

CLAIMS

1. A bispecific antibody or an antibody fragment thereof, having the first arm specifically binding to PD-1 and the second arm specifically binding to CD19, and specifically binding to PD-1 and CD19, respectively, wherein the first arm specifically binding to PD-1 comprises any one of VH selected from

(A) a VH having

- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 18,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 19, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 20,

(B) a VH having

- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 6,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 7, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 8,

(C) a VH having

- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 9,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 10, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 11,

(D) a VH having

- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 12,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 13, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 14,

(E) a VH having

- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 15,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 16, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 17, and

the second arm specifically binding to CD19 comprises any one of VH selected from

(A) a VH having

- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 35,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 36, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 37,

(B) a VH having

- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No.38,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No.39, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No.40,

(C) a VH having

- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No.41,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No.42, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No.43,

(D) a VH having

- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No.44,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No.45, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No.46, and

(E) a VH having

- (a) a VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No.47,
- (b) a VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No.48, and
- (c) a VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No.49, and

wherein one to five arbitrary amino acid residues may be substituted with conservative amino acids thereof in any one or more of CDRs selected from the VH-CDR1, VH-CDR2 and VH-CDR3 in the VH of the first arm specifically binding to PD-1, respectively; and/or one to five arbitrary amino acid residues may be substituted with conservative amino acids thereof in any one or more of CDRs selected from the VH-CDR1, VH-CDR2 and VH-CDR3 in the VH of the second arm specifically binding to CD19, and

wherein the first arm specifically binding to PD-1 and the second arm specifically binding to CD19 have the VL having

- (a) the VL-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 26,
- (b) the VL-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 27, and
- (c) the VL-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 28, respectively.

2. The bispecific antibody or antibody fragment thereof according to claim 1, wherein the first arm specifically binding to PD-1 comprises any one of VH selected from

(A) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 18,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 19,
- and

- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 20,

(B) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 6,
- (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 7, and
- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 8,

(C) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 9,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 10,
- and

- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 11,

(D) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 12,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 13,
- and

- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 14,

(E) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 15,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 16,
- and

- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 17,
- and

the second arm specifically binding to CD19 comprises any one of VH selected from

(A) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 35,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 36,
- and

- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 37,

(B) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No.38,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No.39,
- and

- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No.40,

(C) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No.41,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No.42,
- and

- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No.43,

(D) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No.44,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No.45, and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No.46, and

(E) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No.47,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No.48, and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No.49, and wherein the first arm specifically binding to PD-1 and the second arm specifically binding to CD19 have the VL having

(a) the VL-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 26,

(b) the VL-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 27, and

(c) the VL-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 28, respectively.

3. The bispecific antibody or antibody fragment thereof according to claim 1 or 2,

wherein (i) the VH of the first arm specifically binding to PD-1 has

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 18,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 19, and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 20, and

(ii) the VH of the second arm specifically binding to CD19 is any one selected from

(A) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 35,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 36, and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 37,

(B) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 38,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 39, and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 40,

(C) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 41,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 42, and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 43,

(D) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 44,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 45, and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 46, and

(E) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 47,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 48, and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 49.

4. The bispecific antibody or antibody fragment thereof according to claim 1 or 2, wherein (i) the VH of the first arm specifically binding to PD-1 has
- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 6,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 7, and
 - (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 8, and
- (ii) the VH of the second arm specifically binding to CD19 is any one selected from
- (A) the VH having
 - (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 35,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 36, and
 - (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 37,
 - (B) the VH having
 - (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 38,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 39, and
 - (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 40,
 - (C) the VH having
 - (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 41,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 42, and
 - (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 43,
 - (D) the VH having
 - (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 44,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 45, and
 - (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 46,
 - (E) the VH having
 - (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 47,
 - (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 48, and
 - (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 49.

5. The bispecific antibody or antibody fragment thereof according to claim 1 or 2,

wherein (i) the VH of the first arm specifically binding to PD-1 has

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 9,
- (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 10,
- and
- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 11,
- and

(ii) the VH of the second arm specifically binding to CD19 is any one selected from

(A) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 35,
- (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 36,
- and
- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 37,

(B) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 38,
- (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 39,
- and
- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 40,

(C) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 41,
- (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 42,
- and
- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 43,

(D) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 44,
- (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 45,
- and
- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 46,

and

(E) the VH having

- (a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 47,
- (b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 48,
- and
- (c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 49.

6. The bispecific antibody or antibody fragment thereof according to claim 1 or 2,

wherein (i) the VH of the first arm specifically binding to PD-1 has

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 12,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 13,

and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 14,

and

(ii) the VH of the second arm specifically binding to CD19 is any one selected from

(A) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 35,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 36,

and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 37,

(B) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 38,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 39,

and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 40,

(C) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 41,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 42,

and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 43,

(D) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 44,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 45,

and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 46,

and

(E) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 47,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 48,

and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 49.

7. The bispecific antibody or antibody fragment thereof according to claim 1 or 2,

wherein (i) the VH of the first arm specifically binding to PD-1 has

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 15,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 16,

and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 17,

and

(ii) the VH of the second arm specifically binding to CD19 is any one selected from

(A) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 35,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 36,

and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 37,

(B) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 38,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 39,

and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 40,

(C) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 41,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 42,

and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 43,

(D) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 44,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 45,

and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 46,

and

(E) the VH having

(a) the VH-CDR1 comprising the amino acid sequence set forth in SEQ ID No. 47,

(b) the VH-CDR2 comprising the amino acid sequence set forth in SEQ ID No. 48,

and

(c) the VH-CDR3 comprising the amino acid sequence set forth in SEQ ID No. 49.

8. The bispecific antibody or antibody fragment thereof according to any one of claims 1 to 7, wherein in the VH of the first arm specifically binding to PD-1, the FR1, FR2 and FR3 regions correspond to the amino acid sequences encoded by the germ-line V gene IGHV7-4-1 which may be with somatic mutation(s), respectively, and wherein the FR4 region comprises the amino acid sequence encoded by the germ-line J gene JH6c which may be with somatic mutation(s), and excludes ~~(excluding any~~ amino acid sequence included in the VH-CDR3 region).

9. The bispecific antibody or antibody fragment thereof according to any one of claims 1 to 8, wherein the FR1, FR2 and FR3 regions in the VH of the second arm specifically binding to CD19 correspond to the amino acid sequences encoded by the germ-line V gene IGHV5-51 which may be with somatic mutation(s), respectively.

10. The bispecific antibody or antibody fragment thereof according to any one of claims 1 to 9, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in any one selected from SEQ ID 5, SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 4, or an amino acid sequence having at least 80% identity to the same VH amino acid sequence.

11. The bispecific antibody or antibody fragment thereof according to any one of claims 1 to 10, wherein the VH of the second arm specifically binding to CD19 comprises the amino acid sequence set forth in any one selected from , SEQ ID No. 62, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 63, SEQ ID No. 64, SEQ ID No. 65 and SEQ ID No. 66, or an amino acid sequence having an identity of at least 80% to the same VH amino acid sequence.

12. The bispecific antibody or antibody fragment thereof according to claim 1 or 2, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in any one selected from SEQ ID No. 5, SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 4 , and the VH of the second arm specifically binding to CD19 comprises the amino acid sequence set forth in any one selected from SEQ ID No. 62, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 63, SEQ ID No. 64, SEQ ID No. 65 and SEQ ID No. 66.

13. The bispecific antibody or antibody fragment thereof according to any one of claims 1 to 3, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in SEQ ID No. 5, and the VH of the second arm specifically binding to CD19 comprises the amino acid sequence set forth in any one selected from SEQ ID No. 62, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 63, SEQ ID No. 64, SEQ ID No. 65 and SEQ ID No. 66.

14. The bispecific antibody or antibody fragment thereof according to any one of claims 1, 2 or 4, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in SEQ ID No. 1, and the VH of the second arm specifically binding to CD19 comprises the amino acid sequence set forth in any one selected from SEQ ID No. 62, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 63, SEQ ID No. 64, SEQ ID No. 65 and SEQ ID No. 66.

15. The bispecific antibody or antibody fragment thereof according to claim 1, 2 or 5, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in SEQ ID No. 2, and the VH of the second arm specifically binding to CD19 comprises the amino acid sequence set forth in any one selected from SEQ ID No. 62, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 63, SEQ ID No. 64, SEQ ID No. 65 and SEQ ID No. 66.

16. The bispecific antibody or antibody fragment thereof according to claim 1, 2, or 6, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in SEQ ID No. 3, and the VH of the second arm specifically binding to CD19 comprises the amino acid sequence set forth in any one selected from SEQ ID No. 62, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, , SEQ ID No. 63, SEQ ID No. 64, SEQ ID No. 65 and SEQ ID No. 66.

17. The bispecific antibody or antibody fragment thereof according to claim 1, 2 or 7, wherein the VH of the first arm specifically binding to PD-1 comprises the amino acid sequence set forth in SEQ ID No. 4, and the VH of the second arm specifically binding to CD19 comprises the amino acid sequence set forth in any one selected from SEQ ID No. 62, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 63, SEQ ID No. 64, SEQ ID No. 65 and SEQ ID No. 66.

18. The bispecific antibody or antibody fragment thereof according to any one of claims 1 to 17, wherein the VLs of the first arm specifically binding to PD-1 and the second arm specifically binding to CD19 comprise the amino acid sequence set forth in SEQ ID No. 25, respectively.

19. A bispecific antibody or an antibody fragment thereof, having the first arm specifically binding to PD-1 and the second arm specifically binding to CD19, and specifically binding to PD-1 and CD19, respectively, wherein (A) the first arm specifically binding to PD-1 has a VH comprising the amino acid sequence set forth in any one selected from SEQ ID No. 5, SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 4, and a VL comprising the amino acid sequence set forth in SEQ ID No. 25, and

(B) the second arm specifically binding to CD19 has a VH comprising the amino acid sequence set forth in any one selected from SEQ ID No. 62, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 63, SEQ ID No. 64, SEQ ID No. 65 and SEQ ID No. 66, and a VL comprising the amino acid sequence set forth in SEQ ID No. 25.

~~20. A bispecific antibody or an antibody fragment thereof, having the first arm specifically binding to PD-1 and the second arm specifically binding to CD19, and specifically binding to PD-1 and CD19, respectively, wherein the first arm specifically binding to PD-1 cross-competes for (1) the binding to PD-1 with the first arm specifically binding to PD-1 having a VH comprising the amino acid sequence set forth in any one selected from SEQ ID No. 5, SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, and SEQ ID No. 4, and a VL comprising the amino acid of SEQ ID No. 25, or (2) the binding to PD-1 with a variable region of a monoclonal antibody specifically binding to PD-1 having the same VH and VL.~~

~~21. A bispecific antibody or an antibody fragment thereof, having the first arm specifically binding to PD-1 and the second arm specifically binding to CD19, and specifically binding to PD-1 and CD19, respectively, wherein the binding to PD-1 with the first arm specifically binding to PD-1 is cross-competed by (1) the first arm specifically binding to PD-1 having a VH comprising the amino acid sequence set forth in any one selected from SEQ ID No. 5, SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 4, and a VL comprising the amino acid of SEQ ID No. 25, or (2) a variable region of a monoclonal antibody specifically binding to PD-1 having the same VH and VL.~~

~~22. The bispecific antibody or antibody fragment thereof according to claim 20 or 21, wherein the second arm specifically binding to CD19 cross-competes for (1) the binding to CD19 with the second arm specifically binding to CD19 having the VH comprising the amino acid sequence set forth in any one selected from SEQ ID No. 62, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33 SEQ ID No. 34, SEQ ID No. 63, SEQ ID No. 64, SEQ ID No. 65 and SEQ ID No. 66, and the VL comprising the amino acid sequence set forth in SEQ ID No. 25, or (2) the binding to CD19 with a variable region of a monoclonal antibody specifically binding to CD19 having the same VH and VL.~~

2023. The bispecific antibody or antibody fragment thereof according to any one of claims 1 to 1922, wherein the first arm specifically binding to PD-1 allows the interaction between PD-1 and PD-L1.

2124. The bispecific antibody or antibody fragment thereof according to any one of claims 1 to 2023, wherein the bispecific antibody is an IgG antibody.

2225. The bispecific antibody or antibody fragment thereof according to claim 2124, wherein the IgG antibody is an IgG₁ antibody or IgG₄ antibody.

2326. The bispecific antibody or antibody fragment thereof according to claim 2124, wherein the IgG antibody is an IgG₁ antibody.

2427. The bispecific antibody or antibody fragment thereof according to claim 2326, wherein the binding to Fc receptor is eliminated ~~or reduced~~.

2528. The bispecific antibody or antibody fragment thereof according to claim 2427, wherein in two heavy chain constant regions of the bispecific antibody, each leucine at position 235 according to the EU numbering system was substituted with glycine, and/or each glycine at position 236 was substituted with arginine.

2629. The bispecific antibody or antibody fragment thereof according to any one of claims 2326 to 2528, wherein in a constant region of heavy chain having the VH of the first arm specifically binding to PD-1, leucine at position 351 according to the EU numbering system

was substituted with lysine and threonine at position 366 was substituted with lysine, and in a constant region of heavy chain having the VH of the second arm specifically binding to CD19, leucine at position 351 was substituted with aspartic acid and leucine at position 368 was substituted with glutamic acid.

2730. The bispecific antibody or antibody fragment thereof according to any one of claims 2326 to 2528, wherein in a constant region of heavy chain having the VH of the first arm specifically binding to PD-1, leucine at position 351 according to the EU numbering system was substituted with aspartic acid, and leucine at position 368 was substituted with glutamic acid, and in a constant region of heavy chain having the VH of the second arm specifically binding to CD19, leucine at position 351 was substituted with lysine, and threonine at position 366 was substituted with lysine.

2831. The bispecific antibody or antibody fragment thereof according to any one of claims 2326 to 2730, wherein in two heavy chain constant regions of the bispecific antibody, each lysine at position 447 according to the EU numbering system was deleted.

2932. The bispecific antibody or antibody fragment thereof according to any one of claims 1 to 2427, wherein the heavy chain having the VH of the first arm specifically binding to PD-1 has a heavy chain constant region comprising the amino acid sequence set forth in SEQ ID No. 23.

3033. The bispecific antibody or antibody fragment thereof according to any one of claims 1 to 2528, 2730 and 2932, wherein the heavy chain having the VH of the second arm specifically binding to CD19 has a heavy chain constant region comprising the amino acid sequence set forth in any one selected from SEQ ID No. 24, SEQ ID No. 71, SEQ ID No. 72, SEQ ID No. 73, SEQ ID No. 74 and SEQ ID No. 75.

3134. The bispecific antibody or antibody fragment thereof according to any one of claims 1 to 3033, wherein the light chain having the VL of the first arm specifically binding to PD-1 and/or the light chain having the VL of the second arm specifically binding to CD19 have/has a light chain constant region comprising the amino acid sequence set forth in SEQ ID No. 29.

3235. A bispecific antibody or an antibody fragment thereof, having the first arm specifically

binding to PD-1 and the second arm specifically binding to CD19, and specifically binding to PD-1 and CD19, respectively, wherein

- (A) a heavy chain having a VH of the first arm specifically binding to PD-1 has a VH comprising the amino acid sequence set forth in any one selected from SEQ ID No. 5, SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, and SEQ ID No. 4, and the heavy chain constant region comprising the amino acid sequence set forth in SEQ ID No. 23,
- (B) a light chain having a VL of the first arm specifically binding to PD-1 has a VL comprising the amino acid sequence set forth in SEQ ID No. 25, and the light chain constant region comprising the amino acid sequence set forth in SEQ ID No. 29,
- (C) a heavy chain having a VH of the second arm specifically binding to CD19 has a VH comprising the amino acid sequence set forth in any one selected from SEQ ID No. 62, SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 63, SEQ ID No. 64, SEQ ID No. 65 and SEQ ID No. 66, and the heavy chain constant region comprising the amino acid sequence set forth in SEQ ID No. 24, and
- (D) a light chain having a VL of the second arm specifically binding to CD19 has a VL comprising the amino acid sequence set forth in SEQ ID No. 25, and the light chain constant region comprising the amino acid sequence set forth in SEQ ID No. 29.

3336. A bispecific antibody having the first arm specifically binding to PD-1 and the second arm specifically binding to CD19, and specifically binding to PD-1 and CD19, respectively, wherein

- (A) a heavy chain having the VH of the first arm specifically binding to PD-1 has the VH comprising the amino acid sequence set forth in SEQ ID No. 5, and the heavy chain constant region comprising the amino acid sequence set forth in SEQ ID No. 23,
- (B) a light chain having the VL of the first arm specifically binding to PD-1 has the VL comprising the amino acid sequence set forth in SEQ ID No. 25, and the light chain constant region comprising the amino acid sequence set forth in SEQ ID No. 29,
- (C) a heavy chain having the VH of the second arm specifically binding to CD19 has the VH comprising the amino acid sequence set forth in SEQ ID No. 62, and the heavy chain constant region comprising the amino acid sequence set forth in SEQ ID No. 24, and
- (D) a light chain having the VL of the second arm specifically binding to CD19 has the VL comprising the amino acid sequence set forth in SEQ ID No. 25, and the light chain constant region comprising the amino acid sequence set forth in SEQ ID No. 29.

~~3437.~~ A pharmaceutical composition comprising the bispecific antibody or antibody fragment thereof selected from any one of claims 1 to ~~3336~~, and a pharmaceutically acceptable carrier.

~~3538.~~ Use of the bispecific antibody or antibody fragment thereof according to any one of claims 1 to ~~3437~~ as in active ingredient in the manufacture of a medicament for preventing, suppressing the progression of symptoms of, suppressing the recurrence of, and/or treating autoimmune diseases.

~~3639.~~ The use according to claim ~~3538~~, wherein autoimmune disease is Behcet's disease, systemic lupus erythematosus, chronic discoid lupus erythematosus, multiple sclerosis, scleroderma, polymyositis, dermatomyositis, periarteritis nodosa, aortitis syndrome, malignant rheumatoid arthritis, rheumatoid arthritis, juvenile idiopathic arthritis, spondyloarthritis, mixed connective tissue disease, Sjogren's syndrome, adult Still's disease, vasculitis, allergic granulomatous vasculitis, hypersensitivity vasculitis, rheumatoid vasculitis, large vessel vasculitis, ANCA associated vasculitis, Cogan's syndrome, RS3PE syndrome, temporal arteritis, polymyalgia rheumatica, fibromyalgia, antiphospholipid antibody syndrome, eosinophilic fasciitis, IgG4-related disease, Guillain-Barre syndrome, myasthenia gravis, chronic atrophic gastritis, autoimmune hepatitis, non-alcoholic steatohepatitis, primary biliary cirrhosis, Goodpasture's syndrome, rapidly progressive glomerulonephritis, megaloblastic anemia, autoimmune hemolytic anemia, pernicious anemia, autoimmune neutropenia, idiopathic thrombocytopenic purpura, Basedow disease, Hashimoto disease, autoimmune adrenal insufficiency, primary hypothyroidism, Addison's disease, idiopathic Addison's disease, type I diabetes mellitus, slowly progressive type I diabetes mellitus, focal scleroderma, psoriasis, psoriatic arthritis, bullous pemphigoid, pemphigus, pemphigoid, gestational herpes, linear IgA bullous dermatosis, acquired epidermolysis bullosa, alopecia areata, vitiligo, vitiligo vulgaris, neuromyelitis optica, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, sarcoidosis, giant cell arteritis, amyotrophic lateral sclerosis, Harada disease, autoimmune optic neuropathy, idiopathic azoospermia, habitual abortion, inflammatory bowel disease, celiac disease, ankylosing spondylitis, severe asthma, chronic urticaria, transplantation immunity, familial mediterranean fever, eosinophilic chronic rhinosinusitis, dilated cardiomyopathy, systemic mastocytosis, or inclusion body myositis.

~~3740.~~ The use according to claim ~~3538~~ or claim ~~3639~~, wherein any one or more drugs selected

~~from an insulin formulation, sulfonylurea agent, quick acting insulin secretion promoter, biguanide preparation, insulin resistance improving agent, α glucosidase inhibitor, diabetic neuropathy therapeutic agent, GLP 1 analog preparation, DPP 4 inhibitor, steroid agent, interferon β 1a, interferon β 1b, glatiramer acetate, mitoxantrone, azathioprine, cyclophosphamide, cyclosporin, methotrexate, cladribine, adrenocorticotrophic hormone (ACTH), corticotropin, mizoribine, tacrolimus, fingolimod, alemtuzumab, immunosuppressive agent, belimumab, anti-rheumatic drug, anti-cytokine drug and abatacept are to be administered along with the medicament.~~

~~3841. An agent comprising the bispecific antibody or antibody fragment thereof selected from any one of claims 1 to 3437, as an active ingredient for use in preventing, suppressing the progression of symptoms of, suppressing the recurrence of, and/or treating graft versus host disease (GVHD).~~