SUMMARY

The present disclosure relates to combination therapy comprising an OX40 binding agonist and an agent that decreases or inhibits TIGIT expression and/or activity.

Disclosed is a method for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of an OX40 binding agonist and an agent that decreases or inhibits TIGIT expression and/or activity. In one aspect, there is provided use of an OX40 agonist antibody, or antigen-binding fragment thereof, in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament is to be administered with a TIGIT antagonist antibody, or antigen-binding fragment thereof.

Disclosed is a method for reducing or inhibiting cancer relapse or cancer progression in an individual comprising administering to the individual an effective amount of an OX40 binding agonist and an agent that decreases or inhibits TIGIT expression and/or activity. In another aspect, there is provided use of an OX40 agonist antibody, or antigen-binding fragment thereof, in the manufacture of a medicament for reducing or inhibiting cancer relapse or cancer progression in an individual, wherein the medicament is to be administered with a TIGIT antagonist antibody, or antigen-binding fragment thereof.

Disclosed is a method for treating or delaying progression of an immune related disease in an individual comprising administering to the individual an effective amount of an OX40 binding agonist and an agent that decreases or inhibits TIGIT expression and/or activity. Disclosed is use of an OX40 binding agonist in the manufacture of a medicament for treating or delaying progression of an immune related disease in an individual, wherein the medicament is to be administered with an agent that decreases or inhibits TIGIT expression and/or activity. Disclosed is a method for reducing or inhibiting progression of an immune related disease in an individual comprising administering to the individual an effective amount of an OX40 binding agonist and an agent that decreases or inhibits TIGIT expression and/or activity. Disclosed is use of an OX40 binding agonist in the manufacture of a medicament for reducing or inhibiting progression of an immune related disease in an individual, wherein the medicament is to be administered with an agent that decreases or inhibits TIGIT expression and/or activity. In some embodiments of these disclosures, the immune related disease is associated with a T cell dysfunctional disorder. In some embodiments, the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation. In some embodiments, the T cell dysfunctional disorder is characterized by T cell anergy or decreased ability to secrete cytokines, proliferate, or execute cytolytic activity. In some embodiments, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some embodiments, the T cells are CD4+ and CD8+ T cells. In some embodiments, the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.

Disclosed is a method of increasing, enhancing, or stimulating an immune response or function in an individual comprising administering to the individual an effective amount of an OX40 binding agonist and an agent that decreases or inhibits TIGIT expression and/or activity. Disclosed is use of an OX40 binding agonist in the manufacture of

a medicament for increasing, enhancing, or stimulating an immune response or function in an individual, wherein the medicament is to be administered with an agent that decreases or inhibits TIGIT expression and/or activity.

Disclosed is a method of treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of an OX40 binding agonist and an agent that modulates CD226 expression and/or activity. Disclosed is use of an OX40 binding agonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament is to be administered with an agent that modulates CD226 expression and/or activity.

Disclosed is a method for reducing or inhibiting cancer relapse or cancer progression in an individual comprising administering to the individual an effective amount of an OX40 binding agonist and an agent that modulates CD226 expression and/or activity. Disclosed is use of an OX40 binding agonist in the manufacture of a medicament for reducing or inhibiting cancer relapse or cancer progression in an individual, wherein the medicament is to be administered with an agent that modulates CD226 expression and/or activity.

Disclosed is a method for treating or delaying progression of an immune related disease in an individual comprising administering to the individual an effective amount of an OX40 binding agonist and an agent that modulates CD226 expression and/or activity. Disclosed is use of an OX40 binding agonist in the manufacture of a medicament for treating or delaying progression of an immune related disease in an individual, wherein the medicament is to be administered with an agent that modulates CD226 expression and/or activity. Disclosed is a method for reducing or inhibiting progression of an immune related disease in an individual comprising administering to the individual an effective amount of an OX40 binding agonist and an agent that modulates CD226 expression and/or activity. Disclosed is use of an effective amount of an OX40 binding agonist in the manufacture of a medicament for reducing or inhibiting progression of an immune related disease in an individual, wherein the medicament is to be administered with an agent that modulates CD226 expression and/or activity. In some embodiments of these disclosures, the immune related disease is associated with a T cell dysfunctional disorder. In some

embodiments, the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation. In some embodiments, the T cell dysfunctional disorder is characterized by T cell anergy or decreased ability to secrete cytokines, proliferate, or execute cytolytic activity. In some embodiments, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some embodiments, the T cell is a CD4+ T cell and/or a CD8+ T cell. In some embodiments, the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.

Disclosed is a method of increasing, enhancing, or stimulating an immune response or function in an individual comprising administering to the individual an effective amount of an OX40 binding agonist and an agent that modulates CD226 expression and/or activity. Disclosed is use of an OX40 binding agonist in the manufacture of a medicament for increasing, enhancing, or stimulating an immune response or function in an individual, wherein the medicament is to be administered with an agent that modulates CD226 expression and/or activity.

In some embodiments, the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates CD226 expression and/or activity. In some embodiments, the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates the interaction of CD226 with PVR. In some embodiments, the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates the intracellular signaling mediated by CD226 binding to PVR. In some embodiments, the agent that modulates CD226 expression and/or activity is selected from the group consisting of an agent that inhibits and/or blocks the interaction of CD226 with TIGIT, an antagonist of TIGIT expression and/or activity, an antagonist of PVR expression and/or activity, an agent that inhibits and/or blocks the interaction of TIGIT with PVR, an agent that inhibits and/or blocks the interaction of TIGIT with PVRL2, an agent that inhibits and/or blocks the interaction of TIGIT with PVRL3, an agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to PVR, an agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to PVRL2, an agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to PVRL3, and combinations thereof. In some embodiments, the agent that modulates CD226 expression and/or activity is an agent that inhibits and/or blocks the interaction of CD226 with TIGIT. In some embodiments, the agent that inhibits and/or blocks the interaction of CD226 with TIGIT is a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, or an inhibitory polypeptide. In some embodiments, the agent that inhibits and/or blocks the interaction of CD226 with TIGIT is an anti-TIGIT antibody or antigen-binding fragment thereof. In some embodiments, the agent that inhibits and/or blocks the interaction of CD226 with TIGIT is an inhibitory nucleic acid selected from the group consisting of an antisense polynucleotide, an interfering RNA, a catalytic RNA, and an RNA-DNA chimera. In some embodiments, the agent that modulates CD226 expression and/or activity is an antagonist of TIGIT expression and/or activity. In some embodiments, the antagonist of TIGIT expression and/or activity is a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide. In some embodiments, the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof. In some embodiments, the antagonist of TIGIT expression and/or activity is an inhibitory nucleic acid selected from the group consisting of an antisense polynucleotide, an interfering RNA, a catalytic RNA, and an RNA-DNA chimera. In some embodiments, the antagonist of PVR expression and/or activity is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment

thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide. In some embodiments, the agent that inhibits and/or blocks the interaction of TIGIT with PVR is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide. In some embodiments, the agent that inhibits and/or blocks the interaction of TIGIT with PVRL2 is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide. In some embodiments, the agent that inhibits and/or blocks the interaction of TIGIT with PVRL3 is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide. In some embodiments, the agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to PVR is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide. In some embodiments, the agent that inhibits and/or blocks the interaction of TIGIT with PVRL2 is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide. In some embodiments, the agent that inhibits and/or blocks the interaction of TIGIT with PVRL3 is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

Disclosed is a method of increasing, enhancing, or stimulating an immune response or function in an individual comprising administering to the individual an effective amount of an OX40 binding agonist, an effective amount of an agent that decreases or inhibits TIGIT expression and/or activity, and an agent that decreases or inhibits one or more additional immune co-inhibitory receptors. Disclosed is use of an OX40 binding agonist, in the manufacture of a medicament for increasing, enhancing, or stimulating an immune response or function in an individual; wherein the medicament is to be administered with an agent that decreases or inhibits TIGIT expression and/or activity, and an agent that decreases or inhibits one or more additional immune co-inhibitory receptors. In some embodiments, the one or more additional immune co-inhibitory receptor is selected from the group consisting of PD-L1, PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96. In some embodiments, the one or more additional immune co-inhibitory receptor is selected from the group consisting of PD-L1, PD-1, CTLA-4, LAG3, and TIM3.

Disclosed is a method of increasing, enhancing, or stimulating an immune response or function in an individual comprising administering to the individual an effective amount of an OX40 binding agonist, an effective amount of an agent that decreases or inhibits TIGIT expression and/or activity, and an agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands. Disclosed is use of an OX40 binding agonist, in the manufacture of a medicament for increasing, enhancing, or stimulating an immune response or function in an individual, wherein the medicament is to be administered with an agent that decreases or inhibits TIGIT expression and/or activity, and an agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands. In some embodiments, the one or more additional immune co-stimulatory receptors or their ligands is selected from the group consisting of CD226, CD28, CD27, CD137, HVEM, GITR, MICA, ICOS, NKG2D, and 2B4. In some embodiments, the one or more additional immune co-stimulatory receptors or their ligands is selected from the group consisting of CD226, CD27, CD137, HVEM, and GITR. In some embodiments, the one or more additional immune co-stimulatory receptors or their ligands is CD27.

In some embodiments of any one of the abovedisclosures, the method further comprises administering at least one chemotherapeutic agent. In some embodiments, the individual has cancer. In some embodiments, the CD4 and/or CD8 T cells in the individual have increased or enhanced priming, activation, proliferation, cytokine release, and/or cytolytic activity relative to prior to the administration of

In some embodiments, the agent that decreases or inhibits TIGIT expression and/or activity is administered continuously. In other embodiments, the agent that decreases or inhibits TIGIT expression and/or activity is administered intermittently. In some embodiments, the agent that decreases or inhibits TIGIT expression and/or activity is administered before the OX40 binding agonist. In other embodiments, the agent that decreases or inhibits TIGIT expression and/or activity is administered simultaneous with the OX40 binding agonist. In other embodiments, the agent that decreases or inhibits TIGIT expression and/or activity is administered after the OX40 binding agonist. In some embodiments, the OX40 binding agonist is administered before the agent that modulates CD226 expression and/or activity. In other embodiments, the OX40 binding agonist is administered simultaneous with the agent that modulates CD226 expression and/or activity. In other embodiments, the OX40 binding agonist is administered after the agent that modulates CD226 expression and/or activity. In some embodiments, the agent that decreases or inhibits TIGIT expression and/or activity is administered before the agent that decreases or inhibits one or more additional immune co-inhibitory receptors. In other embodiments, the agent that decreases or inhibits TIGIT expression and/or activity is administered simultaneous with the agent that decreases or inhibits one or more additional immune co-inhibitory receptors. In other embodiments, the agent that decreases or inhibits TIGIT expression and/or activity is administered after the agent that decreases or inhibits one or more additional immune co-inhibitory receptors. In some embodiments, the agent that decreases or inhibits TIGIT expression and/or activity is administered before the agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands. In other embodiments, the agent that decreases or inhibits TIGIT expression and/or activity is administered simultaneous with the agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands. In some embodiments, the agent that decreases or inhibits TIGIT expression and/or activity is administered after the agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands. In some embodiments, the OX40 binding agonist is administered before the agent that decreases or inhibits one or more additional immune co-inhibitory receptors. In some embodiments, the OX40 binding agonist is administered simultaneous with the agent that decreases or inhibits one or more additional immune co-inhibitory receptors. In other embodiments, the OX40 binding agonist is administered after the agent that decreases or inhibits one or more additional immune co-inhibitory receptors. In some embodiments, the OX40 binding agonist is administered before the agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands. In other embodiments, the OX40 binding agonist is administered simultaneous with the agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands. In other embodiments, the OX40 binding agonist is administered after the agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands.

Disclosed is a kit comprising an OX40 binding agonist and a package insert comprising instructions for using the OX40 binding agonist in combination with an agent that decreases or inhibits TIGIT expression and/or activity to treat or delay progression of cancer in an individual.

In another aspect, there is provided a kit comprising an OX40 agonist antibody, or antigen-binding fragment thereof, and a TIGIT antagonist antibody, or antigen-binding fragment thereof, and a package insert comprising instructions

for using the OX40 agonist antibody, or antigen-binding fragment thereof, and the TIGIT antagonist antibody, or antigen-binding fragment thereof, to treat or delay progression of cancer in an individual.

Disclosed is a kit comprising an agent that decreases or inhibits TIGIT expression and/or activity and a package insert comprising instructions for using the agent that decreases or inhibits TIGIT expression and/or activity in combination with an OX40 binding agonist to treat or delay progression of cancer in an individual.

Disclosed is a kit comprising an OX40 binding agonist and a package insert comprising instructions for using the OX40 binding agonist in combination with an agent that decreases or inhibits TIGIT expression and/or activity to enhance immune function of an individual having cancer.

In another aspect there is provided a kit comprising an OX40 agonist antibody, or antigen-binding fragment thereof, and a TIGIT antagonist antibody, or antigen-binding fragment thereof, and a package insert comprising instructions for using the OX40 agonist antibody, or antigen-binding fragment thereof, and the TIGIT antagonist antibody, or antigen-binding fragment thereof, to enhance immune function of an individual having cancer.

Disclosed is a kit comprising an agent that decreases or inhibits TIGIT expression and/or activity and a package insert comprising instructions for using the agent that decreases or inhibits TIGIT expression and/or activity in combination with an OX40 binding agonist to enhance immune function of an individual having cancer.

Disclosed is a kit comprising an OX40 binding agonist and a package insert comprising instructions for using the OX40 binding agonist in combination with an agent that modulates CD226 expression and/or activity to treat or delay progression of cancer in an individual.

Disclosed is a kit comprising an OX40 binding agonist and an agent that modulates CD226 expression and/or activity, and a package insert comprising instructions for using the OX40 binding agonist and the agent that modulates CD226 expression and/or activity to treat or delay progression of cancer in an individual.

Disclosed is a kit comprising an agent that modulates CD226 expression and/or activity and a package insert comprising instructions for using the agent modulates CD226 expression and/or activity in combination with an OX40 binding agonist to treat or delay progression of cancer in an individual.

Disclosed is a kit comprising an OX40 binding agonist and a package insert comprising instructions for using the OX40 binding agonist in combination with an agent that modulates CD226 expression and/or activity to enhance immune function of an individual having cancer.

Disclosed is a kit comprising an OX40 binding agonist and an agent that modulates CD226 expression and/or activity, and a package insert comprising instructions for using the OX40 binding agonist and the agent that modulates CD226 expression and/or activity to enhance immune function of an individual having cancer.

Disclosed is a kit comprising an agent that modulates CD226 expression and/or activity and a package insert comprising instructions for using the agent that modulates CD226 expression and/or activity in combination with an OX40 binding agonist to enhance immune function of an individual having cancer.

CLAIMS

What is claimed is:

1. Use of an OX40 agonist antibody, or antigen-binding fragment thereof, in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament is to be administered with a TIGIT antagonist antibody, or antigen-binding fragment thereof.

2. Use of an OX40 agonist antibody, or antigen-binding fragment thereof, in the manufacture of a medicament for reducing or inhibiting cancer relapse or cancer progression in an individual, wherein the medicament is to be administered with a TIGIT antagonist antibody, or antigen-binding fragment thereof.

3. The use of claim 1 or 2, wherein the medicament is to be administered with at least one chemotherapeutic agent.

4. The use of claim 1 or 2, wherein (i) the individual has cancer; wherein optionally

(ii) CD4 and/or CD8 T cells in the individual have increased or enhanced priming, activation, proliferation, cytokine release, and/or cytolytic activity relative to prior to administration of the OX40 agonist antibody, or antigen-binding fragment thereof, and the TIGIT antagonist antibody, or antigen-binding fragment thereof, to the individual; wherein optionally

(iii) the number of CD4 and/or CD8 T cells is elevated relative to prior to administration of the OX40 agonist antibody, or antigen-binding fragment thereof, and the TIGIT antagonist antibody, or antigen-binding fragment thereof, to the individual; wherein optionally

(iv) the number of activated CD4 and/or CD8 T cells is elevated relative to prior to administration of the OX40 agonist antibody, or antigen-binding fragment thereof, and the TIGIT antagonist antibody, or antigen-binding fragment thereof, to the individual; and wherein optionally

(v) activated CD4 and/or CD8 T cells are characterized by IFN-γ^+ producing CD4 and/or CD8 T cells and/or enhanced cytolytic activity relative to prior to administration of the OX40 agonist antibody, or antigen-binding fragment thereof, and the TIGIT antagonist antibody, or antigen-binding fragment thereof, to the individual.

5. The use of claim 4, wherein the CD4 and/or CD8 T cells exhibit increased release of IFN- γ, TNF-α, and/or interleukins; wherein optionally

the CD4 and/or CD8 T cells are effector memory T cells; and wherein optionally

the CD4 and/or CD8 effector memory T cells are characterized by IFN-γ+ producing CD4 and/or CD8 T cells and/or enhanced cytolytic activity; or

are characterized by having the expression of $CD44^{high}$ $CD62L^{low}$.

6. The use of claim 1 or 2, wherein the cancer has elevated levels of T cell infiltration.

7. The use of claim 1 or 2, wherein (i) the TIGIT antagonist antibody, or antigen-binding fragment thereof,

comprises one of the following sets of six HVR sequences:

(a) KSSQSLYYSGVKENLLA (SEQ ID NO:1), ASIRFT (SEQ ID NO:2), QQGINNPLT (SEQ ID NO:3), GFTFSSFTMH (SEQ ID NO:4), FIRSGSGIVFYADAVRG (SEQ ID NO:5), and RPLGHNTFDS (SEQ ID NO:6); or

(b) RSSQSLVNSYGNTFLS (SEQ ID NO:7), GISNRFS (SEQ ID NO:8), LQGTHQPPT (SEQ ID NO:9), GYSFTGHLMN (SEQ ID NO:10), LIIPYNGGTSYNQKFKG (SEQ ID NO:11), and GLRGFYAMDY (SEQ ID NO:12).

8. The use of claim 1 or 2, wherein the TIGIT antagonist antibody, or antigen-binding fragment thereof,

comprises:

(a) a light chain comprising the amino acid sequence set forth in DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLLIYYASIRFTGV PDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTKLEIKR (SEQ ID NO:13) and a heavy chain comprising the amino acid sequence set forth in EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRSGSGIVFYADA VRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDSWGQGTLVTVSS (SEQ ID NO:15); or

(b) a light chain comprising the amino acid sequence set forth in DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISNRFSGVP DRFSGSGSGTDFTLKISTIKPEDLGMYYCLQGTHQPPTFGPGTKLEVK (SEQ ID NO:14), and a heavy chain comprising the amino acid sequence set forth in EVQLQQSGPELVKPGTSMKISCKASGYSFTGHLMNWVKQSHGKNLEWIGLIIPYNGGTSYNQK FKGKATLTVDKSSSTAYMELLSLTSDDSAVYFCSRGLRGFYAMDYWGQGTSVTVSS (SEQ ID NO: 16); wherein optionally

the antibody is a humanized antibody, a chimeric antibody, a bispecific antibody, a heteroconjugate antibody, or an immunotoxin.

9. The use of claim 1 or 2, wherein the TIGIT antagonist antibody, or antigen-binding fragment thereof, comprises:

(a) a light chain comprising an amino acid sequence at least 90% identical to the amino acid sequence set forth in DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLLIYYASIRFTGV PDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTKLEIKR (SEQ ID NO:13) and a heavy chain comprising an amino acid sequence at least 90% identical to the amino acid sequence set forth in EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRSGSGIVFYADA

VRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDSWGQGTLVTVSS (SEQ ID NO:15); or

(b) a light chain comprising an amino acid sequence at least 90% identical to the amino acid sequence set forth in

DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISNRFSGVP DRFSGSGSGTDFTLKISTIKPEDLGMYYCLQGTHQPPTFGPGTKLEVK (SEQ ID NO:14) and a heavy chain comprising an amino acid sequence at least 90% identical to the amino acid sequence set forth in

EVQLQQSGPELVKPGTSMKISCKASGYSFTGHLMNWVKQSHGKNLEWIGLIIPYNGGTSYNQK FKGKATLTVDKSSSTAYMELLSLTSDDSAVYFCSRGLRGFYAMDYWGQGTSVTVSS (SEQ ID NO:16).

10. The use of claim 1 or 2, wherein the TIGIT antagonist antibody, or antigen-binding fragment thereof, binds to the same epitope as an antibody comprising one of the following sets of six HVR sequences:

(a) KSSQSLYYSGVKENLLA (SEQ ID NO:1), ASIRFT (SEQ ID NO:2), QQGINNPLT (SEQ ID NO:3), GFTFSSFTMH (SEQ ID NO:4), FIRSGSGIVFYADAVRG (SEQ ID NO:5), and RPLGHNTFDS (SEQ ID NO:6); or

(b) RSSQSLVNSYGNTFLS (SEQ ID NO:7), GISNRFS (SEQ ID NO:8), LQGTHQPPT (SEQ ID NO:9), GYSFTGHLMN (SEQ ID NO:10), LIIPYNGGTSYNQKFKG (SEQ ID NO:11), and GLRGFYAMDY (SEQ ID NO:12).

11. The use of claim 1 or 2, wherein the OX40 agonist antibody, or antigen-binding fragment thereof, comprises a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells and has diminished activity relative to an OX40 agonist antibody, or antigen-binding fragment thereof, comprising a native sequence IgG1 Fc portion; wherein optionally

the OX40 agonist antibody, or antigen-binding fragment thereof, comprises a variant Fc portion comprising a DANA mutation.

12. The use of claim 1 or 2, wherein

the OX40 agonist antibody, or antigen-binding fragment thereof, comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 22; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 23; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 24; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 25; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27; or

wherein the OX40 agonist antibody, or antigen-binding fragment thereof, comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 22; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 23; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 24; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 25; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26; and (f) HVR-L3 comprising the amino acid

sequence of SEQ ID NO: 46; or

wherein the OX40 agonist antibody, or antigen-binding fragment thereof, comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 22; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 23; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 24; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 25; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

13. The use of claim 1 or 2, wherein the OX40 agonist antibody, or antigen-binding fragment thereof, comprises a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 76; wherein optionally

a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in SEQ ID NO: 76; and wherein

the OX 40 agonist antibody, or antigen-binding fragment thereof, comprises a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 77;

wherein optionally a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in SEQ ID NO: 77.

14. The use of claim 13, wherein the OX40 agonist antibody, or antigen-binding fragment thereof, comprises a VH sequence of SEQ ID NO: 76

and a VL sequence of SEQ ID NO: 77.

15. The use of claim 1 or 2, wherein the OX40 agonist antibody, or antigen-binding fragment thereof, comprises a VH sequence of SEQ ID NO: 114 and a VL sequence of SEQ ID NO: 115.

16. The use of claim 1 or 2, wherein the OX40 agonist antibody, or antigen-binding fragment thereof, comprises a VH sequence of SEQ ID NO: 116 and a VL sequence of SEQ ID NO: 117.

17. The use of claim 1 or 2, wherein the OX40 agonist antibody, or antigen-binding fragment thereof, comprises:

(a) a heavy chain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 200 and a light chain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 201; or

(b) a heavy chain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 203 and a light chain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 204; or

(c) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 205 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 206; or

(d) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 207 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 208; or

(e) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 209 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 210; or

(f) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 211 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 212; or

(g) a heavy chain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 213 and a light chain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 214; or

(h) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 215 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 216; or

(i) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 217 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 218; or

(j) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 219 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 220; or

(k) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 219 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 221; or

(l) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 222 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 220; or

(m) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 222 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 221; or

(n) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 223 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 220; or

(o) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 223 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 221; or

(p) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 224 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 225; or

(q) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 224 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 226; or

(r) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 227 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 225; or

(s) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 227 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 226; or

(t) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 228 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 225; or

(u) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 228 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 226.

18. The use of claim 1 or 2, wherein the OX40 agonist antibody is antibody L106, antibody ACT35, MEDI6469, or MEDI0562.

19. The use of claim 1 or 2, wherein the OX40 agonist antibody is a full-length IgG1 antibody.

20. The use of claim 1 or 2, wherein the cancer is non-small cell lung cancer, small cell lung cancer, renal cell cancer, colorectal cancer, ovarian cancer, breast cancer, pancreatic cancer, gastric carcinoma, bladder cancer, esophageal cancer, mesothelioma, melanoma, head and neck cancer, thyroid cancer, sarcoma, prostate cancer, glioblastoma, cervical cancer, thymic carcinoma, leukemia, lymphomas, myelomas, mycosis fungoides, Merkel cell cancer, or a hematologic malignancy.

21. The use of claim 1 or 2, wherein the TIGIT antagonist antibody, or antigen-binding fragment thereof, is to be administered continuously; or

intermittently.

22. The use of claim 1 or 2, wherein the TIGIT antagonist antibody, or antigen-binding fragment thereof, is to be administered before the OX40 agonist antibody, or antigen-binding fragment thereof; or

simultaneously with the OX40 agonist antibody, or antigen-binding fragment thereof; or

after the OX40 agonist antibody, or antigen-binding fragment thereof.

23. A kit comprising an OX40 agonist antibody, or antigen-binding fragment thereof, and a TIGIT antagonist antibody, or antigen-binding fragment thereof, and a package insert comprising instructions for using the OX40 agonist antibody, or antigen-binding fragment thereof, and the TIGIT antagonist antibody, or antigen-binding fragment thereof, to treat or delay progression of cancer in an individual.

24. A kit comprising an OX40 agonist antibody, or antigen-binding fragment thereof, and a TIGIT antagonist antibody, or antigen-binding fragment thereof, and a package insert comprising instructions for using the OX40 agonist antibody, or antigen-binding fragment thereof, and the TIGIT antagonist antibody, or antigen-binding fragment thereof, to enhance immune function of an individual having cancer.