

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

Summary

In one aspect of the present disclosure, there is provided an anti-human Tim-3 (SEQ ID NO: 1) antibody for use in simultaneous, separate, or sequential combination
10 with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3
15 having the amino acid sequence of SEQ ID NO: 7.

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

Detailed description

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

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

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

WE CLAIM:

- 5 1. An anti-human Tim-3 (SEQ ID NO: 1) antibody for use in simultaneous, separate, or sequential combination with an anti-human PD-1 (SEQ ID NO: 34) antibody, in the treatment of cancer, wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO:
10 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7.
- 15 2. The anti-human Tim-3 antibody for use of claim 1, wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9.
- 20 3. The anti-human Tim-3 antibody for use of claim 2, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11.
- 25 4. The anti-human Tim-3 antibody for use of any one of Claims 1-3, wherein the anti-human PD-1 antibody is nivolumab, or pembrolizumab.
- 30 5. The anti-human Tim-3 antibody for use of any one of Claims 1-3, wherein the anti-human PD-1 antibody comprises HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21.

6. The anti-human Tim-3 antibody for use of Claim 5, wherein the anti-human PD-1 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 22 and a light chain variable region having the amino acid sequence of SEQ ID NO: 23.
7. The anti-human Tim-3 antibody for use of Claim 6, wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 24 and a light chain having the amino acid sequence of SEQ ID NO: 26.
8. The anti-human Tim-3 antibody for use of Claim 6, wherein the anti-human PD-1 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 25 and a light chain having the amino acid sequence of SEQ ID NO: 26.
9. The anti-human Tim-3 antibody for use of any one of Claims 1-8, wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, esophageal cancer, soft tissue sarcoma, or liver cancer.
10. The anti-human Tim-3 antibody for use of Claim 9, wherein the lung cancer is non-small cell lung cancer.
11. The anti-human Tim-3 antibody for use of any one of Claims 1-10, wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is to be administered in simultaneous, separate, or sequential combination with ionizing radiation.
12. The anti-human Tim-3 antibody for use of any one of Claims 1-11, wherein at least one of the anti-human Tim-3 antibody and anti-human PD-1 antibody is to be administered in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents.

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

14. The use of Claim 13, wherein the anti-human Tim-3 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO: 8 and a light chain variable region having the amino acid sequence of SEQ ID NO: 9.

15. The use of Claim 14, wherein the anti-human Tim-3 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11.

16. The use of any one of Claims 13-15, wherein the anti-human PD-1 antibody is nivolumab, or pembrolizumab.

17. The use of any one of Claims 13-15, wherein the anti-human PD-1 antibody comprises HCDR1 having the amino acid sequence of SEQ ID NO: 16, HCDR2 having the amino acid sequence of SEQ ID NO: 17, HCDR3 having the amino acid sequence of SEQ ID NO: 18, LCDR1 having the amino acid sequence of SEQ ID NO: 19, LCDR2 having the amino acid sequence of SEQ ID NO: 20, and LCDR3 having the amino acid sequence of SEQ ID NO: 21.

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