also modulate immune responses by direct interaction with ligands on dendritic cells (DCs), such as CD40L ligation and CTLA4 interaction with B7 molecules on DCs that elicits the induction of indoleamine 2,3-dioxygenase (IDO). DCs are professional APCs capable of inducing immunity or tolerance against self or non-self antigens. DC-expanded Tregs suppress alloreactivity responses in vitro, and when adoptively transferred, appropriate Tregs inhibited diabetes in NODscid mice or experimentally induced asthma. Specific interactions of ligands on DC with Tregs can also abrogate their suppressive function, such as engagement of GITR in mice, suggesting DC may have a pluralistic role in modulating Treg function.

The molecules CTLA4 and GITR are representative of ligands defined within the CD28-B7 and TNF-superfamilies of co-stimulatory/-inhibitory molecules, respectively. These molecules are highly expressed on Tregs but are typically upregulated on activated T cells. More recently, a protein designated TIGIT (for T-cell immunoreceptor with Ig and ITIM domains) was identified as a cell surface-bound protein specifically expressed in T cells that possessing an IgV domain, a transmembrane domain, and two putative immunoreceptor tyrosine inhibitory (ITIM) motifs. TIGIT was shown to be particularly expressed on Treg and memory T cell subsets, as well as NK cells. As there is an unmet need for new therapeutics and methods of treatment of immune-related disorders and particularly cancers, described herein are unexpectedly efficacious therapeutic compositions, such as the anti-TIGIT antibodies and compositions thereof, and methods of treatment of immune-related disorders and cancers, which involve modulating the interaction of TIGIT with its binding partners.

SUMMARY

The present invention provides anti-TIGIT (T-cell immunoreceptor with Ig and ITIM domains) antibodies and variants thereof with improved properties, including, for example, binding affinity, cross-reactivity, pharmacokinetics, and/or expression. In particular, the present invention provides anti-TIGIT antibodies and variants thereof that possess, for example, high binding affinity to human TIGIT; cross-reactivity between human TIGIT, cynomolgus monkey (cyno) TIGIT, and/or rabbit TIGIT; desirable clearance properties in cyno; and biochemical and biophysical properties that confer the antibodies and variants thereof with high stability.

Disclosed is an antibody that specifically binds to human TIGIT, wherein the antibody binds to an epitope on human TIGIT comprising one or more of amino acid residues Ser78, Ser80, and Lys82 of human TIGIT. In one embodiment, the epitope comprises amino acid residues Ser80 and Lys82 of human TIGIT. In another embodiment, the epitope comprises amino acid residues Ser78, Ser80, and Lys82 of human TIGIT. In another embodiment, the epitope further comprises amino acid residue Ala67 of human TIGIT. In another embodiment, the epitope further comprises one or more additional amino acid residues selected from the group consisting of Glu60, Leu65, and Ile68 of human TIGIT. In another embodiment, the epitope further comprises one or more additional amino acid residues selected from the group consisting of Gln56, Asn70, Leu73, and His111 of human TIGIT. In another embodiment, the epitope further comprises one or more additional amino acid residues selected from the group consisting of Thr55, Asn58, Asp63, Gln64, His76, Ile77, and Pro79 of human TIGIT. In another embodiment, the epitope consists of amino acid residues Thr55, Gln56, Asn58, Glu60, Asp63, Gln64,

Leu65, Ala67, Ile68, Asn70, Leu73, His76, Ile77, Ser78, Pro79, Ser80, Lys82, and His111 of human TIGIT.

Disclosed is an antibody that specifically binds to human TIGIT, wherein the antibody binds to an epitope on human TIGIT comprising one or more of amino acid residues Thr55, Ser80, and Lys82 of human TIGIT. In one embodiment, the epitope comprises amino acid residue Lys82 of human TIGIT. In another embodiment, the epitope comprises amino acid residues Thr55, Ser80, and Lys82 of human TIGIT. In another embodiment, the epitope further comprises amino acid residue Gln56 of human TIGIT. In another embodiment, the epitope further comprises amino acid residue Ile77 or Pro79 of human TIGIT. In another embodiment, the epitope further comprises amino acid residues Ile77 and Pro79 of human TIGIT. In another embodiment, the epitope further comprises amino acid residue Asn58 or Glu60 of human TIGIT. In another embodiment, the epitope further comprises amino acid residues Asn58 and Glu60 of human TIGIT. In another embodiment, the epitope further comprises one or more additional amino acid residues selected from the group consisting of Leu65, Ile68, Leu73, His76, Ser78, and His111 of human TIGIT. In another embodiment, the epitope further comprises amino acid residues Leu65, Ile68, Leu73, His76, Ser78, and His111 of human TIGIT. In yet another embodiment, the epitope consists of Thr55, Gln56, Asn58, Glu60, Leu65, Ile68, Leu73, His76, Ile77, Ser78, Pro79, Ser80, Lys82, and His111 of human TIGIT.

Disclosed is an antibody that specifically binds to human TIGIT, wherein the antibody comprises a paratope comprising one or more amino acid residues selected from the group consisting of heavy chain variable region amino acid residues Asn32, Tyr52, Arg52b, Phe53, Lys54, Tyr56, Asp58, Tyr99, Asp100, Leu100a, Leu100b, and Ala100c and light chain variable region amino acid residues Tyr27d, Tyr92, Ser93, Thr94, and Phe96, wherein optionally the paratope consists of heavy chain variable region amino acid residues Asn32, Tyr52, Arg52b, Phe53, Lys54, Tyr56, Asp58, Tyr99, Asp100, Leu100a, Leu100b, and Ala100c and light chain variable region amino acid residues Tyr27d, Tyr92, Ser93, Thr94, and Phe96. In any of the above embodiments, the antibody may be capable of binding to rabbit TIGIT.

Disclosed is an antibody that specifically binds to human TIGIT, wherein the antibody binds to an epitope on human TIGIT comprising one or more amino acid residues selected from the group consisting of Gln53, His111, and Tyr113 of human TIGIT. In some embodiments, the epitope further comprises Gln56 of human TIGIT. In some embodiments, the epitope further comprises Glu60, Leu65, Ile68, Asn70, Leu73, and His76 of human TIGIT.

In another aspect, the invention features an antibody that specifically binds to human TIGIT, wherein the antibody comprises the following six hypervariable regions (HVRs): an HVR-H1 comprising the amino acid sequence of SNSAAWN (SEQ ID NO: 1); an HVR-H2 comprising the amino acid sequence of KTYYRFKWYSDYAVSVKG (SEQ ID NO: 2); an HVR-H3 comprising the amino acid sequence of ESTTYDLLAGPFDY (SEQ ID NO: 3); an HVR-L1 comprising the amino acid sequence of KSSQTVLYSSNNKKYLA (SEQ ID NO: 4); an HVR-L2 comprising the amino acid sequence of WASTRES (SEQ ID NO: 5); and an HVR-L3 comprising the amino acid sequence of QQYYSTPFT (SEQ ID NO: 6). In some embodiments, the antibody further comprises the following light chain variable region framework regions (FRs): an FR-L1 comprising the amino acid sequence of

DIVMTQSPDSLAVSLGERATINC (SEQ ID NO: 7); an FR-L2 comprising the amino acid sequence of WYQQKPGQPPNLLIY (SEQ ID NO: 8); an FR-L3 comprising the amino acid sequence of GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC (SEQ ID NO: 9); and an FR-L4 comprising the amino acid sequence of FGPGTKVEIK (SEQ ID NO: 10). In some embodiments, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of X_1VQLQQSGPGLVKPSQTLSLTCAISGDSVS (SEQ ID NO: 11), wherein X_1 is Q or E; an FR-H2 comprising the amino acid sequence of WIRQSPSRGLEWLG (SEQ ID NO: 12); an FR-H3 comprising the amino acid sequence of RITINPDTSKNQFSLQLNSVTPEDTAVFYCTR (SEQ ID NO: 13); and an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 14). In some embodiments, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of EVQLQQSGPGLVKPSQTLSLTCAISGDSVS (SEQ ID NO: 15); an FR-H2 comprising the amino acid sequence of WIRQSPSRGLEWLG (SEQ ID NO: 12); an FR-H3 comprising the amino acid sequence of RITINPDTSKNQFSLQLNSVTPEDTAVFYCTR (SEQ ID NO: 13); and an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 14). In some embodiments, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of QVQLQQSGPGLVKPSQTLSLTCAISGDSVS (SEQ ID NO: 16); an FR-H2 comprising the amino acid sequence of WIRQSPSRGLEWLG (SEQ ID NO: 12); an FR-H3 comprising the amino acid sequence of RITINPDTSKNQFSLQLNSVTPEDTAVFYCTR (SEQ ID NO: 13); and an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 14). In some embodiments, the antibody is capable of binding to rabbit TIGIT.

Disclosed is an antibody that specifically binds to human TIGIT, wherein the antibody comprises the following six HVRs: an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17); an HVR-H2 comprising the amino acid sequence of WINTNTGNPTYVQGFTG (SEQ ID NO: 18); an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19); an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20); an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and an HVR-L3 comprising the amino acid sequence of QHLHGYPX_1N (SEQ ID NO: 22), wherein X_1 is C or S. In some embodiments, the antibody comprises the following six HVRs: an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17); an HVR-H2 comprising the amino acid sequence of WINTNTGNPTYVQGFTG (SEQ ID NO: 18); an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19); an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20); an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and an HVR-L3 comprising the amino acid sequence of QHLHGYPSN (SEQ ID NO: 23). In some embodiments, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of EVQLVQSGSDLKKPGASVRVSCKASGYTFT (SEQ ID NO: 24); an FR-H2 comprising the amino acid sequence of WVRQAPGHGLEWMG (SEQ ID NO: 25); an FR-H3 comprising the amino acid sequence of RFVFSLDTSVNTAYLQISSLKAEDTAVYFCAR (SEQ ID NO: 26); and an FR-H4 comprising the amino acid sequence of WGQGTMVTVSS (SEQ ID NO: 27). In some embodiments, antibody comprises the following six HVRs: an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17); an HVR-H2 comprising the amino acid sequence of

WINTNTGNPTYVQGFTG (SEQ ID NO: 18); an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19); an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20); an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and an HVR-L3 comprising the amino acid sequence of QHLHGYPCN (SEQ ID NO: 28). In some embodiments, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of QVQLVQSGSDLKKPGASVRVSCKASGYTFT (SEQ ID NO: 29); an FR-H2 comprising the amino acid sequence of WVRQAPGHGLEWMG (SEQ ID NO: 25); an FR-H3 comprising the amino acid sequence of RFVFSLDTSVNTAYLQISSLKAEDTAVYFCAR (SEQ ID NO: 26); and an FR-H4 comprising the amino acid sequence of WGQGTMVTVSS (SEQ ID NO: 27). In some embodiments, the antibody further comprises the following light chain variable region FRs: an FR-L1 comprising the amino acid sequence of DIQLTQSPTFLSASVGDRVTITC (SEQ ID NO: 30); an FR-L2 comprising the amino acid sequence of WYQQNPGKAPKLLIY (SEQ ID NO: 31); an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTEFTLTISSLQPEDFVTYYC (SEQ ID NO: 32); and an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 33).

In another aspect, the invention features an antibody that specifically binds to human TIGIT, wherein the antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 34 and a light chain variable region (VL) region comprising the amino acid sequence of SEQ ID NO: 36. In another aspect, the invention features an antibody that specifically binds to human TIGIT, wherein the antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 35 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 36. Disclosed is an antibody that specifically binds to human TIGIT, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 34 or 35; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b). In some embodiments, antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 34; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b). In some embodiments, the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 35; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b). In some embodiments, the antibody is capable of binding to rabbit TIGIT.

Disclosed is an antibody that specifically binds to human TIGIT, wherein the antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 37 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 38. Disclosed is an antibody that specifically binds to human TIGIT, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 37; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 38; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b).

Disclosed is an antibody that specifically binds to human TIGIT, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 39; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 40; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b).

In any one of the embodiments described above, the antibody may be capable of binding to both human TIGIT and cynomolgus monkey (cyno) TIGIT, but not murine TIGIT. In some embodiments, the antibody binds human TIGIT with a Kd of about 10 nM or lower and cyno TIGIT with a Kd of about 10 nM

or lower. In some embodiments, the antibody binds human TIGIT with a Kd of about 0.1 nM to about 1 nM and cyno TIGIT with a Kd of about 0.5 nM to about 1 nM. In some embodiments, the antibody binds human TIGIT with a Kd of about 0.1 nM or lower and cyno TIGIT with a Kd of about 0.5 nM or lower.

In any one of the embodiments described above, the antibody may be an antagonist antibody or an agonist antibody.

In some embodiments, the antagonist antibody specifically binds TIGIT and inhibits or blocks TIGIT interaction with poliovirus receptor (PVR). In some embodiments, the antagonist antibody inhibits intracellular signaling mediated by TIGIT binding to PVR. In some embodiments, the antagonist antibody inhibits or blocks binding of human TIGIT to human PVR with an IC50 value of 10 nM or lower. In some embodiments, the antagonist antibody inhibits or blocks binding of human TIGIT to human PVR with an IC50 value of 1 nM to about 10 nM. In some embodiments, the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 50 nM or lower. In some embodiments, the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 1 nM to about 50 nM. In some embodiments, the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 1 nM to about 5 nM.

In some embodiments, the agonist antibody specifically binds TIGIT and stimulates the interaction of PVR with CD226 or CD96. In some embodiments, the agonist antibody specifically binds TIGIT and stimulates the interaction of PVR with CD226 and CD96. In some embodiments, the agonist antibody specifically binds TIGIT and stimulates the interaction of human PVR with human CD226 and human CD96. In some embodiments, the agonist antibody specifically binds TIGIT and stimulates the interaction of cyno PVR with cyno CD226 and cyno CD96.

Disclosed is an isolated antibody that competes for binding to TIGIT with an antibody of any one of the above embodiments.

Disclosed is an isolated antibody that binds to the same epitope as an antibody of any one of the above embodiments.

In some embodiments, the antibody is monoclonal. In some embodiments, the antibody is human, humanized, or chimeric. In some embodiments, the antibody is a full-length antibody. In some embodiments, the antibody has a clearance following administration (e.g., injection, e.g., intravenous injection) of less than about 10 ml/kg/day (e.g., about 3 ml/kg/day to about 10 ml/kg/day). In some embodiments, the antibody antibody has a clearance of about 3 ml/kg/day to about 8 ml/kg/day. In some embodiments, administration of the antibody is to a mammal (e.g., a monkey, such as a cynomolgus monkey, or a human). In some embodiments, the antibody is an antibody fragment that binds TIGIT. In some embodiments, the antibody fragment is selected from the group consisting of Fab, Fab', Fab'-SH, Fv, single chain variable fragment (scFv), and $(Fab')_2$ fragments. In some embodiments, the antibody is an IgG class antibody. In some embodiments, the IgG class antibody is an IgG1 subclass antibody. In some embodiments, an antibody described herein can be for use as a medicament. In some embodiments, an antibody described herein may be for use in treating or delaying progression of a cancer in a subject in need thereof. In some embodiments, the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma,

a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycoses fungoides, a merkel cell cancer, and a hematologic malignancy. In some embodiments, an antibody described herein may be for use in treating or delaying progression of multiple myeloma (MM). In some embodiments, an antibody described herein may be for use in treating or delaying progression of an immune-related disease in a subject in need thereof. In some embodiments, the immune-related disease is associated with a T cell dysfunctional disorder. In some embodiments, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some embodiments, the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity. In some embodiments, an antibody described herein may be for use in increasing, enhancing, or stimulating an immune response or function in a subject in need thereof.

Disclosed is a polynucleotide (e.g., an isolated polynucleotide) encoding any of the antibodies described herein. In one aspect, the invention features a polynucleotide encoding any of the antibodies described herein. Disclosed is a vector (e.g., an expression vector) comprising the polynucleotide for expressing the antibody. In another aspect, the invention features a vector comprising the polynucleotide as described herein. Disclosed are host cells comprising the preceding polynucleotides and/or vectors. In another aspect, the invention features a host cell comprising the vector as described herein. In some embodiments, the host cell is a eukaryotic (e.g., a mammalian cell). In some embodiments, the eukaryotic cell is a 293 cell, a Chinese hamster ovary (CHO) cell, a yeast cell, or a plant cell. In some embodiments, the host cell is a prokaryotic cell. In some embodiments, the prokaryotic cell is *E. coli.*

Disclosed is a method of producing any of the antibodies described herein, the method comprising culturing a host cell that comprises any of the preceding vectors (e.g., expression vectors) in a culture medium. In another aspect, the invention features a method of producing any of the antibodies as described herein, the method comprising culturing the host cell as described herein in a culture medium. In some embodiments, the method further comprises recovering the antibody from the host cell or the culture medium. In some embodiments, the host cell is a eukaryotic cell, for example, a mammalian cell, for example, a 293 cell, a Chinese hamster ovary (CHO) cell, a yeast cell, or a plant cell. In some embodiments, the host cell is a prokaryotic cell. In some embodiments, the prokaryotic cell is *E. coli.*

Disclosed is an immunoconjugate comprising any one of the antibodies described herein and an agent (e.g., a therapeutic agent, e.g., a cytotoxic agent). In another aspect, the invention features an immunoconjugate comprising the any of the antibodies as described herein and a cytotoxic agent.

In another aspect, the invention features a composition comprising an antibody described herein. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier, excipient, or diluent. In some embodiments, the composition is for diagnostic use (e.g., to detect TIGIT expression levels, e.g., TIGIT protein expression levels). In some embodiments, the composition is a pharmaceutical composition. In some embodiments, the composition further comprises a PD-1 axis binding antagonist or an additional therapeutic agent.

In another aspect, the invention features the antibody as described herein for use as a medicament. In another aspect, the invention features the antibody as described herein for use in treating or delaying progression of a cancer in a subject in need thereof. In another aspect, the invention features the antibody as described herein for use in treating or delaying progression of an immune-related disease associated with a T cell dysfunctional disorder characterized by T cell exhaustion in a subject in need thereof. In another aspect, the invention features the antibody as described herein for use in increasing, enhancing, or stimulating a T cell-mediated immune response or function in a subject in need thereof. In another aspect, the invention features the use of an antibody described herein in the manufacture of a medicament for treating or delaying progression of a cancer in a subject in need thereof. In some embodiments, the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a

cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycoses fungoides, a merkel cell cancer, and a hematologic malignancy. In some embodiments, the myeloma is MM. In some embodiments, the medicament is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodiments, the subject is a human.

In another aspect, the invention features the use of an antibody described herein in the manufacture of a medicament for treating or delaying progression of an immune-related disease associated with a T cell dysfunctional disorder characterized by T cell exhaustion in a subject in need thereof. In some embodiments, the immune-related disease is associated with a T cell dysfunctional disorder. In some embodiments, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some embodiments, the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity. In some embodiments, the medicament is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodiments, the subject is a human.

In another aspect, the invention features the use of an antibody described herein in the manufacture of a medicament for increasing, enhancing, or stimulating a T cell-mediated immune response or function in a subject in need thereof. In some embodiments, the medicament is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodiments, the subject is a human.

Disclosed is a method for treating or delaying progression of a cancer in a subject, the method comprising administering to the subject an effective amount of any one or more (e.g., 1, 2, 3, 4, 5, or 6 or more) of the antibodies described herein, thereby treating or delaying the progression of the cancer in the subject. In some embodiments, the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycoses fungoides, a merkel cell cancer, and a hematologic malignancy. In some embodiments, the myeloma is MM.

Disclosed is a method for treating or delaying progression of an immune-related disease in a subject, the method comprising administering to the subject an effective amount of one or more (e.g., 1, 2, 3, 4, 5, or 6 or more) of the antibodies described herein, thereby treating or delaying the progression of the immune-related disease in the subject. In some embodiments, the immune-related disease is associated with a T cell dysfunctional disorder. In some embodiments, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some embodiments, the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.

Disclosed is a method of increasing, enhancing, or stimulating an immune response or function in a subject, the comprising administering to the subject an effective amount

three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 278, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 281, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 287. In some embodiments, the OX40 agonist antibody comprises a VL sequence having at least 90% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 326-351. In some embodiments, the OX40 agonist antibody comprises a VL having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 326. In some embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in SEQ ID NO: 326. In some embodiments, the OX40 agonist antibody comprises a VL comprising one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 290; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 291; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 292. In some embodiments, the OX40 agonist antibody comprises (a) a VH sequence of SEQ ID NO: 300; (b) a VL sequence of SEQ ID NO: 326; or (c) a VH sequence as in (a) and a VL sequence as in (b). In some embodiments, the OX40 agonist antibody comprises (a) a VH sequence of SEQ ID NO: 319; (b) a VL sequence of SEQ ID NO: 345; or (c) a VH sequence as in (a) and a VL sequence as in (b). In some embodiments, the OX40 agonist antibody comprises (a) a VH sequence of SEQ ID NO: 320; (b) a VL sequence of SEQ ID NO: 346; or (c) a VH sequence as in (a) and a VL sequence as in (b). In some embodiments, the OX40 agonist antibody is antibody L106, antibody ACT35, MEDI6469, or MEDI0562. In some embodiments, the OX40 agonist antibody is a full-length IgG1 antibody. In some embodiments, the OX40 immunoadhesin is a trimeric OX40-Fc protein.

In some embodiments, any one of the methods of treatment described above may further comprise administering to the subject an agent that decreases or inhibits one or more additional immune co-inhibitory receptors. In some embodiments, the one or more additional immune co-inhibitory receptor is selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96. In some embodiments, any one of the methods of treatment described above may further comprise administering to the subject an additional therapeutic agent. In some embodiments, the additional therapeutic agent is a chemotherapeutic agent. In some embodiments, antibody is administered subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodiments, the subject is a human.

In another aspect, the invention features a kit comprising the antibody as described herein and a package insert comprising instructions for using the antibody for treating or delaying progression of a cancer in a subject. Disclosed is a kit comprising any one or more (e.g., 1, 2, 3, 4, 5, or 6 or more) of the antibodies described herein and package insert comprising instructions for using the antibody for treating or delaying progression of a cancer in a subject. In some embodiments, the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycoses fungoides, a merkel cell cancer, and a hematologic malignancy. In some embodiments, the subject is a human. In some embodiments, the myeloma is MM.

In another aspect, the invention features a kit comprising the antibody as described herein and a package insert comprising instructions for using the antibody for treating or delaying progression of an immune-related disease associated with a T cell dysfunctional disorder characterized by T cell exhaustion in a subject. Disclosed is a kit comprising any one or more (e.g., 1, 2, 3, 4, 5, or 6 or more) of the antibodies described herein and a package insert comprising instructions for using the

antibody for treating or delaying progression of an immune-related disease in a subject. In some embodiments, the immune-related disease is associated with a T cell dysfunctional disorder. In some embodiments, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some embodiments, the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity. In some embodiments, the subject is a human.

In another aspect, the invention features a kit comprising the antibody as described herein and a package insert comprising instructions for increasing, enhancing, or stimulating a T cell-mediated immune response or function in a subject. Disclosed is a kit comprising any one or more (e.g., 1, 2, 3, 4, 5, or 6 or more) of the antibodies described herein and a package insert comprising instructions for increasing, enhancing, or stimulating an immune response or function in a subject. In some embodiments, the subject is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1A is a schematic diagram of a CHO-TIGIT binding assay.

FIGURE 1B is a graph showing the results of the CHO-TIGIT binding assay depicted in Figure 1A using human TIGIT-expressing CHO cells and the indicated OMT-derived anti-TIGIT antibodies at varying concentrations, as analyzed by FACS.

FIGURE 1C is a graph showing the results of the CHO-TIGIT binding assay depicted in Figure 1A using cynomolgus monkey (cyno) TIGIT-expressing CHO cells and the indicated OMT-derived anti-TIGIT antibodies at varying concentrations, as analyzed by FACS.

FIGURE 1D is a graph showing the results of the CHO-TIGIT binding assay depicted in Figure 1A using human TIGIT-expressing CHO cells and the indicated SD-derived anti-TIGIT antibodies at varying concentrations, as analyzed by FACS.

FIGURE 1E is a graph showing the results of the CHO-TIGIT binding assay depicted in Figure 1A using cyno TIGIT-expressing CHO cells and the indicated SD-derived anti-TIGIT antibodies at varying concentrations, as analyzed by FACS.

FIGURE 2A is a graph showing the binding of the indicated OMT-derived anti-TIGIT antibodies to human CD4 T cells as a function of antibody concentration.

FIGURE 2B is a graph showing the binding of the indicated OMT-derived anti-TIGIT antibodies to human CD8 T cells as a function of antibody concentration.

FIGURE 2C is a graph showing the binding of the indicated SD-derived anti-TIGIT antibodies to human CD4 T cells as a function of antibody concentration.

FIGURE 2D is a graph showing the binding of the indicated SD-derived anti-TIGIT antibodies to human CD8 T cells as a function of antibody concentration.

FIGURE 3A is a graph showing the results of a blocking ELISA assay using human PVR-Fc fusion protein coated-plates, human TIGIT, and the indicated anti-TIGIT antibodies (10A7 and 4.1D3.Q1E in Fab or IgG format) or anti-CSF1 Fab control, as a function of antibody/Fab concentration.

FIGURE 3B is a graph showing the results of a blocking ELISA assay using cyno PVR-Fc fusion protein coated-plates, cyno TIGIT, and the indicated anti-TIGIT antibodies (10A7 and 4.1D3.Q1E in Fab or IgG format) or anti-CSF1 Fab control, as a function of antibody/Fab concentration.

CLAIMS

What is claimed is:

1. An antibody that specifically binds to human TIGIT, wherein the antibody comprises the following six hypervariable regions (HVRs):

an HVR-H1 comprising the amino acid sequence of SNSAAWN (SEQ ID NO: 1);

an HVR-H2 comprising the amino acid sequence of KTYYRFKWYSDYAVSVKG (SEQ ID NO: 2);

an HVR-H3 comprising the amino acid sequence of ESTTYDLLAGPFDY (SEQ ID NO: 3);

an HVR-L1 comprising the amino acid sequence of KSSQTVLYSSNNKKYLA (SEQ ID NO: 4);

an HVR-L2 comprising the amino acid sequence of WASTRES (SEQ ID NO: 5); and

an HVR-L3 comprising the amino acid sequence of QQYYSTPFT (SEQ ID NO: 6).

2. The antibody of claim 1, wherein the antibody further comprises the following light chain variable region framework regions (FRs):

an FR-L1 comprising the amino acid sequence of DIVMTQSPDSLAVSLGERATINC (SEQ ID NO: 7);

an FR-L2 comprising the amino acid sequence of WYQQKPGQPPNLLIY (SEQ ID NO: 8);

an FR-L3 comprising the amino acid sequence of GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC (SEQ ID NO: 9); and

an FR-L4 comprising the amino acid sequence of FGPGTKVEIK (SEQ ID NO: 10); wherein optionally the antibody further comprises the following heavy chain variable region FRs:

an FR-H1 comprising the amino acid sequence of X_1VQLQQSGPGLVKPSQTLSLTCAISGDSVS (SEQ ID NO: 11), wherein X_1 is Q or E;

an FR-H2 comprising the amino acid sequence of WIRQSPSRGLEWLG (SEQ ID NO: 12);

an FR-H3 comprising the amino acid sequence of RITINPDTSKNQFSLQLNSVTPEDTAVFYCTR (SEQ ID NO: 13); and

an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 14).

3. The antibody of claim 2, wherein X_1 is Q.

4. The antibody of claim 2, wherein X_1 is E.

5. The antibody of claim 1 or 2, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 34 or 35; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b).

6. An antibody that specifically binds to human TIGIT, wherein the antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 34 and a light chain variable region (VL) region comprising the amino acid sequence of SEQ ID NO: 36.

7. An antibody that specifically binds to human TIGIT, wherein the antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 35 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 36.

8. The antibody of any one of claims 1-7, wherein the antibody is capable of binding to rabbit TIGIT.

9. The antibody of any one of claims 1-8, wherein the antibody is capable of binding to both human TIGIT and cynomolgus monkey (cyno) TIGIT, but not murine TIGIT; wherein optionally the antibody binds human TIGIT with a Kd of about 10 nM or lower and cyno TIGIT with a Kd of about 10 nM or lower; wherein optionally the antibody binds human TIGIT with a Kd of about 0.1 nM to about 1 nM and cyno TIGIT with a Kd of about 0.5 nM to about 1 nM; and wherein optionally the antibody binds human TIGIT with a Kd of about 0.1 nM or lower and cyno TIGIT with a Kd of about 0.5 nM or lower.

10. The antibody of any one of claims 1-9, wherein the antibody is an antagonist antibody; wherein optionally the antagonist antibody specifically binds TIGIT and inhibits or blocks TIGIT interaction with poliovirus receptor (PVR); and wherein optionally the antagonist antibody inhibits intracellular signaling mediated by TIGIT binding to PVR.

11. The antibody of claim 10, wherein (i) the antagonist antibody inhibits or blocks binding of human TIGIT to human PVR with an IC50 value of 10 nM or lower; wherein optionally (ii) the antagonist antibody inhibits or blocks binding of human TIGIT to human PVR with an IC50 value of 1 nM to about 10 nM; and wherein optionally (iii) the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 50 nM or lower.

12. The antibody of claim 11 (iii), wherein the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 1 nM to about 50 nM; wherein optionally the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 1 nM to about 5 nM.

13. The antibody of any one of claims 1-12, wherein the antibody is monoclonal.

14. The antibody of any one of claims 1-12, wherein the antibody is human, humanized, or chimeric.

15. The antibody of claim 14, wherein at least a portion of the framework sequence is a human consensus framework sequence.

16. The antibody of any one of claims 1-15, wherein the antibody is a full-length antibody.

17. The antibody of any one of claims 1-16, wherein the antibody has a clearance following intravenous injection of about 3 mL/kg/day to about 10 mL/kg/day; wherein optionally the antibody has a clearance following intravenous injection of about 3 mL/kg/day to about 8 mL/kg/day.

18. The antibody of any one of claims 1-15, wherein the antibody is an antibody fragment that binds TIGIT; wherein optionally the antibody fragment is selected from the group consisting of Fab, Fab', Fab'-SH, Fv, single chain variable fragment (scFv), and $(Fab')_2$ fragments.

19. The antibody of any one of claims 1-18, wherein the antibody is an IgG class antibody; wherein optionally the IgG class antibody is an IgG1 subclass antibody.

20. A polynucleotide encoding the antibody of any one of claims 1-19.

21. A vector comprising the polynucleotide of claim 20.

22. A host cell comprising the vector of claim 21.

23. The host cell of claim 22, wherein the host cell is:
(a) prokaryotic, wherein optionally the host cell is *Escherichia coli*; or
(b) eukaryotic, wherein optionally the host cell is a 293 cell, a CHO cell, a yeast cell, or a plant cell.

24. A method of producing the antibody of any one of claims 1-19, the method comprising culturing the host cell of claim 22 in a culture medium.

25. The method of claim 24, wherein the method further comprises recovering the antibody from the host cell or culture medium.

26. An immunoconjugate comprising the antibody of any one of claims 1-19 and a cytotoxic agent.

27. A composition comprising the antibody of any one of claims 1-19.

28. The composition of claim 27, further comprising a pharmaceutically acceptable carrier, excipient, or diluent; wherein optionally the composition is a pharmaceutical composition.

29. The composition of claim 27 or 28, wherein the composition further comprises a PD-1 axis binding antagonist or an additional therapeutic agent.

30. The antibody of any one of claims 1-19 for use as a medicament.

31. The antibody of any one of claims 1-19 for use in treating or delaying progression of a cancer in a subject in need thereof.

32. The antibody of claim 31, wherein the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, a mycosis fungoides, a Merkel cell cancer, and a hematologic malignancy; wherein optionally the myeloma is multiple myeloma (MM).

33. The antibody of any one of claims 1-19 for use in treating or delaying progression of an immune-related disease associated with a T cell dysfunctional disorder characterized by T cell exhaustion in a subject in need thereof.

34. The antibody of claim 33, wherein the immune-related disease is an unresolved acute infection or a chronic infection.

35. The antibody of any one of claims 1-19 for use in increasing, enhancing, or stimulating a T cell-mediated immune response or function in a subject in need thereof.

36. Use of the antibody of any one of claims 1-19 in the manufacture of a medicament for treating or delaying progression of a cancer in a subject in need thereof.

37. The use of claim 36, wherein the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, a mycosis fungoides, a Merkel cell cancer, and a hematologic malignancy; wherein optionally the myeloma is MM.

38. Use of the antibody of any one of claims 1-19 in the manufacture of a medicament for treating or delaying progression of an immune-related disease associated with a T cell dysfunctional disorder characterized by T cell exhaustion in a subject in need thereof.

39. The use of claim 38, wherein the immune-related disease is an unresolved acute infection or a chronic infection.

40. Use of the antibody of any one of claims 1-19 in the manufacture of a medicament for increasing, enhancing, or stimulating a T cell-mediated immune response or function in a subject in need thereof.

41. The use of any one of claims 36-40, wherein the medicament is to be administered with a PD-1 axis binding antagonist; wherein optionally the PD-1 axis binding antagonist is to be administered prior to or subsequent to the administration of the antibody, or concurrently with the antibody.

42. The use of claim 41, wherein (i) the PD-1 axis binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PD-L1 binding antagonist, and a PD-L2 binding antagonist; wherein optionally (ii) the PD-1 axis binding antagonist is a PD-1 binding antagonist; wherein optionally (iii) the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners; and wherein optionally (iv) the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1, PD-1 to PD-L2, or PD-1 to both PD-L1 and PD-L2.

43. The use of any one of claims 42 (ii)-42 (iv), wherein the PD-1 binding antagonist is an anti-PD-1 antibody.

44. The use of claim 42 (ii) or 42 (iii), wherein the PD-1 binding antagonist is selected from the group consisting of MDX 1106 (nivolumab), MK-3475 (pembrolizumab), MEDI-0680 (AMP-514), PDR001, REGN2810, and BGB-108.

45. The use of claim 42 (i), wherein the PD-1 axis binding antagonist is a PD-L1 binding antagonist; wherein optionally the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1, PD-L1 to B7-1, or PD-L1 to both PD-1 and B7-1.

46. The use of claim 45, wherein the PD-L1 binding antagonist is an anti-PD-L1 antibody.

47. The use of claim 46, wherein the anti-PD-L1 antibody is selected from the group consisting of: MPDL3280A (atezolizumab), YW243.55.S70, MDX-1105, MEDI4736 (durvalumab), and MSB0010718C (avelumab).

48. The use of claim 47, wherein the anti-PD-L1 antibody is MPDL3280A.

49. The use of claim 42 (i), wherein the PD-1 axis binding antagonist is a PD-L2 binding antagonist.

50. The use of claim 49, wherein the PD-L2 binding antagonist is an anti-PD-L2 antibody, or an immunoadhesin.

51. The use of any one of claims 36-50, wherein the medicament is to be administered with an OX40 binding agonist; wherein optionally the OX40 binding agonist is to be administered prior to or subsequent to the administration of the antibody and/or the PD-1 axis binding antagonist, or concurrently with the antibody and/or the PD-1 axis binding antagonist.

52. The use of claim 51, wherein (i) the OX40 binding agonist is selected from the group consisting of an OX40 agonist antibody, an OX40L agonist fragment, an OX40 oligomeric receptor, and an OX40 immunoadhesin; wherein optionally (ii) the OX40 agonist antibody depletes cells that express human OX40; wherein optionally the cells that express human OX40 are CD4+ effector T cells, or are regulatory T (Treg) cells.

53. The use of claim 52 (ii), wherein the depleting is by ADCC and/or phagocytosis.

54. The use of claim 52 or 53, wherein the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 1 nM; wherein optionally the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.45 nM; and wherein optionally the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.4 nM.

55. The use of any one of claims 52-54, wherein the OX40 agonist antibody binds human OX40 with an EC50 of less than or equal to 0.3 μg/mL; wherein optionally the OX40 agonist antibody binds human OX40 with an EC50 of less than or equal to 0.2 μg/mL.

56. The use of any one of claims 52-55, wherein the OX40 agonist antibody increases CD4+ effector T cell proliferation and/or increases cytokine production by the CD4+ effector T cell as compared to proliferation and/or cytokine production prior to treatment with the OX40 agonist antibody; wherein optionally the OX40 agonist antibody increases memory T cell proliferation and/or cytokine production by a memory T cell.

57. The use of claim 56, wherein the cytokine production is IFN-γ production.

58. The use of any one of claims 52-57, wherein the OX40 agonist antibody inhibits Treg function.

59. The use of claim 58, wherein the OX40 agonist antibody inhibits Treg suppression of effector T cell function; wherein optionally the effector T cell function is effector T cell proliferation and/or cytokine production; wherein optionally the effector T cell is a CD4+ effector T cell.

60. The use of any one of claims 52-59, wherein the OX40 agonist antibody increases OX40 signal transduction in a target cell that expresses OX40; wherein optionally the OX40 signal transduction is detected by monitoring NFkB downstream signaling.

61. The use of any one of claims 52-60, wherein the OX40 agonist antibody comprises a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells and has diminished activity relative to the OX40 agonist antibody comprising a native sequence IgG1 Fc portion; wherein optionally the OX40 agonist antibody comprises a variant IgG1 Fc polypeptide comprising a DANA mutation.

62. The use of any one of claims 52-61, wherein the OX40 agonist antibody is antibody L106, antibody ACT35, MEDI6469, or MEDI0562.

63. The use of any one of claims 52-62, wherein the OX40 agonist antibody is a full-length IgG1 antibody.

64. The use of claim 52, wherein the OX40 immunoadhesin is a trimeric OX40-Fc protein.

65. The use of any one of claims 36-64, wherein the medicament is to be administered with an agent that decreases or inhibits one or more additional immune co-inhibitory receptors.

66. The use of claim 65, wherein the one or more additional immune co-inhibitory receptor is selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96.

67. The use of any one of claims 36-66, wherein the medicament is to be administered with an additional therapeutic agent; wherein optionally the additional therapeutic agent is a chemotherapeutic agent.

68. The use of any one of claims 36-67, wherein the antibody is to be administered subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally; wherein optionally the subject is a human.

69. A kit comprising the antibody of any one of claims 1-19 and a package insert comprising instructions for using the antibody for treating or delaying progression of a cancer in a subject.

70. A kit comprising the antibody of any one of claims 1-19 and a package insert comprising instructions for using the antibody for treating or delaying progression of an immune-related disease associated with a T cell dysfunctional disorder characterized by T cell exhaustion in a subject.

71. A kit comprising the antibody of any one of claims 1-19 and a package insert comprising instructions for increasing, enhancing, or stimulating a T cell-mediated immune response or function in a subject.

72. The kit of any one of claims 69-71, wherein the subject is a human.