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 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 decreases or inhibits TIGIT 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 decreases or inhibits TIGIT expression and/or activity. In another aspect, there is provided 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 decreases or inhibits TIGIT 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 decreases or inhibits TIGIT expression and/or activity. In another aspect, there is provided 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. In another aspect, there is provided 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. In another aspect, there is provided 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. In another aspect, there is provided 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. In another aspect, there is provided 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. In another aspect, there is provided 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. In another aspect, there is provided 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. In another aspect, there is provided 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. In another aspect, there is provided 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. In another aspect, there is provided 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

embodiments, the anti-TIGIT antibody, or antigen-binding fragment thereof, wherein the antibody is selected from the group consisting of a humanized antibody, a chimeric antibody, a bispecific antibody, a heteroconjugate antibody, and an immunotoxin. In some embodiments, the anti-TIGIT antibody, or antigen-binding fragment thereof, comprises at least one HVR that is at least 90% identical to an HVR set forth in any one of 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); RPLGHNTFDS (SEQ ID NO: 6); 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). In some embodiments, the anti-TIGIT antibody, or antigen-binding fragment thereof, comprises a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLLIYYASIRFTGVPDRFTG SGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTKLEIKR (SEQ ID NO:13) or DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISNRFSGVPDRFSGS GSGTDFTLKISTIKPEDLGMYYCLQGTHQPPTFGPGTKLEVK (SEQ ID NO:14); and/or comprises a heavy chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRSGSGIVF YADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDSWGQGTLVTVSS (SEQ ID NO:15) or EVQLQQSGPELVKPGTSMKISCKASGYSFTGHLMNWVKQSHGKNLEWIGLIIPYNGGTS YNQKFKGKATLTVDKSSSTAYMELLSLTSDDSAVYFCSRGLRGFYAMDYWGQGTSVTVSS (SEQ ID NO:16). In some embodiments, the anti-TIGIT 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).

In some embodiments of any one of above disclosures, the OX40 binding agonist is selected from the group consisting of an OX40 agonist antibody, an OX40L agonist fragment, an OX40 oligomeric receptor, and an OX40 immunoadhesin. In some embodiments, the OX40 agonist antibody depletes cells that express human OX40. In some embodiments, the cells that express human OX40 are CD4+ effector T cells. In some embodiments, the cells that express human OX40 are regulatory T (Treg) cells. In some embodiments, the depleting is by ADCC and/or phagocytosis. In some embodiments, the depleting is by ADCC. In some embodiments, the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.45 nM. In some embodiments, the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.4 nM. In some embodiments, the binding affinity of the OX40 agonist antibody is determined using radioimmunoassay. In some embodiments, the OX40 agonist antibody binds human OX40 and cynomolgus OX40. In some embodiments, the binding is determined using a FACS assay. In some embodiments, the binding to human OX40 has an EC50 of less than or equal to 0.3 μg/ml. In some embodiments, the binding to human OX40 has an EC50 of less

than or equal to 0.2 μg/ml. In some embodiments, the binding to cynomolgus OX40 has an EC50 of less than or equal to 1.5 μg/ml. In some embodiments, the binding to cynomolgus OX40 has an EC50 of less than or equal to 1.4 μg/ml. In some embodiments, the OX40 agonist antibody increases CD4+ effector T cell proliferation and/or increases cytokine production by the CD4+ effector T cell as compared to proliferation and/or cytokine (e.g., IFN- γ) production prior to treatment with the OX40 agonist antibody. In other embodiments, the OX40 agonist antibody increases memory T cell proliferation and/or increasing cytokine (e.g., IFN- γ) production by the memory cell. In some embodiments, the OX40 agonist antibody inhibits Treg function. In some embodiments, the OX40 agonist antibody inhibits Treg suppression of effector T cell function. In some embodiments, the effector T cell function is effector T cell proliferation and/or cytokine production. In some embodiments, the effector T cell is a CD4+ effector T cell.

In some embodiments, the OX40 agonist antibody increases OX40 signal transduction in a target cell that expresses OX40. In some embodiments, the OX40 signal transduction is detected by monitoring NFkB downstream signaling. In some embodiments, the OX40 agonist antibody is stable after treatment at 40°C for two weeks. In some embodiments, wherein the OX40 agonist antibody comprising a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells has diminished activity relative to the OX40 agonist antibody comprising a native sequence IgG1 Fc portion. In some embodiments, the OX40 agonist antibody comprises a variant Fc portion comprising a DANA mutation. In some embodiments, antibody cross-linking is required for anti-human OX40 agonist antibody function.

In some embodiments of any one of the above disclosures, the OX40 agonist antibody comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 22, 28, or 29, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 23, 30, 31, 32, 33 or 34, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO: 24, 35, or 39; and (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 25, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27, 42, 43, 44, 45, 46, 47, or 48. In some embodiments, the OX40 agonist antibody 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 an amino acid sequence selected from SEQ ID NO: 27. In some embodiments, the OX40 agonist antibody 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 an amino acid sequence selected from SEQ ID NO: 46. In some embodiments, the OX40 agonist antibody 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 an amino acid sequence selected from SEQ ID NO: 47. In some embodiments, the OX40 agonist antibody comprises a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or

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.

In another aspect, there is provided 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 binding agonist and an agent that decreases or inhibits TIGIT expression and/or activity, and a package insert comprising instructions

for using the OX40 binding agonist and the 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 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.

In another aspect, there is provided 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 binding agonist and an agent that decreases or inhibits TIGIT expression and/or activity, and a package insert comprising instructions for using the OX40 binding agonist and the 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 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.

In another aspect, there is provided 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.

In another aspect, there is provided 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.

In another aspect, there is provided 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.

In another aspect, there is provided 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.

In another aspect, there is provided 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.

In another aspect, there is provided 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 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 decreases or inhibits TIGIT expression and/or activity.

2. 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 decreases or inhibits TIGIT expression and/or activity.

3. 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.

4. 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.

5. The use of claim 3 or 4, wherein the immune related disease is associated with a T cell dysfunctional disorder; wherein optionally

the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation; or

by T cell anergy or decreased ability to secrete cytokines, proliferate, or execute cytolytic activity; or

by T cell exhaustion.

6. The use of any one of claims 3-5, wherein the T cells are CD4+ and CD8+ T cells; wherein optionally

the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.

7. 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.

8. 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.

9. 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.

10. 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.

11. 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.

12. The use of claim 10 or 11, wherein the immune related disease is associated with a T cell dysfunctional disorder; wherein optionally

the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation; or

by T cell anergy or decreased ability to secrete cytokines, proliferate, or execute cytolytic activity; or

by T cell exhaustion.

13. The use of claim 12, wherein the T cell is a CD4+ T cell and/or a CD8+ T cell.

14. The use of any one of claims 10-13, wherein the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.

15. 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.

16. The use of any one of claims 8-15, wherein (i) the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates CD226 expression and/or activity; wherein optionally

(ii) the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates the interaction of CD226 with PVR; wherein optionally

(iii) 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; and wherein optionally

(iv) 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.

17. The use of claim 16(iv), wherein the agent that modulates CD226 expression and/or activity is an agent that inhibits and/or blocks the interaction of CD226 with TIGIT.

18. The use of claim 16(iv) or 17, wherein the agent that inhibits and/or blocks the interaction of CD226 with TIGIT is (i) a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, or an inhibitory polypeptide; or

(ii) an anti-TIGIT antibody or antigen-binding fragment thereof; or

(iii) an inhibitory nucleic acid selected from the group consisting of an antisense polynucleotide, an interfering RNA, a catalytic RNA, and an RNA-DNA chimera.

19. The use of claim 16(iv), wherein the agent that modulates CD226 expression and/or activity is an antagonist of TIGIT expression and/or activity.

20. The use of claim 16(iv) or 19, wherein 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; or

an anti-TIGIT antibody or antigen-binding fragment thereof; or

an inhibitory nucleic acid selected from the group consisting of an antisense polynucleotide, an interfering RNA, a catalytic RNA, and an RNA-DNA chimera.

21. The use of claim 16(iv), wherein 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; or

wherein 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; or

wherein 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; or

wherein 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; or

wherein 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; or

wherein 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 ; or

wherein 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.

22. 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.

23. The use of claim 22, wherein the one or more additional immune co-inhibitory receptor (i) is selected from the group consisting of PD-L1, PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96 or

(ii) is selected from the group consisting of PD-L1, PD-1, CTLA-4, LAG3, and TIM3.

24. 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.

25. The use of claim 24, wherein 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; or

is selected from the group consisting of CD226, CD27, CD137, HVEM, and GITR; or

is CD27.

26. The use of any one of the preceding claims, wherein the medicament is to be administered with at least one chemotherapeutic agent.

27. The use of any one of the preceding claims, 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 the administration of the combination; wherein optionally

(iii) the number of CD4 and/or CD8 T cells is elevated relative to prior to administration of the combination; wherein optionally

(iv) the number of activated CD4 and/or CD8 T cells is elevated relative to prior to administration of the combination; 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 the administration of the combination.

28. The use of any one of claims 27(ii)-27(v), wherein the CD4 and/or CD8 T cells exhibit increased release of cytokines selected from the group consisting of IFN- γ, TNF-α, and 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 γ-IFN$^+$ producing CD4 and/or CD8 T cells and/or enhanced cytolytic activity; or

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

29. The use of any one of claims 1, 2, 8-9, 16(i)-16(ii), and 26-28, wherein the cancer has elevated levels of T cell infiltration.

30. The use of any one of claims 1-7 and 22-29, wherein the agent that decreases or inhibits TIGIT expression and/or activity is selected from the group consisting of 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.

31. The use of claim 30, wherein (i) the antagonist of TIGIT 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; or

wherein (ii) 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; or

wherein (iii) 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; or

wherein (iv) 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; or

wherein (v) 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; or

wherein (vi) 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; or

wherein (vii) the agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to 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; or

, wherein (viii) the agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to 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.

32. The use of claim 30 or 31(i), wherein (i) 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; or

(ii) wherein the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody, or antigen-binding fragment thereof.

33. The use of claim 18(ii) or 32(ii), wherein (i) the anti-TIGIT antibody, or antigen-binding fragment thereof, comprises at least one HVR comprising an amino acid sequence selected from the amino acid 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); wherein optionally

(ii) the anti-TIGIT 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).

34. The use of any one of claims 18(ii) and 32(ii)-33, wherein (i) the anti-TIGIT antibody, or antigen-binding fragment thereof, comprises a light chain comprising the amino acid sequence set forth in DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLLIYYASIRFTGVPDRFTG SGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTKLEIKR (SEQ ID NO:13) or DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISNRFSGVPDRFSGS GSGTDFTLKISTIKPEDLGMYYCLQGTHQPPTFGPGTKLEVK (SEQ ID NO:14); wherein optionally

(ii) the anti-TIGIT antibody, or antigen-binding fragment thereof, comprises a heavy chain comprising the amino acid sequence set forth in EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRSGSGIVFYADA VRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDSWGQGTLVTVSS (SEQ ID NO:15) or EVQLQQSGPELVKPGTSMKISCKASGYSFTGHLMNWVKQSHGKNLEWIGLIIPYNGGTSYNQK FKGKATLTVDKSSSTAYMELLSLTSDDSAVYFCSRGLRGFYAMDYWGQGTSVTVSS (SEQ ID NO:16); wherein optionally

(iii) the anti-TIGIT antibody, or antigen-binding fragment thereof, comprises a light chain comprising the amino acid sequence set forth in DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLLIYYASIRFTGV PDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTKLEIKR (SEQ ID NO:13) or DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISNRFSGVP DRFSGSGSGTDFTLKISTIKPEDLGMYYCLQGTHQPPTFGPGTKLEVK (SEQ ID NO:14), and a heavy chain comprising the amino acid sequence set forth in EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRSGSGIVFYADAVRGRFT ISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDSWGQGTLVTVSS (SEQ ID NO:15) or EVQLQQSGPELVKPGTSMKISCKASGYSFTGHLMNWVKQSHGKNLEWIGLIIPYNGGTSYNQKFKGKAT LTVDKSSSTAYMELLSLTSDDSAVYFCSRGLRGFYAMDYWGQGTSVTVSS (SEQ ID NO: 16); wherein optionally

(iv) the antibody is selected from the group consisting of a humanized antibody, a chimeric antibody, a bispecific antibody, a heteroconjugate antibody, and an immunotoxin; and wherein optionally

(v) the anti-TIGIT antibody, or antigen-binding fragment thereof, comprises at least one HVR that is at least 90% identical to an HVR set forth in any one of 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); RPLGHNTFDS (SEQ ID NO: 6); 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).

35. The use of any one of claims 18(ii), 32(ii)-33(ii), and 34(v), wherein the anti-TIGIT antibody, or antigen-binding fragment thereof, comprises a light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLLIYYASIRFTGVPDRFTG SGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTKLEIKR (SEQ ID NO:13) or DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISNRFSGVPDRFSGS GSGTDFTLKISTIKPEDLGMYYCLQGTHQPPTFGPGTKLEVK (SEQ ID NO:14); and/or comprises a heavy chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRSGSGIVFYADAVRGRFT ISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDSWGQGTLVTVSS (SEQ ID NO:15) or EVQLQQSGPELVKPGTSMKISCKASGYSFTGHLMNWVKQSHGKNLEWIGLIIPYNGGTSYNQKFKGKAT LTVDKSSSTAYMELLSLTSDDSAVYFCSRGLRGFYAMDYWGQGTSVTVSS (SEQ ID NO:16).

36. The use of any one of claims 18(ii) and 32(ii)-34(v), wherein the anti-TIGIT 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).

37. The use of any one of the preceding claims, wherein (i) the OX40 binding agonist is selected from the group consisting of an OX40 agonist antibody, an OX40L agonist fragment, an OX40 oligomeric receptor, and an OX40 immunoadhesin; wherein optionally

(ii) the OX40 agonist antibody depletes cells that express human OX40; and wherein optionally

(iii) the cells that express human OX40 are CD4+ effector T cells; or

are regulatory T (Treg) cells.

38. The use of any one of the preceding claims, wherein the depleting is by ADCC and/or phagocytosis; wherein optionally

the depleting is by ADCC.

39. The use of any one of the preceding claims, wherein the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.45 nM; wherein optionally

the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.4 nM; and wherein optionally

the binding affinity of the OX40 agonist antibody is determined using radioimmunoassay.

40. The use of any one of the preceding claims, wherein the OX40 agonist antibody binds human OX40 and cynomolgus OX40; wherein optionally

binding is determined using a FACS assay; and wherein optionally

binding to human OX40 has an EC50 of less than or equal to 0.3 μg/ml; or

less than or equal to 0.2 μg/ml.

41. The use of claim 40, wherein binding to cynomolgus OX40 has an EC50 of less than or equal to 1.5 μg/ml; wherein optionally

binding to cynomolgus OX40 has an EC50 of less than or equal to 1.4 μg/ml.

42. The use of any one of the preceding claims, wherein the OX40 agonist antibody increases CD4+ effector T cell proliferation and/or increases cytokine production by the CD4+ effector T cell as compared to proliferation and/or cytokine production prior to treatment with the OX40 agonist antibody; wherein optionally

the cytokine is IFN- γ.

43. The use of any one of the preceding claims, wherein the OX40 agonist antibody increases memory T cell proliferation and/or increasing cytokine production by the memory cell; wherein optionally

the cytokine is IFN- γ.

44. The use of any one of the preceding claims, wherein (i) the OX40 agonist antibody inhibits Treg function; wherein optionally

(ii) the OX40 agonist antibody inhibits Treg suppression of effector T cell function; and wherein optionally

(iii) effector T cell function is effector T cell proliferation and/or cytokine production.

45. The use of claim 44(ii) or 44(iii), wherein the effector T cell is a CD4+ effector T cell.

46. The use of any one of the preceding claims, wherein the OX40 agonist antibody increases OX40 signal transduction in a target cell that expresses OX40; wherein optionally

OX40 signal transduction is detected by monitoring NFkB downstream signaling.

47. The use of any one of the preceding claims, wherein the OX40 agonist antibody is stable after treatment at 40°C for two weeks.

48. The use of any one of the preceding claims, wherein the OX40 agonist antibody comprising a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells has diminished activity relative to the OX40 agonist antibody comprising a native sequence IgG1 Fc portion; wherein optionally

the OX40 agonist antibody comprises a variant Fc portion comprising a DANA mutation.

49. The use of any one of the preceding claims, wherein antibody cross-linking is required for anti-human OX40 agonist antibody function.

50. The use of any one of the preceding claims, wherein the OX40 agonist antibody comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 22, 28, or 29, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 23, 30, 31, 32, 33 or 34, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO: 24, 35, or 39; and (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 25, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27, 42, 43, 44, 45, 46, 47, or 48; wherein optionally

the OX40 agonist antibody 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 an amino acid sequence selected from SEQ ID NO: 27; or

wherein the OX40 agonist antibody 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 an amino acid sequence selected from SEQ ID NO: 46; or

wherein the OX40 agonist antibody 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 an amino acid sequence selected from SEQ ID NO: 47.

51. The use of any one of the preceding claims, wherein the OX40 agonist antibody 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, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 128, 134, or 136.

52. The use of any one of the preceding claims, wherein the OX40 agonist antibody comprises a VL 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, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 129, 135, or 137.

53. The use of any one of the preceding claims, wherein the OX40 agonist antibody 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

the OX40 agonist antibody retains the ability to bind to human OX40; wherein optionally

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

the OX40 agonist antibody comprises a VH comprising one, two, or three HVRs selected from: (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, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 24.

54. The use of any one of the preceding claims, wherein the OX40 agonist antibody comprises a VL 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

the OX40 agonist antibody retains the ability to bind to human OX40; wherein optionally

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

the OX40 agonist antibody comprises a VL comprising one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 25; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27.

55. The use of any one of the preceding claims, wherein the OX40 agonist antibody comprises a

VH sequence of SEQ ID NO: 76; wherein optionally

the OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 77; and wherein optionally

the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 76 and a VL sequence of SEQ ID NO: 77.

56. The use of any one of claims 1-54, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 114; or

wherein the OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 115.

57. The use of any one of claims 1-54, and 56, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 114 and a VL sequence of SEQ ID NO: 115.

58. The use of any one of claims 1-54, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 116 or

wherein the OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 117.

59. The use of any one of claims 1-54, and 58, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 116 and a VL sequence of SEQ ID NO: 117.

60. The use of any one of claims 37(i)-49, wherein the OX40 agonist antibody 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; (b) 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 (c) both a heavy chain as in (a) and a light chain as in (b); or

wherein the OX40 agonist antibody 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: 203; (b) 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) both a heavy chain as in (a) and a light chain as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 205; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 206; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 207; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 208; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence

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

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 211; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 212; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody 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: 213; (b) 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 (c) both a heavy chain as in (a) and a light chain as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 215; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 216; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 217; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 218; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 219; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 220; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 219; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 221; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 222; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 220; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 222; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 221; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 223; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 220; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 223; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 221; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 224; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 225; or (c) both a VH as in (a) and a VL as in (b); or

, wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 224; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 226; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 227; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 225; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 227; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 226; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 228; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 225; or (c) both a VH as in (a) and a VL as in (b); or

wherein the OX40 agonist antibody comprises (a) a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 228; (b) a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 226; or (c) both a VH as in (a) and a VL as in (b).

61. The use of any one of claims 37(i)-49, wherein the OX40 agonist antibody is antibody L106, antibody ACT35, MEDI6469, or MEDI0562.

62. The use of any one of claims 37(i)-61, wherein the OX40 agonist antibody is a full-length IgG1 antibody.

63. The use of claim 37(i), wherein the OX40 immunoadhesin is a trimeric OX40-Fc protein.

64. The use of any one of claims 1, 2, 8-9, 16(i)-16(ii), and 26-63, wherein the cancer is selected from the group consisting of 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, mycoses fungoids, merkel cell cancer, and other hematologic malignancies.

65. The use of any one of claims 1-7 and 22-64, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered continuously; or

intermittently.

66. The use of any one of claims 1-7 and 22-65, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered before the OX40 binding agonist; or

simultaneously with the OX40 binding agonist; or

after the OX40 binding agonist.

67. The use of any one of claims 8-21and 26-64, wherein the OX40 binding agonist is to be administered before the agent that modulates CD226 expression and/or activity; or

simultaneously with the agent that modulates CD226 expression and/or activity; or

after the agent that modulates CD226 expression and/or activity.

68. The use of any one of claims 22-23 and 26-64, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered before the agent that decreases or inhibits one or more additional immune co-inhibitory receptors; or

simultaneously with the agent that decreases or inhibits one or more additional immune co-inhibitory receptors; or

after the agent that decreases or inhibits one or more additional immune co-inhibitory receptors.

69. The use of any one of claims 24-64, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered before the agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands; or

simultaneously with the agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands; or

after the agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands.

70. The use of any one of claims 22-23(ii) and 26-64, wherein the OX40 binding agonist is to be administered before the agent that decreases or inhibits one or more additional immune co-inhibitory receptors; or

simultaneously with the agent that decreases or inhibits one or more additional immune co-inhibitory receptors; or

after the agent that decreases or inhibits one or more additional immune co-inhibitory receptors.

71. The use of any one of claims 24-64, wherein the OX40 binding agonist is to be administered before the agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands; or

simultaneously with the agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands; or

after the agent that increases or activates one or more additional immune co-stimulatory receptors or their ligands.

72. 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.

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

74. 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.

75. 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.

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

77. 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.

78. 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.

79. 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.

80. 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.

81. 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.

82. 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.

83. 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.