SUMMARY

[0010] The present disclosure describes a combination treatment comprising a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity.
[0011] Provided herein are methods for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity.
[0012] Provided herein are also methods for reducing or inhibiting cancer relapse or cancer progression in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity.
[0013] Provided herein are also methods for treating or delaying progression of an immune related disease in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity.
[0014] Provided herein are also methods for reducing or inhibiting progression of an immune related disease in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity.
[0014a] In one aspect, the present disclosure refers to use of an anti-PD-1 antagonist antibody that inhibits binding of PD-L1 to PD-1 in the manufacture of a medicament for: treating or delaying progression of cancer in an individual; reducing or inhibiting cancer relapse or cancer progression in an individual; treating or delaying progression of a viral infection in an individual; or reducing or inhibiting progression of a viral infection in an individual, wherein the individual is to be administered an effective amount of an anti-TIGIT antagonist antibody that inhibits and/or blocks interaction of CD226 with TIGIT.
[0014b] In one aspect, the present disclosure refers to use of an anti-PD-1 antagonist antibody that inhibits binding of PD-L1 to PD-1 and an anti-TIGIT antagonist antibody that inhibits and/or blocks interaction of CD226 with TIGIT in the manufacture of a medicament for: treating or delaying progression of cancer in an individual; reducing or inhibiting cancer relapse or cancer progression in an individual; treating or delaying progression of a viral infection in an individual; or reducing or inhibiting progression of a viral infection in an individual.
[0014c] In one aspect, the present disclosure refers to use of an anti-TIGIT antagonist antibody that inhibits and/or blocks interaction of CD226 with TIGITin the manufacture of a medicament for: treating or delaying progression of cancer in an individual; reducing or inhibiting cancer relapse or cancer progression in an individual; treating or delaying progression of a viral infection in an individual; or reducing or inhibiting progression of a viral infection in an individual, wherein the individual is to be administered an effective amount of an anti-PD-1 antagonist antibody that inhibits binding of PD-L1 to PD-1.
[0015] In some examples, the immune related disease is associated with a T cell dysfunctional disorder. In some examples, the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation. In some examples, the T cell dysfunctional disorder is characterized by T cell anergy or decreased ability to secrete cytokines, proliferate or execute cytolytic activity. In some examples, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some examples, the T cells are CD4+ and CD8+ T cells. In some examples, the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection and tumor immunity.
[0016] Provided herein are also methods of increasing, enhancing or stimulating an immune response or function in an individual by administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity.

[0017] Provided herein are also methods of treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that modulates the CD226 expression and/or activity.

[0018] Provided herein are also methods for reducing or inhibiting cancer relapse or cancer progression in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that modulates the CD226 expression and/or activity.

[0019] Provided herein are also methods for treating or delaying progression of an immune related disease in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that modulates the CD226 expression and/or activity.

[0020] Provided herein are also methods for reducing or inhibiting progression of an immune related disease in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and agent that modulates the CD226 expression and/or activity.

[0021] In some examples, the immune related disease is associated with a T cell dysfunctional disorder. In some examples, the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation. In some examples, the T cell dysfunctional disorder is characterized by T cell anergy, or decreased ability to secrete cytokines, proliferate or execute cytolytic activity. In some examples, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some examples, the T cells are CD4+ and CD8+ T cells. In some examples, the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection and tumor immunity.

[0022] Provided herein are also methods of increasing, enhancing or stimulating an immune response or function in an individual by administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that modulates the CD226 expression and/or activity.

[0023] In some examples, the agent that modulates the CD226 expression and/or activity is capable of increasing and/or stimulating CD226 expression and/or activity.

[0024] In some examples, the agent that modulates the CD226 expression and/or activity is selected from 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 intracellular signaling mediated by TIGIT binding to PVR.

[0025] In some examples, 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, and an inhibitory polypeptide. In some examples, the agent that inhibits and/or blocks the interaction of CD226 with TIGIT is an anti-TIGIT antibody or antigen-binding fragment thereof.

[0026] In some examples, 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 examples, the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof.

[0027] In some examples, the antagonist of PVR 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.

[0028] In some examples, the agent that inhibits and/or blocks the interaction of TIGIT with PVR is a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

[0029] In some examples, the agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to PVR is a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

[0030] The present disclosure also describes a combination treatment comprising 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.

[0031] Provided herein are methods of increasing, enhancing or stimulating an immune response or function in an individual by administering to the individual 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.

[0032] In some examples, the one or more additional immune co-inhibitory receptor is selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA and VISTA. In some examples, the one or more additional immune co-inhibitory receptor is selected from the group of PD-1, CTLA-4, LAG3 and TIM3.

[0033] The present disclosure also describes a combination treatment comprising 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 receptor.

[0034] Provided herein are methods of increasing, enhancing or stimulating an immune response or function in an individual by administering to the individual 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 receptor.

[0035] In some examples, the one or more additional immune co-stimulatory receptor is selected from the group consisting of CD226, OX-40, CD28, CD27, CD137, HVEM, and GITR. In some examples, the one or more additional immune co-stimulatory receptor is selected from the group of CD226, OX-40, CD27, CD137, HVEM and GITR. In some examples, the one or more additional immune co-stimulatory receptor is selected from the group consisting of OX-40 and CD27.

[0036] In some examples, any of the above methods further comprise administering at least one chemotherapeutic agent.

[0037] In some examples, the individual in any of the above methods has cancer. In some examples, the individual in any of the above methods is a human.

[0038] In some examples, 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 the combination.

[0039] In some examples, the number of CD4 and/or CD8 T cells is elevated relative to prior to administration of the combination. In some examples, the number of activated CD4 and/or CD8 T cells is elevated relative to prior to administration of the combination. In some examples, the activated CD4 and/or CD8 T cells is characterized by γ-IFN^{+} producing CD4 and/or CD8 T cells and/or enhanced cytolytic activity relative to prior to the administration of the combination. In some examples, the CD4 and/or CD8 T cells exhibit increased release of cytokines selected from the group consisting of IFN-γ, TNF-α, and interleukins.

[0040] In some examples, the CD4 and/or CD8 T cell is an effector memory T cell. In some examples, the CD4 and/or CD8 effector memory T cell is characterized by γ-IFN^{+} producing CD4 and/or CD8 T cells and/or enhanced cytolytic activity. In some examples, the CD4 and/or CD8 effector memory T cell is characterized by having the expression of CD44^{high} CD62L^{low}.

[0041] In some examples, the cancer in any of the above methods has elevated levels of T cell infiltration.

[0042] In some examples, 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, and an agent that inhibits the interaction and/or the intracellular signaling mediated by TIGIT binding to PVR.

[0043] In some examples, 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.

[0044] In some examples, 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.

[0045] In some examples, the agent that inhibits 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.

[0046] In some examples, the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof.

[0047] In some examples, 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 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 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).

[0048] In some examples, the anti-TIGIT antibody or antigen-binding fragment thereof comprises a light chain comprising the amino acid sequence set forth in DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQS PKLLIYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDG TKLEIKR (SEQ ID NO:13) or DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISNR

FSGVPDRFSGSGSGTDFTLKISTIKPEDLGMYYCLQGTHQPPTFGPGTKLEVK (SEQ ID NO:14).

[0049] In some examples, the anti-TIGIT antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence set forth in EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRSGSGI VFYADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDSWGQG TLVTVSS (SEQ ID NO:15) or EVQLQQSGPELVKPGTSMKISCKASGYSFTGHLMNWVKQSHGKNLEWIGLIIPYNGG TSYNQKFKGKATLTVDKSSSTAYMELLSLTSDDSAVYFCSRGLRGFYAMDYWGQG TSVTVSS (SEQ ID NO:16).

[0050] In some examples, the anti-TIGIT antibody or antigen-binding fragment thereof comprises a light chain comprising the amino acid sequence set forth in DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQS PKLLIYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDG TKLEIKR (SEQ ID NO:13) or DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISNR FSGVPDRFSGSGSGTDFTLKISTIKPEDLGMYYCLQGTHQPPTFGPGTKLEVK (SEQ ID NO:14) and the antibody heavy chain comprises the amino acid sequence set forth in EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRSGSGI VFYADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDSWGQG TLVTVSS (SEQ ID NO:15) or EVQLQQSGPELVKPGTSMKISCKASGYSFTGHLMNWVKQSHGKNLEWIGLIIPYNGG TSYNQKFKGKATLTVDKSSSTAYMELLSLTSDDSAVYFCSRGLRGFYAMDYWGQG TSVTVSS (SEQ ID NO:16).

[0051] In some examples, the anti-TIGIT antibody or antigen-binding fragment thereof, wherein the antibody is selected from a humanized antibody, a chimeric antibody, a bispecific antibody, a heteroconjugate antibody, and an immunotoxin.

[0052] In some examples, the anti-TIGIT antibody or antigen-binding fragment thereof comprises at least one HVR is at least 90% identical to an HVR set forth in any 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), and RPLGHNTFDS (SEQ ID NO:6) or 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)..

[0053] In some examples, the anti-TIGIT antibody or fragment thereof comprises the light chain and/or heavy chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQS PKLLIYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDG TKLEIKR (SEQ ID NO:13) or DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISNR FSGVPDRFSGSGSGTDFTLKISTIKPEDLGMYYCLQGTHQPPTFGPGTKLEVK (SEQ ID NO:14), or EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRSGSGI VFYADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDSWGQG TLVTVSS (SEQ ID NO:15) or EVQLQQSGPELVKPGTSMKISCKASGYSFTGHLMNWVKQSHGKNLEWIGLIIPYNGG TSYNQKFKGKATLTVDKSSSTAYMELLSLTSDDSAVYFCSRGLRGFYAMDYWGQG TSVTVSS (SEQ ID NO:16), respectively.

[0054] In some examples, the PD-1 axis binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PD-L1 binding antagonist and a PD-L2 binding antagonist.

[0055] In some examples, the PD-1 axis binding antagonist is a PD-1 binding antagonist. In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners. In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1. In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2. In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2. In some examples, the PD-1 binding antagonist is an antibody. In some examples, the PD-1 binding antagonist is MDX-1106 (nivolumab). In some examples, the PD-1 binding antagonist is Merck 3475 (lambrolizumab). In some examples, the PD-1 binding antagonist is CT-011 (pidilizumab). In some examples, the PD-1 binding antagonist is AMP-224.

[0056] In some examples, the PD-1 axis binding antagonist is a PD-L1 binding antagonist. In some examples, the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1. In some examples, the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1. In some examples, the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1. In some examples, the PD-L1 binding antagonist is an antibody.

[0057] In some examples, the PD-L1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105 and MEDI 4736.

[0058] In some examples, the anti-PD-L1 antibody comprises a heavy chain comprising HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO:17), HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO:18), and HVR-H3 sequence of RHWPGGFDY (SEQ ID NO:19); and a light chain comprising HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO:20), HVR-L2 sequence of SASFLYS (SEQ ID NO:21), and HVR-L3 sequence of QQYLYHPAT (SEQ ID NO:22).

[0059] In some examples, the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGG STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG TLVTVSA (SEQ ID NO:23) and a light chain variable region comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID NO:24).

[0060] In some examples, the PD-1 axis binding antagonist is a PD-L2 binding antagonist. In some examples, the PD-L2 binding antagonist is an antibody. In some examples, the PD-L2 binding antagonist is an immunoadhesin.

[0061] In some examples, the cancer being treated 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.

[0062] In some examples, the agent that decreases or inhibits TIGIT expression and/or activity is administered continuously. In some examples, the agent that decreases or inhibits TIGIT expression and/or activity is administered intermittently. In some examples, the agent that decreases or inhibits TIGIT expression and/or activity is administered before the PD-1 axis binding antagonist. In some examples, the agent that decreases or inhibits TIGIT expression and/or activity is administered simultaneous with the PD-1 axis binding antagonist. In some examples, the agent that decreases or inhibits TIGIT expression and/or activity is administered after the PD-1 axis binding antagonist.

[0063] Also provided herein are kits comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with an agent that decreases or inhibits TIGIT expression and/or activity to treat or delay progression of cancer in an individual.

[0063a] In one aspect, the present disclosure refers to a kit comprising an anti-PD-1 antagonist antibody and an anti-TIGIT antagonist antibody as a combined preparation for simultaneous, separate, or sequential use for: treating or delaying progression of cancer in an individual; reducing or inhibiting cancer relapse or cancer progression in an individual; treating or delaying progression of a viral infection in an individual; or reducing or inhibiting progression of a viral infection in an individual, wherein the anti-PD-1 antagonist antibody inhibits binding of PD-L1 to PD-1 and the anti-TIGIT antagonist antibody inhibits and/or blocks interaction of CD226 with TIGIT.

[0064] Also provided herein are kits comprising a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the agent that decreases or inhibits TIGIT expression and/or activity to treat or delay progression of cancer in an individual.

[0065] Also provided herein are kits 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 a PD-1 axis binding antagonist to treat or delay progression of cancer in an individual.

[0066] Also provided herein are kits comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with an agent that decreases or inhibits TIGIT expression and/or activity to enhance immune function of an individual having cancer.

[0067] Also provided herein are kits comprising a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the agent that decreases or inhibits TIGIT expression and/or activity to enhance immune function of an individual having cancer.

[0068] Also provided herein are kits 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 a PD-1 axis binding antagonist to enhance immune function of an individual having cancer.

[0069] Also provided herein are kits comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with an agent that modulates the CD226 expression and/or activity to treat or delay progression of cancer in an individual.

[0070] Also provided herein are kits comprising a PD-1 axis binding antagonist and an agent that modulates the CD226 expression and/or activity, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the agent that modulates the CD226 expression and/or activity to treat or delay progression of cancer in an individual.

[0071] Also provided herein are kits comprising an agent that modulates the CD226 expression and/or activity and a package insert comprising instructions for using the agent modulates the CD226 expression and/or activity in combination with a PD-1 axis binding antagonist to treat or delay progression of cancer in an individual.

[0072] Also provided herein are kits comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with an agent that modulates the CD226 expression and/or activity to enhance immune function of an individual having cancer.

[0073] Also provided herein are kits comprising a PD-1 axis binding antagonist and an agent that modulates the CD226 expression and/or activity, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the agent that modulates the CD226 expression and/or activity to enhance immune function of an individual having cancer.

[0074] Also provided herein are kits comprising an agent modulates the CD226 expression and/or activity and a package insert comprising instructions for using the agent that modulates the CD226 expression and/or activity in combination with a PD-1 axis binding antagonist to enhance immune function of an individual having cancer.

[0075] In some examples, the kits comprising the PD-1 axis binding antagonist is an anti-PD-L1 antibody. In some examples, the kits comprising the PD-1 axis binding antagonist is an anti-PD-1 antibody. In some examples, the kits comprising 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, and an agent that inhibits the interaction and/or the intracellular signaling mediated by TIGIT binding to PVR. In some examples, the kits comprising the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof.

[0076] In some examples, the kits comprises an agent that modulates the CD226 expression and/or activity which is capable of increasing and/or stimulating CD226 expression and/or activity. In some examples, the kits comprising the agent that modulates the CD226 expression and/or activity is selected from 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 intracellular signaling mediated by TIGIT binding to PVR. In some examples, the kits comprising the

agent that inhibits and/or blocks the interaction of CD226 with TIGIT and/or the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof.

[0077] In certain examples, the present disclosure provides a method for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides use of an effective amount of a PD-1 axis binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the PD-1 axis binding agent is used in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides use of an effective amount of an agent that decreases or inhibits TIGIT expression and/or activity in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the an agent that decreases or inhibits TIGIT expression and/or activity is used in combination with a PD-1 axis binding antagonist. In other examples, the present disclosure provides a pharmaceutical composition comprising a PD-1 axis binding antagonist for use in treating or delaying progression of cancer in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that decreases or inhibits TIGIT expression and/or activity for use in treating or delaying progression of cancer in combination with a PD-1 axis binding antagonist.

[0078] In other examples, the present disclosure provides a method for reducing or inhibiting cancer relapse or cancer progression in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides use of an effective amount of a PD-1 axis binding antagonist in the manufacture of a medicament for reducing or inhibiting cancer relapse or cancer progression in an individual, wherein the PD-1 axis binding agent is used in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides use of an effective amount of an agent that decreases or inhibits TIGIT expression and/or activity in the manufacture of a medicament for reducing or inhibiting cancer relapse or cancer progression in an individual, wherein the agent that decreases or inhibits TIGIT expression and/or activity is used in combination with a PD-1 axis binding antagonist. In other examples, the present disclosure provides a pharmaceutical composition comprising a PD-

1 axis binding antagonist for use in reducing or inhibiting cancer relapse or cancer progression in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that decreases or inhibits TIGIT expression and/or activity for use in reducing or inhibiting cancer relapse or cancer progression in combination with a PD-1 axis binding antagonist.

[0079] In other examples, the present disclosure provides a method for treating or delaying progression of an immune related disease in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides use of an effective amount of a PD-1 axis binding antagonist in the manufacture of a medicament for treating or delaying progression of an immune related disease in an individual, wherein the PD-1 axis binding agent is used in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides use of an effective amount of an agent that decreases or inhibits TIGIT expression and/or activity in the manufacture of a medicament for treating or delaying progression of an immune related disease in an individual, wherein the agent that decreases or inhibits TIGIT expression and/or activity is used in combination with a PD-1 axis binding antagonist. In other examples, the present disclosure provides a pharmaceutical composition comprising a PD-1 axis binding antagonist for use in treating or delaying progression of an immune related disease in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that decreases or inhibits TIGIT expression and/or activity for use in treating or delaying progression of an immune related disease in combination with a PD-1 axis binding antagonist.

[0080] In other examples, the present disclosure provides a combination comprising an effective amount of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity.

[0081] In other examples, the present disclosure provides a method for reducing or inhibiting progression of an immune related disease in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides use of an effective amount of a PD-1 axis binding antagonist in the manufacture of a medicament for reducing or inhibiting progression of an immune related disease in an

individual, wherein the PD-1 axis binding agent is used in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides use of an effective amount of an agent that decreases or inhibits TIGIT expression and/or activity in the manufacture of a medicament for reducing or inhibiting progression of an immune related disease in an individual, wherein the agent that decreases or inhibits TIGIT expression and/or activity is used in combination with a PD-1 axis binding antagonist. In other examples, the present disclosure provides a pharmaceutical composition comprising a PD-1 axis binding antagonist for use in reducing or inhibiting progression of an immune related disease in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that decreases or inhibits TIGIT expression and/or activity for use in reducing or inhibiting progression of an immune related disease in combination with a PD-1 axis binding antagonist.

[0082] In certain examples that may be combined with any of the preceding examples, the immune related disease is associated with a T cell dysfunctional disorder. In certain examples that may be combined with any of the preceding examples, the immune related disease is a viral infection. In certain examples that may be combined with any of the preceding examples, the viral infection is a chronic viral infection. In certain examples that may be combined with any of the preceding examples, the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation. In certain examples that may be combined with any of the preceding examples, the T cell dysfunctional disorder is characterized by T cell anergy or decreased ability to secrete cytokines, proliferate or execute cytolytic activity. In certain examples that may be combined with any of the preceding examples, the T cell dysfunctional disorder is characterized by T cell exhaustion. In certain examples that may be combined with any of the preceding examples, the T cells are CD4+ and CD8+ T cells. In certain examples that may be combined with any of the preceding examples, the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.

[0083] In other examples, the present disclosure provides a method of increasing, enhancing or stimulating an immune response or function in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides use of an effective amount of a PD-1 axis binding antagonist in the manufacture of a

medicament for enhancing or stimulating an immune response or function in an individual, wherein the PD-1 axis binding agent is used in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides use of an effective amount of an agent that decreases or inhibits TIGIT expression and/or activity in the manufacture of a medicament for enhancing or stimulating an immune response or function in an individual, wherein the agent that decreases or inhibits TIGIT expression and/or activity is used in combination with a PD-1 axis binding antagonist. In other examples, the present disclosure provides a pharmaceutical composition comprising a PD-1 axis binding antagonist for use in enhancing or stimulating an immune response or function in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that decreases or inhibits TIGIT expression and/or activity for use in enhancing or stimulating an immune response or function in combination with a PD-1 axis binding antagonist. In other examples, the present disclosure provides a combination comprising an effective amount of a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity.

[0084] In other examples, the present disclosure provides a method of treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides use of an effective amount of a PD-1 axis binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the PD-1 axis binding agent is used in combination with an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides use of an effective amount of an agent that modulates CD226 expression and/or activity in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the agent that modulates CD226 expression and/or activity is used in combination with a PD-1 axis binding antagonist. In other examples, the present disclosure provides a pharmaceutical composition comprising a PD-1 axis binding antagonist for use in treating or delaying progression of cancer in combination with an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that modulates CD226 expression and/or activity for use in treating or delaying progression of cancer in combination with a PD-1 axis binding antagonist.

[0085] In other examples, the present disclosure provides a method for reducing or inhibiting cancer relapse or cancer progression in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides use of an effective amount of a PD-1 axis binding antagonist in the manufacture of a medicament for reducing or inhibiting cancer relapse or cancer progression in an individual, wherein the PD-1 axis binding agent is used in combination with an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides use of an effective amount of an agent that modulates CD226 expression and/or activity in the manufacture of a medicament for reducing or inhibiting cancer relapse or cancer progression in an individual, wherein the agent that modulates CD226 expression and/or activity is used in combination with a PD-1 axis binding antagonist. In other examples, the present disclosure provides a pharmaceutical composition comprising a PD-1 axis binding antagonist for use in reducing or inhibiting cancer relapse or cancer progression in combination with an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that modulates CD226 expression and/or activity for use in reducing or inhibiting cancer relapse or cancer progression in combination with a PD-1 axis binding antagonist.

[0086] In other examples, the present disclosure provides a method for treating or delaying progression of an immune related disease in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides use of an effective amount of a PD-1 axis binding antagonist in the manufacture of a medicament for treating or delaying progression of an immune related disease in an individual, wherein the PD-1 axis binding agent is used in combination with an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides use of an effective amount of an agent that modulates CD226 expression and/or activity in the manufacture of a medicament for treating or delaying progression of an immune related disease in an individual, wherein the agent that modulates CD226 expression and/or activity is used in combination with a PD-1 axis binding antagonist. In other examples, the present disclosure provides a pharmaceutical composition comprising a PD-1 axis binding antagonist for use in treating or delaying progression of an immune related disease in combination with an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that modulates CD226

expression and/or activity for use in treating or delaying progression of an immune related disease in combination with a PD-1 axis binding antagonist.

[0087] In other examples, the present disclosure provides a combination comprising an effective amount of a PD-1 axis binding antagonist and an agent that modulates CD226 expression and/or activity.

[0088] In other examples, the present disclosure provides a method for reducing or inhibiting progression of an immune related disease in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides use of an effective amount of a PD-1 axis binding antagonist in the manufacture of a medicament for reducing or inhibiting progression of an immune related disease in an individual, wherein the PD-1 axis binding agent is used in combination with an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides use of an effective amount of an agent that modulates CD226 expression and/or activity in the manufacture of a medicament for reducing or inhibiting progression of an immune related disease in an individual, wherein the agent that modulates CD226 expression and/or activity is used in combination with a PD-1 axis binding antagonist. In other examples, the present disclosure provides a pharmaceutical composition comprising a PD-1 axis binding antagonist for use in reducing or inhibiting progression of an immune related disease in combination with an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that modulates CD226 expression and/or activity for use in reducing or inhibiting progression of an immune related disease in combination with a PD-1 axis binding antagonist.

[0089] In certain examples that may be combined with any of the preceding examples, the immune related disease is associated with a T cell dysfunctional disorder. In certain examples that may be combined with any of the preceding examples, the immune related disease is a viral infection. In certain examples that may be combined with any of the preceding examples, the viral infection is a chronic viral infection. In certain examples that may be combined with any of the preceding examples, the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation. In certain examples that may be combined with any of the preceding examples, the T cell dysfunctional disorder is characterized by T cell anergy, or decreased ability to secrete cytokines, proliferate or execute cytolytic activity. In certain examples that may be combined with any of the preceding examples, the T cell

dysfunctional disorder is characterized by T cell exhaustion. In certain examples that may be combined with any of the preceding examples, the T cells are CD4+ and CD8+ T cells. In certain examples that may be combined with any of the preceding examples, the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection and tumor immunity.

[0090] In other examples, the present disclosure provides a method of increasing, enhancing, or stimulating an immune response or function in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides use of an effective amount of a PD-1 axis binding antagonist in the manufacture of a medicament for enhancing or stimulating an immune response or function in an individual, wherein the PD-1 axis binding agent is used in combination with an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides use of an effective amount of an agent that modulates CD226 expression and/or activity in the manufacture of a medicament for enhancing or stimulating an immune response or function in an individual, wherein the an agent that modulates CD226 expression and/or activity is used in combination with a PD-1 axis binding antagonist. In other examples, the present disclosure provides a pharmaceutical composition comprising a PD-1 axis binding antagonist for use in enhancing or stimulating an immune response or function in combination with an agent that modulates CD226 expression and/or activity. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that modulates CD226 expression and/or activity for use in enhancing or stimulating an immune response or function in combination with a PD-1 axis binding antagonist. In other examples, the present disclosure provides a combination comprising an effective amount of a PD-1 axis binding antagonist and an agent that modulates CD226 expression and/or activity.

[0091] In certain examples that may be combined with any of the preceding examples, the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates CD226 expression and/or activity. In certain examples that may be combined with any of the preceding examples, the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates the interaction of CD226 with PVR. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, the agent that modulates CD226 expression and/or activity is an agent that inhibits and/or blocks the interaction of CD226 with TIGIT. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, the agent that inhibits and/or blocks the interaction of CD226 with TIGIT is an anti-TIGIT antibody or antigen-binding fragment thereof. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, the antisense polynucleotide targets TIGIT. In certain examples that may be combined with any of the preceding examples, the interfering RNA targets TIGIT. In certain examples that may be combined with any of the preceding examples, the catalytic RNA targets TIGIT. In certain examples that may be combined with any of the preceding examples, the RNA-DNA chimera targets TIGIT. In certain examples that may be combined with any of the preceding examples, the agent that modulates CD226 expression and/or activity is an antagonist of TIGIT expression and/or activity. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, the antagonist of TIGIT expression and/or

activity is an anti-TIGIT antibody or antigen-binding fragment thereof. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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.

[0092] In other examples, the present disclosure provides 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 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 other examples, the present disclosure provides use of an effective amount of an agent that decreases or inhibits TIGIT expression and/or activity in the manufacture of a medicament for enhancing or stimulating an immune response or function in an individual, wherein the agent that decreases or inhibits TIGIT expression and/or activity is used in combination with an agent that decreases or inhibits one or more additional immune co-inhibitory receptors. In other examples, the present disclosure provides use of an effective amount of an agent that decreases or inhibits one or more additional immune co-inhibitory receptors in the manufacture of a medicament for enhancing or stimulating an immune response or function in an individual, wherein the agent that decreases or inhibits one or more additional immune co-inhibitory receptors is used in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that decreases or inhibits TIGIT expression and/or activity for use in enhancing or stimulating an immune response or function in combination with an agent that decreases or inhibits one or more additional immune co-inhibitory receptors. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that decreases or inhibits one or more additional immune co-inhibitory receptors for use in enhancing or stimulating an immune response or function in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides a combination comprising 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 certain examples that may be combined with any of the preceding examples, the one or more additional immune co-inhibitory receptor is selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96. In certain examples that may be combined with any of the preceding examples, the one or more additional immune co-inhibitory receptor is selected from the group consisting of PD-1, CTLA-4, LAG3 and TIM3.

[0093] In other examples, the present disclosure provides 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 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. In other examples, the present disclosure provides use of an effective amount of an agent that decreases or inhibits TIGIT expression and/or activity in the manufacture of a medicament for enhancing or stimulating an immune response or function in an individual, wherein the agent that decreases or inhibits TIGIT expression and/or activity is used in combination with an agent that increases or activates one or more additional immune co-stimulatory receptors. In other examples, the present disclosure provides use of an effective amount of an a agent that increases or activates one or more additional immune co-stimulatory receptors in the manufacture of a medicament for enhancing or stimulating an immune response or function in an individual, wherein the a agent that increases or activates one or more additional immune co-stimulatory receptors is used in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that decreases or inhibits TIGIT expression and/or activity for use in enhancing or stimulating an immune response or function in combination with an agent that increases or activates one or more additional immune co-stimulatory receptors. In other examples, the present disclosure provides a pharmaceutical composition comprising an agent that increases or activates one or more additional immune co-stimulatory receptors for use in enhancing or stimulating an immune response or function in combination with an agent that decreases or inhibits TIGIT expression and/or activity. In other examples, the present disclosure provides a combination comprising 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. In certain examples that may be combined with any of the preceding examples, the one or more additional immune co-stimulatory receptors is selected from the group consisting of CD226, OX-40, CD28, CD27, CD137, HVEM, GITR, MICA, ICOS, NKG2D, and 2B4. In certain examples that may be combined with any of the preceding examples, the one or more additional immune co-stimulatory receptors is selected from the group consisting of CD226, OX-40, CD27, CD137, HVEM and GITR. In certain examples that may be combined with any of the preceding examples, the one or more additional immune co-stimulatory receptors is selected from the group consisting of OX-40 and CD27.

[0094] In certain examples that may be combined with any of the preceding examples, the method further comprises administering at least one chemotherapeutic agent. In certain examples that may be combined with any of the preceding examples,

the individual has cancer. In certain examples that may be combined with any of the preceding examples, the individual is a human. In certain examples that may be combined with any of the preceding examples, 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. In certain examples that may be combined with any of the preceding examples, the number of CD4 and/or CD8 T cells is elevated relative to prior to administration of the combination. In certain examples that may be combined with any of the preceding examples, the number of activated CD4 and/or CD8 T cells is elevated relative to prior to administration of the combination. In certain examples that may be combined with any of the preceding examples, activated CD4 and/or CD8 T cells are characterized by γ-IFN$^+$ producing CD4 and/or CD8 T cells and/or enhanced cytolytic activity relative to prior to the administration of the combination. In certain examples that may be combined with any of the preceding examples, the CD4 and/or CD8 T cells exhibit increased release of cytokines selected from the group consisting of IFN- γ, TNF-α and interleukins. In certain examples that may be combined with any of the preceding examples, the CD4 and/or CD8 T cells are effector memory T cells. In certain examples that may be combined with any of the preceding examples, 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. In certain examples that may be combined with any of the preceding examples, the CD4 and/or CD8 effector memory T cells are characterized by having the expression of CD44^{high} CD62L^{low}. In certain examples that may be combined with any of the preceding examples, the cancer has elevated levels of T cell infiltration. In certain examples that may be combined with any of the preceding examples, 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. In certain examples that may be combined with any of the

preceding examples, 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. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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. In certain examples that may be combined with any of the preceding examples, 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. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, the antisense polynucleotide targets TIGIT.

[0095] In certain examples that may be combined with any of the preceding examples, the interfering RNA targets TIGIT. In certain examples that may be combined with any of the preceding examples, the catalytic RNA targets TIGIT. In certain examples that may be combined with any of the preceding examples, the RNA-DNA chimera targets TIGIT. In certain examples that may be combined with any of the preceding examples, the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof. In certain examples that may be combined with any of the preceding examples, 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 (1) 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
(2) 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 certain examples that may be combined with any of the preceding examples, the anti-TIGIT antibody or antigen-binding fragment thereof, wherein the antibody light chain comprises the amino acid sequence set forth in DIVMTQSPSSLAVSPGEKVTMTC**KSSQSLYYSGVKENLLA**WYQQKPGQS PKLLIYY**ASIRFT**GVPDRFTGSGSGTDYTLTITSVQAEDMGQYFC**QQGINNPLT**FGD GTKLEIKR (SEQ ID NO:13) or
DVVLTQTPLSLSVSFGDQVSISC**RSSQSLVNSYGNTFLS**WYLHKPGQSPQLLIF**GISN RFS**GVPDRFSGSGSGTDFTLKISTIKPEDLGMYYC**LQGTHQPPT**FGPGTKLEVK (SEQ ID NO:14). In certain examples that may be combined with any of the preceding examples, the anti-TIGIT antibody or antigen-binding fragment thereof, wherein the antibody heavy chain comprises the amino acid sequence set forth in
EVQLVESGGGLTQPGKSLKLSCEAS**GFTFSSFTMH**WVRQSPGKGLEWVA**FIRSGSG IVFYADAVRG**RFTISRDNAKNLLFLQMNDLKSEDTAMYYCAR**RPLGHNTFDS**WGQ GTLVTVSS (SEQ ID NO:15) or
EVQLQQSGPELVKPGTSMKISCKAS**GYSFTGHLMN**WVKQSHGKNLEWIG**LIIPYNG GTSYNQKFKG**KATLTVDKSSSTAYMELLSLTSDDSAVYFCSR**GLRGFYAMDY**WG

QGTSVTVSS (SEQ ID NO:16). In certain examples that may be combined with any of the preceding examples, the anti-TIGIT antibody or antigen-binding fragment thereof, wherein the antibody light chain comprises the amino acid sequence set forth in DIVMTQSPSSLAVSPGEKVTMTC**KSSQSLYYSGVKENLLA**WYQQKPGQS PKLLIYY**ASIRFT**GVPDRFTGSGSGTDYTLTITSVQAEDMGQYFC**QQGINNPLT**FGD GTKLEIKR (SEQ ID NO:13) or DVVLTQTPLSLSVSFGDQVSISC**RSSQSLVNSYGNTFLS**WYLHKPGQSPQLLIF**GISN RFS**GVPDRFSGSGSGTDFTLKISTIKPEDLGMYYC**LQGTHQPPT**FGPGTKLEVK (SEQ ID NO:14), and the antibody heavy chain comprises the amino acid sequence set forth in EVQLVESGGGLTQPGKSLKLSCEAS**GFTFSSFTMH**WVRQSPGKGLEWVA**FIRSGSG IVFYADAVRG**RFTISRDNAKNLLFLQMNDLKSEDTAMYYCAR**RPLGHNTFDS**WGQ GTLVTVSS (SEQ ID NO:15) or EVQLQQSGPELVKPGTSMKISCKAS**GYSFTGHLMN**WVKQSHGKNLEWIG**LIIPYNG GTSYNQKFKG**KATLTVDKSSSTAYMELLSLTSDDSAVYFCSR**GLRGFYAMDY**WG QGTSVTVSS (SEQ ID NO: 16). In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 (1) 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 (2) 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 certain examples that may be combined with any of the preceding examples, the anti-TIGIT antibody or fragment thereof comprises the light chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in DIVMTQSPSSLAVSPGEKVTMTC**KSSQSLYYSGVKENLLA**WYQQKPGQS PKLLIYY**ASIRFT**GVPDRFTGSGSGTDYTLTITSVQAEDMGQYFC**QQGINNPLT**FGD GTKLEIKR (SEQ ID NO:13) or DVVLTQTPLSLSVSFGDQVSISC**RSSQSLVNSYGNTFLS**WYLHKPGQSPQLLIF**GISN**

RFSGVPDRFSGSGSGTDFTLKISTIKPEDLGMYYC**LQGTHQPPT**FGPGTKLEVK (SEQ ID NO:14); and/or the heavy chain comprising amino acid sequences at least 90% identical to the amino acid sequences set forth in EVQLVESGGGLTQPGKSLKLSCEAS**GFTFSSFTMH**WVRQSPGKGLEWVA**FIRSGSG IVFYADAVRG**RFTISRDNAKNLLFLQMNDLKSEDTAMYYCAR**RPLGHNTFDS**WGQ GTLVTVSS (SEQ ID NO:15) or EVQLQQSGPELVKPGTSMKISCKAS**GYSFTGHLMN**WVKQSHGKNLEWIG**LIIPYNG GTSYNQKFKG**KATLTVDKSSSTAYMELLSLTSDDSAVYFCSR**GLRGFYAMDY**WG QGTSVTVSS (SEQ ID NO:16). In certain examples that may be combined with any of the preceding examples, the PD-1 axis binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PD-L1 binding antagonist and a PD-L2 binding antagonist. In certain examples that may be combined with any of the preceding examples, the PD-1 axis binding antagonist is a PD-1 binding antagonist. In certain examples that may be combined with any of the preceding examples, the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners. In certain examples that may be combined with any of the preceding examples, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1. In certain examples that may be combined with any of the preceding examples, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2. In certain examples that may be combined with any of the preceding examples, the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2. In certain examples that may be combined with any of the preceding examples, the PD-1 binding antagonist is an antibody. In certain examples that may be combined with any of the preceding examples, the PD-1 binding antagonist is MDX-1106. In certain examples that may be combined with any of the preceding examples, the PD-1 binding antagonist is MK-3475. In certain examples that may be combined with any of the preceding examples, the PD-1 binding antagonist is CT-011. In certain examples that may be combined with any of the preceding examples, the PD-1 binding antagonist is AMP-224. In certain examples that may be combined with any of the preceding examples, the PD-1 axis binding antagonist is a PD-L1 binding antagonist. In certain examples that may be combined with any of the preceding examples, the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1. In certain examples that may be combined with any of the preceding examples, the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1. In certain examples that may be combined with any of the preceding examples, the PD-L1 binding antagonist

inhibits the binding of PD-L1 to both PD-1 and B7-1. In certain examples that may be combined with any of the preceding examples, the PD-L1 binding antagonist is an anti-PD-L1 antibody. In certain examples that may be combined with any of the preceding examples, the PD-L1 binding antagonist is selected from the group consisting of YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736. In certain examples that may be combined with any of the preceding examples, the anti-PD-L1antibody comprises a heavy chain comprising HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO:17), HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO:18), and HVR-H3 sequence of RHWPGGFDY (SEQ ID NO:19); and a light chain comprising HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO:20), HVR-L2 sequence of SASFLYS (SEQ ID NO:21), and HVR-L3 sequence of QQYLYHPAT (SEQ ID NO:22). In certain examples that may be combined with any of the preceding examples, the anti-PD-L1antibody comprises a heavy chain variable region comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGG STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG TLVTVSA (SEQ ID NO:23), EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGG STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG TLVTVSSASTK (SEQ ID NO:40), or EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGG STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG TLVTVSS (SEQ ID NO:41), and a light chain variable region comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID NO:24). In certain examples that may be combined with any of the preceding examples, the PD-1 axis binding antagonist is a PD-L2 binding antagonist. In certain examples that may be combined with any of the preceding examples, the PD-L2 binding antagonist is an antibody. In certain examples that may be combined with any of the preceding examples, the PD-L2 binding antagonist is an immunoadhesin. In certain examples that may be combined with any of the preceding examples, 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. In certain examples that may be combined with any of the preceding examples, the agent that decreases or inhibits TIGIT expression and/or activity is administered continuously. In certain examples that may be combined with any of the preceding examples, the agent that decreases or inhibits TIGIT expression and/or activity is administered intermittently. In certain examples that may be combined with any of the preceding examples, the agent that decreases or inhibits TIGIT expression and/or activity is administered before the PD-1 axis binding antagonist. In certain examples that may be combined with any of the preceding examples, the agent that decreases or inhibits TIGIT expression and/or activity is administered simultaneous with the PD-1 axis binding antagonist. In certain examples that may be combined with any of the preceding examples, the agent that decreases or inhibits TIGIT expression and/or activity is administered after the PD-1 axis binding antagonist. In certain examples that may be combined with any of the preceding examples, the PD-1 axis binding antagonist is administered before the agent that modulates CD226 expression and/or activity. In certain examples that may be combined with any of the preceding examples, the PD-1 axis binding antagonist is administered simultaneous with the agent that modulates CD226 expression and/or activity. In certain examples that may be combined with any of the preceding examples, the PD-1 axis binding antagonist is administered after the agent that modulates CD226 expression and/or activity. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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. In certain examples that may be combined with any of the preceding examples, 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. In certain examples that may be combined with any of the preceding examples, 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.

[0096] In other examples, the present disclosure provides a kit comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with an agent that decreases or inhibits TIGIT expression and/or activity to treat or delay progression of cancer in an individual.

[0097] In other examples, the present disclosure provides a kit comprising a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the agent that decreases or inhibits TIGIT expression and/or activity to treat or delay progression of cancer in an individual.

[0098] In other examples, the present disclosure provides 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 a PD-1 axis binding antagonist to treat or delay progression of cancer in an individual.

[0099] In other examples, the present disclosure provides a kit comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with an agent that decreases or inhibits TIGIT expression and/or activity to enhance immune function of an individual having cancer.

[0100] In other examples, the present disclosure provides a kit comprising a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the agent that decreases or inhibits TIGIT expression and/or activity to enhance immune function of an individual having cancer.

[0101] In other examples, the present disclosure provides 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 a PD-1 axis binding antagonist to enhance immune function of an individual having cancer.

[0102] In other examples, the present disclosure provides a kit comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with an agent that modulates CD226 expression and/or activity to treat or delay progression of cancer in an individual.

[0103] In other examples, the present disclosure provides a kit comprising a PD-1 axis binding antagonist and an agent that modulates CD226 expression and/or activity, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the agent that modulates CD226 expression and/or activity to treat or delay progression of cancer in an individual.

[0104] In other examples, the present disclosure provides 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 a PD-1 axis binding antagonist to treat or delay progression of cancer in an individual.

[0105] In other examples, the present disclosure provides a kit comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with an agent that modulates CD226 expression and/or activity to enhance immune function of an individual having cancer.

[0106] In other examples, the present disclosure provides a kit comprising a PD-1 axis binding antagonist and an agent that modulates CD226 expression and/or activity, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the agent that modulates CD226 expression and/or activity to enhance immune function of an individual having cancer.

[0107] In other examples, the present disclosure provides a kit comprising an agent 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 a PD-1 axis binding antagonist to enhance immune function of an individual having cancer.

[0108] In certain examples that may be combined with any of the preceding examples, the PD-1 axis binding antagonist is an anti-PD-L1 antibody. In certain examples that may be combined with any of the preceding examples, the anti-PD-L1 antibody is selected from the group consisting of YW243.55.S70, MPDL3280A, MDX-1105 and MEDI4736. In certain examples that may be combined with any of the preceding examples, the anti-PD-L1antibody comprises a heavy chain comprising HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO:17), HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO:18), and HVR-H3 sequence of RHWPGGFDY

(SEQ ID NO:19); and a light chain comprising HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO:20), HVR-L2 sequence of SASFLYS (SEQ ID NO:21), and HVR-L3 sequence of QQYLYHPAT (SEQ ID NO:22). In certain examples that may be combined with any of the preceding examples, the anti-PD-L1antibody comprises a heavy chain variable region comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGG STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG TLVTVSA (SEQ ID NO:23), EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGG STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG TLVTVSSASTK (SEQ ID NO:40), or EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGG STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG TLVTVSS (SEQ ID NO:41), and a light chain variable region comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID NO:24). In certain examples that may be combined with any of the preceding examples, the PD-1 axis binding antagonist is an anti-PD-1 antibody. In certain examples that may be combined with any of the preceding examples, the anti-PD-1 antibody is MDX-1106, MK-3475, or CT-011. In certain examples that may be combined with any of the preceding examples, the PD-1 axis binding antagonist is AMP-224. In certain examples that may be combined with any of the preceding examples, the PD-1 axis binding antagonist is a PD-L2 binding antagonist. In certain examples that may be combined with any of the preceding examples, the PD-L2 binding antagonist is an antibody. In certain examples that may be combined with any of the preceding examples, the PD-L2 binding antagonist is an immunoadhesin.

[0109] In other examples, the present disclosure provides 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 agent that decreases or inhibits one or more additional immune co-inhibitory receptors to treat or delay progression of cancer in an individual. In other examples, the present disclosure provides a kit comprising 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, and a package insert comprising instructions for using the agent that decreases or inhibits TIGIT expression and/or activity and the agent that decreases or inhibits one or more additional immune co-inhibitory receptors to treat or delay progression of cancer in an individual. In other examples, the present disclosure provides a kit comprising an agent that decreases or inhibits one or more additional immune co-inhibitory receptors and a package insert comprising instructions for using the agent that decreases or inhibits one or more additional immune co-inhibitory receptors 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 other examples, the present disclosure provides 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 agent that decreases or inhibits one or more additional immune co-inhibitory receptors to enhance immune function of an individual having cancer. In other examples, the present disclosure provides a kit comprising 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, and a package insert comprising instructions for using the agent that decreases or inhibits TIGIT expression and/or activity and the agent that decreases or inhibits one or more additional immune co-inhibitory receptors to enhance immune function of an individual having cancer. In other examples, the present disclosure provides a kit comprising an agent that decreases or inhibits one or more additional immune co-inhibitory receptors and a package insert comprising instructions for using the agent that decreases or inhibits one or more additional immune co-inhibitory receptors in combination with an agent that decreases or inhibits TIGIT expression and/or activity to enhance immune function of an individual having cancer. In certain examples that may be combined with any of the preceding examples, the one or more additional immune co-inhibitory receptor is selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96. In certain examples that may be combined with any of the preceding examples, the one or more additional immune co-inhibitory receptor is selected from the group consisting of PD-1, CTLA-4, LAG3 and TIM3.

[0110] In other examples, the present disclosure provides 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 agent that increases or activates one or more additional immune co-stimulatory receptors to treat or delay progression of cancer in an individual. In other

examples, the present disclosure provides a kit comprising 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, and a package insert comprising instructions for using the agent that decreases or inhibits TIGIT expression and/or activity and the agent that increases or activates one or more additional immune co-stimulatory receptors to treat or delay progression of cancer in an individual. In other examples, the present disclosure provides a kit comprising an agent that increases or activates one or more additional immune co-stimulatory receptors and a package insert comprising instructions for using the agent that increases or activates one or more additional immune co-stimulatory receptors 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 other examples, the present disclosure provides 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 agent that increases or activates one or more additional immune co-stimulatory receptors to enhance immune function of an individual having cancer. In other examples, the present disclosure provides a kit comprising 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, and a package insert comprising instructions for using the agent that decreases or inhibits TIGIT expression and/or activity and the agent that increases or activates one or more additional immune co-stimulatory receptors to enhance immune function of an individual having cancer. In other examples, the present disclosure provides a kit comprising an agent that increases or activates one or more additional immune co-stimulatory receptors and a package insert comprising instructions for using the agent that increases or activates one or more additional immune co-stimulatory receptors in combination with an agent that decreases or inhibits TIGIT expression and/or activity to enhance immune function of an individual having cancer. In certain examples that may be combined with any of the preceding examples, the or more additional immune co-stimulatory receptor is selected from the group consisting of CD226, OX-40, CD28, CD27, CD137, HVEM, GITR, MICA, ICOS, NKG2D, and 2B4. In certain examples that may be combined with any of the preceding examples, the one or more additional immune co-stimulatory receptor is selected from the group consisting of CD226, OX-40, CD27, CD137, HVEM and GITR. In certain examples that may be combined with any of the preceding examples, the one or more additional immune co-stimulatory receptor is selected from the group consisting of OX-40 and CD27.

[0111] In certain examples that may be combined with any of the preceding examples, the individual is a human. In certain examples that may be combined with any of the preceding examples, 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, and an agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to PVRL3. In certain examples that may be combined with any of the preceding examples, the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof. In certain examples that may be combined with any of the preceding examples, the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates CD226 expression and/or activity. In certain examples that may be combined with any of the preceding examples, the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates the interaction of CD226 with PVR. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, 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, and an agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to PVRL3. In certain examples that may be combined with any of the preceding examples, the agent that modulates CD226 expression and/or activity is an agent that inhibits and/or blocks the interaction of CD226 with TIGIT. In certain examples that may be combined with any of the preceding examples, 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 certain examples that may be combined with any of the preceding examples, the agent that inhibits and/or blocks the interaction of CD226 with TIGIT is an anti-TIGIT antibody or antigen-binding fragment thereof. In certain examples that may be combined with any of the preceding examples, 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 (1) 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 (2) 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 certain examples that may be combined with any of the preceding examples, the anti-TIGIT antibody or antigen-binding fragment thereof, wherein the antibody light chain comprises the amino acid sequence set forth in DIVMTQSPSSLAVSPGEKVTMTC**KSSQSLYYSGVKENLLA**WYQQKPGQS PKLLIYY**ASIRFT**GVPDRFTGSGSGTDYTLTITSVQAEDMGQYFC**QQGINNPLT**FGD GTKLEIKR (SEQ ID NO:13) or DVVLTQTPLSLSVSFGDQVSISC**RSSQSLVNSYGNTFLS**WYLHKPGQSPQLLIF**GISN RFS**GVPDRFSGSGSGTDFTLKISTIKPEDLGMYYC**LQGTHQPPT**FGPGTKLEVK (SEQ ID NO:14). In certain examples that may be combined with any of the preceding examples, the anti-TIGIT antibody or antigen-binding fragment thereof, wherein the antibody heavy chain comprises the amino acid sequence set forth in EVQLVESGGGLTQPGKSLKLSCEAS**GFTFSSFTMH**WVRQSPGKGLEWVA**FIRSGSG IVFYADAVRG**RFTISRDNAKNLLFLQMNDLKSEDTAMYYCAR**RPLGHNTFDS**WGQ GTLVTVSS (SEQ ID NO:15) or EVQLQQSGPELVKPGTSMKISCKAS**GYSFTGHLMN**WVKQSHGKNLEWIG**LIIPYNG GTSYNQKFKG**KATLTVDKSSSTAYMELLSLTSDDSAVYFCSR**GLRGFYAMDY**WG QGTSVTVSS (SEQ ID NO:16). In certain examples that may be combined with any of the preceding examples, the anti-TIGIT antibody or antigen-binding fragment thereof, wherein the antibody light chain comprises the amino acid sequence set forth in DIVMTQSPSSLAVSPGEKVTMTC**KSSQSLYYSGVKENLLA**WYQQKPGQS PKLLIYY**ASIRFT**GVPDRFTGSGSGTDYTLTITSVQAEDMGQYFC**QQGINNPLT**FGD