

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 T-cell immunoreceptor with Ig and ITIM domains (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

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, triple negative breast cancer, a solid tumor with high microsatellite instability (MSI) (including microsatellite instability-high colorectal cancer (MSI CRC)) or a microsatellite stable colorectal cancer (MSS CRC); 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,

WHAT IS CLAIMED IS:

1. Use of an antibody that specifically binds the extracellular domain of human T-cell immunoreceptor with Ig and ITIM domains (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. 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).
4. The use of claim 3, wherein there is tumor growth recurrence after treatment with a PD-1 antagonist or a PD-L1 antagonist.
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 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).

6. 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).
7. The use of claims 5 and 6, 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.
8. 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, triple negative breast cancer, a solid tumor with high microsatellite instability (MSI) (including microsatellite instability-high colorectal cancer (MSI CRC)) or a microsatellite stable colorectal cancer (MSS CRC); 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).

9. The use of claim 8, wherein there is tumor growth recurrence after treatment with a PD-1 antagonist or a PD-L1 antagonist.
10. The use of claims 2, 3, 4, 7, 8 and 9, wherein the subject has previously been treated with an anti-PD-1 antibody or an anti-PD-L1 antibody.
11. The use of claims 1-10, 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.
12. The use of claims 1-11, wherein the antibody that binds human TIGIT comprises a heavy chain variable region comprising SEQ ID NO:10 and a light chain variable region comprising SEQ ID NO:11.
13. The use of claims 1-12, wherein the antibody that binds human TIGIT is 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.
14. The use of claims 1-11, 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.
15. The use of claims 1-12, wherein the antibody that binds human TIGIT is to be administered in combination with an anti-PD-1 antibody.

16. The use of claim 15, wherein anti-PD-1 antibody is nivolumab.
17. The use of claims 1-16, wherein the antibody that binds human TIGIT is to be intravenously administered to said subject.
18. The use of claims 1-17, 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.
19. The use of claim 18, wherein the antibody that binds human TIGIT is to be administered about once every two weeks or once every three weeks.
20. The use of any one of claims 1-19, wherein the antibody that binds human TIGIT is to be administered at a dose of about 0.1mg/kg to about 25 mg/kg.