

CLAIMS

1. A method of cancer treatment, the method comprising administering to a subject an effective amount of a non-competitive anti-OX40 antibody or antigen-binding fragment thereof in combination with an anti-PD1 antibody or antigen binding fragment thereof.

2. The method of claim 1, wherein the method comprises administering to a subject an effective amount of an antibody or antigen-binding fragment thereof, which specifically binds to human OX40 and comprises:

(i) a heavy chain variable region that comprises (a) a HCDR (Heavy Chain Complementarity Determining Region) 1 of SEQ ID NO: 3, (b) a HCDR2 of SEQ ID NO:24, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises (d) a LCDR (Light Chain Complementarity Determining Region) 1 of SEQ ID NO:25, (e) a LCDR2 of SEQ ID NO:19, and (f) a LCDR3 of SEQ ID NO:8;

(ii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:18, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:19, and (f) a LCDR3 of SEQ ID NO: 8;

(iii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:13, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:7, and (f) a LCDR3 of SEQ ID NO:8; or

(iv) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:4, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:7, and (f) a LCDR3 of SEQ ID NO:8, in combination with an anti-PD1 antibody.

3. The method of claim 2, wherein the OX40 antibody or antigen-binding fragment thereof comprises:

(i) a heavy chain variable region (VH) that comprises SEQ ID NO:26, and a light chain variable region (VL) that comprises SEQ ID NO: 28;

(ii) a heavy chain variable region (VH) that comprises SEQ ID NO: 20, and a light chain variable region (VL) that comprises SEQ ID NO: 22;

(iii) a heavy chain variable region (VH) that comprises SEQ ID NO: 14, and a light chain variable region (VL) that comprises SEQ ID NO: 16; or

(iv) a heavy chain variable region (VH) that comprises SEQ ID NO:9, and a light chain variable region (VL) that comprises SEQ ID NO:11.

4. The method of claim 1, wherein the anti-PD1 antibody comprises an antibody or an antigen binding fragment thereof which specifically binds human PD1, and comprises:

a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO: 32, (b) HCDR2 of SEQ ID NO: 33, and (c) HCDR3 of SEQ ID NO: 34; and a light chain variable region that comprises (d) LCDR1 of SEQ ID NO:35, (e) LCDR2 of SEQ ID NO: 36, and (f) LCDR3 of SEQ ID NO: 37.

5. The method of claim 4, wherein the anti-PD1 antibody or antigen binding fragment thereof which specifically binds human PD1, and comprises a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO:39 and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 41.

6. The method of claims 4 or 5 wherein the anti-PD1 antibody comprises an IgG4 constant domain comprising any one of SEQ ID NO: 42-47.

7. The method of claim 6, wherein the IgG4 constant domain comprises SEQ ID NO 46 or 47.

8. The method of claim 1, wherein the anti-OX40 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

9. The method of claim 1, wherein the anti-PD1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

10. A method of cancer treatment, the method comprising administering to a subject an effective amount of a non-competitive anti-OX40 antibody or antigen-binding fragment thereof in combination with an anti-PDL1 antibody or antigen binding fragment thereof.

11. The method of claim 10, wherein the method comprises administering to a subject an effective amount of an antibody or antigen-binding fragment thereof, which specifically binds to human OX40 and comprises:

(i) a heavy chain variable region that comprises (a) a HCDR (Heavy Chain Complementarity Determining Region) 1 of SEQ ID NO: 3, (b) a HCDR2 of SEQ ID NO:24, and (c) a HCDR3

of SEQ ID NO:5; and a light chain variable region that comprises (d) a LCDR (Light Chain Complementarity Determining Region) 1 of SEQ ID NO:25, (e) a LCDR2 of SEQ ID NO:19, and (f) a LCDR3 of SEQ ID NO:8;

(ii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:18, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:19, and (f) a LCDR3 of SEQ ID NO: 8;

(iii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:13, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:7, and (f) a LCDR3 of SEQ ID NO:8; or

(iv) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:4, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:7, and (f) a LCDR3 of SEQ ID NO:8, in combination with an anti-PDL1 antibody.

12. The method of claim 11, wherein the anti-PDL1 antibody comprises an antibody or an antigen binding fragment thereof which specifically binds human PDL1, and comprises: a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO: 50, (b) HCDR2 of SEQ ID NO: 51, and (c) HCDR3 of SEQ ID NO: 52; and a light chain variable region that comprises (d) LCDR1 of SEQ ID NO:53, (e) LCDR2 of SEQ ID NO: 54, and (f) LCDR3 of SEQ ID NO: 55.

13. The method of claim 12, wherein the anti-PDL1 antibody or antigen binding fragment thereof which specifically binds human PDL1, and comprises a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO:56 and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 57.

14. The method of claim 12 or 13, wherein the anti-PDL1 antibody comprises an IgG4 constant domain comprising any one of SEQ ID NO: 42-47.

15. The method of claim 14, wherein the IgG4 constant domain comprises SEQ ID NO 46 or 47.

16. The method of claim 10, wherein the anti-OX40 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.
17. The method of claim 10, wherein the anti-PDL1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.
18. The method of claim 1 or claim 10, wherein the cancer is selected from the group consisting of breast cancer, colon cancer, pancreatic cancer, head and neck cancer, gastric cancer, kidney cancer, liver cancer, small cell lung cancer, non-small cell lung cancer, ovarian cancer, skin cancer, mesothelioma, lymphoma, leukemia, myeloma or sarcoma.
19. The method of claim 18, wherein the cancer is a metastatic cancer.
20. The method of any one of claims 1-19, wherein the treatment results in a sustained anti-cancer response in the subject after cessation of the treatment.
21. A method of increasing, enhancing, or stimulating an immune response or function, the method comprising administering to a subject an effective amount of a non-competitive anti-OX40 antibody or antigen-binding fragment thereof in combination with an anti-PD1 antibody or antigen binding fragment thereof.
22. The method of claim 21, wherein the method comprises administering to a subject an effective amount of an antibody or antigen-binding fragment thereof, which specifically binds to human OX40 and comprises:
- (i) a heavy chain variable region that comprises (a) a HCDR (Heavy Chain Complementarity Determining Region) 1 of SEQ ID NO: 3, (b) a HCDR2 of SEQ ID NO:24, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises: (d) a LCDR (Light Chain Complementarity Determining Region) 1 of SEQ ID NO:25, (e) a LCDR2 of SEQ ID NO:19, and, (f) a LCDR3 of SEQ ID NO:8;
 - (ii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:18, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:19, and (f) a LCDR3 of SEQ ID NO: 8;
 - (iii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:13, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that

comprises: (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:7, and (f) a LCDR3 of SEQ ID NO:8; or;

(iv) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:4, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:7, and (f) a LCDR3 of SEQ ID NO:8, in combination with an anti-PD1 antibody.

23. The method of claim 22, wherein the OX40 antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain variable region (VH) that comprises SEQ ID NO:26, and a light chain variable region (VL) that comprises SEQ ID NO: 28;
- (ii) a heavy chain variable region (VH) that comprises SEQ ID NO: 20, and a light chain variable region (VL) that comprises SEQ ID NO: 22;
- (iii) a heavy chain variable region (VH) that comprises SEQ ID NO: 14, and a light chain variable region (VL) that comprises SEQ ID NO: 16; or
- (iv) a heavy chain variable region (VH) that comprises SEQ ID NO:9, and a light chain variable region (VL) that comprises SEQ ID NO:11.

24. The method of claim 21, wherein the anti-PD1 antibody comprises an antibody or an antigen binding fragment thereof which specifically binds human PD1, and comprises: a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO: 32, (b) HCDR2 of SEQ ID NO: 33, and (c) HCDR3 of SEQ ID NO: 34; and a light chain variable region that comprises (d) LCDR1 of SEQ ID NO:35, (e) LCDR2 of SEQ ID NO: 36, and (f) LCDR3 of SEQ ID NO: 37.

25. The method of claim 21, wherein the anti-PD1 antibody comprises an antibody antigen binding domain which specifically binds human PD1, and comprises a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO:39 and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 41.

26. The method of claim 24, wherein the anti-PD1 antibody comprises an IgG4 constant domain comprising any one of SEQ ID NO: 42-47.

27. The method of claim 26, wherein the IgG4 constant domain comprises SEQ ID NO 46 or 47.

28. The method of claim 21, wherein the anti-OX40 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.
29. The method of claim 21, wherein the anti-PD1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.
30. The method of claim 21 wherein stimulating an immune response is associated with T cells.
31. The method of claim 21, wherein stimulating an immune response is characterized by increased responsiveness to antigenic stimulation.
32. The method of claim 30, wherein the T cells have increased cytokine secretion, proliferation, or cytolytic activity.
33. The method of any one of claims 30-32, wherein the T cells are CD4⁺ and CD8⁺ T cells.
34. The method of any one of claims 21-33, wherein the administration results in a sustained immune cell response in the subject after cessation of the treatment.
35. A method of increasing, enhancing, or stimulating an immune response or function, the method comprising administering to a subject an effective amount of a non-competitive anti-OX40 antibody or antigen-binding fragment thereof in combination with an anti-PDL1 antibody or antigen binding fragment thereof.
36. The method of claim 35, wherein the method comprises administering to a subject an effective amount of an antibody or antigen-binding fragment thereof, which specifically binds to human OX40 and comprises:
- (i) a heavy chain variable region that comprises (a) a HCDR (Heavy Chain Complementarity Determining Region) 1 of SEQ ID NO: 3, (b) a HCDR2 of SEQ ID NO:24, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises (d) a LCDR (Light Chain Complementarity Determining Region) 1 of SEQ ID NO:25, (e) a LCDR2 of SEQ ID NO:19, and (f) a LCDR3 of SEQ ID NO:8;
 - (ii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:18, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that

comprises: (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:19, and (f) a LCDR3 of SEQ ID NO: 8;

(iii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:13, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:7, and (f) a LCDR3 of SEQ ID NO:8; or

(iv) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:4, and (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:7, and (f) a LCDR3 of SEQ ID NO:8, in combination with an anti-PDL1 antibody.

37. The method of claim 35, wherein the anti-PDL1 antibody comprises an antibody or an antigen binding fragment thereof which specifically binds human PDL1, and comprises: a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO: 50, (b) HCDR2 of SEQ ID NO: 51, and (c) HCDR3 of SEQ ID NO: 52; and a light chain variable region that comprises (d) LCDR1 of SEQ ID NO:53, (e) LCDR2 of SEQ ID NO: 54, and (f) LCDR3 of SEQ ID NO: 55.

38. The method of claim 35, wherein the anti-PDL1 antibody or antigen binding fragment thereof which specifically binds human PDL1, and comprises a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO:56 and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 57.

39. The method of claim 37, wherein the anti-PDL1 antibody comprises an IgG4 constant domain comprising any one of SEQ ID NO: 42-47.

40. The method of claim 39, wherein the IgG4 constant domain comprises SEQ ID NO 46 or 47.

41. The method of claim 35, wherein the anti-OX40 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

42. The method of claim 35, wherein the anti-PDL1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

43. The method of claim 35 wherein stimulating an immune response is associated with T cells.
44. The method of claim 35, wherein stimulating an immune response is characterized by increased responsiveness to antigenic stimulation.
45. The method of claim 43, wherein the T cells have increased cytokine secretion, proliferation, or cytolytic activity.
46. The method of any one of claims 43 or 45, wherein the T cells are CD4⁺ and CD8⁺ T cells.
47. The method of any one of claims 35-46, wherein the administration results in a sustained immune cell response in the subject after cessation of the treatment.