

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-TIM3 antibody or antigen binding fragment thereof.

2. The method of claim 1, wherein the OX40 antibody 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-TIM3 antibody or antigen binding fragments thereof.

3. The method of claim 1, wherein the OX40 antibody or antigen-binding 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-TIM3 antibody or antigen binding fragment thereof comprises an antibody antigen binding domain which specifically binds human TIM3, and comprises a heavy chain variable region comprising: HCDR1 of SEQ ID NO: 32, HCDR2 of SEQ ID NO: 33, and HCDR3 of SEQ ID NO:34; and a light chain variable region comprising: LCDR1 of SEQ ID NO:35, LCDR2 of SEQ ID NO: 36, and LCDR3 of SEQ ID NO: 37.
5. The method of claim 1, wherein the anti-TIM3 antibody comprises an antibody antigen binding domain which specifically binds human TIM3, and comprises a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO:38 and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO:40.
6. The method of claim 1, wherein the anti-OX40 antibody or antigen binding fragment is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.
7. The method of claim 1, wherein the anti-TIM3 antibody or antigen binding fragment is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.
8. The method of claim 1, wherein the cancer is breast cancer, colon 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.
9. The method of claim 8, wherein the breast cancer is metastatic breast cancer.
10. The method of any one of claims 1-9, wherein the treatment results in a sustained anti-cancer response in the subject after cessation of the treatment.
11. 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-TIM3 antibody or antigen binding fragment thereof.

12. The method of claim 11, wherein the OX40 antibody 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-TIM3 antibody.

13. The method of claim 11, 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.

14. The method of claim 11, wherein the anti-TIM3 antibody or antigen binding fragment thereof comprises an antibody antigen binding domain which specifically binds human TIM3, and comprises a heavy chain variable region comprising: HCDR1 of SEQ ID NO: 32, HCDR2 of SEQ ID NO: 33, and HCDR3 of SEQ ID NO:34; and a light chain variable region

comprising: LCDR1 of SEQ ID NO:35, LCDR2 of SEQ ID NO: 36, and LCDR3 of SEQ ID NO: 37.

15. The method of claim 11, wherein the anti-TIM3 antibody comprises an antibody antigen binding domain which specifically binds human TIM3, and comprises a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO:38 and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO:40.

16. The method of claim 11, wherein the anti-OX40 antibody or antigen binding fragment is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

17. The method of claim 11, wherein the anti-TIM3 antibody or antigen binding fragment is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.

18. The method of claim 11, wherein stimulating an immune response is associated with T cells, NK cells and macrophages.

19. The method of claim 18, wherein stimulated the immune response is characterized by increased responsiveness to antigenic stimulation.

20. The method of claim 18, wherein the T cells have increased cytokine secretion, proliferation, or cytolytic activity.

21. The method of any one of claims 18-20, wherein the T cells are CD4⁺ and CD8⁺ T cells.

22. The method of any one of claims 11-21, wherein the administration results in a sustained immune response in the subject after cessation of the treatment.