

BRIEF SUMMARY OF THE INVENTION

[0010] The present ~~invention~~disclosure describes a combination treatment comprising a PD-1 axis binding antagonist and an agent that decreases or inhibits TIGIT expression and/or activity.

[0010a] In one aspect, there is provided use 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 medicament is to be administered with 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.

[0011a] In one aspect, there is provided use 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 medicament is to be administered with 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.

[0012a] In one aspect, there is provided use 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 medicament is to be administered with 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.

[0013a] In one aspect, there is provided use 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 medicament is to be administered with 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.

[0015] In some embodiments, the immune related disease is associated with a T cell dysfunctional disorder. In some embodiments, the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation. In some embodiments, the T cell dysfunctional disorder is characterized by T cell anergy or decreased ability to secrete cytokines, proliferate or execute cytolytic activity. In some embodiments, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some embodiments, the T cells are CD4+ and CD8+ T cells. In some embodiments, the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection and tumor immunity.

[0015a] In one aspect, there is provided use of a PD-1 axis binding antagonist in the manufacture of a medicament for increasing, enhancing or stimulating an immune response or function in an individual, wherein the medicament is to be administered with an agent that decreases or inhibits TIGIT expression and/or activity.

[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.

[0016a] In one aspect, there is provided use 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 medicament is to be administered with an agent that modulates CD226 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.

[0017a] In one aspect, there is provided use 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 medicament is to be administered with an agent that modulates 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.

[0018a] In one aspect, there is provided use 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 medicament is to be administered with an agent that modulates 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.

[0019a] In one aspect, there is provided use 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 medicament is to be administered with agent that modulates 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 embodiments, the immune related disease is associated with a T cell dysfunctional disorder. In some embodiments, the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation. In some embodiments, the T cell dysfunctional disorder is characterized by T cell anergy, or decreased ability to secrete cytokines, proliferate or execute cytolytic activity. In some embodiments, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some embodiments, the T cells are CD4+ and CD8+ T cells. In some embodiments, the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection and tumor immunity.

[0021a] In one aspect, there is provided use of a PD-1 axis binding antagonist in the manufacture of a medicament for increasing, enhancing, or stimulating an immune response or function in an individual, wherein the medicament is to be administered with an agent that modulates CD226 expression and/or activity.

[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 embodiments, 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 embodiments, 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 embodiments, the agent that inhibits and/or blocks the interaction of CD226 with TIGIT is a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide. In some embodiments, the agent that inhibits and/or blocks the interaction of CD226 with TIGIT is an anti-TIGIT antibody or antigen-binding fragment thereof.

[0026] In some embodiments, the antagonist of TIGIT expression and/or activity is a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide. In some embodiments, the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof.

[0027] In some embodiments, 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 embodiments, 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 embodiments, 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 ~~invention~~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.

[0030a] In one aspect, there is provided use of an agent that decreases or inhibits TIGIT expression and/or activity in the manufacture of a medicament for increasing, enhancing, or stimulating an immune response or function in an individual, wherein the medicament is to be administered with an agent that decreases or inhibits 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 embodiments, 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 embodiments, 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 ~~invention~~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.

[0033a] In one aspect, there is provided use of an agent that decreases or inhibits TIGIT expression and/or activity in the manufacture of a medicament for increasing, enhancing, or stimulating an immune response or function in an individual, wherein the medicament is to be administered with an agent that increases or activates one or more additional immune co-stimulatory receptors.

[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 embodiments, 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 embodiments, 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 embodiments, the one or more additional immune co-stimulatory receptor is selected from the group consisting of OX-40 and CD27.

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

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

[0038] In some embodiments, the CD4 and/or CD8 T cells in the individual have increased or enhanced priming, activation, proliferation, cytokine release and/or cytolytic activity relative to prior to the administration of the combination.

[0039] In some embodiments, the number of CD4 and/or CD8 T cells is elevated relative to prior to administration of the combination. In some embodiments, the number of activated CD4 and/or CD8 T cells is elevated relative to prior to administration of the combination. In some embodiments, 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 embodiments, 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 embodiments, the CD4 and/or CD8 T cell is an effector memory T cell. In some embodiments, 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 embodiments, the CD4 and/or CD8 effector memory T cell is characterized by having the expression of CD44^{high} CD62L^{low}.

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

[0042] In some embodiments, 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 embodiments, 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 embodiments, the antagonist of PVR expression and/or activity is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

[0045] In some embodiments, 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 embodiments, the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof.

[0047] In some embodiments, 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 embodiments, 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
DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLNKPGQSPQLLIFGISNR

[0063] In one aspect, there is provided a~~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.

[0064] In one aspect, there is provided a~~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] In one aspect, there is provided a~~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] In one aspect, there is provided a~~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] In one aspect, there is provided a~~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] In one aspect, there is provided a~~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] In one aspect, there is provided a~~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] In one aspect, there is provided a~~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] In one aspect, there is provided a~~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] In one aspect, there is provided a~~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] In one aspect, there is provided a~~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] In one aspect, there is provided a~~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 embodiments, the kits comprising the PD-1 axis binding antagonist is an anti-PD-L1 antibody. In some embodiments, the kits comprising the PD-1 axis binding antagonist is an anti-PD-1 antibody. In some embodiments, 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 embodiments, the kits comprising the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof.

[0076] In some embodiments, 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 embodiments, 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 embodiments, 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 aspectsembodiments, 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 embodimentsaspects, 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 embodimentsaspects, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 embodiments that may be combined with any of the preceding embodiments, the immune related disease is associated with a T cell dysfunctional disorder. In certain embodiments that may be combined with any of the preceding embodiments, the immune related disease is a viral infection. In certain embodiments that may be combined with any of the preceding embodiments, the viral infection is a chronic viral infection. In certain embodiments that may be combined with any of the preceding embodiments, the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation. In certain embodiments that may be combined with any of the preceding embodiments, the T cell dysfunctional disorder is characterized by T cell anergy or decreased ability to secrete cytokines, proliferate or execute cytolytic activity. In certain embodiments that may be combined with any of the preceding embodiments, the T cell dysfunctional disorder is characterized by T cell exhaustion. In certain embodiments that may be combined with any of the preceding embodiments, the T cells are CD4+ and CD8+ T cells. In certain embodiments that may be combined with any of the preceding embodiments, the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.

[0083] In other aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 embodiments that may be combined with any of the preceding embodiments, the immune related disease is associated with a T cell dysfunctional disorder. In certain embodiments that may be combined with any of the preceding embodiments, the immune related disease is a viral infection. In certain embodiments that may be combined with any of the preceding embodiments, the viral infection is a chronic viral infection. In certain embodiments that may be combined with any of the preceding embodiments, the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation. In certain embodiments that may be combined with any of the preceding embodiments, the T cell dysfunctional disorder is characterized by T cell anergy, or decreased ability to secrete cytokines, proliferate or execute cytolytic activity. In certain embodiments that may be combined with any of the preceding embodiments, the T cell

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

[0090] In other ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates CD226 expression and/or activity. In certain embodiments that may be combined with any of the preceding embodiments, the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates the interaction of CD226 with PVR. In certain embodiments that may be combined with any of the preceding embodiments, the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates the intracellular signaling mediated by CD226 binding to PVR. In certain embodiments that may be combined with any of the preceding embodiments, the

[0092] In other aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 aspectsembodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the one or more additional immune co-stimulatory receptors is selected from the group consisting of OX-40 and CD27.

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

expression and/or activity is administered simultaneous with the agent that increases or activates one or more additional immune co-stimulatory receptors. In certain embodiments that may be combined with any of the preceding embodiments, the agent that decreases or inhibits TIGIT expression and/or activity is administered after the agent that increases or activates one or more additional immune co-stimulatory receptors.

[0096] In other ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 ~~aspects~~embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the PD-1 axis binding antagonist is an anti-PD-L1 antibody. In certain embodiments that may be combined with any of the preceding embodiments, the anti-PD-L1 antibody is selected from the group consisting of YW243.55.S70, MPDL3280A, MDX-1105 and MEDI4736. In certain embodiments that may be combined with any of the preceding embodiments, 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). In certain embodiments that may be combined with any of the preceding embodiments, the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWRQAPGKGLEWVAWISPYGG
STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG
TLVTVSA (SEQ ID NO:23),

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWRQAPGKGLEWVAWISPYGG
STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG
TLVTVSSASTK (SEQ ID NO:40), or

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWRQAPGKGLEWVAWISPYGG
STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG
TLVTVSS (SEQ ID NO:41), and a light chain variable region comprising the amino acid sequence of

DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYS
VPSRFSGSGSGTDFTLTISLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID

NO:24). In certain embodiments that may be combined with any of the preceding embodiments, the PD-1 axis binding antagonist is an anti-PD-1 antibody. In certain embodiments that may be combined with any of the preceding embodiments, the anti-PD-1 antibody is MDX-1106, MK-3475, or CT-011. In certain embodiments that may be combined with any of the preceding embodiments, the PD-1 axis binding antagonist is AMP-224. In certain embodiments that may be combined with any of the preceding embodiments, the PD-1 axis binding antagonist is a PD-L2 binding antagonist. In certain embodiments that may be combined with any of the preceding embodiments, the PD-L2 binding antagonist is an antibody. In certain embodiments that may be combined with any of the preceding embodiments, the PD-L2 binding antagonist is an immunoadhesin.

[0109] In other aspects, ~~there is provided 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 aspects, ~~there is provided 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 aspects, ~~there is provided 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 aspects, ~~there is provided 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 aspects, ~~there is provided 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 aspects, ~~there is provided 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 aspects, ~~there is provided 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

aspects, ~~there is provided 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 aspects, ~~there is provided 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 aspects, ~~there is provided 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 aspects, ~~there is provided 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 aspects, ~~there is provided 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 embodiments that may be combined with any of the preceding embodiments, the one 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the one or more additional immune co-stimulatory receptor is selected from the group consisting of OX-40 and CD27.

CLAIMS

What is claimed is:

1. ~~A method for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount~~Use 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 medicament is to be administered with~~and an agent that decreases or inhibits TIGIT expression and/or activity.~~
2. ~~A method for reducing or inhibiting cancer relapse or cancer progression in an individual comprising administering to the individual an effective amount~~Use 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 medicament is to be administered with~~and an agent that decreases or inhibits TIGIT expression and/or activity.~~
3. ~~A method for treating or delaying progression of an immune related disease in an individual comprising administering to the individual an effective amount~~Use 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 medicament is to be administered with~~and an agent that decreases or inhibits TIGIT expression and/or activity.~~
4. ~~A method for reducing or inhibiting progression of an immune related disease in an individual comprising administering to the individual an effective amount~~Use 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 medicament is to be administered with~~and an agent that decreases or inhibits TIGIT expression and/or activity.~~
5. The ~~use method~~ of claim 3 or 4, wherein the immune related disease is associated with a T cell dysfunctional disorder.
6. The ~~use method~~ of claim 5, wherein the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation.
7. The ~~use method~~ of claim 5, wherein the T cell dysfunctional disorder is characterized by T cell anergy or decreased ability to secrete cytokines, proliferate or execute cytolytic activity.
8. The ~~use method~~ of claim 5, wherein the T cell dysfunctional disorder is characterized by T cell exhaustion.
9. The ~~use method~~ of any one of claims 3-8, wherein the T cells are CD4⁺ and CD8⁺ T cells.
10. The ~~use method~~ of any one of claims 3-9, wherein the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.
11. ~~A method of increasing, enhancing or stimulating an immune response or function in an individual comprising administering to the individual an effective amount~~Use of a PD-1 axis binding antagonist in the manufacture of a medicament for increasing, enhancing or stimulating an immune response or function in an individual, wherein the medicament is to be administered with~~and an agent that decreases or inhibits TIGIT expression and/or activity.~~
12. ~~A method of treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount~~Use 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 medicament is to be administered with~~and an~~

agent that modulates CD226 expression and/or activity.

13. ~~A method for reducing or inhibiting cancer relapse or cancer progression in an individual comprising administering to the individual an effective amount~~Use 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 medicament is to be administered withand an agent that modulates CD226 expression and/or activity.

14. ~~A method for treating or delaying progression of an immune related disease in an individual comprising administering to the individual an effective amount~~Use 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 medicament is to be administered withand an agent that modulates CD226 expression and/or activity.

15. ~~A method for reducing or inhibiting progression of an immune related disease in an individual comprising administering to the individual an effective amount~~Use 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 medicament is to be administered withand agent that modulates CD226 expression and/or activity.

16. The ~~use~~method of claim 14 or 15, wherein the immune related disease is associated with a T cell dysfunctional disorder.

17. The ~~use~~method of claim 16, wherein the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation.

18. The ~~use~~method of claim 16, wherein the T cell dysfunctional disorder is characterized by T cell anergy, or decreased ability to secrete cytokines, proliferate or execute cytolytic activity.

19. The ~~use~~method of claim 16, wherein the T cell dysfunctional disorder is characterized by T cell exhaustion.

20. The ~~use~~method of any one of claims 16-19, wherein the T cells are CD4+ and CD8+ T cells.

21. The ~~use~~method of any one of claims 14-20, wherein the immune related disease is selected from the group consisting of unresolved acute infection, chronic infection and tumor immunity.

22. ~~A method of increasing, enhancing, or stimulating an immune response or function in an individual comprising administering to the individual an effective amount~~Use of a PD-1 axis binding antagonist in the manufacture of a medicament for increasing, enhancing, or stimulating an immune response or function in an individual, wherein the medicament is to be administered withand an agent that modulates CD226 expression and/or activity.

23. The ~~use~~method of any one of claims 12-22, wherein the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates CD226 expression and/or activity.

24. The ~~use~~method of any one of claims 12-23, wherein the agent that modulates CD226 expression and/or activity is an agent that increases and/or stimulates the interaction of CD226 with PVR.

25. The ~~use~~method of any one of claims 12-24, wherein 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.

26. The ~~usemethod~~ of any one of claims 12-25, wherein 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.

27. The ~~usemethod~~ of claim 26, wherein the agent that modulates CD226 expression and/or activity is an agent that inhibits and/or blocks the interaction of CD226 with TIGIT.

28. The ~~usemethod~~ of claim 26 or 27, wherein 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.

29. The ~~usemethod~~ of claim 26 or 27, wherein the agent that inhibits and/or blocks the interaction of CD226 with TIGIT is an anti-TIGIT antibody or antigen-binding fragment thereof.

30. The ~~usemethod~~ of claim 26 or 27, wherein 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.

31. The ~~usemethod~~ of claim 26, wherein the agent that modulates CD226 expression and/or activity is an antagonist of TIGIT expression and/or activity.

32. The ~~usemethod~~ of claim 26 or 31, wherein the antagonist of TIGIT expression and/or activity is a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

33. The ~~usemethod~~ of claim 26 or 31, wherein the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof.

34. The ~~usemethod~~ of claim 26 or 31, wherein 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.

35. The ~~use~~method of claim 26, wherein the antagonist of PVR expression and/or activity is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

36. The ~~use~~method of claim 26, wherein the agent that inhibits and/or blocks the interaction of TIGIT with PVR is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

37. The ~~use~~method of claim 26, wherein the agent that inhibits and/or blocks the interaction of TIGIT with PVRL2 is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

38. The ~~use~~method of claim 26, wherein the agent that inhibits and/or blocks the interaction of TIGIT with PVRL3 is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

39. The ~~use~~method of claim 26, wherein the agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to PVR is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

40. The ~~use~~method of claim 26, wherein the agent that inhibits and/or blocks the interaction of TIGIT with PVRL2 is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

41. The ~~use~~method of claim 26, wherein the agent that inhibits and/or blocks the interaction of TIGIT with PVRL3 is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

42. ~~A method of increasing, enhancing, or stimulating an immune response or function in an individual comprising administering to the individual an effective amount~~Use of an agent that decreases or inhibits TIGIT expression and/or activity in the manufacture of a medicament for increasing, enhancing, or stimulating an immune response or function in an individual, wherein the medicament is to be administered with~~and~~ an agent that decreases or inhibits one or more additional immune co-inhibitory receptors.

43. The ~~use~~method of claim 42, wherein 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.

44. The ~~use~~method of claim 42, wherein the one or more additional immune co-inhibitory receptor is selected from the group consisting of PD-1, CTLA-4, LAG3 and TIM3.

45. ~~A method of increasing, enhancing, or stimulating an immune response or function in an individual comprising administering to the individual an effective amount~~Use of an agent that decreases or inhibits TIGIT expression and/or activity in the manufacture of a medicament for increasing, enhancing, or stimulating an immune response or function in an individual, wherein the medicament is to be administered with and an agent that increases or activates one or more additional immune co-stimulatory receptors.

46. The ~~use~~method of claim 45, wherein 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.

47. The ~~use~~method of claim 45, wherein the one or more additional immune co-stimulatory receptors is selected from the group consisting of CD226, OX-40, CD27, CD137, HVEM and GITR.

48. The ~~use~~method of claim 45, wherein the one or more additional immune co-stimulatory receptors is selected from the group consisting of OX-40 and CD27.

49. The ~~use~~method of any one of the preceding claims, further comprising administering at least one chemotherapeutic agent.

50. The ~~use~~method of any one of the preceding claims, wherein the individual has cancer.

51. The ~~use~~method of any one of the preceding claims, wherein 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.

52. The ~~use~~method of any one of the preceding claims, wherein the number of CD4 and/or CD8 T cells is elevated relative to prior to administration of the combination.

53. The ~~use~~method of any one of the preceding claims, wherein the number of activated CD4 and/or CD8 T cells is elevated relative to prior to administration of the combination.

54. The ~~use~~method of any one of the preceding claims, wherein 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.

55. The ~~use~~method of any one of claims 51-54, wherein the CD4 and/or CD8 T cells exhibit increased release of cytokines selected from the group consisting of IFN- γ , TNF- α and interleukins.

56. The ~~use~~method of any one of claims 51-55, wherein the CD4 and/or CD8 T cells are

effector memory T cells.

57. The ~~use~~method of claim 56, wherein 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.

58. The ~~use~~method of claim 56, wherein the CD4 and/or CD8 effector memory T cells are characterized by having the expression of CD44^{high} CD62L^{low}.

59. The ~~use~~method of any one of claims 1, 2, 12, 13, 23-41, and 49-58, wherein the cancer has elevated levels of T cell infiltration.

60. The ~~use~~method of any one of claims 1-11 and 42-59, wherein the agent that decreases or inhibits TIGIT expression and/or activity is selected from the group consisting of an antagonist of TIGIT expression and/or activity, an antagonist of PVR expression and/or activity, an agent that inhibits and/or blocks the interaction of TIGIT with PVR, an agent that inhibits and/or blocks the interaction of TIGIT with PVRL2, an agent that inhibits and/or blocks the interaction of TIGIT with PVRL3, an agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to PVR, an agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to PVRL2, an agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to PVRL3, and combinations thereof.

61. The ~~use~~method of claim 60, wherein 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.

62. The ~~use~~method of claim 60, wherein the antagonist of PVR expression and/or activity is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

63. The ~~use~~method of claim 60, wherein the agent that inhibits and/or blocks the interaction of TIGIT with PVR is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

64. The ~~use~~method of claim 60, wherein the agent that inhibits and/or blocks the interaction of TIGIT with PVRL2 is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.

65. The ~~use~~method of claim 60, wherein the agent that inhibits and/or blocks the interaction of TIGIT with PVRL3 is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.
66. The ~~use~~method of claim 60, wherein the agent that inhibits and/or blocks the intracellular signaling mediated by TIGIT binding to PVR is selected from the group consisting of a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide.
67. The ~~use~~method of claim 60, wherein 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.
68. The ~~use~~method of claim 60, wherein 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.
69. The ~~use~~method of claim 60 or 61, wherein 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.
70. The ~~use~~method of claim 60 or 61, wherein the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof.
71. The ~~use~~method of claim 29 or 70, wherein 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) KSSQSLYYSQGVKENLLA (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).
72. The ~~use~~method of any one of claims 29, 70, and 71, wherein the anti-TIGIT antibody or antigen-binding fragment thereof, wherein the antibody light chain comprises the amino acid sequence set forth in
DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSQGVKENLLAWYQQKPGQS
PKLLIYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGD

GTKLEIKR (SEQ ID NO:13) or

DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISN
RFSGVPDRFSGSGSGTDFTLKISTIKPEDLGMYYC**LOGTHQPPT**FGPGTKLEVK

(SEQ ID NO:14).

73. The ~~use~~method of any one of claims 29 and 70-72, wherein the anti-TIGIT antibody or antigen-binding fragment thereof, wherein the antibody heavy chain comprises the amino acid sequence set forth in

EVQLVESGGGLTQPGKSLKLSCEAS**GFTFSSFTM**HWVRQSPGKGLEWVAFIRSGSG
IVFYADAVRGRFTISRDNANKNLLFLQMNDLKSEDTAMYVCARR**PLGHNTF**DSWGQ
GTLVTVSS (SEQ ID NO:15) or

EVQLQQSGPELVKPGTSMKISCKAS**GYSFTGHLMN**WVKQSHGKNLEWIGLIIPYNG
GTSYNQKFKGKATLTVDKSSSTAYMELLSTSDDSAVYFCSR**GLRGFYAM**DYWG
QGTSVTVSS (SEQ ID NO:16).

74. The ~~use~~method of any one of claims 29, 70, and 71, wherein the anti-TIGIT antibody or antigen-binding fragment thereof, wherein the antibody light chain comprises the amino acid sequence set forth in

DIVMTQSPSSSLAVSPGEKVTMTCKSSQSLYYS**GVKENLL**AWYQQKPGQS

PKLLIYYASIR**FTG**VDPDRFTGSGSGTDYTLTITSVQAEDMGQYFC**QQGINNPLT**FGD

GTKLEIKR (SEQ ID NO:13) or

DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISN
RFSGVPDRFSGSGSGTDFTLKISTIKPEDLGMYYC**LOGTHQPPT**FGPGTKLEVK

(SEQ ID NO:14), and the antibody heavy chain comprises the amino acid sequence set forth in

EVQLVESGGGLTQPGKSLKLSCEAS**GFTFSSFTM**HWVRQSPGKGLEWVAFIRSGSG
IVFYADAVRGRFTISRDNANKNLLFLQMNDLKSEDTAMYVCARR**PLGHNTF**DSWGQ
GTLVTVSS (SEQ ID NO:15) or

EVQLQQSGPELVKPGTSMKISCKAS**GYSFTGHLMN**WVKQSHGKNLEWIGLIIPYNG
GTSYNQKFKGKATLTVDKSSSTAYMELLSTSDDSAVYFCSR**GLRGFYAM**DYWG
QGTSVTVSS (SEQ ID NO: 16).

75. The ~~use~~method of any one of claims 29 and 70-74, wherein 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.

76. The ~~use~~method of any one of claims 29 and 70-75, wherein 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).

77. The ~~use~~method of any one of claims 72, 73, and 74, wherein 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

DIVMTQSPSSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQS
PKLLIYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGD
GTKLEIKR (SEQ ID NO:13) or

DVVLVTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISN
RFSQVPDRFSGSGSGTDFTLKISTIKPEDLGMYCYCLQGTHQPPTFGPGTKLEVK
(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

EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRSGSG
IVFYADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYVCARRPLGHNTFDSWGQ
GTLVTVSS (SEQ ID NO:15) or

EVQLQQSGPELVKPGTSMKISCKASGYSFTGHLMNWVKQSHGKNLEWIGLIIPYNG
GTSYNQKFKGKATLTVDKSSSTAYMELLSLTSDDSAVYFCRGLRGFYAMDYWG
QGTSVTVSS (SEQ ID NO:16).

78. The ~~use~~method of any one of claims 1-41, 43, 44, and 49-77, wherein 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.

79. The ~~use~~method of claim 78, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.

80. The ~~use~~method of claim 79, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.

81. The ~~use~~method of claim 79 or 80, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1.

82. The ~~use~~method of claim 79 or 80, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2.

83. The ~~use~~method of claim 79 or 80, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2.
84. The ~~use~~method of any one of claims 79-83, wherein the PD-1 binding antagonist is an antibody.
85. The ~~use~~method of any one of claims 79-84, wherein the PD-1 binding antagonist is MDX-1106.
86. The ~~use~~method of any one of claims 79-84, wherein the PD-1 binding antagonist is MK-3475.
87. The ~~use~~method of any one of claims 79-84, wherein the PD-1 binding antagonist is CT-011.
88. The ~~use~~method of any one of claims 79-83, wherein the PD-1 binding antagonist is AMP-224.
89. The ~~use~~method of claim 78, wherein the PD-1 axis binding antagonist is a PD-L1 binding antagonist.
90. The ~~use~~method of claim 89, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1.
91. The ~~use~~method of claim 89, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1.
92. The ~~use~~method of claim 89, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.
93. The ~~use~~method of any one of claims 89-92, wherein the PD-L1 binding antagonist is an anti-PD-L1 antibody.
94. The ~~use~~method of any one of claims 89-93, wherein the PD-L1 binding antagonist is selected from the group consisting of YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.
95. The ~~use~~method of claim 93, wherein 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).
96. The ~~use~~method of claim 93, wherein the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGG

STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG
 TLVTVSA (SEQ ID NO:23),
 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWRQAPGKGLEWVAWISPYGG
 STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG
 TLVTVSSASTK (SEQ ID NO:40), or
 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWRQAPGKGLEWVAWISPYGG
 STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG
 TLVTVSS (SEQ ID NO:41), and a light chain variable region comprising the amino acid
 sequence of
 DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSG
 VPSRFSGSGSGTDFTLTISLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID
 NO:24).

97. The ~~use method~~ of claim 78, wherein the PD-1 axis binding antagonist is a PD-L2 binding antagonist.
98. The ~~use method~~ of claim 97, wherein the PD-L2 binding antagonist is an antibody.
99. The ~~use method~~ of claim 97, wherein the PD-L2 binding antagonist is an immunoadhesin.
100. The ~~use method~~ of any one of claims 1, 2, 12, 13, 23-41, and 49-99, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, renal cell cancer, colorectal cancer, ovarian cancer, breast cancer, pancreatic cancer, gastric carcinoma, bladder cancer, esophageal cancer, mesothelioma, melanoma, head and neck cancer, thyroid cancer, sarcoma, prostate cancer, glioblastoma, cervical cancer, thymic carcinoma, leukemia, lymphomas, myelomas, mycoses fungoids, merkel cell cancer, and other hematologic malignancies.
101. The ~~use method~~ of any one of claims 1-11 and 42-100, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered continuously.
102. The ~~use method~~ of any one of claims 1-11 and 42-100, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered intermittently.
103. The ~~use method~~ of any one of claims 1-11 and 49-102, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered before the PD-1 axis binding antagonist.
104. The ~~use method~~ of any one of claims 1-11 and 49-102, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered simultaneous with the PD-1 axis binding antagonist.
105. The ~~use method~~ of any one of claims 1-11 and 49-102, wherein the agent that decreases or

inhibits TIGIT expression and/or activity is to be administered after the PD-1 axis binding antagonist.

106. The ~~use~~method of any one of claims 12-41 and 49-100, wherein the PD-1 axis binding antagonist is to be administered before the agent that modulates CD226 expression and/or activity.

107. The ~~use~~method of any one of claims 12-41 and 49-100, wherein the PD-1 axis binding antagonist is to be administered simultaneous with the agent that modulates CD226 expression and/or activity.

108. The ~~use~~method of any one of claims 12-41 and 49-100, wherein the PD-1 axis binding antagonist is to be administered after the agent that modulates CD226 expression and/or activity.

109. The ~~use~~method of any one of claims 42-44 and 49-100, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered before the agent that decreases or inhibits one or more additional immune co-inhibitory receptors.

110. The ~~use~~method of any one of claims 42-44 and 49-100, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered simultaneous with the agent that decreases or inhibits one or more additional immune co-inhibitory receptors.

111. The ~~use~~method of any one of claims 42-44 and 49-100, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered after the agent that decreases or inhibits one or more additional immune co-inhibitory receptors.

112. The ~~use~~method of any one of claims 45-100, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered before the agent that increases or activates one or more additional immune co-stimulatory receptors.

113. The ~~use~~method of any one of claims 45-100, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered simultaneous with the agent that increases or activates one or more additional immune co-stimulatory receptors.

114. The ~~use~~method of any one of claims 45-100, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered after the agent that increases or activates one or more additional immune co-stimulatory receptors.

115. 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.

116. 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