CLAIMS

1. An antibody comprising an antigen-binding region capable of binding to human PD-L1, wherein the antibody inhibits the binding of human PD-L1 to human PD-1 and comprises a VH sequence as set forth in SEQ ID NO:18 and a VL sequence as set forth in SEQ ID NO:22~~a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 19, 20 and 21, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:23, the sequence DDN, and the sequence as set forth in SEQ ID NO:24, respectively~~ **[547]**.

2. The antibody according to claim 1, wherein said antibody binds to an epitope on PD-L1 (SEQ ID NO: 94), said epitope comprising the amino acid residue at position 58 (E58) and/or the amino acid residue at position 113 (R113) of SEQ ID NO: 94.

~~3. The antibody according to any one of the preceding claims, wherein said antigen-binding region capable of binding to human PD-L1 comprises a VH sequence which has at least 90%, at least 95%, at least 97%, at least 99%, or 100% amino acid sequence identity to the VH sequence set forth in SEQ ID NO:18.~~

~~4. The antibody according to any one of the preceding claims, wherein said antigen-binding region capable of binding to human PD-L1 comprises a VL sequence which has at least 90%, at least 95%, at least 97%, at least 99%, or 100% amino acid sequence identity to the VL sequence set forth in: SEQ ID NO:22.~~

~~5. The antibody according to any one of the preceding claims, wherein said antigen-binding region capable of binding to human PD-L1 comprises a VH sequence which has at least 90%, at least 95%, at least 97%, at least 99%, or 100% amino acid sequence identity to the VH sequence set forth in: SEQ ID NO:18 and a VL sequence which has at least 90%, at least 95%, at least 97%, at least 99% or 100% amino acid sequence identity to the VL sequence set forth in: SEQ ID NO:22 **[547]**.~~

~~6. The antibody according to claim 5, wherein said VH and VL sequences each comprise three CDR sequences, CDR1, CDR2 and CDR3, respectively, and four framework sequences, FR1, FR2, FR3 and FR4, respectively, and wherein the respective combined~~

~~FR1, FR2, FR3 and FR4 framework sequences of the VH have at least 90%, at least 95%, at least 97%, or at least 99% amino acid sequence identity to the respective combined FR1, FR2, FR3 and FR4 framework sequences of said VH sequences and wherein the VH CDR sequences are not mutated and wherein the respective combined FR1, FR2, FR3 and FR4 framework sequences of the VL have at least 90%, at least 95%, at least 97%, or at least 99% amino acid sequence identity to the respective combined FR1, FR2, FR3 and FR4 framework sequences of said VL sequences and wherein the VL CDR sequences are not mutated.~~

3~~7~~. The antibody according to ~~any one of the preceding claims~~claim 1 or 2, wherein said antibody is capable of inducing dose-dependent lysis of epithelial cells of an adenocarcinoma, such as MDA-MB-231 through antibody-dependent cell-mediated cytotoxicity (ADCC).

4~~8~~. The antibody according to claim ~~7~~3, wherein said antibody is capable of reducing the number of cells in a culture of said epithelial cells by at least 5%, such as at least 6%, 7%, 8%, 9% or at least 10% as a result of cell lysis.

~~9. The antibody according to any one of the preceding claims, wherein said antigen-binding region capable of binding to human PD-L1 comprises a VH sequence as set forth in SEQ ID NO:18 and a VL sequence as set forth in SEQ ID NO:22 **[547]**.~~

5~~10~~. The antibody according to any one of the preceding claims, wherein said antibody is monovalent.

6~~11~~. The antibody according to any one of claims 1 to 4~~9~~, wherein said antibody is a bivalent bispecific antibody, which, in addition to said (first) antigen-binding region capable of binding to human PD-L1, comprises a (second) antigen-binding region capable of binding to a second antigen or to a different epitope of human PD-L1, wherein said second antigen is not human CD3ε.

7~~12~~. A bispecific antibody comprising an antigen-binding region capable of binding to human PD-L1 and an antigen-binding region capable of binding to human CD3ε (epsilon), wherein the antigen-binding region capable of binding to human PD-L1 has the features set forth in any one of the ~~preceding claims~~claims 1-5.

8~~13~~. The bispecific antibody according to claim ~~12~~7, wherein the antigen-binding region capable of binding to human CD3ε comprises (a) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 26, 27, and 28, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:30, the sequence GTN, and the sequence as set forth in SEQ ID NO:31, respectively.

~~14. The bispecific antibody according to claim 12 or 13, comprising an antigen binding region capable of binding to human PD-L1 comprising a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 19, 20 and 21, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences having the sequences as set forth in SEQ ID NO:23, the sequence DDN, and the sequence as set forth in SEQ ID NO:24 **[547]**, respectively, and an antigen binding region capable of binding to human CD3ε comprising (a) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 26, 27, and 28, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:30, the sequence GTN, and the sequence as set forth in SEQ ID NO:31, respectively.~~

9~~15~~. The bispecific antibody according to ~~any one of claims 12 to 14~~claim 7 or 8, wherein the antigen-binding region capable of binding to human CD3ε comprises a VH sequence as set forth in SEQ ID NO:25 and a VL sequence as set forth in SEQ ID NO:29.

~~16. The bispecific antibody according to claim 12, wherein said bispecific antibody is capable of mediating concentration-dependent cytotoxicity of MDA-MB-231 cells, PC-3 cells and/or HELA cells when using PBMCs or purified T cells as effector cells, e.g. when assayed as described in Example 11 herein.~~

10~~17~~. The bispecific antibody according to claim ~~16~~7, wherein the antigen-binding region capable of binding to human CD3ε comprises:

(i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 99, 27, and 28, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having the

sequences as set forth in SEQ ID NO:30, the sequence GTN, and the sequence as set forth in SEQ ID NO:31, respectively, or

(ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 100, 27, and 28, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:30, the sequence GTN, and the sequence as set forth in SEQ ID NO:31, respectively, or

(iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 26, 27, and 101, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:30, the sequence GTN, and the sequence as set forth in SEQ ID NO:31, respectively, or

(iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 26, 27, and 102, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:30, the sequence GTN, and the sequence as set forth in SEQ ID NO:31, respectively, or

(v) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 26, 27, and 103, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:30, the sequence GTN, and the sequence as set forth in SEQ ID NO:31, respectively, or

(vi) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 26, 27, and 104, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:30, the sequence GTN, and the sequence as set forth in SEQ ID NO:31, respectively, or

(vii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 26, 27, and 105, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:30, the sequence GTN, and the sequence as set forth in SEQ ID NO:31, respectively.

11~~8~~. The bispecific antibody according to claim ~~16 or 17~~10, wherein the antigen-binding region capable of binding to human CD3ε comprises:

(i) a VH sequence as set forth in SEQ ID NO:39 and a VL sequence as set forth in SEQ ID NO:29, or

(ii) a VH sequence as set forth in SEQ ID NO:40 and a VL sequence as set forth in SEQ ID NO:29, or

(iii) a VH sequence as set forth in SEQ ID NO:41 and a VL sequence as set forth in SEQ ID NO:29, or

(iv) a VH sequence as set forth in SEQ ID NO:42 and a VL sequence as set forth in SEQ ID NO:29, or

(v) a VH sequence as set forth in SEQ ID NO:43 and a VL sequence as set forth in SEQ ID NO:29, or

(vi) a VH sequence as set forth in SEQ ID NO:44 and a VL sequence as set forth in SEQ ID NO:29, or

(vii) a VH sequence as set forth in SEQ ID NO:45 and a VL sequence as set forth in SEQ ID NO:29.

12~~9~~. A multispecific antibody comprising a first antigen-binding region capable of binding to human PD-L1 and a second antigen-binding region capable of binding to a second antigen or to a different epitope of human PD-L1, wherein said antigen-binding region capable of binding to human PD-L1 has the features set forth in any one of claims 1-~~16~~6.

~~20. The multispecific antibody according to claim 19, wherein said antigen binding region capable of binding to human PD-L1 comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences, wherein the VH CDR3 sequence is set forth in: SEQ ID NO:21 **[547]**.~~

~~21. The multispecific antibody according to claim 20, wherein said first antigen binding region capable of binding to human PD-L1 comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences as set forth in SEQ ID NOs: 19, 20 and 21, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:23, the sequence DDN, and the sequence as set forth in SEQ ID NO:24, respectively **[547]**.~~

~~22. The multispecific antibody according to any one of claims 25 to 26, wherein said first antigen-binding region capable of binding to human PD-L1 comprises a VH sequence which has at least 90%, at least 95%, at least 97%, at least 99%, or 100% amino acid sequence identity to the VH sequence set forth in: SEQ ID NO:18 and a VL sequence which has at least 90%, at least 95%, at least 97%, at least 99% or 100% amino acid sequence identity to the VL sequence set forth in: SEQ ID NO:22 **[547]**.~~

~~23. The multispecific antibody according to any one of claims 20 to 22, wherein said first antigen-binding region capable of binding to human PD-L1 comprises a VH sequence as set forth in SEQ ID NO:18 and a VL sequence as set forth in SEQ ID NO:22 **[547]**.~~

13~~24~~. The multispecific antibody according to ~~any one of claims 20 to 30~~claim 12, wherein the antibody is bispecific.

~~25~~14. The multispecific antibody according to claim ~~24~~13, wherein the antibodyis bivalent.

~~38~~15. The multispecific antibody according to any one of claims ~~20~~ 12 to ~~25~~14, wherein the antibody is capable of binding a second antigen and said second antigen is not human CD3ε.

~~26~~16. The antibody according to any one of the preceding claims, wherein the antibody is a full-length antibody.

~~27~~17. The antibody according to claim ~~24~~16, wherein the antibody is a full-length IgG1 antibody.

~~28~~18. The antibody according to any one of the ~~preceding~~ claims 1-15, wherein the antibody is an antibody fragment.

~~29~~19. The antibody according to any one of the preceding claims, wherein each of the antigen-binding regions comprises a heavy chain variable region (VH) and a light chain variable region (VL), and wherein said variable regions each comprise three CDR sequences, CDR1, CDR2 and CDR3, respectively, and four framework sequences, FR1, FR2, FR3 and FR4, respectively.

~~30~~20. The antibody according to claim ~~29~~19, wherein the antibody comprises two heavy chain constant regions (CH), and two light chain constant regions (CL).

~~31~~21. The antibody according to any one of the preceding claims, wherein the antibody comprises a first and second heavy chain, wherein each of said first and second heavy chains comprises at least a hinge region, a CH2 and a CH3 region, wherein in said first heavy chain 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 (according to EU numbering) has been substituted, and in said second heavy chain 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 (according to EU numbering) has been substituted, and wherein said first and said second heavy chains are not substituted in the same positions.

~~32~~22. The antibody according to claim ~~31~~21, wherein (i) the amino acid in the position corresponding to F405 (according to EU numbering) is L in said first heavy chain, and the amino acid in the position corresponding to K409 (according to EU numbering) is R in said second heavy chain, or (ii) the amino acid in the position corresponding to K409 (according to EU numbering) is R in said first heavy chain, and the amino acid in the position corresponding to F405 (according to EU numbering) is L in said second heavy chain.

~~33~~23. The antibody according to any one of the preceding claims, wherein said antibody comprises a first and a second heavy chain and wherein one or both heavy chains are modified so that the antibody induces Fc-mediated effector function to a lesser extent relative to an antibody which is identical, except for comprising non-modified first and second heavy chains.

~~34~~24. The antibody according to claim ~~33~~23, wherein said Fc-mediated effector function is measured by determining Fc-mediated CD69 expression, by binding to Fcγ receptors, by binding to C1q, or by induction of Fc-mediated cross-linking of FcRs.

~~35~~25. The antibody according to claim ~~33~~ 23 or ~~34~~24, wherein the heavy and light chain constant sequences have been modified so that said antibody reduces Fc-mediated CD69 expression by at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at

least 99% or 100% when compared to a wild-type antibody wherein said Fc-mediated CD69 expression is determined in a PBMC-based functional assay.

~~36~~26. The antibody according to any one of the preceding claims, wherein said antibody comprises a first and a second heavy chain, wherein in at least one of said first and second heavy chains 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.

~~37~~27. The antibody according to claim ~~36~~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.

~~38~~28. The antibody according to claim ~~37~~27, wherein the antibody is a bispecific antibody comprising a first and second heavy chain and wherein the positions corresponding to positions L234 and L235 in a human IgG1 heavy chain according to EU numbering of both the first heavy chain and the second heavy chain 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 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 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.

~~39~~29. The antibody according to claim ~~36~~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 chains.

~~40~~30. The antibody according to claim ~~39~~29, wherein the antibody is a bispecific antibody comprising a first and second heavy chain and wherein the positions corresponding to positions L234, L235, and D265 in a human IgG1 heavy chain according to EU numbering of both the first heavy chain and the second heavy chain 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 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 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.

~~41~~31. The antibody according to any one of the preceding claims, wherein the antibody does not bind to human PD-L2.

~~42. The antibody according to any one of the preceding claims, wherein the antibody binds human PD-L1 with a K_D of 10^{-8} M or less, such as 10^{-9} M or less, e.g. 10^{-10} M or less, when determined as described in Example 8 herein.~~

~~43. The antibody according to any one of the preceding claims, wherein the antibody mediates concentration dependent cytotoxicity of MDA-MB-231 cells, PC-3 cells and/or HELA cells when using purified T cells as effector cells, when assayed as described in Example 11 herein.~~

~~44~~32. A nucleic acid construct comprising:

(i) a nucleic acid sequence encoding a heavy chain sequence of an antibody comprising an antigen-binding region capable of binding to human PD-L1 as defined in any one of claims 1 to ~~31~~6, and/or

(ii) a nucleic acid sequence encoding a light chain sequence of an antibody comprising an antigen-binding region capable of binding to human PD-L1 as defined in any one of claims 1 to ~~31~~6.

~~45~~33. The nucleic acid construct according to claim ~~44~~32, further comprising

(i) a nucleic acid sequence encoding a heavy chain sequence of an antibody comprising an antigen-binding region capable of binding to human CD3ε as defined in any one of claims ~~18~~ 7 to ~~23~~11, and

(ii) a nucleic acid sequence encoding a light chain sequence of an antibody comprising an antigen-binding region capable of binding to human CD3ε as defined in any one of claims ~~18~~ 7 to ~~23~~11.

~~46~~34. An expression vector comprising a nucleic acid construct as defined in claim ~~44~~ 32 or ~~45~~33.

~~47~~35. A host cell comprising a nucleic acid construct as defined in claim ~~44~~ 32 or ~~45~~ 33 or an expression vector as defined in claim ~~46~~34.

~~48~~36. The host cell according to claim ~~47~~35, wherein said host cell is a mammalian cell, such as a Chinese hamster ovary cell.

~~49~~37. A pharmaceutical composition comprising an antibody according to any one of claims 1 to ~~43~~ 31 and a pharmaceutically-acceptable carrier.

~~50~~38. The antibody according to any one of claims 1 to ~~43~~ 31 or the pharmaceutical composition according to claim ~~49~~ 37 for use as a medicament.

~~51~~39. The antibody according to any one of claims 1 to ~~43~~ 31 or the pharmaceutical composition according to claim ~~49~~ 37 for use in the treatment of cancer.

~~52~~40. The antibody according to any one of claims 1 to ~~43~~ 31 or the pharmaceutical composition according to claim ~~49~~ 37 for use in the treatment of a cancer disease characterised by the presence of solid tumors.

~~53~~41. The antibody according to any one of claims 1 to ~~44~~ 31 or the pharmaceutical composition according to claim ~~49~~ 37 for use in the treatment of a cancer disease selected from the group consisting of: melanoma, ovarian cancer, lung cancer, colon cancer and head and neck cancer.

~~54~~42. Use of an antibody according to any one of claims 1 to ~~43~~ 31 for the manufacture of a medicament~~, such as a medicament~~ for the treatment of cancer, e.g. a cancer disease characterized by the presence of solid tumors or a cancer disease selected from the group consisting of: melanoma, ovarian cancer, lung cancer, colon cancer and head and neck cancer.

~~55~~43. The antibody or the pharmaceutical composition for according to any one of claims ~~49~~ 37 to ~~53~~ 41 or the use of an antibody according to claim ~~67~~ 42 wherein the use comprises combination with one or more further therapeutic agent, such as a chemotherapeutic agent.

~~56~~44. A method for producing an antibody according to any one of claims 1 to ~~43~~31, wherein the antibody is a bispecific antibody, comprising the steps of:

a) culturing a host cell producing a first antibody comprising an antigen-binding region capable of binding to human PD-L1 as defined in any one of claims 1 to ~~8~~ 6 and purifying said first antibody from the culture;

b) culturing a host cell producing a second antibody comprising an antigen-binding region capable of binding to a different epitope of PD-L1 or a different antigen, e.g. a human CD3ε-binding region as defined in any one of claims ~~3~~ 7 to ~~7~~11, and 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 bispecific antibody.

~~57. An anti idiotypic antibody which binds to the antigen binding region capable of binding to human PD-L1 as defined in any one of claims 1 to 43.~~