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(54) **Titre :** ANTICORPS ANTI-TIM-3 POUR UNE COMBINAISON AVEC DES ANTICORPS ANTI-PD-1
(54) **Title:** ANTI-TIM-3 ANTIBODIES FOR COMBINATION WITH ANTI-PD-1 ANTIBODIES

(57) **Abrégé/Abstract:**

The present invention relates to antibodies that bind human T-cell immunoglobulin- and mucin-domain-containing protein-3 (Tim-3), and may be useful for treating solid and hematological tumors in combination with anti-human PD-1 antibodies, chemotherapy, and ionizing radiation.

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- (54) **Title:** ANTI-TIM-3 ANTIBODIES FOR COMBINATION WITH ANTI-PD-1 ANTIBODIES
- (57) **Abstract:** The present invention relates to antibodies that bind human T-cell immunoglobulin- and mucin-domain-containing protein-3 (Tim-3), and may be useful for treating solid and hematological tumors in combination with anti-human PD-1 antibodies, chemotherapy, and ionizing radiation.

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ANTI-TIM-3 ANTIBODIES FOR COMBINATION WITH ANTI-PD-1 ANTIBODIES

The present invention is in the field of medicine. Particularly, the present invention relates to antibodies directed to human T-cell immunoglobulin- and mucin-
5 domain-containing protein-3 (Tim-3) (SEQ ID NO: 1) that can be combined with antibodies directed to human PD-1 (SEQ ID NO: 34), compositions comprising such anti-human Tim-3 antibodies or anti-human PD-1 antibodies, and methods of using such anti-human Tim-3 antibodies in combination with anti-human PD-1 antibodies for the treatment of solid and hematological tumors alone or in further combination with
10 chemotherapy, ionizing radiation, and other cancer therapeutics.

Tumor cells escape detection and elimination by the immune system through multiple mechanisms some of which include the manipulation of immune checkpoint pathways. Immune checkpoint pathways are used in self-tolerance maintenance and in the regulation of T cell activation, but cancer cells can manipulate these pathways to
15 prolong tumor survival. The PD-1/human programmed cell death 1 ligand 1 (PD-L1) pathway is one such immune checkpoint. Human PD-1 (SEQ ID NO: 34) is expressed on T cells, and the binding of PD-L1 or PD-L2 to PD-1 has been shown to inhibit T cell proliferation and cytokine production. Moreover, some tumors are known to express PD-L1 and PD-L2 and such expression can contribute to the inhibition of the intratumoral
20 immune response.

In addition to the PD-1/PD-L1 pathway, T cells recognizing tumor antigens can also express other checkpoint receptors, such as Tim-3. In particular, T cells expressing Tim-3 can exhibit an exhausted phenotype characterized by an impairment in cytotoxic functions, effector cytokine production, and proliferation. In this regard, it has been
25 shown that anti-Tim-3 antibodies can restore anti-tumor immunity in some murine cancer models. Moreover, it has also been shown that some patients who develop adaptive resistance to anti-PD-1 treatment display an upregulation of Tim-3 on their T cells.

Antibodies directed to human Tim-3 are known. Humanized antibodies against human Tim-3 are described in WO15117002. MBG453, an anti-human Tim-3 antibody,
30 is currently being tested in human clinical trials as a single agent and in combination with an anti-human PD-1 antibody. However, no antibody targeting Tim-3 has been approved

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for therapeutic use in humans nor has any anti-human Tim-3 antibody been shown to display efficacy against human tumors when combined with an anti-human PD-1 antibody. Thus, there remains a need for anti-human Tim-3 antibodies that can be combined with anti-human PD-1 antibodies as well as other therapies for treating human
5 cancers.

Tim-3 (SEQ ID NO:1) has been shown to interact with galectin-9 (SEQ ID NO:15), phosphatidylserine ($C_{13}H_{24}NO_{10}P$), high-mobility group Box 1 (HMGB1), and carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1) (SEQ ID NO:14). Because all of the aforementioned Tim-3 ligands are not exclusive ligands of Tim-3, it is
10 desirable to provide therapeutic anti-Tim-3 antibodies that differentially block the activity of said ligands as these ligands can regulate the immune system independently of Tim-3. Such a strategy can provide alternative ways to more specifically modulate Tim-3 activity, allowing for tailored immuno-oncology based therapies for patients. Furthermore, such anti-Tim-3 antibodies can provide options for combinatorial therapies
15 with anti-human PD-1 antibodies. Thus, there also remains a need to provide antibodies that bind human Tim-3 and inhibit Tim-3's interactions with some of Tim-3's ligands, but not others, and that can be combined with anti-human PD-1 antibodies.

The anti-human Tim-3 antibodies described herein can block human Tim-3 (SEQ ID NO: 1) from binding to human galectin-9 (SEQ ID NO:15) and phosphatidylserine
20 while simultaneously not blocking the binding of human Tim-3 and human CEACAM1 (SEQ ID NO:14). Surprisingly, the anti-Tim-3 antibodies of the present invention can be combined with an anti-human PD-1 antibody to enhance tumor clearance. Surprisingly, the anti-Tim-3 antibodies described herein block human Tim-3 interactions with phosphatidylserine ($C_{13}H_{24}NO_{10}P$) and galectin-9 (SEQ ID NO:15), but not human Tim-
25 3's interactions with CEACAM1 (SEQ ID NO:14) and can be combined with an anti-human PD-1 antibody to treat cancer.

While antibodies targeting PD-1 (SEQ ID NO:34) for cancer immunotherapy have proven effective for some cancers, some cancers become less sensitive to PD-1 therapy over time or do not respond at all. In some embodiments, the present invention provides
30 an anti-human Tim-3 antibody that can be administered to patients who have progressed or are progressing under anti-human PD-1 antibody therapy. In some embodiments, the

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present invention provides an anti-human Tim-3 antibody that can be administered in combination with an anti-human PD-1 antibody to patients who have no previously received anti-human PD-1 antibody therapy.

The present invention includes anti-human Tim-3 (SEQ ID NO: 1) antibodies comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9; and/or a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11 for simultaneous, separate, or sequential combination with an anti-human PD-1 antibody.

Non-limiting examples of known anti-human PD-1 antibodies include PDR001 (described in US20150210769; CAS registry number 1859072-53-9), MEDI0680, REGN2810, BGB-A317, nivolumab (CAS registry number 946414-94-4; wherein nivolumab comprises a heavy chain having the amino acid sequence of SEQ ID NO: 30 and a light chain having the amino acid sequence of SEQ ID NO: 31), and pembrolizumab (CAS registry number 137-4853-91-4; wherein pembrolizumab comprises a heavy chain having the amino acid sequence of SEQ ID NO: 32 and a light chain having the amino acid sequence of SEQ ID NO: 33). Furthermore, said known anti-human PD-1 antibodies can be expressed in a variety of cell lines and produced via various manufacturing processes and may exhibit some difference(s) as a result.

Non-limiting examples of other anti-human PD-1 (SEQ ID NO: 34) antibodies include anti-human PD-1 antibodies comprising at least one of the following: (a) HCDR1 having the amino acid sequence of SEQ ID: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the

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amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody in simultaneous,
5 separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid
10 sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1
15 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody in simultaneous,
20 separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11.

A method of treating cancer comprising administering to a patient in need, thereof
25 an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1
30 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO:

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7; wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or pembrolizumab.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody in simultaneous,
5 separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9; wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or
10 pembrolizumab.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises comprises
15 a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or pembrolizumab.

A method of treating cancer comprising administering to a patient in need, thereof
20 an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1
25 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the
30 amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy

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chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19,

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LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises: a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic

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cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, esophageal cancer, soft tissue sarcoma, or liver cancer.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is melanoma. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is lung cancer. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is melanoma. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the lung cancer is non-small cell lung cancer. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally,

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wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is head and neck cancer. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is colorectal cancer. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is pancreatic cancer. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is gastric cancer. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is kidney cancer. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an

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effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is bladder cancer. A method of treating cancer comprising

5 administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence

10 of SEQ ID NO: 11; and wherein the cancer is prostate cancer. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody

15 comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is breast cancer. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective

20 amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is ovarian cancer. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3

25 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is esophageal cancer. A method of treating

30 cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous,

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separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is soft tissue sarcoma. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is liver cancer.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is administered in simultaneous, separate, or sequential combination with ionizing radiation and/or one or more chemotherapeutic agents.

A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region

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having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26; wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is administered in simultaneous, separate, or sequential combination with ionizing radiation and/or one or more chemotherapeutic agents.

An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7.

An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9.

An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11.

An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ

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ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7; wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or pembrolizumab.

5 An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9; wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or
10 pembrolizumab.

An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or pembrolizumab.
15

An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 25;
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acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the

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amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

5 An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26.

10 An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises a heavy chain
15 having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy
20 chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, esophageal cancer, soft tissue sarcoma, or liver cancer.

25 An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is melanoma. An
30 effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present

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invention for use in simultaneous, separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and

5 wherein the cancer is lung cancer. An an anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer

10 is melanoma. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the lung cancer is

15 non-small cell lung cancer. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer

20 is head and neck cancer. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is

25 colorectal cancer. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is

30 pancreatic cancer. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human

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PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is gastric cancer. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention

5 for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is kidney cancer. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention

10 for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is bladder cancer. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention

15 for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is prostate cancer. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention

20 for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is breast cancer. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention

25 for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is ovarian cancer. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention

30 for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody

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comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is esophageal cancer. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is soft tissue sarcoma. An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is liver cancer.

An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is administered in simultaneous, separate, or sequential combination with ionizing radiation and/or one or more chemotherapeutic agents.

An anti-human Tim-3 (SEQ ID NO: 1) antibody of the present invention for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody; optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the

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amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26; wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is administered in simultaneous, separate, or sequential combination with ionizing radiation and/or one or more chemotherapeutic agents.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO:

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34) antibody, wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7; wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or pembrolizumab.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9; wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or pembrolizumab.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, wherein the anti-human Tim-3 antibody comprises comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or pembrolizumab.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of

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SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

10 Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region
15 having the amino acid sequence of SEQ ID NO: 9; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having
20 the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a
25 light chain having the amino acid sequence of SEQ ID NO: 26.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, wherein the anti-human Tim-3 antibody comprises a heavy chain having
30 the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises: (a)

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HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the

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amino acid sequence of SEQ ID NO: 11; and wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, esophageal cancer, soft tissue sarcoma, or liver cancer.

- 5 Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the
- 10 amino acid sequence of SEQ ID NO: 11; and wherein the cancer is melanoma. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the
- 15 amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is lung cancer. 1. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally,
- 20 wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is melanoma. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and
- 25 an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the lung cancer is non-small cell lung cancer. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the
- 30 medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3

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antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is head and neck cancer. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is colorectal cancer. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is pancreatic cancer. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is gastric cancer. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is kidney cancer. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light

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chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is bladder cancer. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is prostate cancer. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is breast cancer. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is ovarian cancer. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is esophageal cancer. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is soft

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tissue sarcoma. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody
5 comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; and wherein the cancer is liver cancer.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered
10 simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO: 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is administered in simultaneous, separate, or
15 sequential combination with ionizing radiation and/or one or more chemotherapeutic agents.

Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered simultaneously, separately, or sequentially with and an anti-human PD-1 (SEQ ID NO:
20 34) antibody, optionally, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid
25 sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid
30 sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a

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light chain having the amino acid sequence of SEQ ID NO: 26; wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is administered in simultaneous, separate, or sequential combination with ionizing radiation and/or one or more chemotherapeutic agents.

5 A kit for the treatment of cancer, the kit comprising a first pharmaceutical composition comprising an anti-human Tim-3 (SEQ ID NO:1) antibody of the present invention and a second pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody. A kit for the treatment of cancer, the kit comprising a first pharmaceutical composition comprising an anti-human Tim-3 (SEQ ID NO:1) antibody
10 of the present invention and a second pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, esophageal cancer, soft tissue sarcoma, or liver cancer.

15 A kit for the treatment of cancer, the kit comprising a first pharmaceutical composition comprising an anti-human Tim-3 (SEQ ID NO:1) antibody and a second pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID
20 NO: 11.

A kit for the treatment of cancer, the kit comprising a first pharmaceutical composition comprising an anti-human Tim-3 (SEQ ID NO:1) antibody and a second pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid
25 sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or pembrolizumab.

A kit for the treatment of cancer, the kit comprising a first pharmaceutical composition comprising an anti-human Tim-3 (SEQ ID NO:1) antibody and a second
30 pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid

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sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

A kit for the treatment of cancer, the kit comprising a first pharmaceutical composition comprising an anti-human Tim-3 (SEQ ID NO:1) antibody and a second pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

A kit for the treatment of cancer, the kit comprising a first pharmaceutical composition comprising an anti-human Tim-3 (SEQ ID NO:1) antibody and a second pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

An anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the

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treatment of cancer, wherein the anti-human Tim-3 antibody blocks binding of human Tim-3 to human phosphatidylserine, but does not block binding of human Tim-3 to human CEACAM1 (SEQ ID: 14). An anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody blocks binding of human Tim-3 to human phosphatidylserine, but does not block binding of human Tim-3 to human CEACAM1 (SEQ ID: 14); wherein the anti-human Tim-3 antibody also blocks binding of human Tim-3 to human galectin-9 (SEQ ID: 15).

An anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody blocks binding of human Tim-3 to human phosphatidylserine, but does not block binding of human Tim-3 to human CEACAM1 (SEQ ID: 14); wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, esophageal cancer, soft tissue sarcoma, or liver cancer. An anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody blocks binding of human Tim-3 to human phosphatidylserine, but does not block binding of human Tim-3 to human CEACAM1 (SEQ ID: 14); wherein the anti-human Tim-3 antibody also blocks binding of human Tim-3 to human galectin-9 (SEQ ID: 15); wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, esophageal cancer, soft tissue sarcoma, or liver cancer.

An anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody blocks binding of human Tim-3 to human phosphatidylserine, but does not block binding of human Tim-3 to human CEACAM1 (SEQ ID: 14); wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or pembrolizumab. An anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential

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combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody blocks binding of human Tim-3 to human phosphatidylserine, but does not block binding of human Tim-3 to human CEACAM1 (SEQ ID: 14); wherein the anti-human Tim-3 antibody also blocks binding of human
 5 Tim-3 to human galectin-9 (SEQ ID: 15); wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or pembrolizumab.

An anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody blocks binding of human
 10 Tim-3 to human phosphatidylserine, but does not block binding of human Tim-3 to human CEACAM1 (SEQ ID: 14); wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the
 15 amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain
 20 having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26. An anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody blocks binding of human Tim-3 to human phosphatidylserine, but does not block binding
 25 of human Tim-3 to human CEACAM1 (SEQ ID: 14); wherein the anti-human Tim-3 antibody also blocks binding of human Tim-3 to human galectin-9 (SEQ ID: 15); wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid
 30 sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain

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variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

An anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody contacts at least one amino acid residue of the following on human Tim-3 (SEQ ID NO:1): 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive). An anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody contacts at least one amino acid residue of the following on human Tim-3 (SEQ ID NO:1): 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the anti-human Tim-3 antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues. An anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody contacts at least one amino acid residue of the following on human Tim-3 (SEQ ID NO:1): 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the anti-human Tim-3 antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the

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residues; more preferably at least thirteen of the residues; or more preferably all of the residues; wherein the anti-human Tim-3 antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive), and 122. An anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination
 5 with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody contacts at least one amino acid residue of the following on human Tim-3 (SEQ ID NO:1): 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the anti-human Tim-3 antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more
 10 preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the
 15 residues; wherein the anti-human Tim-3 antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive), and 122; wherein the residues in contact are within six (6) angstroms or less of the anti-human Tim-3 antibody, as determined by X-ray crystallography.

A first pharmaceutical composition comprising an anti-human Tim-3 (SEQ ID
 20 NO:1) antibody for use in simultaneous, separate, or sequential combination with a second pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11. A first pharmaceutical composition
 25 comprising an anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with a second pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID
 30 NO: 11; wherein the anti-human PD-1 antibody is PDR001, REGN2810, MEDI0680, BGB-A317, nivolumab, or pembrolizumab. A first pharmaceutical composition

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comprising an anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with a second pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11. A first pharmaceutical composition comprising an anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with a second pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises: (a) HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21; (b) a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26; or (d) a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

A first pharmaceutical composition comprising an anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with a second pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26.

A first pharmaceutical composition comprising an anti-human Tim-3 (SEQ ID NO:1) antibody for use in simultaneous, separate, or sequential combination with a

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second pharmaceutical composition comprising an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11; wherein the anti-human PD-1 antibody
5 comprises a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

The antibodies of the present invention are engineered, non-naturally occurring polypeptide complexes. A DNA molecule of the present invention is a non-naturally occurring DNA molecule that comprises a polynucleotide sequence encoding a
10 polypeptide having the amino acid sequence of one of the polypeptides in an antibody of the present invention.

The antibodies of the present invention are an IgG type antibody and have “heavy” chains and “light” chains that are cross-linked via intra- and inter-chain disulfide bonds. Each heavy chain is comprised of an N-terminal HCVR and a heavy chain
15 constant region (“HCCR”). Each light chain is comprised of a LCVR and a light chain constant region (“LCCR”). When expressed in certain biological systems, antibodies having native human Fc sequences are glycosylated in the Fc region. Typically, glycosylation occurs in the Fc region of the antibody at a highly conserved N-glycosylation site. N-glycans typically attach to asparagine. Antibodies may be
20 glycosylated at other positions as well.

Optionally, certain anti-Tim-3 antibodies described herein contain an Fc portion that is derived from human IgG1. IgG1 is well known to bind to the proteins of the Fc-gamma receptor family (FcγR) as well as C1q. Interaction with these receptors can induce antibody-dependent cell cytotoxicity (ADCC) and complement-dependent
25 cytotoxicity (CDC). Therefore, optionally, certain anti-Tim-3 antibodies described herein are a fully human monoclonal antibody lacking Fc effector function (IgG1, Fc-null). To achieve an Fc-null IgG1 antibody, selective mutagenesis of residues is necessary within the CH2 region of its IgG1 Fc region. Amino acid substitutions L234A, L235E, and G237A are introduced into IgG1 Fc to reduce binding to FcγRI, FcγRIIa, and FcγRIII,
30 and substitutions A330S and P331S are introduced to reduce C1q-mediated complement fixation. To reduce the potential induction of an immune response when dosed in

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humans, certain amino acids may require back-mutations to match antibody germline sequences.

Optionally, the anti-human PD-1 antibodies of the present invention can contain an Fc portion which is derived from human IgG₄ Fc region because of a reduced ability to engage Fc receptor-mediated inflammatory mechanisms or to activate complement resulting in reduced effector function. Certain anti-human PD-1 antibodies of the present invention contain an IgG₄-Fc portion that has a serine to proline mutation at position 228. Further, certain anti-human PD-1 antibodies of the present invention contain an IgG₄-PAA Fc portion. The IgG₄-PAA Fc portion has a serine to proline mutation at position 228, a phenylalanine to alanine mutation at position 234, and a leucine to alanine mutation at position 235. The S228P mutation is a hinge mutation that prevents half-antibody formation (phenomenon of dynamic exchange of half-molecules in IgG₄ antibodies). The F234A and L235A mutations further reduce effector function of the already low human IgG₄ isotype. Further, certain anti-human PD-1 antibodies of the present invention contain an IgG₄-PAA Fc portion with the C-terminal lysine removed (des-Lys) from the heavy chain.

The HCVR and LCVR regions can be further subdivided into regions of hyper-variability, termed complementarity determining regions (“CDRs”), interspersed with regions that are more conserved, termed framework regions (“FR”). Each HCVR and LCVR is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Herein, the three CDRs of the heavy chain are referred to as “HCDR1, HCDR2, and HCDR3” and the three CDRs of the light chain are referred to as “LCDR1, LCDR2 and LCDR3”. The CDRs contain most of the residues which form specific interactions with the antigen. There are currently three systems of CDR assignments for antibodies that are used for sequence delineation. The North CDR definition (North *et al.*, “A New Clustering of Antibody CDR Loop Conformations”, Journal of Molecular Biology, 406, 228-256 (2011)) is based on affinity propagation clustering with a large number of crystal structures. For the purposes of the present invention, the North CDR definitions are used.

An isolated DNA encoding a HCVR region can be converted to a full-length heavy chain gene by operably linking the HCVR-encoding DNA to another DNA

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molecule encoding heavy chain constant regions. The sequences of human, as well as other mammalian, heavy chain constant region genes are known in the art. DNA fragments encompassing these regions can be obtained *e.g.*, by standard PCR amplification.

5 An isolated DNA encoding a LCVR region may be converted to a full-length light chain gene by operably linking the LCVR-encoding DNA to another DNA molecule encoding a light chain constant region. The sequences of human, as well as other mammalian, light chain constant region genes are known in the art. DNA fragments encompassing these regions can be obtained by standard PCR amplification. The light
10 chain constant region can be a human kappa or lambda constant region. Preferably for anti-human Tim-3 antibodies of the present invention, the light chain constant region is a human kappa constant region.

 The polynucleotides of the present invention will be expressed in a host cell after the sequences have been operably linked to an expression control sequence. The
15 expression vectors are typically replicable in the host organisms either as episomes or as an integral part of the host chromosomal DNA. Commonly, expression vectors will contain selection markers, *e.g.*, tetracycline, neomycin, and dihydrofolate reductase, to permit detection of those cells transformed with the desired DNA sequences.

 The antibodies of the present invention may readily be produced in mammalian
20 cells, non-limiting examples of which includes CHO, NS0, HEK293 or COS cells. The host cells are cultured using techniques well known in the art.

 The vectors containing the polynucleotide sequences of interest (*e.g.*, the polynucleotides encoding the polypeptides of the antibody and expression control sequences) can be transferred into the host cell by well-known methods, which vary
25 depending on the type of cellular host.

 Various methods of protein purification may be employed and such methods are known in the art and described, for example, in Deutscher, *Methods in Enzymology* 182: 83-89 (1990) and Scopes, *Protein Purification: Principles and Practice*, 3rd Edition, Springer, NY (1994).

30 In other embodiments of the present invention, the antibody, or the nucleic acids encoding the same, is provided in isolated form. As used herein, the term “isolated”

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refers to a protein, peptide, or nucleic acid which is free or substantially free from any other macromolecular species found in a cellular environment. "Substantially free" as used herein means the protein, peptide, or nucleic acid of interest comprises more than 80% (on a molar basis) of the macromolecular species present, preferably more than 90%,
5 and more preferably more than 95%.

The antibodies of the present invention, or pharmaceutical compositions comprising the same, may be administered by parenteral routes (e.g., subcutaneous and intravenous). The antibodies of the present invention may be administered to a patient along with pharmaceutically acceptable carriers, diluents, or excipients in single or
10 multiple doses. Pharmaceutical compositions of the present invention can be prepared by methods well known in the art (e.g., *Remington: The Science and Practice of Pharmacy*, 22nd ed. (2012), A. Loyd et al., Pharmaceutical Press) and comprise an antibody, as disclosed herein, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

15 Dosage regimens may be adjusted to provide the optimum desired response (e.g., a therapeutic effect). Treatment dosages may be titrated to optimize safety and efficacy. Dosing schedules, for intravenous (*i.v.*) or non-intravenous administration, localized or systemic, or combinations, thereof will typically range from a single bolus dosage or continuous infusion to multiple administrations per day (e.g., every 4-6 hours), or as
20 indicated by the treating physician and the patient's condition.

The term "treating" (or "treat" or "treatment") refers to slowing, interrupting, arresting, alleviating, stopping, reducing, or reversing the progression or severity of an existing symptom, disorder, condition, or disease.

"Effective amount" means the amount of an antibody of the present invention or
25 pharmaceutical composition comprising an antibody of the present invention that will elicit the biological or medical response of or desired therapeutic effect on a tissue, system, animal, mammal or human that is being sought by the researcher, medical doctor, or other clinician. An effective amount of the antibody may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the
30 antibody to elicit a desired response in the individual. An effective amount is also one in

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which any toxic or detrimental effect of the antibody is outweighed by the therapeutically beneficial effects.

Antibody generation, expression, and purification

The antibodies of the present invention may be generated by known methods including, but not limited to, by using phage display, transgenic animals, and/or humanization. For generation of anti-human Tim-3 antibodies, the human Tim-3 protein can be pretreated with PNGaseF enzyme prior to use. Additionally, the antibodies derived as described above may be further screened using the assays described herein.

The polypeptides of the variable regions of the heavy chain and light chain, the complete heavy chain and light chain amino acid sequences for Antibodies A, D, and E and the nucleotide sequences encoding the same, are listed in the section entitled "Amino Acid and Nucleotide Sequences." In addition, the SEQ ID NOs for the light chain, heavy chain, light chain variable region, and heavy chain variable region of Antibodies A, D, and E are shown in Table 1 below.

The antibodies of the present invention, including, but not limited to, Antibodies A, D, and E can be made and purified essentially as follows. An appropriate host cell, such as HEK 293 or CHO, can be either transiently or stably transfected with an expression system for secreting antibodies using an optimal predetermined HC:LC vector ratio or a single vector system encoding both HC (heavy chain) and LC (light chain). Clarified media, into which the antibody has been secreted, may be purified using any of many commonly-used techniques. For example, the medium may be conveniently applied to a MabSelect column (GE Healthcare), or KappaSelect column (GE Healthcare) for Fab fragment, that has been equilibrated with a compatible buffer, such as phosphate buffered saline (pH 7.4). The column may be washed to remove nonspecific binding components. The bound antibody may be eluted, for example, by pH gradient (such as 20 mM Tris buffer pH 7 to 10 mM sodium citrate buffer pH 3.0, or phosphate buffered saline pH 7.4 to 100 mM glycine buffer pH 3.0). Antibody fractions may be detected, such as by UV absorbance or SDS-PAGE, and then may be pooled. Further purification is optional, depending on the intended use. The antibody may be concentrated and/or sterile filtered using common techniques. Soluble aggregate and multimers may be effectively removed by common techniques, including size exclusion, hydrophobic interaction, ion

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exchange, multimodal, or hydroxyapatite chromatography. The purity of the antibody after these chromatography steps is typically greater than 95%. The product may be immediately frozen at -70°C or may be lyophilized.

5 **Table 1**

Corresponding SEQ ID	Antibody A (anti-Tim-3 Antibody)	Antibody D (Anti-PD-1 Antibody - S228P IgG4)	Antibody E (Anti-PD-1 Antibody - PAA IgG4 des-Lys)
HCDR1	2	16	16
HCDR2	3	17	17
HCDR3	4	18	18
LCDR1	5	19	19
LCDR2	6	20	20
LCDR3	7	21	21
HCVR	8	22	22
LCVR	9	23	23
Heavy chain	10	24	25
Light chain	11	26	26
DNA Heavy Chain	12	27	28
DNA Light Chain	13	29	29

WINN Assay

The antibodies of the present invention can be tested for *in vivo* immunomodulatory activity with the WINN assay. In the WINN assay, human NSCLC tumor cells NCI-H292 and human immune cells (allogeneic) are mixed and co-implanted into an immunodeficient mouse, and then followed by dosing with an immunomodulatory agent. The ability of the immunomodulatory agent to inhibit or delay tumor formation or support intra-tumoral persistence can be assessed as follows.

On day 0, NSG mice from Jackson Laboratories (7 weeks of age, female, in groups of 8-10 mice) are implanted into the flank subcutaneously with either 2×10^6 H292 cells, or a mixture of 2×10^6 H292 cells and 1×10^6 human PBMCs in HBSS (0.2 ml total

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volume). Starting on Day 0, mice are treated with an i.p. injection of control human IgG at 10 mg/kg or Antibody A at 1 mg/kg or 10 mg/kg, one time per week for six weeks. Animal well-being and behavior, including grooming and ambulation, are monitored at least twice per week.

5 Tumor sections from the model can be analyzed for CD3-positive and CD8-positive T cell persistence by measuring the presence of CD3-positive and CD8-positive T cells by staining for CD3 and CD8 and analyzing with the Aperio ScanScope™. The IHC Nuclear Image Analysis macro detects nuclear staining for a target chromogen for the individual cells in those regions that are chosen by the user and quantifies their
10 intensities. Three to five annotations are made from viable tumor area and used in adjusting the parameters until the algorithm results generate consistent cell identification. The macro is then saved and the slides logged in for analysis. The % CD3-positive and CD8-positive cells as a percent of the total number of cells are calculated by the Aperio software.

15 In experiments performed essentially as described in this WINN assay, by IHC analysis, mice co-implanted with NCI-H292 tumors and PBMCs and dosed with Antibody A at 10 mg/kg results in a significant increase (30%) of human CD3-positive CD8-positive intratumoral T cells as compared to mice co-implanted with NCI-H292 tumors and PBMCs and treated with the control IgG (6.5 %) ($P = 0.03$).

20 Established human tumor xenograft model in NSG mice humanized with primary human T cells

The efficacy of the antibodies of the present invention can be tested in the NCI-HCC827 human NSCLC (non-small cell lung cancer) xenograft model to assess the ability to delay or destroy established tumors in the model. On day 0, 1×10^7 NCI-HCC827 cells are implanted subcutaneously into the flank of NSG mice (7 weeks of age, female, 8 mice per group). When tumors reach a volume of $\sim 400 \text{ mm}^3$ ($\sim$ days 30-32), the
25 mice are infused (i.v.) with 2.5×10^6 previously expanded human T cells. Previously expanded human T cells are generated by isolating human T cells from whole blood and expanding using Dynabeads® Human T-Activator CD3/CD28 for 10 days. Previously
30 expanded human T cells may be cryopreserved for later use. One day after T cell infusion, mice are dosed at 10 mg/kg by weekly (4 total doses) i.p. injection with human

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IgG or Antibody A. Animal well-being and behavior, including grooming and ambulation are monitored at least twice per week.

Body weight and tumor volume are measured twice a week. Tumor volumes were measured twice per week starting on day 4 post-cell implantation using electronic calipers as described above. Tumor Volume (mm^3) = $\pi/6 * \text{Length} * \text{Width}^2$. The antitumor efficacy is expressed as T/C ratio in percent and calculated as summarized below: %T/C is calculated by the formula $100 \Delta T / \Delta C$ if $\Delta T > 0$ of the geometric mean values. ΔT = mean tumor volume of the drug-treated group on the final day of the study – mean tumor volume of the drug-treated group on initial day of dosing; ΔC = mean tumor volume of the control group on the final day of the study – mean tumor volume of the control group on initial day of dosing. Additionally, % Regression is calculated using the formula = $100 \times \Delta T / T_{\text{initial}}$ if $\Delta T < 0$. Animals with no measurable tumors are considered as Complete Responders (CR) and tumors with >50% regressions are Partial Responders (PR).

In experiments performed essentially as described above, treatment with Antibody A (anti-human Tim-3) significantly inhibits tumor growth in the humanized NSG mice, compared to treatment with human IgG (Table 2). On day 76, treatment with Antibody A results in a T/C = 2%. On day 110, Antibody A treatment results in a 3/8 CR.

Table 2: Tumor volume (mm^3) in the NCI-HCC827 human NSCLC xenograft model

Day	Human IgG Control		Antibody A	
	Mean	SEM	Mean	SEM
21	152	13	164	85
28	289	24	309	160
30	332	28	358	186
34	388	32	403	209
36	414	34	505	262
40	706	59	628	326
43	752	62	733	380
47	858	71	763	396
50	932	77	747	387

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	Human IgG Control		Antibody A	
Day	Mean	SEM	Mean	SEM
55	982	81	807	418
57	1212	100	843	437
62	1324	110	553	287
65	1524	126	726	376
69	1492	124	602	312
72	1827	151	539	279
76	2030	168	375	196
79			375	196
83			414	218
85			331	175
90			192	103
93			235	128
97			173	95
100			118	65
103			125	69
106			120	67
110			131	73

L55 Assay

The antibodies of the present invention can be tested for *in vivo* immunomodulatory activity with the L55 assay. In this regard, the efficacy of Antibody A and of the combination of Antibody A and the anti-PD-1 antibody, Antibody D, to enhance T cell responses to allo-antigens can be evaluated using the L55 (non-small cell lung cancer) established xenograft model. L55 cells are cultured in RPMI-1640 media with 10% fetal bovine serum and 1mM Na⁺ Pyruvate and L-Glutamine. On day 0, NSG mice from Jackson Laboratories (7 weeks of age, female, in groups of 8 mice) are implanted into the flank subcutaneously with 5 x10⁶ L55 human NSCLC cells in HBSS (0.2 ml total volume). When the tumors reach ~200-300 mm (~day 21-25), the mice are randomized. Human PBMC cells are isolated from whole blood and infused intravenously (8 x10⁶ PBMC in 0.2 ml PBS per mouse) into L55 tumor-bearing mice on day 28. On the same day, mice are treated with an intraperitoneal injection of human IgG or Antibody A at 10 mg/kg, once weekly for four weeks in total (dosed on d28, d35, d42, d48). Antibody D treatment at 10 mg/kg starts on day 31 and is administered once weekly

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for three more weeks (dosed on d31, d38, d45, d48). Animal well-being and behavior, including grooming and ambulation, are monitored at least twice per week. Body weight and tumor volume are measured twice a week. Tumor volumes are measured twice per week starting on day 4, post cell implantation using electronic calipers. Tumor volume is

5 calculated using the formula: Tumor Volume (mm^3) = $\pi/6$ * Length * Width².

In experiments performed essentially as described in this assay, combination treatment with Antibody A (anti-human Tim-3) and Antibody D (anti-human PD-1) significantly delay tumor growth in the humanized NSG mice, compared to treatment with either Antibody A or Antibody D alone (Table 3).

10 **Table 3**

	Human IgG Control		Antibody A		Antibody D		Antibody A + Antibody D	
Day	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
16	113.7	3.6	109	5.5	110.7	4.6	103.9	6.3
24	251.6	19.7	236.9	12.1	238.9	17.5	228	21.9
28	364.0	27.7	344.1	17.6	342.6	25.1	358.5	34.4
31	483.7	36.9	441.7	22.6	457.3	33.5	447	42.8
35	480.0	36.6	491.9	25.2	538.6	39.6	388.7	37.3
38	545.7	41.6	582.6	29.8	655.3	48.1	492.3	47.2
42	657.8	50.2	651.2	33.3	607.5	44.5	391.5	37.5
44	916.0	69.8	756.6	38.7	896.9	65.8	520.4	49.9
48	1027.5	78.3	766.8	39.3	772.6	56.7	599.6	57.5
50	1173.0	89.4	911	46.6	943.8	69.2	720.3	69
55	1298.1	98.9	1170.6	59.9	1125.8	82.6	816.6	78.3
58			1839.9	94.2	1530.7	112.2	931.0	89.2
62							1019.5	97.7
65							1147.7	110
69							1272.5	122

Modified Mixed Lymphocyte Reaction

The function of blocking Tim-3 signals by antibodies of the present invention may be evaluated by measuring the release of cytokines during T cell activation. The levels of

15 certain cytokines, such as IFN- γ , are expected to increase if T cell activation is promoted by treatment with antibodies of the present invention.

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CD14⁺ monocytes are isolated by negative selection from fresh human PBMC obtained from a healthy donor (AllCells) using human monocyte isolation kit II (Miltenyi Biotec). Human monocyte-derived dendritic cells are generated by culturing the CD14⁺ monocytes in complete RPMI-1640 medium in the presence of 62.5 ng/ml hGM-CSF and 20 ng/ml human IL-4 for 3 days. Fresh human PBMC were isolated from different healthy donor (AllCells). The two types of cells are then mixed in individual wells of a 96-well plate with 100 μ l complete AIM-V medium containing 7.5×10^4 PBMC cells and 1.5×10^4 immature DC per well. 100 μ l complete AIM-V medium is added containing 100 nM human IgG1, 100 nM Antibody A, 0.64nM or 0.32 nM nivolumab, 100 nM Antibody A and 0.64 or 0.32 nM Nivolumab combination in 8 replicates. After incubation for 6 days at 37°C at 5% CO₂, supernatants are harvested and measured for human IFN- γ with an ELISA kit (R&D Systems). An unpaired t-test is used to compare groups.

In experiments performed essentially as described above, the addition of Antibody A or nivolumab increases the secretion of IFN- γ as compared to the addition of human IgG1. The combination of Antibody A with nivolumab significantly increases the secretion of IFN- γ as compared to the addition of nivolumab alone at the dose of 0.32 nM dose ($P = 0.0013$), as illustrated in Table 4 below.

Table 4

	Control IgG (100 nM)			Antibody A (100 nM)		
Nivolumab	0 nM	0.32 nM	0.64 nM	0 nM	0.32 nM	0.64 nM
IFN-gamma (pg/ml)	157.554 ± 79.3	180.326 ± 37.3	232.65 6 ± 58.7	201.419 $\pm$ 120.7	310.84 6 ± 66.1	369.109 $\pm$ 179.4

ELISA analysis: Antibody A binds to recombinant Tim-3

The ability of antibodies of the present invention to bind human Tim-3 can be measured with an ELISA assay. For the Tim-3 binding assay, a 96-well plate (Nunc) is coated with human Tim-3-Fc (R&D Systems) overnight at 4°C. Wells are blocked for 2 h with blocking buffer (PBS containing 3% bovine serum albumin). Wells are washed three times with PBS containing 0.1% Tween-20. Antibody A or control IgG (100 μ l) is

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then added and incubated at room temperature for 1 h. After washing, the plate is incubated with 100 µl of goat anti-human IgG F(ab')₂-HRP conjugate (Jackson Immuno Research) at room temperature for 1 h. The plates are washed and then incubated with 100 µl of 3,3', 5,5'-tetra-methylbenzidine. The absorbance at 450 nm is read on a microplate reader. The half maximal effective concentration (EC₅₀) is calculated using GraphPad Prism 6 software.

In experiments performed essentially as described above, Antibody A binds human Tim-3 with an EC₅₀ of 2.07×10^{-11} M.

Flow cytometric analysis: Antibody A binds to cell surface Tim-3

The ability for antibodies of the present invention to bind to cell surface human Tim-3 can be measured with a flow cytometric assay. Tim-3 DO11.10 cells, a human Tim-3 expressing DO11.10 cell line, are used for this assay.

Tim-3 DO11.10 cells can be obtained as follows. Full-length Tim-3 gene can be purchased from Origene Technologies, Inc. and cloned into a pLVX-IRES-Neo lentivirus vector from Clontech Laboratories, Inc. using PCR. Lenti-X™ system from Clontech Laboratories, Inc. is used to generate high titers of recombinant, replication-incompetent virions. The virions are either used to infect the target cells immediately or are aliquoted and frozen at -80 until use. The murine T cell hybridoma, DO11.10 cell line, can be obtained from the National Jewish Health®. The DO11.10 cells are cultured and maintained according to a protocol accompanying this cell line. On day 0, DO11.10 cells are counted and spun down to remove culture media. Cell pellets are mixed with virions containing the human TIM-3 gene or vector control and incubated at 37°C for 24 hours. Polybrene is added when mixing cells and virions until a final concentration of 8 µg/ml is achieved. After 24 hours, DO11.10 cells are pelleted again and resuspended in fresh culture media and incubated at 37°C for 3 days. Next, the DO11.10 cells are pelleted every 3 days and resuspended in selection media containing 1 mg/ml Geneticin® to select stably transduced cells. Tim-3 expression is monitored by flow cytometry using antibodies obtained from R&D Systems. After 2 to 3 weeks in selection media, the resulting Tim-3 expressing DO11.10 cells are sorted to establish a single cell clone.

DO11.10 and Tim-3 DO11.10 cells are added to a 96 well V-bottom plate at 1×10^5 cells per well (100 µl/well) in staining buffer (DPBS containing 3% BSA). Cells

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are Fc blocked on ice for 1 hour in staining buffer with 30 µg/mL human IgG. Antibody A or control human IgG is labelled with A488 (Molecular Probes®) and 12 point titrations (1:3 serial dilutions) of both antibodies are prepared in staining buffer with a starting concentration of 66.7 nM. Labelled antibodies are added to the cells and

5 incubated for 1 hour at 4°C in the dark. Cells are washed two times with PBS by spinning for 5 min at 1200 RPM and decanting the supernatant. Live/Dead cell dye 7-AAD (1:1000 in PBS) is added to each well at 3 µl/well and cells are incubated for 15 min on ice. Cells are washed two times with PBS and resuspended in 100 µl DPBS containing 0.5% BSA and analyzed on an Intellicyte iQue. All stainings are done in

10 triplicate. Data are analyzed with FlowJo software to identify populations of live cells and determine the median fluorescence intensity of each sample using the AF488 (FL1) detection channel. The individual MFI (i.e. mean fluorescence intensity) values are placed into GraphPad Prism software to generate concentration response curves from which EC50 values are extrapolated.

15 In experiments performed essentially as described above, Antibody A binds to cellular bound human Tim-3 on Tim-3 DO11.10 cells in a dose dependent manner with an EC50 value of 0.09 nM.

Flow cytometric analysis: Antibody A blocks the interaction of phosphatidylserine with human Tim-3 The ability for certain antibodies of the present invention to block

20 phosphatidylserine binding to Tim-3 can be measured by FACS analysis. For this receptor-ligand blocking assay, 1×10^6 /ml of DO11.10 cells are treated with 12 µM camptothecin (Sigma®) for 3 hours at 37°C to induce apoptosis. FITC-Annexin V (Becton Dickinson®) is used as a positive control to detect the existence of phosphatidylserine. Biotinylated hTIM-3-Fc binds strongly to camptothecin-treated cells

25 but does not bind to non-treated cells. Camptothecin-treated cells are washed with cold PBS and resuspended in binding buffer (Becton Dickinson®) at 1×10^6 cells/ml. Fc receptors are blocked by adding 50 µg/ml mouse IgG and rat IgG to the cells and incubating at room temperature for 30 min. 6 point titrations (1:3 serial dilutions) of Antibody A are prepared in binding buffer with a starting concentration of 90 nM and

30 added to 1 ml of cells and cells are then incubated for 60 min at room temperature. hTIM-3-Fc Biotin is then added at 0.05 µg/well to the appropriate samples in a 200 µl

volume and incubated for 30 min at room temperature. Cells are then washed twice with binding buffer by centrifugation at 1200 RPM for 5 min. 2.4 µl/well of a streptavidin-FITC (Biolegend®) containing solution (1:10 dilution in DPBS) and 5 µl/well of propidium iodide are added to each well and incubated for 30 min at room temperature in the dark. Cells are washed twice with binding buffer and resuspended in 100 µl of PBS. Samples are read on the IntelliCyt iQue Flow Cytometer and Data were analyzed with FlowJo software. The individual MFI (i.e. mean fluorescence intensity) values are placed into GraphPad Prism software to generate concentration response curves from which IC50 values are extrapolated.

10 In experiments performed essentially as described above, Antibody A blocks the interaction of human Tim-3 with phosphatidylserine in a dose-dependent manner with an IC50 value of 0.32 nM and as further illustrated in Table 4.

Table 4

	Untreated DO11.10 + hTIM-3-Fc Biotin	Camptothecin-treated DO11.10+ hTIM-3-Fc Biotin						
Antibody A (nM)	0	90	30	10	3.3	1.1	0.37	0
MFI	1747	1815	19655	32574	52885	96566	197146	214044

15 **Galectin-9 Blocking Assay: Antibody A blocks the interaction of human galectin-9 with human Tim-3**

20 The ability for antibodies of the present invention to block human galectin-9 binding to human Tim-3 can be measured as follows. For this receptor-ligand blocking assay, a 96-well streptavidin-coated MSD plate (Meso Scale Diagnostics) is blocked for 2 hours with 150 µl blocking buffer (PBST containing 5% bovine serum albumin). Wells are washed three times with 200 µl PBS containing 0.2% Tween-20. Recombinant human galectin-9 (R&D Systems) is biotinylated using EZ-Link™ biotin (Thermo Scientific™) and then 25 µl of 0.21 µg/ml of the human recombinant galectin-9-biotin is then added and incubated at room temperature for 2 hours. Plates are washed three times

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with PBS containing 0.2% Tween-20. Human Tim-3-Fc protein (R&D Systems) is ruthenylated using sulfo-tag NHS-ester reagent (Meso Scale Discovery®) and a small aliquot is stored at -80 until use. Antibodies are serially diluted (starting at 13.5 µg/ml) and 50 µl of each antibody combined with 50 µl of diluted hTim-3-Fc-ruth at 0.05 µg/ml and incubated for 1 hour at room temperature. 50 µl of each combination is then added to the plate and incubated for 1.5 hours at room temperature. Plates are washed three times with PBS containing 0.2% Tween-20. 150 µl of 1X read buffer (Meso Scale Diagnostics) is then added to each well of the plate and the plate is read on a Sector Imager 2400 (Meso Scale Diagnostics).

10 In experiments performed essentially as described above, Antibody A blocks the interaction of human Tim-3 with human galectin-9 with an IC50 value of 5.6 nM as compared to control a polyclonal anti-human Tim-3 antibody (R&D Systems) with an IC50 value of 7.8 nM. However, The polyclonal anti-human Tim-3 antibody can block up to 100% human Tim-3's interactions with human galectin-9 while Antibody A only
15 achieve partial blockage in this assay.

CEACAM-1 Blocking Assay: Antibody A does not block the interaction of human CEACAM1 with human Tim-3

The ability for antibodies of the present invention to block human CEACAM1 binding to human Tim-3 can be measured as follows. For this receptor-ligand blocking
20 assay, a 96-well Immulon 4HBX plate (Thermo Scientific) is coated with 100 µl/well of 1 µg/ml human Tim-3-Fc at 4°C. The plate is washed three times with PBS containing 0.2% Tween-20 and blocked with 200 µl/well of PBS with 3% BSA for 1 hour at room temperature. Blocking buffer is then removed and 50 µl of titrated Abs (including polyclonal anti-human Tim-3, R&D Systems, Antibody A, and control human IgG),
25 starting at 600 nM are added to the plate and incubated for 1 hour at room temperature. 50 µl of 20 µg/ml of CEACAM1 (BIOTANG) is then added directly to the wells and incubated for 1 hour at room temperature (final concentration of antibody is 300 nM and of CEACAM1 is 10 µg/ml). The plate is washed three times with PBS containing 0.2% Tween-20 and 100 µl of 0.2 µg/ml of biotinylated human CEACAM1 antibody (R&D
30 Systems) is added and then incubated for 1 hour at room temperature. The plate is washed three times with PBS containing 0.2% Tween-20 and then 100 µl of streptavidin

peroxidase (Jackson ImmunoResearch Laboratories) is added and then incubated for 1 hour at room temperature. The plate is washed six times with PBS containing 0.2% Tween-20 and developed using 100 µl/well of a 1:1 TMB substrate solution A and B (KPL) for 10 min at room temperature. The reaction is then stopped with 100 µl/well of 0.1N H₂SO₄ and the plate is read on a SpectraMax® plate reader at 450 nm.

In experiments performed essentially as described above, Antibody A does not significantly block the binding of CEACAM1 to human Tim-3, as illustrated in Table 5 below.

Table 5

Concentration of Antibody (nM)	0.015	0.046	0.137	0.41	1.24	3.71	11.1	33.3	100	300
Human IgG Control (O.D.)	2.05	2.02	2.13	2.03	2.04	2.03	2.05	2.07	2.12	2.08
Polyclonal Anti-Tim-3 (O.D.)	1.96	1.88	1.89	1.88	1.85	1.80	1.51	1.16	0.99	0.99
Antibody A (O.D.)	1.87	1.88	1.87	1.82	1.80	1.78	1.79	1.79	1.73	1.74

Epitope

A Fab for Antibody A is generated by enzymatically clipping Antibody A with immobilized (agarose resin) papain (ThermoFisher Scientific) followed by a standard ProA column (GE Healthcare Life Sciences) purification to pull out the free, soluble Fc and the unclipped IgG. Flow through containing the Fab is collected to concentrate and buffer exchange. The hTim-3-IgV-FLAG is purified from the 293HEK supernatant with a standard anti-FLAG resin (Sigma-Aldrich) protocol. The hTim-3-IgV domain represents amino acid residues S22 to K130 of human Tim-3 (SEQ ID:1). Flow through is rerun in the resin column multiple times. After each run, SDS-PAGE (NuPAGE Novex 4-12% Bis-Tris Gels; Invitrogen) and HPLC (TSKgel G3000 SW XL (Dimensions: 7.8mm, ID 30 CM, 5 µM; TOSHO BioSCIENCE) is utilized to determine quality of the

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hTim-3-FLAG protein. Proteins of the best rounds are combined together to generate the final batch.

hTim-3-IgV-FLAG, at 2.17 mg/mL in TBS buffer pH 7.2, and Antibody A-Fab, at 6.79 mg/mL, are combined in a 1:1 molar ratio and the complex is isolated via size
 5 exclusion chromatography with a final concentration of 6.9 mg/mL in 20 mM hepes pH 7.4 and 150 mM sodium chloride. The Tim-3-anti-Tim-3 complex is screened in five Qiagen grid screens at both 8°C and 21°C using the sitting drop vapor diffusion method. Drops are set up using an Art Robbins Phoenix liquid handling robot which dispenses 0.3 µL crystallization solution on top of 0.3 µL protein. 100-200 µm intergrown prisms are
 10 obtained at 21°C in 20% PEG 3350 and 0.2 M lithium chloride. Crystals are harvested and cryoprotected in a solution made of the crystallization condition supplemented with 20% ethylene glycol prior to flash freezing in liquid nitrogen. A dataset is collected at Argonne National Laboratory diffracting to 2.2 Å in space group P21 with cell parameters $a = 74.62 \text{ Å}$, $b = 57.85 \text{ Å}$, and $c = 74.71 \text{ Å}$.

15 The structure of the Antibody A-Fab in complex with human Tim-3 is determined by Molecular Replacement using the program Phaser. High resolution and publicly available Fab structures and the published structure of murine Tim-3 can be used as Molecular Replacement models. The structure is refined using the program Refmac and the model rebuilt using the program COOT. Final refinement R-factors are
 20 $R_{\text{work}}=20.2\%$, $R_{\text{free}}=23.4\%$. There are no Ramachandran violators, and 96.4% of the residues are in the favored region of the Ramachandran plot. There is density indicating glycosylation at Asn99 of Tim-3 (SEQ ID NO:1).

Biacore T200 is utilized to determine the binding kinetics of hTim-3-IgV-FLAG to the captured AntibodyA-Fab. In HBS-EP as a running buffer, 1:1 binding of this
 25 complex at 25°C has a k_{on} of $3.62\text{E}+05 \text{ 1/Ms}$, k_{off} of $2.86\text{E}-03 \text{ 1/s}$, and a K_D of $7.92\text{E}-09 \text{ M}$.

In experiments performed essentially as described in this assay, Antibody A-Fab/hTim-3 complex is resolved and the epitope/paratope is illustrated in Table 6 below. Table 6 below lists the residues on Antibody A-Fab that are within 6Å of the listed
 30 residues on hTim-3 (SEQ ID NO:1). The heavy chain of the Antibody A-Fab has 62 contacts (cutoff 6 Å) with hTim-3 while the light chain has 34 contacts (cutoff 6 Å).

Table 6

Tim-3 (Epitope)	Antibody A Heavy Chain (Paratope)	Antibody A Light Chain (Paratope)
P50	S54	--
K55	--	Y32
G56	--	Y32
A57	--	Y30, Y32, N92
C58	--	Y32, A91, N92, S93
P59	Y99, T102	Y32, A91, N92, S93
V60	Y59, Y99, T102	Y32, Q89, Q90,A91, N92, S93, F94, P95, P96
F61	Y33, S35, W47, A50, Y59, Y99, A100, T102, F104	A91, F94, P96
E62	S31, Y33, Y59, Y99, R101	--
C63	Y99, R101, T102	Y32
G64	T102	Y32
N65	T102	N31, Y32, A50
E72	S54	--
I107	--	T30
R111	Y33, Y59	--
Q113	Y33, S52, G53, S54, G55, G56, S57,Y59	--
I114	G56, S57	--

P115	G56, S57	--
G116	G56, S57, T58, Y59	--
I117	G56, S57, T58, Y59, Y60, K65	--
M118	S57, T58, Y59, Y60, A61, D62, K65	F94
N119	T58, Y59	--
D120	Y33, S57, Y59	--
K122	--	N92, F94

Kinetics/Affinity study for Antibody A

A Biacore T100 instrument can be used to measure the kinetics of human Tim-3-
5 IgV-Fc single arm antigen (SAG) binding to captured Antibody A. Human Fab Binder
surfaces are prepared by amine-coupling Human Fab Binder (GE Healthcare) to a Biacore
CM5 sensor chip surface. Test antibodies are captured by the chip using HBS-EP buffer
(GE Healthcare) as the running buffer. Tim-3 SAG is diluted into running buffer starting
at 30 nM with a dilution factor of 3 to give concentrations of 0.04, 0.12, 0.37, 1.11, 3.33,
10 10 and 30 nM. Diluted Tim-3 SAG analyte or buffer is injected at 30 µl/min for 180
seconds and the complex dissociation is monitored for 1200 seconds. The binding surface
is regenerated with injection of 10mM Glycine-HCl pH 2.1 at 30 µl/min, 30 seconds of
two injections for five lower concentrations, and two injections at 60 seconds for two
higher concentrations between each analyte binding cycle. Experimental data for a given
15 antigen/Ab interaction are fit using a *1:1 Langmuir with mass transport* Model.

In experiments performed essentially as described above, Antibody A binds to
human Tim-3 with the kinetics and affinity constants illustrated in Table 7.

Table 7

Antibody	K _{on} (1/Ms)	K _{off} (1/s)	K _D (M)	R _{max}	Chi ²
Antibody A	2.33E+06	9.27E-04	3.98E-10	17.09	0.319

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Surface Plasmon Resonance (SPR)

Immobilization of human PD-1-Fc (R&D Systems) as a ligand on to sensor chip surface is performed at 25°C. Anti-Antibodies of the present invention are used as
 5 analyte, and injected over the human PD-1-Fc immobilized sensor chip surface. All sample analytes are run in 3-fold series dilutions from their starting concentration (90 nM), 8 total dilutions with one duplicate at a middle concentration and a zero. The analysis is performed at 37°C. The contact time for each sample is 180 sec at 30 µl/min. The dissociation time: 300 seconds for 5 lower concentrations and 1200 (Fab), or 2400
 10 (T=0) or 3000 (4 weeks 4°C, 25°C, 40°C) seconds for 3 higher concentrations. The immobilized surface is regenerated for 6-8 seconds with 0.4% SDS at 30 µl/min, and then stabilized for 5 seconds. Binding kinetics are analyzed using the Biacore T200 Evaluation software (Version 3.0). Data are referenced to a blank flow cell, and the data are fit to a 1:1 binding model.

15 In experiments performed essentially as described in this assay, Antibody D binds with a K_D to human PD-1 of 102 pM, nivolumab with a K_D of 246 pM, and pembrolizumab with a K_D of 181 pM. As shown in Table 8, Antibody D maintained binding activity at 4 weeks under elevated temperature conditions.

Table 8 : Binding by SPR of Antibody D at extended times and temperatures

Binding to human PD-1-Fc	K_{on} (1/Ms)	K_{off} (1/s)	K_D (pM)
Antibody D	2.86E+05	2.98E-05	104
Antibody D, 4 weeks 4°C	3.77E+05	3.86E-05	103
Antibody D, 4 weeks 25°C	3.54E+05	3.60E-05	102
Antibody D, 4 weeks 40°C	3.58E+05	4.22E-05	118

Blocking of human PD-1 interaction with PD-L1 and PD-L2.

For the receptor-ligand blocking assay, varying amounts of the indicated anti-PD-1 antibody or control IgG are mixed with a fixed amount of biotinylated PD-1-Fc fusion protein (100 ng/mL) and incubated at room temperature for 1 hour. The mixture is
 25 transferred to 96-well plates pre-coated with PD-L1-Fc (100 ng/well) or PD-L2-Fc (100 ng/well) and then incubated at room temperature for an additional 1 hour. Plates are washed and streptavidin HRP conjugate is added. Plates are read at an absorbance at 450

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nm. IC₅₀ represents the antibody concentration required for 50% inhibition of PD-1 binding to PD-L1 or binding to PD-L2.

In experiments performed essentially as described, Antibody D blocks the interaction of PD-1 with PD-L1 with an IC₅₀ of 0.30 nM, and the interaction of PD-1
5 with PD-L2 with an IC₅₀ of 0.34 nM.

Binding to human PD-1 on CHO cells

The binding of an antibody of the present invention to human PD-1 may be measured by flow cytometry.

CHO cells (0.2×10^6) are incubated with antibody from 200 nM titrated 19x by a
10 factor of 2 to the lowest concentration of 3.185 pM for 30 min in PBS 1% BSA on ice. Cells are then washed 3x, and are incubated with a secondary antibody (PE-labelled, at final concentration of 5 µg/ml) in PBS 1% BSA for 30 min on ice (protected from light). Cells are washed 3x and analyzed via flow cytometry. Flow cytometry is performed on an Accuri C6 system (BD Biosciences) and MFIs are calculated on the C6 software.
15 EC₅₀s are calculated on Graphpad software.

In experiments performed essentially as described in this assay, Antibody G binds PD-1 in a dose-dependent manner, with an EC₅₀ value (n=1) of 1.756 nM and pembrolizumab binds PD-1 with an EC₅₀ value (n=1) of 1.429 nM. Antibody D binds PD-1 in a dose-dependent manner, with an EC₅₀ value (n=1) of 0.9784 nM,
20 pembrolizumab with an EC₅₀ value (n=1) of 0.9510 nM, and nivolumab with an EC₅₀ value (n=1) of 0.9675 nM. Antibody D binds with a similar EC₅₀ to human PD-1 as nivolumab and pembrolizumab under these conditions.

Blocking of human PD-1 to PD-L2 in CHO cells.

The ability of an anti-human PD-1 antibody of the present invention to block
25 binding of human PD-1 to PD-L1 and PD-L2 can be measured by flow cytometry.

CHO cells (0.2×10^6) are incubated with the experimental antibody 100 nM for 30 min in PBS 1% BSA on ice. Cells are then washed 3X, and are incubated with PD-L2 linked with NHS-Fluorescein (Promega) in PBS 1% BSA for 30 min on ice (protected from light). Cells are washed 3x and analyzed via flow cytometry. Flow cytometry is
30 performed on an Accuri C6 system (BD Biosciences) and mean fluorescence intensity (MFI) is calculated on the C6 software.

In experiments performed essentially as described in this assay, Antibody D, in IgG1 format and expressed in yeast, blocked human PD-L2-FITC binding, resulting in an MFI of 24,697.7 as compared to control IgG which resulted in an MFI of 182,959.1. Pembrolizumab and nivolumab resulted in less blocking of PD-L2 binding to PD-1 than
5 Antibody D with an MFI of 46,245.9.

Table 7: Blocking of human PD-1 on CHO cells

Test Sample	MFI (PD-L2-FITC)
Cells only	33,449.7
No IgG	199,716.0
IgG Control	182,959.1
Nivolumab	54,509.8
Pembrolizumab	46,245.9
Antibody D in IgG1 format	24,697.7

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Amino Acid and Nucleotide Sequences

5 SEQ ID NO: 1 (human Tim-3) (Homo Sapiens)

MFSHLPFDCVLLLLLLLLLRSSEVEYRAEVGQNAYLPCFYTPAAPGNLVPVCWG
KGACPVFECGNVLRDTERDVNYWTSRYWLNGDFRKGDVSLTIENVTLADSGIY
CCRIQIPGIMNDEKFNKLVIK

10

SEQ ID NO: 2 (HCDR1 of Antibody A) (Artificial Sequence)

AASGFTFSSYYMS

SEQ ID NO: 3 (HCDR2 of Antibody A) (Artificial Sequence)

15 AISGSGGSTYYADSVKG

SEQ ID NO: 4 (HCDR3 of Antibody A) (Artificial Sequence)

ARYARTAFDL

20 SEQ ID NO: 5 (LCDR1 of Antibody A) (Artificial Sequence)

QASQDIYNYLN

SEQ ID NO: 6 (LCDR2 of Antibody A) (Artificial Sequence)

YAASSLQS

25

SEQ ID NO: 7 (LCDR3 of Antibody A) (Artificial Sequence)

QQANSFPPT

SEQ ID NO: 8 (HCVR of Antibody A) (Artificial Sequence)

30 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYYMSWVRQAPGKGLEWVSAISGS
GGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYARTAFDLW
GQGTLVTVSS

SEQ ID NO: 9 (LCVR of Antibody A) (Artificial Sequence)

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DIVMTQSPSSLSASVGDGVITTCQASQDIYNYLNWYQQKPGKAPKLLIYAASSLQ
SGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQANSFPPTFGQGTKLEIK

SEQ ID NO: 10 (HC of Antibody A) (Artificial Sequence)

5 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYYMSWVRQAPGKGLEWVSAISGS
GGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYARTAFDLW
GQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK
SCDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
10 FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPSSIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHY
TQKSLSLSPGK

15 SEQ ID NO: 11 (LC of Antibody A) (Artificial Sequence)

DIVMTQSPSSLSASVGDGVITTCQASQDIYNYLNWYQQKPGKAPKLLIYAASSLQ
SGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQANSFPPTFGQGTKLEIKRTVAA
PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
SKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
20

SEQ ID NO: 12 (DNA of HC of Antibody A) (Artificial Sequence)

GAGGTGCAGCTGTTGGAGTCTGGCGGAGGGCTGGTGCAGCCGGGAGGCAGCC
TCAGGCTGAGCTGCGCTGCGAGCGGGTTTACTTTCTCGTCGTACTATATGTCG
TGGGTGAGACAAGCACCAGGTAAAGGACTTGAGTGGGTGTCCGCTATCTCAG
25 GCAGCGGAGGATCCACCTACTACGCGGATTCAGTCAAGGGAAGATTCATCTAT
CTCGCGCGACAATTCCAAGAACACCCTGTACCTCCAGATGAACTCGCTGCGG
GCAGAAGATACGGCCGTGTACTACTGTGCCCCGCTACGCCCCGGACCGCCTTCG
ACTTGTGGGGTTCAGGGAACCCTGGTCACTGTCTCCTCAGCTAGCACCAAGGG
CCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGGCACAG
30 CGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTC
GTGGAACCTCAGGCGCACTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTA
CAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAG
CTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACC
AAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACCTCACACATGCC
35 CACCGTGCCCAGCACCTGAAGCCGAGGGGGGCACCGTCAGTCTTCTCTTCCCC
CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTACACATGCG
TGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTATGT
GGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTA
CAACAGCACGTACCGTGTGGTCAGCGTCCTACCGTCCTGCACCAAGACTGG
40 CTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCATCCT
CCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT
GTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAAGTCAGCCTG
ACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGA

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GCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTC
 CGACGGCTCCTTCTTCCTCTATTCCAAGCTCACCGTGGACAAGAGCAGGTGGC
 AGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCA
 CTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGCAA

5

SEQ ID NO: 13 (DNA of LC of Antibody A) (Artificial Sequence)

GACATCGTGATGACTCAAAGCCCTTCAAGCCTCTCGGCGTCAGTCGGTGATGG
 CGTGACCATTACCTGTCAAGCATCCCAAGACATCTACAACACTTGAATTGGT
 ACCAGCAGAAGCCAGGGAAAGCCCCGAAGCTGCTGATCTACGCCGCCTCCTC
 10 ACTTCAGAGCGGAGTGCCATCCCGCTTTTCCGGATCGGGGAGCGGAACGGAT
 TTCACTCTGACCATCTCGTCGCTGCAACCGGAGGACTTCGCGACTTACTATTG
 CCAGCAGGCTAACTCGTTCCCGCCCACTTTCGGACAGGGGCACCAAGCTCGAA
 ATCAAACGAACGTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
 GCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATC
 15 CCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAA
 CTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC
 AGCAGCACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTAC
 GCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCA
 ACAGGGGAGAGTGT

20

SEQ ID NO: 14 (Human CEACAM1) (Homo Sapiens)

MGHLSAPLHRVRVPWQGLLLTASLLTFWNPPTTAQLTTESMPFNVAEGKEVLLL
 VHNLPQQLFGYSWKGERVDGNRQIVGYAIGTQQATPGPANSGRETIYPNASLLI
 25 QNVTQNDTGFYTLQVIKSDLVNEEATGQFHVYPELPKPSISSNNSNPVEDKDAVA
 FTCEPETQDTTYLWWINNQSLPVSRLQLSNGNRTLTLSSVTRNDTGPYECEIQNP
 VSANRSDPVTNLNVTYGPDTPTISPSDTYYRPGANLSLSCYAASNPPAQYSWLINGT
 FQQSTQELFIPNITVNNSGSYTCHANNSVTGCNRTTVKTIIVTELSPVVAKPQIKAS
 KTTVTGDKDSVNLTCSTNDTGISIRWFFKNQSLPSSERMKLSQGNTTLSINPVKRE
 30 DAGTYWCEVFNPISKNQSDPIMLVNLYNALPQENGLSPGAIAGIVIGVVALVALI
 AVALACFLHFGKTGRASDQRDLTEHKPSVSNHTQDHSNDPPNKMNEVTYSTLNF
 EAQQPTQPTSASPSLTATEIHYSEVKKQ

35 SEQ ID NO:15 (Human Galectin-9) (Homo Sapiens)

MAFSGSQAPYLSPAVPFSGTIQGGGLQDGLQITVNGTVLSSSGTRFAVNFQTGFSGN
 DIAFHFNPRFEDGGYVVCNTRQNGSWGPEERKTHMPFQKGMPFDLCFLVQSSDF
 KVMVNGILFVQYFHRVPFHRVDTISVNGSVQLSYISFQPPGVWPANPAPITQTVIH
 40 TVQSAPGQMFSTPAIPPMMPHPAYPMPFITTLGGLYPSKSILLSGTVLPSAQRFH
 INLCSGNHIAFHLNPRFDENAVVRNTQIDNSWGSEERSLPRKMPFVRGQSFSVWIL
 CEAHCLKVAVDGQHLFEYYHRLRLNLTINRLEVGGDIQLTHVQT

SEQ ID NO: 16 (HCDR1 of Antibody D and Antibody E) (Artificial Sequence)

45 KASGGTFSSYAIS

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SEQ ID NO: 17 (HCDR2 of Antibody D and Antibody E) (Artificial Sequence)

LIIPMFDTAGYAQKFQG

5 SEQ ID NO: 18 (HCDR3 of Antibody D and Antibody E) (Artificial Sequence)

ARAEHSSTGTFDY

SEQ ID NO: 19

RASQGISSWLA (LCDR1 of Antibody D and Antibody E) (Artificial Sequence)

10

SEQ ID NO: 20 (LCDR2 of Antibody D and Antibody E) (Artificial Sequence)

SAASSLQS

SEQ ID NO: 21 (LCDR3 of Antibody D and Antibody E) (Artificial Sequence)

15

QQANHLPFT

SEQ ID NO: 22 (HCVR of Antibody D and Antibody E) (Artificial Sequence)

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGLIIPM

FDTAGYAQKFQGRVAITVDESTSTAYMELSSLRSEDVAVYYCARAEHSSTGTFD

20

YWGQGTLVTVSS

SEQ ID NO: 23 (LCVR of Antibody D and Antibody E) (Artificial Sequence)

DIQMTQSPSSVSASVGDRVITTCRASQGISSWLAWYQQKPGKAPKLLISAASSLQS

GVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQANHLPFTFGGGTKVEIK

25

SEQ ID NO: 24 (HC of Antibody D – S228P IgG4) (Artificial Sequence)

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGLIIPM

FDTAGYAQKFQGRVAITVDESTSTAYMELSSLRSEDVAVYYCARAEHSSTGTFD

YWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS

30

GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV

ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQ

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FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY
TQKSLSLGLGK

5

SEQ ID NO: 25 (HC of Antibody E – PAA IgG4 des-Lys) (Artificial Sequence)

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGLIIPM
FDTAGYAQKFQGRVAITVDESTSTAYMELSSLRSEDVAVYYCARAEHSSTGTFD
YWGQGTLLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
10 GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV
ESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY
15 TQKSLSLGLG

SEQ ID NO: 26 (LC of Antibody D and Antibody E) (Artificial Sequence)

DIQMTQSPSSVSASVGDRVITTCRASQGISSWLAWYQQKPGKAPKLLISAASSLQS
GVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQANHLPTFTGGGKVEIKRTVAA
20 PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
SKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 27 (DNA of HC of Antibody D - S228P IgG4) (Artificial Sequence)

CAAGTGCAGCTGGTGCAGTCCGGCGCTGAGGTGAAAAAACCCGGATCCTCCG
25 TCAAGGTGTCCTGTAAAGCCAGCGGCGGCACATTCAGCAGCTACGCCATCTC
CTGGGTGAGGCAAGCTCCTGGACAGGGCCTGGAATGGATGGGCCTGATCATC
CCCATGTTTCGACACCGCCGGCTACGCTCAGAAATTCCAGGGCCGGGTCGCCA
TTACAGTGGATGAGAGCACACAGCCTACATGGAGCTCAGCTCCCTGAG
GAGCGAAGATAACCGCCGTCTACTATTGTGCCCCGGGCTGAGCATAGCAGCACC
30 GGCACCTTCGACTATTGGGGCCAGGGAACCCTGGTCACAGTGAGCTCCGCTTC
CACAAAAGGCCCCAGCGTGTTTCCCCTGGCCCCTTGTAGCAGGTCCACCTCCG

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AAAGCACAGCCGCTCTGGGCTGCCTGGTCAAGGATTACTTCCCCGAGCCCGT
GACCGTGTCTGGAATAGCGGGCGCTCTCACATCCGGAGTGCATACCTTTCCTG
CCGTGCTCCAGTCCTCCGGCCTGTACTCCCTGAGCTCCGTGGTGACCGTCCCT
TCCAGCTCCCTGGGACCAAGACCTATACCTGTAACGTGGACCACAAGCCCTC
5 CAATACCAAGGTGGATAAGCGGGTCGAGTCCAAGTACGGACCCCCCTTGCCCT
CCTTGTCCTGCTCCTGAATTCCTCGGCGGACCTAGCGTCTTTCTCTTCCCCCCC
AAGCCCAAGGATACCCTGATGATCTCCAGGACCCCCGAGGTGACATGCGTCG
TGGTCGATGTGTCCCAGGAGGATCCTGAAGTGCAGTTCAACTGGTACGTGGA
CGGCGTCGAAGTGCATAACGCCAAGACCAAGCCCAGGGAGGAGCAGTTCAA
10 CTCCACCTATCGGGTGGTGAGCGTGCTGACCGTGCTGCATCAGGACTGGCTCA
ACGGCAAAGAGTACAAGTGCAAGGTCTCCAACAAGGGACTCCCCTCCAGCAT
CGAGAAGACCATTAGCAAGGCCAAAGGCCAACCCAGGGAGCCTCAGGTATAT
ACGCTGCCCCCAGCCAGGAGGAGATGACCAAAAACCAGGTCAGCCTCACCT
GTCTGGTCAAGGGCTTCTACCCTAGCGACATTGCTGTCGAGTGGGAGAGCAA
15 CGGCCAGCCCGAGAACAACCTATAAAACCACCCCCCCTGTCCTGGACTCCGAC
GGATCCTTCTTCCTGTACTCCAGGCTGACAGTCGACAAGTCCCGGTGGCAAGA
GGGAAACGTCTTCTCCTGCTCCGTGATGCACGAAGCTCTCCACAACCACTACA
CCCAGAAGAGCCTCAGCCTGTCCCTGGGCAAATGATGA

20 SEQ ID NO: 28 (DNA of HC of Antibody E - PAA IgG4 des-Lys) (Artificial
Sequence)

CAGGTGCAGCTGGTCCAGTCAGGGGCTGAAGTGAAGAAGCCCGGCAGCTCCG
TGAAGGTGTCTTGCAAGGCCAGCGGCGGAACATTCTCCAGTTACGCCATCTCT
TGGGTGCGGCAGGCTCCAGGCCAGGGCCTGGAGTGGATGGGCCTGATCATCC
25 CCATGTTCGACACCGCCGGGTATGCCCAGAAGTTTCAGGGCAGAGTGGCAAT
CACAGTGGACGAGAGCACCTCCACAGCCTACATGGAGCTGTCTAGCCTGAGA
TCCGAGGATACCGCCGTGTATTATTGTGCCCGGGCCGAACACAGCTCTACAG
GGACTTTCGACTACTGGGGCCAGGGCACCCCTGGTGACAGTGTCTCTGCTAGC
ACCAAGGGCCCATCGGTCTTCCCGCTCGCGCCCTGCTCCAGGAGCACCTCCGA
30 GAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG
ACGGTGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGG

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CTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC
TCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCA
GCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCC
ACCCTGCCCAGCACCTGAGGCCGCCGGGGGACCATCAGTCTTCCTGTTCCCCC
5 CAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGT
GGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTATGTT
GATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTC
AACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCT
GAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCC
10 ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGT
ACACCCTGCCCCCATCCCAAGAAGAAATGACCAAAAACCAAGTCAGCCTGAC
CTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAAAGC
AATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCG
ACGGCTCCTTCTTCCTCTACTCCCGTCTAACCGTGGACAAGAGCAGGTGGCAG
15 GAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTA
CACACAGAAGAGCCTCTCCCTGTCTCTGGGT

SEQ ID NO: 29 (DNA of LC of Antibody D and Antibody E) (Artificial Sequence)
GACATCCAGATGACACAGTCCCCTAGCTCCGTGTCCGCTTCCGTGGGAGACA
20 GGGTGACAATCACATGCAGGGCTTCCCAGGGCATCAGCAGCTGGCTGGCTTG
GTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCAGCGCTGCTAGC
TCCCTGCAGTCCGGAGTGCCTTCCAGGTTCTCCGGCTCCGGAAGCGGCACCGA
CTTCACCCTGACCATCTCCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACT
GCCAACAGGCCAACCACCTGCCCTTCACCTTCGGCGGGCGGCACCAAGGTGGA
25 GATCAAGAGGACCGTGGCCGCCCCCTCCGTGTTTCATCTTTCCCCCCCAGCGACG
AGCAGCTGAAGAGCGGCACCGCCTCCGTGGTGTGCCTGCTGAACAACCTCTA
TCCCCGGGAGGCCAAGGTGCAGTGGAAGGTCGACAATGCCCTGCAGAGCGGC
AACTCCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACTCCC
TGAGCTCCACCCTGACACTGTCCAAGGCCGACTACGAGAAGCACAAAGGTGTA
30 CGCCTGCGAGGTGACACACCAGGGCCTGAGCTCCCCCGTGACCAAGTCCTTC
AACAGGGGCGAGTGCTGATGA

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SEQ ID NO: 30 (Nivolumab Heavy Chain) (Artificial Sequence)

QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWY
 DGSKRYYADSVKGRFTISRDN SKNTLFLQMNSLRAEDTAVYYCATNDDYWGQG
 5 TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
 VHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNV DHKPSNTKVDKRVESKYGP
 PCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD
 GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK
 TISKAKGQPREPQVYTLPPS QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
 10 NYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSL
 SLGK

SEQ ID NO: 31 (Nivolumab Light Chain) (Artificial Sequence)

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRAT
 15 GIPARFSGSGSGTDFTLTISSELEPEDFAVYYCQQSSNWPRTFGQGTKVEIKRTVAA
 PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
 SKDSTYSLSSLTLSKADYEEKHKVYACEVTHQGLSSPVT KSFNRGEC

SEQ ID NO: 32 (Pembrolizumab Heavy Chain) (Artificial Sequence)

20 QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGIN
 PSNGGTNFNEKFKNRVTLTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMG
 FDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
 NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNV DHKPSNTKVDK
 25 RVESKYGP PCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE
 VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS
 NKGLPSSIEKTISKAKGQPREPQVYTLPPS QEEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN
 30 HYTQKSLSLSLGK

SEQ ID NO: 33 (Pembrolizumab Light Chain) (Artificial Sequence)

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EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLAS
YLESQVPAFSGSGSGTDFTLTISSELPEDFAVYYCQHSRDLPLTFGGGTKVEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV
TEQDSKDSSTLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC

5

SEQ ID NO:34 (Human PD-1) (Homo Sapiens)

MQIPQAPWPVWAVLQLGWRPGWFLDSPDRPWNPPTFSPALLVVTEGDNATFT
CSFSNTSEFVLNWYRMSPSNQTDKLAAPEDRSQPGQDCRFRVTQLPNGRDFH
10 MSVVRARRNDSGTLYCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPA
GQFQTLVVG VVGGLLGSLVLLVWVLAVICSRAARGTIGARRTGQPLKEDPSAVP
VFSVDYGELDFQWREKTPEPPVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPR
SAQPLRPEDGHCSWPL

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WE CLAIM:

1. A method of treating cancer comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 (SEQ ID NO: 1) antibody in simultaneous,
5 separate, or sequential combination with an effective amount of an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the
10 amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7.
2. The method of Claim 1, wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9.
- 15 3. The method of Claim 2, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11.
4. The method of any one of Claims 1-3, wherein the anti-human PD-1 antibody is nivolumab, or pembrolizumab.
- 20 5. The method of any one of Claims 1-3, wherein the anti-human PD-1 antibody comprises HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having
25 the amino acid sequence of SEQ ID NO: 21.
6. The method of Claim 5, wherein the anti-human PD-1 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23.
7. The method of Claim 6, wherein the anti-human PD-1 antibody comprises a heavy
30 chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26.

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8. The method of Claim 6, wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.
9. The method of any one of Claims 1-8, wherein the cancer is melanoma, lung cancer,
5 head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, esophageal cancer, soft tissue sarcoma, or liver cancer.
10. The method of Claim 9, wherein the lung cancer is non-small cell lung cancer.
11. The method of any one of Claims 1-10, wherein at least one of the anti-human Tim-3
10 antibody and anti-human PD-1 antibody is administered in simultaneous, separate, or sequential combination with ionizing radiation.
12. The method of any one of Claims 1-11, wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is administered in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents.
13. An anti-human Tim-3 (SEQ ID NO: 1) antibody for use in simultaneous, separate, or
15 sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO:
20 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7.
14. The anti-human Tim-3 antibody for use of claim 13, wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of
25 SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9.
15. The anti-human Tim-3 antibody for use of claim 14, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11.
- 30 16. The anti-human Tim-3 antibody for use of any one of Claims 13-15, wherein the anti-human PD-1 antibody is nivolumab, or pembrolizumab.

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17. The anti-human Tim-3 antibody for use of any one of Claims 13-15, wherein the anti-human PD-1 antibody comprises HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21.
18. The anti-human Tim-3 antibody for use of Claim 17, wherein the anti-human PD-1 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23.
19. The anti-human Tim-3 antibody for use of Claim 18, wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26.
20. The anti-human Tim-3 antibody for use of Claim 18, wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.
21. The anti-human Tim-3 antibody for use of any one of Claims 13-20, wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, esophageal cancer, soft tissue sarcoma, or liver cancer.
22. The anti-human Tim-3 antibody for use of Claim 21, wherein the lung cancer is non-small cell lung cancer.
23. The anti-human Tim-3 antibody for use of any one of Claims 13-22, wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is administered in simultaneous, separate, or sequential combination with ionizing radiation.
24. The anti-human Tim-3 antibody for use of any one of Claims 13-23, wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is administered in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents.
25. Use of an anti-human Tim-3 (SEQ ID NO:1) antibody for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be

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administered simultaneously, separately, or sequentially with an anti-human PD-1 (SEQ ID NO: 34) antibody; wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO:5, LCDR2 having the amino acid sequence of SEQ ID NO:6, and LCDR3 having the amino acid sequence of SEQ ID NO:7.

26. The use of Claim 25, wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9.

27. The use of Claim 26, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11.

28. The use of any one of Claims 25-27, wherein the anti-human PD-1 antibody is nivolumab, or pembrolizumab.

29. The use of any one of Claims 25-27, wherein the anti-human PD-1 antibody comprises HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21.

30. The use of Claim 29, wherein the anti-human PD-1 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23.

31. The use of Claim 30, wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26.

32. The use of Claim 30, wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.

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33. The use of any one of Claims 25-32, wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, esophageal cancer, soft tissue sarcoma, or liver cancer.
- 5 34. The use of Claim 33, wherein the lung cancer is non-small cell lung cancer.
35. The use of any one of Claims 25-34, wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is administered in simultaneous, separate, or sequential combination with ionizing radiation.
- 10 36. The use of any one of Claims 25-35, wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is administered in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents.