METHODS FOR TREATMENT OF CANCER COMPRISING TIGIT-BINDING AGENTS

FIELD OF THE INVENTION

[001] The present invention generally relates to methods for treating cancer using agents that bind human TIGIT, particularly antibodies that specifically bind the extracellular domain of TIGIT.

BACKGROUND OF THE INVENTION

[002] The basis for immunotherapy is the manipulation and/or modulation of the immune system, including both innate immune responses and adaptive immune responses. The general aim of immunotherapy is to treat diseases by controlling the immune response to a "foreign agent", for example a pathogen or a tumor cell. However, in some instances immunotherapy is used to treat autoimmune diseases which may arise from an abnormal immune response against proteins, molecules, and/or tissues normally present in the body. Immunotherapy may include agents and methods to induce or enhance specific immune responses or to inhibit or reduce specific immune responses.

[003] The immune system is a highly complex system made up of a great number of cell types, including but not limited to, T-cells, B-cells, natural killer cells, antigen-presenting cells, dendritic cells, monocytes, and macrophages. These cells possess complex and subtle systems for controlling their interactions and responses. The cells utilize both activating and inhibitory mechanisms and feedback loops to keep responses in check and not allow negative consequences of an uncontrolled immune response (e.g., autoimmune diseases).

[004] The concept of cancer immunosurveillance is based on the theory that the immune system can recognize tumor cells, mount an immune response, and suppress the development and/or progression of a tumor. However, it is clear that many cancer/tumor cells have developed mechanisms to evade the immune system which can allow for uninhibited growth of those cells. Cancer/tumor immunotherapy focuses on the development of new and novel agents that can activate and/or boost the immune system to achieve a more effective attack against tumor cells resulting in increased killing of tumor cells and/or inhibition of tumor growth.

SUMMARY

[004a] In one aspect, the present disclosure refers to the use of an antibody that specifically binds the extracellular domain of human TIGIT in the manufacture of a medicament for inhibiting tumor growth in a subject, wherein the tumor is a microsatellite instability-high colorectal cancer, a microsatellite stable

colorectal cancer, a triple negative breast cancer, a Merkel cell carcinoma, an endometrial cancer, or an esophageal cancer; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[004b] In another aspect, the present disclosure refers to the use of an antibody that specifically binds the extracellular domain of human TIGIT in the manufacture of a medicament for inhibiting tumor growth in a subject, wherein the tumor is resistant or refractory to treatment with a PD-1 antagonist or a PD-L1 antagonist; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[004c] In another aspect, the present disclosure refers to the use of an antibody that specifically binds the extracellular domain of human TIGIT in the manufacture of a medicament for inhibiting tumor growth in a subject, wherein the tumor expresses poliovirus receptor (PVR) and/or poliovirus receptor-related 2 (PVRL2); and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[004d] In another aspect, the present disclosure refers to the use of an antibody that specifically binds the extracellular domain of human TIGIT in the manufacture of a medicament for inhibiting tumor growth in a subject, wherein the tumor comprises tumor-infiltrating lymphocytes (TILs) or regulatory T-cells; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[004e] In another aspect, the present disclosure refers to the use of an antibody that specifically binds the extracellular domain of human TIGIT in the manufacture of a medicament for inhibiting tumor growth in a subject, wherein the tumor is a head and neck cancer, esophageal/gastroesophageal cancer, gastric

cancer, colorectal cancer, anal cancer, hepatocellular cancer/liver cancer, cervical cancer, lung cancer, melanoma, Merkel cell carcinoma, renal cell carcinoma/kidney cancer, bladder cancer, ovarian cancer, pancreatic cancer, endometrial cancer, and triple negative breast cancer, a known MSI high solid tumor (including MSI CRC) or a MSS colorectal cancer; wherein the tumor is resistant or refractory to treatment with an anti-PD-1 antibody or an anti-PD-L1 antibody; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[005] The present disclosure provides methods for treatment of cancer (i.e., inhibiting tumor growth) using agents that bind T-cell immunoreceptor with Ig and ITIM domains (TIGIT), including, but not limited to, antibodies that specifically bind the extracellular domain of TIGIT. In certain examples,

the agent is a TIGIT antagonist. In some examples, a method comprises using a TIGIT-binding agent to induce, activate, promote, increase, enhance, or prolong an immune response to cancer and/or a tumor. In some examples, a method comprises using a TIGIT-binding agent to inhibit tumor growth. In some examples, a method comprises using a TIGIT-binding agent for the treatment of cancer. In some examples, a method comprises using a TIGIT-binding agent in combination with at least one additional therapeutic agent.

[006] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent, wherein the tumor is a colorectal cancer (CRC) such as a microsatellite instability-high colorectal cancer (MSI CRC) or a microsatellite stable colorectal cancer (MSS CRC), a triple negative breast cancer (TNBC), a Merkel cell carcinoma, an endometrial cancer, or an esophageal cancer. In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT, wherein the tumor is a microsatellite instability-high colorectal cancer, a microsatellite stable colorectal cancer, a triple negative breast cancer, a Merkel cell carcinoma, an endometrial cancer, or an esophageal cancer, and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[007] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent, wherein the tumor is a solid tumor with high microsatellite instability (MSI). In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT, and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9). In some examples the solid tumor with high MSI is selected from the group consisting of a MSI CRC, a MSI gastric cancer, a MSI endometrium cancer, a MSI ovarian cancer, a MSI hepatobiliary tract cancer, a MSI urinary tract cancer, a MSI brain cancer, or a MSI skin cancer.

[008] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the tumor is a microsatellite instability-high colorectal cancer, a microsatellite stable colorectal cancer, a triple negative breast cancer, a Merkel cell carcinoma, an endometrial cancer, or an esophageal cancer. In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the tumor is a colorectal cancer (CRC) such as a microsatellite instability-high colorectal cancer or a microsatellite stable colorectal cancer, a triple negative breast cancer, a Merkel cell carcinoma, an endometrial cancer, or an esophageal cancer, and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9). In some examples, the combination therapy comprises an anti-PD-1 antibody. In some examples, the combination therapy comprises an anti-PD-L1 antibody.

[009] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the tumor is a solid tumor with high MSI. In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the tumor is a solid tumor with a high microsatellite instability, and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9). In some examples, the combination therapy comprises an anti-PD-1 antibody. In some examples, the combination therapy comprises an anti-PD-L1 antibody. In some examples the solid tumor with high MSI is selected from the group consisting of a MSI CRC, a MSI gastric cancer, a MSI endometrium cancer, a MSI ovarian cancer, a MSI hepatobiliary tract cancer, a MSI urinary tract cancer, a MSI brain cancer or a MSI skin cancer.

[010] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent, wherein the tumor is resistant or refractory to treatment with a PD-1 antagonist or a PD-L1 antagonist. In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT, wherein the tumor is resistant or refractory to treatment with a PD-1 antagonist or a PD-L1 antagonist; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9). In some examples, the tumor was resistant or refractory to treatment with a PD-1 antagonist or a PD-L1 antagonist. As used herein, a tumor is resistant or refractory to treatment with an agent wherein there is tumor growth progression during or after treatment with the agent. In some examples, a tumor is resistant or refractory to treatment with an agent that is administered as a single agent. In some examples, a tumor is resistant or refractory to treatment with an agent that is administered as a first-line treatment or a second-line treatment. In some examples, the tumor is resistant or refractory to treatment with an anti-PD-1 antibody (e.g., as a single agent). In some examples, the tumor is resistant or refractory to treatment with an anti-PD-L1 antibody (e.g., as a single agent). In some examples, the tumor resistant or refractory to treatment with a PD-1 antagonist or a PD-L1 antagonists is selected from the group consisting of melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer (e.g. MSI or DNA mismatch repair defective (dMMR) metastatic CRC) and hepatocellular carcinoma.

[011] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the tumor is resistant or refractory to treatment with a PD-1 antagonist or a PD-L1 antagonist as a single agent. In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the tumor is resistant or refractory to treatment with a PD-1 antagonist or a PD-L1 antagonist as a single agent; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2

comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9). In some examples, a tumor is resistant or refractory to treatment with an agent that is administered as a first-line treatment or a second-line treatment. In some examples, a tumor is resistant or refractory to treatment with a PD-1 antagonist as a single agent, but is responsive to treatment with this agent in combination with a TIGIT-binding agent. In some examples, a tumor is resistant or refractory to treatment with a PD-L1 antagonist as a single agent, but is responsive to treatment with this agent in combination with a TIGIT-binding agent. In some examples, the tumor is resistant or refractory to treatment with an anti-PD-1 antibody (e.g., as a single agent). In some examples, the tumor is resistant or refractory to treatment with an anti-PD-L1 antibody (e.g., as a single agent). In some examples, the combination therapy comprises an anti-PD-1 antibody. In some examples, the combination therapy comprises an anti-PD-L1 antibody. In some examples, the tumor resistant or refractory to treatment with a PD-1 antagonist or a PD-L1 antagonists is selected from the group consisting of melanoma, NSCLC, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer (e.g. MSI or dMMR metastatic CRC) and hepatocellular carcinoma.

[012] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent, wherein the subject has previously been treated with a PD-1 antagonist or a PD-L1 antagonist as a single agent. In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT, wherein the subject has previously been treated with a PD-1 antagonist or a PD-L1 antagonist as a single agent; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9). In some examples, the subject has previously been treated with a PD-1 antagonist or a PD-L1 antagonist, wherein there was disease progression on or after treatment. In some examples, there is tumor growth recurrence after treatment with a PD-1 antagonist or a PD-L1 antagonist. As used herein, tumor growth recurrence is defined as the return of cancer after treatment and after a period of time during which the cancer was not detected. The cancer may come back where it was first found or it may be found somewhere else in the body. In some examples, the recurrence is local recurrence, regional recurrence, or distant recurrence. In some examples, the subject has previously been treated with an anti-PD-1 antibody. In some examples, the subject has previously been treated with an anti-PD-L1 antibody. In some examples, the tumor is selected from the group consisting of melanoma, NSCLC, renal cell carcinoma, squamous cell carcinoma of the

head and neck, urothelial carcinoma, colorectal cancer (e.g. MSI or dMMR metastatic CRC) and hepatocellular carcinoma.

[013] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the subject has previously been treated with a PD-1 antagonist or a PD-L1 antagonist as a single agent. In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the subject has previously been treated with a PD-1 antagonist or a PD-L1 antagonist as a single agent; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9). In some examples, the subject has previously been treated with a PD-1 antagonist or a PD-L1 antagonist, wherein there was disease progression on or after treatment. In some examples, there is tumor growth recurrence after treatment with a PD-1 antagonist or a PD-L1 antagonist. In some examples, the recurrence is local recurrence, regional recurrence, or distant recurrence. In some examples, the combination therapy "resensitizes" the tumor to treatment with a PD-1 antagonist or a PD-L1 antagonist. In some examples, the subject has previously been treated with an anti-PD-1 antibody. In some examples, the subject has previously been treated with an anti-PD-L1 antibody. In some examples, the combination therapy comprises an anti-PD-1 antibody. In some examples, the combination therapy comprises an anti-PD-L1 antibody. In some examples, the tumor is selected from the group consisting of melanoma, NSCLC, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer (e.g. MSI or dMMR metastatic CRC) and hepatocellular carcinoma.

[014] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent, wherein the tumor expresses poliovirus receptor (PVR) and/or poliovirus receptor-related 2 (PVRL2). In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT, wherein the tumor expresses PVR and/or PVRL2; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY

(SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[015] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the tumor expresses PVR and/or PVRL2. In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the tumor expresses PVR and/or PVRL2; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9). In some examples, the tumor is selected from the group consisting of melanoma, NSCLC, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer (e.g. MSI or dMMR) metastatic CRC and hepatocellular carcinoma.

[016] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent, wherein the tumor comprises tumor-infiltrating lymphocytes (TILs). In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT, wherein the tumor comprises tumor-infiltrating lymphocytes; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[017] In some examples of the disclosure, a method of inhibiting tumor growth in a subject, comprising administering to the subject a therapeutically effective amount of a TIGIT-binding agent in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the tumor comprises tumor-infiltrating lymphocytes. In some examples, a method of inhibiting tumor growth in a subject, comprising administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the tumor comprises tumor-infiltrating lymphocytes; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2

comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[018] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent, wherein the tumor comprises regulatory T-cells (Tregs). In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT, wherein the tumor comprises Tregs; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[019] In some examples of the disclosure, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of a TIGIT-binding agent in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the tumor comprises Tregs. In some examples, a method of inhibiting tumor growth in a subject comprises administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT in combination with a PD-1 antagonist or a PD-L1 antagonist, wherein the tumor comprises Tregs; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[020] In some examples of the methods described herein, the tumor is selected from the group consisting of: lung tumor, liver tumor, breast tumor, renal cell carcinoma/kidney tumor, prostate tumor, gastrointestinal/gastric tumor, melanoma, cervical tumor, bladder tumor, glioblastoma, head and neck tumor, pancreatic tumor, ovarian tumor, colorectal tumor, endometrial tumor, anal tumor and esophageal tumor.

[021] In some examples, the lung tumor comprises NSCLC, such as NSCLC squamous cell or NSCLC adenocarcinoma.

[022] In some examples, the breast tumor comprises triple-negative breast cancer (TNBC).

[023] In some examples, the tumor is a solid tumor with high MSI. In some examples, the solid tumor with high microsatellite instability is a MSI colorectal cancer (MSI CRC), a MSI gastric cancer, a MSI endometrium cancer, a MSI ovarian cancer, a MSI hepatobiliary tract cancer, a MSI urinary tract cancer, a MSI brain cancer or a MSI skin cancer. In some examples, the solid tumor with high MSI is a MSI CRC.

[024] In some examples, the tumor is a microsatellite stable (MSS) tumor. In some examples, the tumor is a microsatellite stable colorectal cancer (MSS CRC).

[025] In some examples, the tumor is selected from the group consisting of a melanoma, a NSCLC, a renal cell carcinoma, a squamous cell carcinoma of the head and neck, a urothelial carcinoma, a colorectal cancer (e.g. MSI or dMMR metastatic CRC) and hepatocellular carcinoma.

[026] In some examples of the methods described herein, the agent is an antibody that specifically binds the extracellular domain of human TIGIT, which comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), and a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), and/or a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[027] In some examples of the methods described herein, the agent is an antibody that specifically binds the extracellular domain of TIGIT, wherein the antibody comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:10 and/or a light chain variable region having at least 90% sequence identity to SEQ ID NO:11. In some examples, an antibody comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:10 and/or a light chain variable region having at least 95% sequence identity to SEQ ID NO:11. In some examples, an antibody comprises a heavy chain variable region comprising SEQ ID NO:10 and a light chain variable region comprising SEQ ID NO:11.

[028] In some examples of the methods described herein, the TIGIT-binding agent is an antibody which is a monoclonal antibody, a humanized antibody, a human antibody, a recombinant antibody, a chimeric antibody, a bispecific antibody, an antibody fragment comprising an antigen-binding site, an IgG antibody, an IgG1 antibody, an IgG2 antibody, or an IgG4 antibody. In some examples, the antibody is monovalent. In some examples, the antibody is bivalent. In some examples, the antibody is monospecific. In some examples, the antibody is bispecific.

[029] In some examples of the methods described herein, an antibody that specifically binds human TIGIT comprises a heavy chain amino acid sequence of SEQ ID NO:13 and a light chain amino acid sequence of SEQ ID NO:15. In some examples, an antibody that specifically binds human TIGIT

comprises a heavy chain amino acid sequence of SEQ ID NO:17 and a light chain amino acid sequence of SEQ ID NO:15.

[030] In some examples of the methods described herein, an antibody that specifically binds human TIGIT, does not bind mouse TIGIT. In some examples an antibody that specifically binds human TIGIT, does not bind rat TIGIT. In some examples an antibody that specifically binds human TIGIT, does not bind rabbit TIGIT. In some examples an antibody that specifically binds human TIGIT, does not bind marmoset TIGIT. In some examples an antibody that specifically binds human TIGIT, does not bind dog TIGIT. In some examples an antibody that specifically binds human TIGIT, does not bind pig TIGIT. In some examples an antibody that specifically binds human TIGIT, does not bind cynomolgus monkey TIGIT. In some examples an antibody that specifically binds human TIGIT, does not bind rhesus monkey TIGIT.

[031] In some examples of the methods described herein, an antibody that specifically binds human TIGIT comprises the heavy chain variable region and the light chain variable region from antibody OMP-313M32. In some examples, the antibody comprises the heavy chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122346. In some examples, the antibody comprises a polypeptide comprising the heavy chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122346. In some examples, the antibody comprises the light chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122347. In some examples, the antibody comprises the light chain encoded by the plasmid deposited with ATCC as Designation No. PTA-122347. In some examples, the antibody comprises the heavy chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122346 and the light chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122347. In some examples, the antibody comprises a polypeptide encoded by the plasmid deposited with ATCC as PTA-122346 and a polypeptide encoded by the plasmid deposited with ATCC as Designation No. PTA-122347.

[032] In some examples of the methods described herein, the TIGIT-binding agent is monovalent. In some examples, the TIGIT-binding agent is bivalent. In some examples, the TIGIT-binding agent is monospecific. In some examples, the TIGIT-binding agent is bispecific. In some examples, the bispecific agent is a heterodimeric agent or heterodimeric molecule. In some examples, a heterodimeric agent comprises an antibody that specifically binds TIGIT. In some examples, the bispecific agent is a homodimeric agent or homodimeric molecule. In some examples, a homodimeric agent comprises an antibody that specifically binds TIGIT.

[033] In some examples of the methods described herein, the TIGIT-binding agent is an antibody that competes for specific binding to human TIGIT with an antibody described herein. In some examples, a

TIGIT-binding agent binds the same epitope on human TIGIT as an antibody described herein. In some examples, a TIGIT-binding agent binds an epitope on human TIGIT that overlaps with the epitope on TIGIT bound by an antibody described herein. In some examples, a TIGIT-binding agent binds an epitope comprising amino acids within SEQ ID NO:27. In some examples, a TIGIT-binding agent binds an epitope comprising amino acids within SEQ ID NO:28. In some examples, a TIGIT-binding agent binds an epitope comprising amino acids within SEQ ID NO:27 and SEQ ID NO:28. In some examples, a TIGIT-binding agent binds an epitope comprising amino acids Q62 and I109 of SEQ ID NO:1. In some examples, a TIGIT-binding agent binds an epitope comprising amino acids Q62 and T119 of SEQ ID NO:1. In some examples, a TIGIT-binding agent binds an epitope comprising amino acids Q64 and I109 of SEQ ID NO:1. In some examples, a TIGIT-binding agent binds an epitope comprising amino acids Q64 and T119 of SEQ ID NO:1. In some examples, a TIGIT-binding agent binds an epitope comprising amino acids Q62, Q64, and I109 of SEQ ID NO:1. In some examples, a TIGIT-binding agent binds an epitope comprising amino acids Q62, Q64, and T119 of SEQ ID NO:1. In some examples, a TIGIT-binding agent binds an epitope comprising amino acids Q62, I109, and T119 of SEQ ID NO:1. In some examples, a TIGIT-binding agent binds an epitope comprising amino acids Q64, I109, and T119 of SEQ ID NO:1. In some examples, a TIGIT-binding agent binds an epitope comprising amino acids Q62, Q64, I109, and T119 of SEQ ID NO:1. In some examples, a TIGIT-binding agent binds an epitope comprising at least one amino acid selected from the group consisting of: N58, E60, Q62, Q64, L65, F107, I109, H111, T117, T119, G120, and R121 of SEQ ID NO:1. In some examples, the epitope is a conformational epitope. In some examples, a TIGIT-binding agent binds an epitope that does not comprise amino acid V100 of SEQ ID NO:1.

[034] In some examples of the methods described herein, the agent that specifically binds TIGIT is an antibody, wherein the antibody is part of a bispecific agent. In some examples, a bispecific agent comprises a first arm which binds TIGIT and a second arm which binds a second target. In some examples, a bispecific agent comprises a first arm that specifically binds TIGIT and a second arm, wherein the first arm comprises an anti-TIGIT antibody. In some examples, a bispecific agent comprises a first arm that binds TIGIT and a second arm which comprises an antigen-binding site from an antibody. In some examples, a bispecific agent comprises a first arm that binds TIGIT and a second arm that specifically binds PD-1, PD-L1, CTLA4, TIM-3, LAG-3, OX-40, or GITR. In some examples, a bispecific agent comprises a first arm that binds TIGIT and a second arm that specifically binds a tumor antigen. In some examples, a bispecific agent comprises a first arm that binds TIGIT and a second arm that comprises an immune response stimulating agent. In some examples, the immune response stimulating agent is selected from the group consisting of: granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage colony stimulating factor (M-CSF), granulocyte colony stimulating factor

(G-CSF), interleukin 2 (IL-2), interleukin 3 (IL-3), interleukin 12 (IL-12), interleukin 15 (IL-15), B7-1 (CD80), B7-2 (CD86), 4-1BB ligand, GITRL, OX-40L, anti-CD3 antibody, anti-CTLA4 antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-GITR antibody, anti-OX-40 antibody, anti-LAG-3 antibody, and anti-TIM-3 antibody.

[035] In some examples, the bispecific agent is a heterodimeric agent or heterodimeric molecule. In some examples, the bispecific agent is a homodimeric agent or homodimeric molecule. In some examples, a heterodimeric molecule comprises a first arm which binds human TIGIT and a second arm which binds a second target. In some examples, a heterodimeric molecule comprises a first arm that specifically binds human TIGIT and a second arm, wherein the first arm comprises an anti-TIGIT antibody. In some examples, a heterodimeric molecule comprises a first arm that binds human TIGIT and a second arm which comprises an antigen-binding site from an antibody that specifically binds a second target. In some examples, a heterodimeric molecule is a bispecific antibody. In some examples, a heterodimeric molecule comprises a first arm that binds human TIGIT and a second arm that specifically binds a tumor antigen. In some examples, a heterodimeric molecule comprises a first arm that binds human TIGIT and a second arm that specifically binds PD-1, PD-L1, CTLA-4, TIM-3, LAG-3, OX-40, 4-1BB, or GITR. In some examples, a heterodimeric molecule comprises a first arm that binds TIGIT and a second arm that comprises an immunotherapeutic agent. In some examples, the immunotherapeutic agent is selected from the group consisting of: granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage colony stimulating factor (M-CSF), granulocyte colony stimulating factor (G-CSF), interleukin 2 (IL-2), interleukin 3 (IL-3), interleukin 12 (IL-12), interleukin 15 (IL-15), B7-1 (CD80), B7-2 (CD86), 4-1BB ligand, GITRL, OX-40L, anti-CD3 antibody, anti-CTLA-4 antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-4-1BB antibody, anti-GITR antibody, anti-OX-40 antibody, anti-LAG-3 antibody, and anti-TIM-3 antibody.

[036] In some examples of the methods described herein, an agent specifically binds TIGIT and inhibits binding of TIGIT to PVR. In some examples, an agent specifically binds TIGIT and inhibits or blocks the interaction between TIGIT and PVR. In some examples, an agent specifically binds TIGIT and inhibits binding of TIGIT to PVRL2. In some examples, an agent specifically binds TIGIT and inhibits or blocks the interaction between TIGIT and PVRL2. In some examples, an agent specifically binds TIGIT and inhibits binding of TIGIT to PVRL3. In some examples, an agent specifically binds TIGIT and inhibits or blocks the interaction between TIGIT and PVRL3. In some examples, the agent is an antagonist of TIGIT. In some examples, an agent specifically binds TIGIT and inhibits TIGIT signaling. In some examples, an agent specifically binds TIGIT and is an antagonist of TIGIT-mediated signaling. In some examples, an agent specifically binds TIGIT and inhibits TIGIT activation. In some examples,

an agent specifically binds TIGIT and inhibits phosphorylation of TIGIT. In some examples, an agent specifically binds TIGIT and decreases cell surface expression of TIGIT.

[037] In some examples of the methods described herein, an agent specifically binds TIGIT and induces, activates, promotes, increases, enhances, and/or prolongs an immune response. In some examples, the immune response is directed to (e.g., kills) a tumor or tumor cell. In some examples, the agent increases cell-mediated immunity. In some examples, the agent increases T-cell activity. In some examples, the agent increases cytolytic T-cell (CTL) activity. In some examples, the agent increases natural killer (NK) cell activity. In some examples, the agent increases IL-2 production and/or the number of IL-2-producing cells. In some examples, the agent increases IFN-gamma production and/or the number of IFN-gamma-producing cells. In some examples, the agent increases a Th1-type immune response. In some examples, the agent decreases IL-4 production and/or the number of IL-4-producing cells. In some examples, the agent decreases IL-10 and/or the number of IL-10-producing cells. In some examples, the agent decreases IL-6 production and/or the number of IL-6-producing cells. In some examples, the agent decreases IL-5 production and/or the number of IL-5-producing cells. In some examples, the agent decreases a Th2-type immune response. In some examples, the agent decreases the number of Treg cells. In some examples, the agent decreases Treg activity. In some examples, the agent inhibits and/or decreases the suppressive activity of Tregs. In some examples, the agent decreases the number of myeloid-derived suppressor cells (MDSCs). In some examples, the agent inhibits and/or decreases the suppressive activity of MDSCs.

[038] In some examples of the methods described herein, an agent specifically binds TIGIT and inhibits tumor growth. In some examples, the agent reduces tumor growth. In some examples, the agent reduces tumor growth to an undetectable size. In some examples, the agent induces long-term anti-tumor immunity.

[039] In another example, the disclosure provides compositions comprising a TIGIT-binding agent for use in the methods described herein. In some examples, the disclosure provides pharmaceutical compositions comprising a TIGIT-binding agent for use in the methods described herein and a pharmaceutically acceptable carrier.

[040] In certain examples of the methods described herein, the TIGIT-binding agent is isolated. In certain examples, the TIGIT-binding agent is substantially pure.

[041] The disclosure also provides polynucleotides comprising a polynucleotide that encodes a TIGIT-binding agent. In some examples, the polynucleotide is isolated. In some examples, the disclosure provides vectors that comprise the polynucleotides, as well as cells that comprise the vectors and/or the polynucleotides. In some examples, the disclosure also provides cells comprising or producing a TIGIT-binding agent. In some examples, the cell is a monoclonal cell line.

[042] In some examples of the methods described herein, a method further comprises administering at least one additional therapeutic agent. In some examples, the additional therapeutic agent is a chemotherapeutic agent. In some examples, the additional therapeutic agent is an antibody. In some examples, the additional therapeutic agent is an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-CTLA4 antibody, an anti-LAG-3 antibody, or an anti-TIM-3 antibody. In some examples, the additional therapeutic agent is an inhibitor of the Notch pathway, the Wnt pathway, or the RSPO/LGR pathway. In some examples, the additional therapeutic agent is an immunotherapeutic agent. As used herein, the phrase "immunotherapeutic agent" is used in the broadest sense and refers to a substance that directly or indirectly affects or modulates the immune system. In some examples, an immunotherapeutic agent is an agent that directly or indirectly stimulates the immune system by inducing activation or increasing activity of any of the immune system's components. As the TIGIT-binding agents are considered immunotherapeutic agents, this additional immunotherapeutic agent may be considered a "second" immunotherapeutic agent. In some examples, the second immunotherapeutic agent is selected from the group consisting of: GM-CSF, M-CSF, G-CSF, IL-2, IL-3, IL-12, IL-15, B7-1 (CD80), B7-2 (CD86), 4-1BB ligand, GITRL, OX-40 ligand, anti-CD3 antibody, anti-CTLA-4 antibody, anti-CD28 antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-4-1BB antibody, anti-GITR antibody, anti-OX-40 antibody, anti-LAG-3 antibody, and anti-TIM-3 antibody. In some examples, the second immunotherapeutic agent is a fusion protein comprising: GM-CSF, M-CSF, G-CSF, IL-2, IL-3, IL-12, IL-15, B7-1 (CD80), B7-2 (CD86), 4-1BB ligand, GITRL, OX-40 ligand, or a fragment thereof. In some examples, the second immunotherapeutic agent is a fusion protein comprising at least one copy of the extracellular domain of GITRL, OX40 ligand, or 4-1BB ligand.

[043] In some examples of the methods described herein, the subject is human. In some examples, the subject has had a tumor or a cancer, at least partially, removed.

[044] In some examples of the methods described herein, the tumor or the cancer expresses PD-L1. In some examples, a method further comprises a step of determining the level of PD-L1 expression in the tumor or cancer. In some examples, determining the level of PD-L1 expression is done prior to treatment or contact with a TIGIT-binding agent. In some examples, if the tumor or cancer has an elevated expression level of PD-L1, a TIGIT-binding agent is administered to the subject.

[045] In some examples, the disclosure comprises a method of inhibiting tumor growth in a subject, comprising administering to the subject a therapeutically effective amount of an antibody that specifically binds the extracellular domain of human TIGIT, wherein the tumor is a head and neck cancer, esophageal/gastroesophageal cancer, gastric cancer, colorectal cancer, anal cancer, hepatocellular cancer/liver cancer, cervical cancer, lung cancer (e.g., NSCLC), melanoma, Merkel cell carcinoma, renal cell carcinoma/kidney cancer, bladder cancer, ovarian cancer, pancreatic cancer, endometrial cancer, and

triple negative breast cancer, a known MSI high solid tumor (including MSI CRC) or a MSS colorectal cancer; wherein the tumor is resistant or refractory to treatment with an anti-PD-1 antibody or an anti-PD-L1 antibody; and wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

[046] In some examples of the methods described herein, the subject has previously been treated with an anti-PD-1 antibody or an anti-PD-L1 antibody. In some examples, the antibody that specifically binds the extracellular domain of human TIGIT is administered to the subject at a dose of about 0.1 mg/kg, about 0.3 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 5 mg/kg, about 7.5 kg/kg, or about 10 mg/kg. In some examples, the antibody that specifically binds the extracellular domain of human TIGIT is administered once about every week, once about every two weeks, once about every three weeks, or once about every four weeks. In some examples, the subject has a histologically confirmed advanced relapsed or refractory solid tumor.

[047] Where aspects or embodiments of the invention are described in terms of a Markush group or other grouping of alternatives, the present invention encompasses not only the entire group listed as a whole, but also each member of the group individually and all possible subgroups of the main group, and also the main group absent one or more of the group members. The present invention also envisages the explicit exclusion of one or more of any of the group members in the claimed invention.

BRIEF DESCRIPTION OF THE FIGURES

[048] Figure 1. Inhibition of tumor growth by anti-TIGIT antibody OMP-313M32 in a humanized mouse model. Humanized mice were injected subcutaneously with patient-derived melanoma tumor cells (OMP-M9, 75,000 cells/mouse). Tumors were allowed to grow 19 days until they had reached an average volume of approximately $50mm^3$. Tumor-bearing mice were randomized into groups (n = 8 mice per group). Tumor-bearing mice were treated with either a control antibody or anti-TIGIT antibody OMP-313M32. Mice were dosed every 5 days at 1mg/kg or 5mg/kg. Tumor growth was monitored and tumor volumes were measured with electronic calipers at the indicated time points.

[049] Figure 2. A schematic diagram showing dose escalation and expansion for the initial phase of a clinical trial using anti-TIGIT antibody 313M32.

WHAT IS CLAIMED IS:

1. Use of an antibody that specifically binds the extracellular domain of human TIGIT in the manufacture of a medicament for inhibiting tumor growth in a subject,
wherein the tumor is a microsatellite instability-high colorectal cancer, a microsatellite stable colorectal cancer, a triple negative breast cancer, a Merkel cell carcinoma, an endometrial cancer, or an esophageal cancer; and
wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

2. The use of claim 1, wherein the tumor is resistant or refractory to treatment with a PD-1 antagonist or a PD-L1 antagonist, and there is tumor growth progression or recurrence during or after treatment with a PD-1 antagonist or a PD-L1 antagonist.

3. The use of claim 1, wherein the antibody that binds human TIGIT comprises:
(i) a heavy chain variable region comprising SEQ ID NO:10 and a light chain variable region comprising SEQ ID NO:11;
(ii) a heavy chain amino acid sequence of SEQ ID NO:13 and a light chain amino acid sequence of SEQ ID NO:15; or
(iii) a heavy chain amino acid sequence of SEQ ID NO:17 and a light chain amino acid sequence of SEQ ID NO:15.

4. The use of claim 1, wherein the antibody that binds human TIGIT comprises a heavy chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122346 and a light chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122347.

5. Use of an antibody that specifically binds the extracellular domain of human TIGIT in the manufacture of a medicament for inhibiting tumor growth in a subject,
wherein the tumor is resistant or refractory to treatment with a PD-1 antagonist or a PD-L1 antagonist; and

wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

6. The use of claim 5, wherein there is tumor growth recurrence after treatment with a PD-1 antagonist or a PD-L1 antagonist.

7. The use of claim 5, wherein the antibody that binds human TIGIT comprises:

(i) a heavy chain variable region comprising SEQ ID NO:10 and a light chain variable region comprising SEQ ID NO:11;

(ii) a heavy chain amino acid sequence of SEQ ID NO:13 and a light chain amino acid sequence of SEQ ID NO:15; or

(iii) a heavy chain amino acid sequence of SEQ ID NO:17 and a light chain amino acid sequence of SEQ ID NO:15.

8. The use of claim 5, wherein the antibody that binds human TIGIT comprises a heavy chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122346 and a light chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122347.

9. Use of an antibody that specifically binds the extracellular domain of human TIGIT in the manufacture of a medicament for inhibiting tumor growth in a subject,
wherein the tumor expresses poliovirus receptor (PVR) and/or poliovirus receptor-related 2 (PVRL2); and
wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

10. The use of claim 9, wherein the antibody that binds human TIGIT comprises:

(i) a heavy chain variable region comprising SEQ ID NO:10 and a light chain variable region comprising SEQ ID NO:11;

(ii) a heavy chain amino acid sequence of SEQ ID NO:13 and a light chain amino acid sequence of SEQ ID NO:15; or

(iii) a heavy chain amino acid sequence of SEQ ID NO:17 and a light chain amino acid sequence of SEQ ID NO:15.

11. The use of claim 9, wherein the antibody that binds human TIGIT comprises a heavy chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122346 and a light chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122347.

12. The use of claim 9, wherein the antibody that binds human TIGIT is to be administered once every week, once every two weeks, once every three weeks, or once every four weeks.

13. Use of an antibody that specifically binds the extracellular domain of human TIGIT in the manufacture of a medicament for inhibiting tumor growth in a subject,
wherein the tumor comprises tumor-infiltrating lymphocytes (TILs) or regulatory T-cells; and
wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

14. The use of claim 13, wherein the antibody that binds human TIGIT comprises:

(i) a heavy chain variable region comprising SEQ ID NO:10 and a light chain variable region comprising SEQ ID NO:11;

(ii) a heavy chain amino acid sequence of SEQ ID NO:13 and a light chain amino acid sequence of SEQ ID NO:15; or

(iii) a heavy chain amino acid sequence of SEQ ID NO:17 and a light chain amino acid sequence of SEQ ID NO:15.

15. The use of claim 13, wherein the antibody that binds human TIGIT comprises a heavy chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122346

and a light chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122347.

16. The use of claim 13, wherein the antibody that binds human TIGIT is to be administered once every week, once every two weeks, once every three weeks, or once every four weeks.

17. Use of an antibody that specifically binds the extracellular domain of human TIGIT in the manufacture of a medicament for inhibiting tumor growth in a subject,
wherein the tumor is a head and neck cancer, esophageal/gastroesophageal cancer, gastric cancer, colorectal cancer, anal cancer, hepatocellular cancer/liver cancer, cervical cancer, lung cancer, melanoma, Merkel cell carcinoma, renal cell carcinoma/kidney cancer, bladder cancer, ovarian cancer, pancreatic cancer, endometrial cancer, and triple negative breast cancer, a known MSI high solid tumor (including MSI CRC) or a MSS colorectal cancer;
wherein the tumor is resistant or refractory to treatment with an anti-PD-1 antibody or an anti-PD-L1 antibody; and
wherein the antibody that binds human TIGIT comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:4), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:5), a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:6), a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:7), a light chain CDR2 comprising SASYRYT (SEQ ID NO:8), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:9).

18. The use of claim 17, wherein the subject has previously been treated with an anti-PD-1 antibody or an anti-PD-L1 antibody.

19. The use of claim 17, wherein the antibody that binds human TIGIT comprises:
(i) a heavy chain variable region comprising SEQ ID NO:10 and a light chain variable region comprising SEQ ID NO:11;
(ii) a heavy chain amino acid sequence of SEQ ID NO:13 and a light chain amino acid sequence of SEQ ID NO:15; or
(iii) a heavy chain amino acid sequence of SEQ ID NO:17 and a light chain amino acid sequence of SEQ ID NO:15.

20. The use of claim 17, wherein the antibody that binds human TIGIT comprises a heavy chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122346

and a light chain variable region encoded by the plasmid deposited with ATCC as Designation No. PTA-122347.