

tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Activated T cells transiently express PD1, but sustained hyperexpression of PD1 and its ligand PDL1 promote immune exhaustion, leading to persistence of viral infections, tumor evasion, increased infections and mortality. PD1 expression is induced by antigen recognition via the T-cell receptor and its expression is maintained primarily through continuous T-cell receptor signaling. After prolonged antigen exposure, the PD1 locus fails to be remethylated, which promotes continuous hyperexpression. Blocking the PD1 pathway can restore the exhausted T-cell functionality in cancer and chronic viral infections (Sheridan, Nature Biotechnology 30 (2012), 729-730). Monoclonal antibodies to PD-1 have been described, for example, in WO 2003/042402, WO 2004/004771, WO 2004/056875, WO 2004/072286, WO 2004/087196, WO 2006/121168, WO 2006/133396, WO 2007/005874, WO 2008/083174, WO 2008/156712, WO 2009/024531, WO 2009/014708, WO 2009/101611, WO 2009/114335, WO 2009/154335, WO 2010/027828, WO 2010/027423, WO 2010/029434, WO 2010/029435, WO 2010/036959, WO 2010/063011, WO 2010/089411, WO 2011/066342, WO 2011/110604, WO 2011/110621, WO 2012/145493, WO 2013/014668, WO 2014/179664, and WO 2015/112900.

Bispecific Fc diabodies having immunoreactivity with PD1 and LAG3 for use in the treatment of cancer or a disease associated with a pathogen such as a bacterium, a fungus or a virus are described in WO 2015/200119. However, there is a need of providing new bispecific antibodies that not only simultaneously bind to PD1 and LAG3 and thus selectively target cells expressing both PD1 and LAG3, but that also avoid blocking of LAG3 on other cells given the broad expression pattern of LAG3. The bispecific antibodies of the present invention do not only effectively block PD1 and LAG3 on T cells overexpressing both PD1 and LAG3, they are very selective for these cells and thereby side effects by administering highly active LAG3 antibodies may be avoided.

SUMMARY

The present disclosure relates to bispecific antibodies comprising at least one antigen binding domain that specifically binds to programmed cell death protein 1 (PD1) and at least one second antigen binding domain that specifically binds to Lymphocyte activation gene-3 (LAG3). These bispecific antibodies are advantageous as they provide better selectivity and, potentially, efficacy than anti-PD1 and anti-LAG3 combination strategies. They are further characterized in that show a reduced sink effect (as shown by reduced internalization by T cells), they preferentially bind to conventional T cells as to Tregs and are able to rescue T cell effector functions from Treg suppression, they show increased tumor-specific T cell effector functions and increased tumor eradication *in vivo*.

In one aspect, the disclosure provides a bispecific antibody comprising a first antigen binding domain that specifically binds to programmed cell death protein 1 (PD1) and a second antigen binding domain that specifically binds to Lymphocyte activation gene-3 (LAG3), wherein

- 5 said first antigen binding domain specifically binding to PD1 comprises
 a VH domain comprising
 (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:1,
 (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:2, and
 (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:3; and
10 a VL domain comprising
 (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:4;
 (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:5, and
 (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:6.

15 In particular, provided is a bispecific antibody comprising a first antigen binding domain
that specifically binds to programmed cell death protein 1 (PD1) and a second antigen binding
domain that specifically binds to Lymphocyte activation gene-3 (LAG3), wherein the bispecific
antibody comprises a Fc domain that is an IgG, particularly an IgG1 Fc domain or an IgG4 Fc
domain and wherein the Fc domain comprises one or more amino acid substitution that reduces
binding to an Fc receptor, in particular towards Fcγ receptor.

20 There is provided a bispecific antibody comprising a first antigen binding domain that
specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3,
wherein the second antigen binding domain that specifically binds to LAG3 comprises

- (a) a VH domain comprising
 (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:14,
25 (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:15, and
 (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:16; and
 a VL domain comprising
 (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:17,
 (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:18, and
30 (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19; or
 (b) a VH domain comprising
 (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:22,
 (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:23, and
 (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:24; and
35 a VL domain comprising

- (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:25,
- (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:26, and
- (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:27; or

(c) a VH domain comprising

- (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:30,
 - (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:31, and
 - (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:32; and
- a VL domain comprising

- (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:33,
- (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:34, and
- (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:35; or

(d) a VH domain comprising

- (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:38,
 - (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:39, and
 - (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:40; and
- a VL domain comprising

- (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:41,
- (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:42, and
- (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:43; or

(e) a VH domain comprising

- (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:46,
 - (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:47, and
 - (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:48; and
- a VL domain comprising

- (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:49,
- (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:50, and
- (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:51.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, wherein the first antigen-binding domain specifically binding to PD1 comprises

- (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 7 and a VL domain comprising the amino acid sequence of SEQ ID NO: 8, or
- (b) a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10, or

(c) a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 11, or

(d) a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 12, or

5 (e) a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 13.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, wherein the first antigen-binding domain specifically binding to PD1 comprises a VH domain
10 comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein the second antigen-binding domain specifically binding to
15 LAG3 comprises

(a) a VH domain comprising the amino acid sequence of SEQ ID NO: 20 and a VL domain comprising the amino acid sequence of SEQ ID NO: 21, or

(b) a VH domain comprising the amino acid sequence of SEQ ID NO: 28 and a VL domain comprising the amino acid sequence of SEQ ID NO: 29, or

20 (c) a VH domain comprising the amino acid sequence of SEQ ID NO: 36 and a VL domain comprising the amino acid sequence of SEQ ID NO: 37, or

(d) a VH domain comprising the amino acid sequence of SEQ ID NO: 44 and a VL domain comprising the amino acid sequence of SEQ ID NO: 45, or

25 (e) a VH domain comprising the amino acid sequence of SEQ ID NO: 52 and a VL domain comprising the amino acid sequence of SEQ ID NO: 53.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein the second antigen-binding domain specifically binding to LAG3 comprises

30 (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 54 and a VL domain comprising the amino acid sequence of SEQ ID NO: 55, or

(b) a VH domain comprising the amino acid sequence of SEQ ID NO: 62 and a VL domain comprising the amino acid sequence of SEQ ID NO: 63, or

(c) a VH domain comprising the amino acid sequence of SEQ ID NO: 64 and a VL domain comprising the amino acid sequence of SEQ ID NO: 65, or

(d) a VH domain comprising the amino acid sequence of SEQ ID NO: 66 and a VL domain comprising the amino acid sequence of SEQ ID NO: 67.

5 Furthermore, provided is a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein

10 the first antigen binding domain specifically binding to PD1 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10,

15 and the second antigen binding domain specifically binding to LAG3 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 20 and a VL domain comprising the amino acid sequence of SEQ ID NO: 21 or a VH domain comprising the amino acid sequence of SEQ ID NO: 52 and a VL domain comprising the amino acid sequence of SEQ ID NO: 53.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein

20 the first antigen binding domain specifically binding to PD1 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10,

and the second antigen binding domain specifically binding to LAG3 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 20 and a VL domain comprising the amino acid sequence of SEQ ID NO: 21.

25 There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein

30 the first antigen binding domain specifically binding to PD1 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10,

and the second antigen binding domain specifically binding to LAG3 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 56 and a VL domain comprising the amino acid sequence of SEQ ID NO: 57.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein the bispecific antibody is a humanized or chimeric antibody. In particular, the bispecific antibody is a humanized antibody.

5 There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein the bispecific antibody comprises an Fc domain of human IgG1 subclass with the amino acid mutations L234A, L235A and P329G (numbering according to Kabat EU index).

10 Furthermore, provided is a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein the bispecific antibody comprises an Fc domain comprising a modification promoting the association of the first and second subunit of the Fc domain. There is provided a bispecific antibody, wherein the first subunit of the Fc domain
15 comprises knobs and the second subunit of the Fc domain comprises holes according to the knobs into holes method. In particular, the first subunit of the Fc domain comprises the amino acid substitutions S354C and T366W (EU numbering) and the second subunit of the Fc domain comprises the amino acid substitutions Y349C, T366S and Y407V (numbering according to Kabat EU index).

20 There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, wherein the bispecific antibody comprises an Fc domain, a first Fab fragment comprising the antigen binding domain that specifically binds to PD1 and a second Fab fragment comprising the antigen binding domain that specifically binds to LAG3.

25 There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, wherein in one of the Fab fragments the the variable domains VL and VH are replaced by each other so that the VH domain is part of the light chain and the VL domain is part of the heavy chain. Particularly, provided is bispecific antibody, wherein in the first Fab fragment comprising
30 the antigen binding domain that specifically binds to PD1 the variable domains VL and VH are replaced by each other.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, wherein the bispecific antibody comprises a Fab fragment wherein in the constant domain CL
35 the amino acid at position 124 is substituted independently by lysine (K),

arginine (R) or histidine (H) (numbering according to Kabat EU Index), and in the constant domain CH1 the amino acids at positions 147 and 213 are substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to Kabat EU index). Particularly, provided is bispecific antibody, wherein in the second Fab fragment comprising the antigen binding domain that specifically binds to LAG3 the constant domain CL the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat EU Index), and in the constant domain CH1 the amino acids at positions 147 and 213 are substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to Kabat EU index).

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, comprising

(a) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 96, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 98, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 97, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:99, or

(b) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 96, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 98, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 100, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:101, or

(c) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 102, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 104, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 103, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:105, or

(d) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 106, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 107, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 103, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:105.

More particularly, provided is a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 96, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 98, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 100, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:101.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein the bispecific antibody comprises a Fab fragment comprising the antigen binding domain that specifically binds to LAG3 which is fused to the C-terminus of the Fc domain.

In particular, provided is a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 96, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 98, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 144, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:101.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein the bispecific antibody comprises a third Fab fragment comprising an antigen binding domain that specifically binds to LAG3. In one example, provided is a bispecific antibody, wherein the two Fab fragments comprising each an antigen binding domain that specifically binds to LAG3 are identical.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein the Fab fragment comprising the antigen binding domain that specifically binds to PD1 is fused via a peptide linker to the C-terminus of one of the heavy chains.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, comprising

- (a) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 118, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 115,
5 a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 119, and two second light chains comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:101, or
- (b) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 120, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 115,
10 a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 121, and two second light chains comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:99, or
- (c) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 122, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 115,
15 a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 103, and two second light chains comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:105.

20 There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein one of the Fab fragments comprising the antigen binding domain that specifically binds to LAG3 is fused via a peptide linker to the C-terminus of one of the heavy chains.

25 There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 96, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 98, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 145, and two
30 second light chains comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:101.

35 There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein the bispecific antibody comprises a fourth Fab fragment comprising an antigen binding domain that specifically binds to PD1. In one example,

provided is a bispecific antibody, wherein the two Fab fragments comprising each an antigen binding domain that specifically binds to PD1 are identical.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein before, wherein the two Fab fragments comprising each an antigen binding domain that specifically binds to PD1 are each fused via a peptide linker to the C-terminus to one of the heavy chains, respectively.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, comprising

(a) two heavy chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 114, two first light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 115, and two second light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 101, or

(b) two heavy chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 116, two first light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 115, and two second light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:99, or

(c) two heavy chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 117, two first light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 115, and two second light chains comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:105.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, wherein the bispecific antibody comprises an Fc domain, two Fab fragments comprising each an antigen binding domain that specifically binds to LAG3 and a single chain Fab (scFab) comprising the antigen binding domain that specifically binds to PD1. In particular, the scFab comprising an antigen binding domain that specifically binds to PD1 is fused via a peptide linker to the C-terminus to one of the heavy chains.

There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, comprising

- 5 (a) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 123, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 119, and two light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 101, or
- 10 (b) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 124, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 121, and two light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 99, or
- 15 (c) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 125, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 103, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 105.

20 There is provided a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, wherein the bispecific antibody comprises an Fc domain, two Fab fragments comprising each an antigen binding domain that specifically binds to LAG3 and a VH and VL domain comprising the antigen binding domain that specifically binds to PD1. In one example, the VH domain of the antigen binding domain that specifically binds to PD1 is fused via a peptide linker to the C-

25 terminus of one of the heavy chains and the VL domain of the antigen binding domain that specifically binds to PD1 is fused via a peptide linker to the C-terminus of the other one of the heavy chains. There is provided a bispecific antibody, comprising a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 126, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 127, and two light chains comprising each an amino acid sequence

30 with at least 95% sequence identity to the sequence of SEQ ID NO: 109.

According to another aspect of the disclosure, there is provided a polynucleotide encoding the bispecific antibody as described herein before. The disclosure further provides a vector, particularly an expression vector, comprising a polynucleotide of the disclosure and a

35 prokaryotic

or eukaryotic host cell comprising the polynucleotide or the vector of the disclosure. According to another aspect of the disclosure, there is provided a prokaryotic or eukaryotic host cell comprising the polynucleotide as described herein before. In some embodiments the host cell is a eukaryotic cell, particularly a mammalian cell.

5 There is provided a method for producing bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein, comprising the steps of a) transforming a host cell with vectors comprising polynucleotides encoding said bispecific antibody, b) culturing the host cell according under conditions suitable for the expression of the bispecific antibody and c)
10 recovering the bispecific antibody from the culture. The disclosure also encompasses a bispecific antibody produced by the method of the disclosure.

 In another aspect, there is provided a method of producing the bispecific antibody as described herein before, comprising culturing the host cell as described herein before under conditions suitable for the expression of the bispecific antibody and recovering the bispecific
15 antibody from the culture.

 The disclosure further provides a pharmaceutical composition comprising a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein, and at least one pharmaceutically acceptable excipient. In another aspect, there is provided a pharmaceutical
20 composition comprising the bispecific antibody as described herein before and at least one pharmaceutically acceptable excipient.

 Also encompassed by the disclosure is the bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein, or the pharmaceutical composition comprising
25 the bispecific antibody, for use as a medicament. In another aspect, there is provided the bispecific antibody as described herein before or the pharmaceutical composition as described herein before for use as a medicament.

 The disclosure provides a bispecific antibody comprising a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding
30 domain that specifically binds to LAG3 as described herein, or the pharmaceutical composition comprising the bispecific antibody, for use
i) in the modulation of immune responses, such as restoring T cell activity,
ii) in stimulating an immune response or function,
iii) in the treatment of infections,
35 iv) in the treatment of cancer,

- v) in delaying progression of cancer,
- vi) in prolonging the survival of a patient suffering from cancer.

5 In another aspect, there is provided the bispecific antibody as described herein before or the pharmaceutical composition as described herein before for use

- i) in the modulation of immune responses, such as restoring T cell activity,
- ii) in stimulating a T cell response,
- iii) in the treatment of infections,
- iv) in the treatment of cancer,
- 10 v) in delaying progression of cancer,
- vi) in prolonging the survival of a patient suffering from cancer.

There is provided the bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein, or the pharmaceutical composition comprising the bispecific antibody, for
15 use in the treatment of a disease in an individual in need thereof. In a specific example, the disclosure provides a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, or the pharmaceutical composition comprising the bispecific antibody, for use in the treatment of cancer. In a further specific example, a bispecific antibody comprising a first antigen

binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, or the pharmaceutical composition comprising the bispecific antibody, for use in the modulation of immune responses is provided. In another example, a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3, or a pharmaceutical composition comprising the bispecific antibody for use in the treatment of a chronic viral infection is provided.

In another aspect, there is provided the bispecific antibody as described herein before or the pharmaceutical composition as described herein before for use in the treatment of cancer.

In another aspect, there is provided the bispecific antibody as described herein before or the pharmaceutical composition as described herein before for use in the treatment of a chronic viral infection.

In another aspect, there is provided the bispecific antibody as described herein before or the pharmaceutical composition as described herein before for use in the prevention or treatment of cancer, wherein the bispecific antibody is to be administered in combination with a chemotherapeutic agent, radiation and/ or other agents for use in cancer immunotherapy.

In another aspect, there is provided the bispecific antibody as described herein before or the pharmaceutical composition as described herein before for use in the prevention or treatment of cancer, wherein the bispecific antibody is to be administered in combination with an anti-CEA/anti-CD3 bispecific antibody.

The disclosure also provides a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein, or a pharmaceutical composition comprising the bispecific antibody for use in the prevention or treatment of cancer, wherein the bispecific antibody is administered in combination with a chemotherapeutic agent, radiation and/or other agents for use in cancer immunotherapy. In a particular example, provided is bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein, or a pharmaceutical composition comprising the bispecific antibody for use in the prevention or treatment of cancer, wherein the bispecific antibody is administered in combination with an anti-CEA/anti-CD3 bispecific antibody.

Also provided is the use of the bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein for the manufacture of a medicament for the treatment of a disease in an individual in need thereof, in particular for the manufacture of a medicament for the treatment of cancer, as well as a method of treating a disease in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein in a pharmaceutically acceptable form.

In another aspect, there is provided use of the bispecific antibody as described herein before or the pharmaceutical composition as described herein before in the manufacture of a medicament for the treatment of cancer or infectious diseases.

In a specific example, the disease is cancer. In another specific example, the disease is a chronic viral infection. In another example, a method of modulating of immune responses in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising the bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein in a pharmaceutically acceptable form is provided. In any of the above examples the individual is preferably a mammal, particularly a human.

The disclosure also provides a bispecific antibody comprising a first antigen binding domain that specifically binds to PD1 and a second antigen binding domain that specifically binds to LAG3 as described herein, or a pharmaceutical composition comprising the bispecific

Claims

1. A bispecific antibody comprising a first antigen binding domain that specifically binds to programmed cell death protein 1 (PD1) and a second antigen binding domain that specifically binds to Lymphocyte activation gene-3 (LAG3), wherein
 - 5 said first antigen binding domain specifically binding to PD1 comprises
 - a VH domain comprising
 - (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:1,
 - (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:2, and
 - (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:3; and
 - 10 a VL domain comprising
 - (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:4;
 - (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:5, and
 - (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:6.
2. The bispecific antibody of claim 1, wherein the bispecific antibody comprises a Fc domain
 - 15 that is an IgG, particularly an IgG1 Fc domain or an IgG4 Fc domain and wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor, in particular towards Fc γ receptor.
3. The bispecific antibody of claims 1 or 2, wherein the second antigen binding domain that specifically binds to LAG3 comprises
 - 20 (a) a VH domain comprising
 - (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:14,
 - (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:15, and
 - (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:16; and
 - a VL domain comprising
 - 25 (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:17,
 - (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:18, and
 - (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:19; or
 - (b) a VH domain comprising
 - (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:22,
 - 30 (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:23, and
 - (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:24; and
 - a VL domain comprising
 - (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:25,
 - (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:26, and
 - 35 (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:27; or

(c) a VH domain comprising

- (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:30,
- (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:31, and
- (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:32; and

5 a VL domain comprising

- (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:33,
- (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:34, and
- (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:35; or

(d) a VH domain comprising

- 10
- (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:38,
 - (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:39, and
 - (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:40; and

a VL domain comprising

- 15
- (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:41,
 - (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:42, and
 - (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:43; or

(e) a VH domain comprising

- 20
- (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:46,
 - (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:47, and
 - (iii) HVR-H3 comprising an amino acid sequence of SEQ ID NO:48; and

a VL domain comprising

- (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:49,
- (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:50, and
- (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:51.

25 4. The bispecific antibody according to any one of claims 1 to 3, wherein the first antigen-binding domain specifically binding to PD1 comprises

(a) a VH domain comprising the amino acid sequence of SEQ ID NO: 7 and a VL domain comprising the amino acid sequence of SEQ ID NO: 8, or

30 (b) a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10, or

(c) a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 11, or

(d) a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 12, or

(e) a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 13.

5. The bispecific antibody according to any one of claims 1 to 4, wherein the first antigen-binding domain specifically binding to PD1 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10.

6. The bispecific antibody according to any one of claims 1 to 5, wherein the second antigen-binding domain specifically binding to LAG3 comprises

(a) a VH domain comprising the amino acid sequence of SEQ ID NO: 20 and a VL domain comprising the amino acid sequence of SEQ ID NO: 21, or

(b) a VH domain comprising the amino acid sequence of SEQ ID NO: 28 and a VL domain comprising the amino acid sequence of SEQ ID NO: 29, or

(c) a VH domain comprising the amino acid sequence of SEQ ID NO: 36 and a VL domain comprising the amino acid sequence of SEQ ID NO: 37, or

(d) a VH domain comprising the amino acid sequence of SEQ ID NO: 44 and a VL domain comprising the amino acid sequence of SEQ ID NO: 45, or

(e) a VH domain comprising the amino acid sequence of SEQ ID NO: 52 and a VL domain comprising the amino acid sequence of SEQ ID NO: 53.

7. The bispecific antibody according to any one of claims 1 to 5, wherein the second antigen-binding domain specifically binding to LAG3 comprises

(a) a VH domain comprising the amino acid sequence of SEQ ID NO: 54 and a VL domain comprising the amino acid sequence of SEQ ID NO: 55, or

(b) a VH domain comprising the amino acid sequence of SEQ ID NO: 62 and a VL domain comprising the amino acid sequence of SEQ ID NO: 63, or

(c) a VH domain comprising the amino acid sequence of SEQ ID NO: 64 and a VL domain comprising the amino acid sequence of SEQ ID NO: 65, or

(d) a VH domain comprising the amino acid sequence of SEQ ID NO: 66 and a VL domain comprising the amino acid sequence of SEQ ID NO: 67.

8. The bispecific antibody according any one of claims 1 to 6, wherein

the first antigen binding domain specifically binding to PD1 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10,

5 and the second antigen binding domain specifically binding to LAG3 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 20 and a VL domain comprising the amino acid sequence of SEQ ID NO: 21 or a VH domain comprising the amino acid sequence of SEQ ID NO: 52 and a VL domain comprising the amino acid sequence of SEQ ID NO: 53.

9. The bispecific antibody according any one of claims 1 to 6 or 8, wherein

10 the first antigen binding domain specifically binding to PD1 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10,

and the second antigen binding domain specifically binding to LAG3 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 20 and a VL domain comprising the amino acid sequence of SEQ ID NO: 21.

10. The bispecific antibody according any one of claims 1 to 5 or 7, wherein

the first antigen binding domain specifically binding to PD1 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 9 and a VL domain comprising the amino acid sequence of SEQ ID NO: 10,

20 and the second antigen binding domain specifically binding to LAG3 comprises a VH domain comprising the amino acid sequence of SEQ ID NO: 56 and a VL domain comprising the amino acid sequence of SEQ ID NO: 57.

11. The bispecific antibody of any one of claims 1 to 10, wherein the bispecific antibody comprises an Fc domain of human IgG1 subclass with the amino acid mutations L234A, 25 L235A and P329G (numbering according to Kabat EU index).

12. The bispecific antibody of any one of claims 1 to 11, wherein the bispecific antibody comprises an Fc domain comprising a modification promoting the association of the first and second subunit of the Fc domain.

13. The bispecific antibody of any one of claims 1 to 13, wherein the first subunit of the Fc domain comprises the amino acid substitutions S354C and T366W (numbering according to 30

Kabat EU index) and the second subunit of the Fc domain comprises the amino acid substitutions Y349C, T366S and Y407V (numbering according to Kabat EU index).

14. The bispecific antibody of any one of claims 1 to 13, wherein the bispecific antibody comprises an Fc domain, a first Fab fragment comprising the antigen binding domain that specifically binds to PD1 and a second Fab fragment comprising the antigen binding domain that specifically binds to LAG3.
15. The bispecific antibody of any one of claims 1 to 14, wherein in one of the Fab fragments the the variable domains VL and VH are replaced by each other so that the VH domain is part of the light chain and the VL domain is part of the heavy chain.
16. The bispecific antibody of claim 14 or 15, wherein in the first Fab fragment comprising the antigen binding domain that specifically binds to PD1 the variable domains VL and VH are replaced by each other.
17. The bispecific antibody of any one of claims 1 to 16, wherein the bispecific antibody comprises a Fab fragment wherein in the constant domain CL the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat EU Index), and in the constant domain CH1 the amino acids at positions 147 and 213 are substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to Kabat EU index).
18. The bispecific antibody of any one of claims 14 to 17, wherein in the second Fab fragment comprising the antigen binding domain that specifically binds to LAG3 the constant domain CL the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat EU Index), and in the constant domain CH1 the amino acids at positions 147 and 213 are substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to Kabat EU index).
19. The bispecific antibody of any one of claims 1 to 18, comprising
 - (a) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 96, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 98, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 97, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:99, or

- (b) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 96, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 98,
a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 100, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:101, or
- (c) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 102, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 104,
a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 103, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:105, or
- (d) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 106, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 107,
a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 103, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:105.
20. The bispecific antibody of any one of claims 1 to 19, comprising a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 96, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 98, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 100, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:101.
21. The bispecific antibody of any one of claims 1 to 18, wherein the bispecific antibody comprises a second Fab fragment comprising the antigen binding domain that specifically binds to LAG3 which is fused to the C-terminus of the Fc domain.
22. The bispecific antibody of any one of claims 1 to 18 or 21, comprising a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 96, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 98, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 144,

and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:101.

23. The bispecific antibody of any one of claims 1 to 18, wherein the bispecific antibody comprises a third Fab fragment comprising an antigen binding domain that specifically binds to LAG3.

24. The bispecific antibody of any one of claims 1 to 18 or 22 or 23, wherein the Fab fragment comprising the antigen binding domain that specifically binds to PD1 is fused via a peptide linker to the C-terminus of one of the heavy chains.

25. The bispecific antibody of any one of claims 1 to 18 or 22 to 24, comprising

(a) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 118, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 115,

a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 119, and two second light chains comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:101, or

(b) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 120, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 115,

a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 121, and two second light chains comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:99, or

(c) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 122, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 115,

a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 103, and two second light chains comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:105.

26. The bispecific antibody of any one of claims 1 to 18 or 22 or 23, wherein one of the Fab fragments comprising the antigen binding domain that specifically binds to LAG3 is fused via a peptide linker to the C-terminus of one of the heavy chains.

27. The bispecific antibody of any one of claims 1 to 18 or 22 or 23 or 26, comprising (a) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the

sequence of SEQ ID NO: 96, a first light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 98, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 145, and two second light chains comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:101.

28. The bispecific antibody of any one of claims 1 to 11, 14 to 18 or 22 to 24, wherein the bispecific antibody comprises a fourth Fab fragment comprising an antigen binding domain that specifically binds to PD1.

29. The bispecific antibody of any one of claims 1 to 11, 14 to 18 or 22 to 24 or 28, wherein the two Fab fragments comprising each an antigen binding domain that specifically binds to PD1 are identical.

30. The bispecific antibody of any one of claims 1 to 11, 14 to 18 or 22 to 24 or 28 or 29, wherein the two Fab fragments comprising each an antigen binding domain that specifically binds to PD1 are each fused via a peptide linker to the C-terminus to one of the heavy chains, respectively.

31. The bispecific antibody of any one of claims 1 to 11, 14 to 18 or 22 to 24 or 28 to 30, comprising

(a) two heavy chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 114, two first light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 115, and two second light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 101, or

(b) two heavy chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 116, two first light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 115, and two second light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:99, or

(c) two heavy chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 117, two first light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 115, and two second light chains comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:105.

32. The bispecific antibody of any one of claims 1 to 13, wherein the bispecific antibody comprises an Fc domain, two Fab fragments comprising each an antigen binding domain that specifically binds to LAG3 and a single chain Fab (scFab) comprising the antigen binding domain that specifically binds to PD1.

5 33. The bispecific antibody of any one of claims 1 to 13 or 32, wherein the scFab comprising an antigen binding domain that specifically binds to PD1 is fused via a peptide linker to the C-terminus to one of the heavy chains.

34. The bispecific antibody of any one of claims 1 to 13 or 32 or 33, comprising

10 (a) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 123, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 119, and two light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 101, or

15 (b) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 124, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 121, and two light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:99, or

20 (c) a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 125, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 103, and a second light chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO:105.

25 35. The bispecific antibody of any one of claims 1 to 13, wherein the bispecific antibody comprises an Fc domain, two Fab fragments comprising each an antigen binding domain that specifically binds to LAG3 and a VH and VL domain comprising the antigen binding domain that specifically binds to PD1.

30 36. The bispecific antibody of any one of claims 1 to 13 or 35, wherein the VH domain of the antigen binding domain that specifically binds to PD1 is fused via a peptide linker to the C-terminus of one of the heavy chains and the VL domain of the antigen binding domain that specifically binds to PD1 is fused via a peptide linker to the C-terminus of the other one of the heavy chains.

37. The bispecific antibody of any one of claims 1 to 13 or 35 or 36, comprising a first heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 126, a second heavy chain comprising an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 127, and two light chains comprising each an amino acid sequence with at least 95% sequence identity to the sequence of SEQ ID NO: 109.
38. A polynucleotide encoding the bispecific antibody of any one of claims 1 to 37.
39. A prokaryotic or eukaryotic host cell comprising the polynucleotide according to claim 38.
40. A method of producing the bispecific antibody according to claims 1 to 37, comprising culturing the host cell of claim 42 under conditions suitable for the expression of the bispecific antibody and recovering the bispecific antibody from the culture.
41. A pharmaceutical composition comprising the bispecific antibody according to any one of claims 1 to 37 and at least one pharmaceutically acceptable excipient.
42. The bispecific antibody according to any one of claims 1 to 37 or the pharmaceutical composition according to claim 41 for use as a medicament.
43. The bispecific antibody according to any one of claims 1 to 37 or the pharmaceutical composition according to claim 41 for use
- i) in the modulation of immune responses, such as restoring T cell activity,
 - ii) in stimulating a T cell response,
 - iii) in the treatment of infections,
 - iv) in the treatment of cancer,
 - v) in delaying progression of cancer,
 - vi) in prolonging the survival of a patient suffering from cancer.
44. The bispecific antibody according to any one of claims 1 to 37 or the pharmaceutical composition according to claim 41 for use in the treatment of cancer.
45. The bispecific antibody according to any one of claims 1 to 37 or the pharmaceutical composition according to claim 41 for use in the treatment of a chronic viral infection.
46. The bispecific antibody according to any one of claims 1 to 37 or the pharmaceutical composition according to claim 41 for use in the prevention or treatment of cancer, wherein

the bispecific antibody is to be administered in combination with a chemotherapeutic agent, radiation and/ or other agents for use in cancer immunotherapy.

47. The bispecific antibody according to any one of claims 1 to 37 or the pharmaceutical composition according to claim 41 for use in the prevention or treatment of cancer, wherein
5 the bispecific antibody is to be administered in combination with an anti-CEA/anti-CD3 bispecific antibody.

48. Use of the bispecific antibody according to any one of claims 1 to 37 or the pharmaceutical composition according to claim 41 in the manufacture of a medicament for the treatment of cancer or infectious diseases.