

## SUMMARY

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

**[0010a]** In one aspect, there is provided use of a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 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-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 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-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 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 and the immune related disease is a viral infection.

**[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-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 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 and the immune related disease is a viral infection.

**[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-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 in the manufacture of a medicament for increasing, enhancing or stimulating an immune response or function in an individual having cancer, 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]** Provided is 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]** Provided is 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]** Provided is 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]** Provided is 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]** Provided is 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 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 having cancer, wherein the medicament is to be administered with an agent that decreases or inhibits one or more additional immune co-inhibitory receptors, wherein the one or more additional immune co-inhibitory receptors are selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96.

**[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 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] Provided is 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  $\gamma$ -IFN<sup>+</sup> 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- $\gamma$ , TNF- $\alpha$ , 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  $\gamma$ -IFN<sup>+</sup> 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<sup>high</sup> CD62L<sup>low</sup>.

**[0063]** Provided is 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.

**[0064]** In one aspect, there is provided a kit comprising a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 and an agent that decreases or inhibits TIGIT expression and/or activity, and a package insert comprising instructions for using the PD-L1 binding antagonist, the PD-1 binding antagonist, or the PD-L2 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]** Provided is a kit comprising an agent that decreases or inhibits TIGIT expression and/or activity and a package insert comprising instructions for using the agent that decreases or inhibits TIGIT expression and/or activity in combination with a PD-1 axis binding antagonist to treat or delay progression of cancer in an individual.

**[0066]** Provided is 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.

**[0067]** In one aspect, there is provided a kit comprising a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 and an agent that decreases or inhibits TIGIT expression and/or activity, and a package insert comprising instructions for using the PD-L1 binding antagonist, the PD-1 binding antagonist, or the PD-L2 binding antagonist and the agent that decreases or inhibits TIGIT expression and/or activity to enhance immune function of an individual having cancer.

**[0068]** Provided is a kit comprising an agent that decreases or inhibits TIGIT expression and/or activity and a package insert comprising instructions for using the agent that decreases or inhibits TIGIT expression and/or activity in combination with a PD-1 axis binding antagonist to enhance immune function of an individual having cancer.

**[0069]** Provided is 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 the CD226 expression and/or activity to treat or delay progression of cancer in an individual.

**[0070]** Provided is a kit 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] Provided is a kit 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] Provided is 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 the CD226 expression and/or activity to enhance immune function of an individual having cancer.

[0073] Provided is a kit 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] Provided is a kit 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

(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  
GVPSTRFSGSGSGTDFTLTISLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (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]** Provided is a kit comprising an agent that decreases or inhibits TIGIT expression and/or activity and a package insert comprising instructions for using the agent that decreases or inhibits TIGIT expression and/or activity in combination with an 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 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, wherein the one or more additional immune co-inhibitory receptors are selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96. Provided is 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. Provided is a kit comprising an agent that decreases or inhibits TIGIT expression and/or activity and a package insert comprising instructions for using the agent that decreases or inhibits TIGIT expression and/or activity in combination with an 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 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, wherein the one or more additional immune co-inhibitory receptors are selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96. Provided is 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]** Provided is a kit comprising an agent that decreases or inhibits TIGIT expression and/or activity and a package insert comprising instructions for using the agent that decreases or inhibits TIGIT expression and/or activity in combination with an agent that increases or activates one or more additional immune co-stimulatory receptors to treat or delay progression of cancer in an individual.

Provided is 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. Provided is 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. Provided is a kit comprising an agent that decreases or inhibits TIGIT expression and/or activity and a package insert comprising instructions for using the agent that decreases or inhibits TIGIT expression and/or activity in combination with an agent that increases or activates one or more additional immune co-stimulatory receptors to enhance immune function of an individual having cancer. Provided is 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. Provided is 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. Use of a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament is to be administered with an agent that decreases or inhibits TIGIT expression and/or activity.
2. Use of a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 in the manufacture of a medicament for reducing or inhibiting cancer relapse or cancer progression in an individual, wherein the medicament is to be administered with an agent that decreases or inhibits TIGIT expression and/or activity.
3. Use of a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 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 and the immune related disease is a viral infection.
4. Use of a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 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 and the immune related disease is a viral infection.
5. The use of claim 3 or 4, wherein the immune related disease is associated with a T cell dysfunctional disorder.
6. The use of claim 5, wherein the T cell dysfunctional disorder is characterized by decreased responsiveness to antigenic stimulation.
7. The use 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 of claim 5, wherein the T cell dysfunctional disorder is characterized by T cell exhaustion.
9. The use of any one of claims 3-8, wherein the T cells are CD8<sup>+</sup> T cells.
10. The use of any one of claims 3-9, wherein the viral infection is an unresolved acute viral infection or a chronic viral infection.

11. Use of a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 in the manufacture of a medicament for increasing, enhancing or stimulating an immune response or function in an individual having cancer, wherein the medicament is to be administered with an agent that decreases or inhibits TIGIT expression and/or activity.
12. 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 having cancer, wherein the medicament is to be administered with an agent that decreases or inhibits one or more additional immune co-inhibitory receptors, wherein the one or more additional immune co-inhibitory receptors are selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96.
13. The use of claim 12, wherein the one or more additional immune co-inhibitory receptors are selected from the group consisting of PD-1, CTLA-4, LAG3 and TIM3.
14. The use of any one of claims 1-13, wherein the medicament is to be administered with at least one chemotherapeutic agent.
15. The use of any one of claims 1-14, 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.
16. The use of any one of claims 1-15, wherein the number of CD4 and/or CD8 T cells is elevated relative to prior to administration of the combination.
17. The use of any one of claims 1-16, wherein the number of activated CD4 and/or CD8 T cells is elevated relative to prior to administration of the combination.
18. The use of any one of claims 1-17, wherein activated CD4 and/or CD8 T cells are characterized by  $\gamma$ -IFN<sup>+</sup> producing CD4 and/or CD8 T cells and/or enhanced cytolytic activity relative to prior to the administration of the combination.
19. The use of any one of claims 15-18, wherein the CD4 and/or CD8 T cells exhibit increased release of cytokines selected from the group consisting of IFN- $\gamma$ , TNF- $\alpha$  and interleukins.
20. The use of any one of claims 15-19, wherein the CD4 and/or CD8 T cells are effector memory T cells.
21. The use of claim 20, wherein the CD4 and/or CD8 effector memory T cells are characterized by  $\gamma$ -IFN<sup>+</sup> producing CD4 and/or CD8 T cells and/or enhanced cytolytic activity.
22. The use of claim 20, wherein the CD4 and/or CD8 effector memory T cells are characterized by having the expression of CD44<sup>high</sup> CD62L<sup>low</sup>.
23. The use of any one of claims 1, 2, and 14-22, wherein the cancer has elevated levels of T cell infiltration.
24. The use of any one of claims 1-11 and 12-23, 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 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, and combinations thereof.

25. The use of claim 24, 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.

26. The use of claim 24, 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.

27. The use of claim 24, 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.

28. The use of claim 24, 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.

29. The use of claim 24, 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.

30. The use of claim 24, 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.

31. The use of claim 24, 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.

32. The use of claim 24, 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.

33. The use of claim 24 or 25, 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.

34. The use of claim 24 or 25, wherein the antagonist of TIGIT expression and/or activity is an anti-TIGIT antibody or antigen-binding fragment thereof.

35. The use of claim 34, wherein the anti-TIGIT antibody or antigen-binding fragment thereof comprises six HVRs comprising the following amino acid sequences (1) KSSQSLYYSGVKENLLA (SEQ ID NO:1), ASIRFT (SEQ ID NO:2), QQGINNPLT (SEQ ID NO:3), GFTFSSFTMH (SEQ ID NO:4), FIRSGSGIVFYADAVRG (SEQ ID NO:5), and RPLGHNTFDS (SEQ ID NO:6); or (2) RSSQSLVNSYGNLFLS (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).

36. The use of claim 34 or 35, wherein the anti-TIGIT antibody or antigen-binding fragment thereof, wherein the antibody light chain comprises the amino acid sequence set forth in DIVMTQSPSSSLAVSPGKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQS PKLLIYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTKLEI KR (SEQ ID NO:13) or DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNLFLSWYLHKPGQSPQLLIFGISNRFSGVP DRFSGSGSGTDFTLKISTIKPEDLGMYCYCLQGTHQPPTFGPGTKLEVK (SEQ ID NO:14), and the antibody heavy chain comprises the amino acid sequence set forth in EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRSGSGIVFYA DAVRGRFTISRDNANKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDSWGQGTLVTVSS (SEQ ID NO:15) or EVQLQQSGPELVKPGTSMKISCKASGYSFTGHLMNWVKQSHGKNLEWIGLIIPYNGGTSYN QKFKGKATLTVDKSSSTAYMELLSLTSDDSAVYFCRGLRGFYAMDYWGQGTSTVTVSS (SEQ ID NO: 16).

37. The use of any one of claims 34-36, 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.

38. The use of claim 34, wherein the anti-TIGIT antibody or antigen-binding fragment thereof comprises six HVRs that are each 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) RSSQSLVNSYGNLFLS (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).

39. The use of claim 38, wherein the anti-TIGIT antibody or fragment thereof comprises a light chain comprising an amino acid sequence at least 90% identical to the amino acid sequence set forth in DIVMTQSPSSSLAVSPGKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQS PKLLIYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTKLEI

KR (SEQ ID NO:13) or

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

EVQLVESGGGLTQPGKSLKLSCEASGFTFSFTMHWVRQSPGKGLEWVAFIRSGSGIVFYA  
DAVRGRFTISRDNANKLLFLQMNDLKSEDTAMYYCARRPLGHNTFDSWGQGTLVTVSS  
(SEQ ID NO:15) or

EVQLQQSGPELVKPGTSMKISCKASGYSTGHLMNWVKQSHGKNLEWIGLIIPYNGGTSYN  
QKFKGKATLTVDKSSSTAYMELLSLTSDDSAVYFCSRGLRGFYAMDYWGQGTSTVTVSS  
(SEQ ID NO:16).

40. The use of any one of claims 1-11 and 14-39, wherein the PD-1 binding antagonist is an antibody.
41. The use of any one of claims 1-11 and 14-40, wherein the PD-1 binding antagonist is MDX-1106.
42. The use of any one of claims 1-11 and 14-40, wherein the PD-1 binding antagonist is MK-3475.
43. The use of any one of claims 1-11 and 14-40, wherein the PD-1 binding antagonist is CT-011.
44. The use of any one of claims 1-11 and 14-39, wherein the PD-1 binding antagonist is AMP-224.
45. The use of any one of claims 1-11 and 14-39, wherein the PD-L1 binding antagonist is an anti-PD-L1 antibody.
46. The use of any one of claims 1-11, 14-39 and 45, wherein the PD-L1 binding antagonist is selected from the group consisting of MPDL3280A, YW243.55.S70, MDX-1105, and MEDI4736.
47. The use of claim 45, 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).
48. The use of claim 45, wherein the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of  
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGG  
STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTV  
SA (SEQ ID NO:23),  
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA  
DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSSAST

K (SEQ ID NO:40), or

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA  
DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSS (SEQ  
ID NO:41), and a light chain variable region comprising the amino acid sequence of  
DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFS  
GSGSGTDFLTITISLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID NO:24).

49. The use of claim 1-11 and 14-39, wherein the PD-L2 binding antagonist is an antibody.

50. The use of claim 1-11 and 14-39, wherein the PD-L2 binding antagonist is an immunoadhesin.

51. The use of any one of claims 1, 2, and 11-50, 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 fungoides, merkel cell cancer, and other hematologic malignancies.

52. The use of any one of claims 1-51, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered continuously.

53. The use of any one of claims 1-51, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered intermittently.

54. The use of any one of claims 1-11 and 14-53, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered before the PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, the PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or the PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1.

55. The use of any one of claims 1-11 and 14-53, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered simultaneous with the PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, the PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or the PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1.

56. The use of any one of claims 1-11 and 14-53, wherein the agent that decreases or inhibits TIGIT expression and/or activity is to be administered after the PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, the PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or the PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1.

57. The use of any one of claims 12-51, 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.

58. The use of any one of claims 12-51, 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.

59. The use of any one of claims 12-51, 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.

60. A kit comprising a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 and an agent that decreases or inhibits TIGIT expression and/or activity, and a package insert comprising instructions for using the PD-L1 binding antagonist, the PD-1 binding antagonist, or the PD-L2 binding antagonist and the agent that decreases or inhibits TIGIT expression and/or activity to treat or delay progression of cancer in an individual.

61. A kit comprising a PD-L1 binding antagonist that inhibits the binding of PD-L1 to PD-1, a PD-1 binding antagonist that inhibits the binding of PD-1 to PD-L1 and/or PD-L2, or a PD-L2 binding antagonist that inhibits the binding of PD-L2 to PD-1 and an agent that decreases or inhibits TIGIT expression and/or activity, and a package insert comprising instructions for using the PD-L1 binding antagonist, the PD-1 binding antagonist, or the PD-L2 binding antagonist and the agent that decreases or inhibits TIGIT expression and/or activity to enhance immune function of an individual having cancer.

62. The kit of claim 60 or 61, wherein the PD-L1 binding antagonist is an anti-PD-L1 antibody.

63. The kit of claim 62, wherein the anti-PD-L1 antibody is selected from the group consisting of MPDL3280A, YW243.55.S70, MDX-1105 and MEDI4736.

64. The kit of claim 62, 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).

65. The kit of claim 62, wherein the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA  
DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSA  
(SEQ ID NO:23),

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA  
DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSSAST  
K (SEQ ID NO:40), or

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA  
DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSS (SEQ

ID NO:41), and a light chain variable region comprising the amino acid sequence of  
DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFS  
GSGSGTDFLTITSSLPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID NO:24).

66. The kit of claim 60 or 61, wherein the PD-1 binding antagonist is an anti-PD-1 antibody.
67. The kit of claim 66, wherein the anti-PD-1 antibody is MDX-1106, MK-3475, or CT-011.
68. The kit of claim 60 or 61, wherein the PD-1 binding antagonist is AMP-224.
69. The kit of claim 60 or 61, wherein the PD-L2 binding antagonist is an antibody.
70. The kit of claim 60 or 61, wherein the PD-L2 binding antagonist is an immunoadhesin.
71. 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, wherein the one or more additional immune co-inhibitory receptors are selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96.
72. 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, wherein the one or more additional immune co-inhibitory receptors are selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96.
73. The kit of claim 71 or 72, wherein the one or more additional immune co-inhibitory receptors are selected from the group consisting of PD-1, CTLA-4, LAG3 and TIM3.