[0014] Figures 3A-3D show the anti-tumor efficacy of monotherapy of anti-GITR or anti-PD-1 antibodies alone (Figs 3C-3D), compared to co-administration of both antibodies (Fig. 3A) in the CT26 tumor model (n=10/group).

[0015] Figures 4A-4D show the effect of anti-GITR and anti PD-1 antibodies dosed alone or with concurrent administration of both antibodies on the anti-tumor response of mice implanted with the MB49 cell line (n=10/group). Treatment was commenced when tumors reached 85-122 mm^3.

[0016] Figures 5A-5B show the dose dependent effect of the combination of anti-GITR (MK-4166) and anti-PD-1 (MK-3475) on Tregs (Fig. 5A) and Treg:CD8 cell ratio (Fig. 5B) in a mixed lymphocyte reaction (MLR).

[0017] Figure 6 shows that incubation with a combination of MK-4166 and MK-3475 results in reduced suppressive activity of Tregs in an MLR.

SUMMARY ~~OF THE INVENTION~~

[0018] The present ~~invention~~ disclosure meets these needs in the art and more by providing a method of treating a tumor in a patient comprising administering to the patient a PD-1 antagonist and a GITR agonist, wherein the PD-1 antagonist and GITR agonist are administered simultaneously or sequentially. In certain embodiments, the PD-1 antagonist is an antibody or antigen binding fragment thereof, that binds PD-1 or PD-L1; and the GITR agonist is an antibody or antigen binding fragment thereof that binds GITR. The GITR agonist and PD-1 or PD-L1 antagonist binds to the human proteins. The antibody or binding fragment thereof is humanized or fully human.

[0018a] In one aspect, there is provided a combination of a PD-1 antagonist and a GITR agonist for use in treating a tumor in a patient, wherein the PD-1 antagonist ~~agonist~~ and GITR agonist are administered simultaneously or sequentially.

[0018b] In another aspect, there is provided a bispecific antibody or antigen binding fragment thereof for use in treating a tumor in a patient, wherein the bispecific antibody or antigen binding fragment thereof comprises a first arm that binds to PD-1 or PD-L1 and antagonizes PD-1 activity, and a second arm that binds to GITR and agonizes GITR activity.

[0019] In further embodiments, the PD-1 antagonist is selected from the group consisting of BMS-936558, MK-3475, and MPDL3280A; and GITR agonist is selected from the group consisting of an antibody having at least one CDR of SEQ ID NOs: 1 - 66; TRX518; and TRX385. The GITR agonist can be an antibody having: a heavy chain CDR1 of SEQ ID NOs: 1-11, CDR2 of SEQ ID NOs: 12-22, and CDR3 of SEQ ID NOs: 23-33;

and/or a light chain CDR1 of SEQ ID NOs: 34-44, CDR2 of SEQ ID NOs: 45-55, and CDR3 of SEQ ID NOs: 56-66. In yet a further embodiment, the GITR agonist is an antibody having: a variable heavy chain of SEQ ID NOs: 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, and 87; and/or a variable light chain of SEQ ID NO: 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, and 88.

[0020] The present ~~invention~~ disclosure also contemplates that the PD-1 antagonist and GITR agonist are administered concurrently at least one time. In certain embodiments, the PD-1 antagonist and GITR agonist are administered concurrently at least 2 times. In certain

embodiments, the tumor is an advanced stage tumor and can be selected from the group consisting squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer such as hepatic carcinoma and hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma (such as multiple myeloma), salivary gland carcinoma, kidney cancer such as renal cell carcinoma and Wilms' tumors, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, and esophageal cancer.

[0021] The present ~~invention~~ disclosure provides method of treating a tumor, by administering to a patient a bispecific antibody comprising a first arm that binds to PD-1 or PD-L1 and antagonizes PD-1 activity, and a second arm that binds to GITR and agonizes GITR activity. In certain embodiments, the first arm is selected from the group consisting of an antigen binding fragment from BMS-936558, MK-3475, and MPDL3280A; and the second arm is selected from the group consisting of an antigen binding fragment from an antibody having at least one CDR of SEQ ID NO: 1 - 66; TRX518; and TRX385. In yet a further embodiment, the second arm has a heavy chain CDR1 of SEQ ID NOs: 1-11, CDR2 of SEQ ID NOs: 12-22, and CDR3 of SEQ ID NOs: 23-33; and/or a light chain CDR1 of SEQ ID NOs: 34-44, CDR2 of SEQ ID NOs: 45-55, and CDR3 of SEQ ID NOs: 56-66. In certain embodiments, the second arm has a variable heavy chain of SEQ ID NOs: 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, and 87; and/or a variable light chain of SEQ ID NO: 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, and 88.

[0022] The present invention ~~provides~~ disclosure a method of treating a tumor wherein the tumor is an advanced stage tumor. In certain embodiments, the advanced stage tumor is selected from the group consisting of squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer such as hepatic carcinoma and hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma (such as multiple myeloma), salivary gland carcinoma, kidney cancer such as renal cell carcinoma and Wilms' tumors, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, and esophageal cancer.

[0023] The present ~~invention~~ disclosure provides a pharmaceutical composition comprising a PD-1 antagonist and a GITR agonist. In another aspect, there is provided a pharmaceutical combination comprising a PD-1 antagonist and a GITR agonist, wherein: a) the PD-1 antagonist is selected from the group consisting of BMS-936558, MK-3475, and MPDL3280A; and b) the GITR agonist comprising: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81; ii. TRX518; and iii. TRX385.

[0023a] Also provided is the use of a PD-1 antagonist in combination with a GITR agonist to treat an advanced stage tumor. In another aspect, there is provided use of a PD-1 antagonist and a GITR agonist in the manufacture of a medicament for the treatment of a tumor in a patient, wherein the PD-1 antagonist and GITR agonist are for administration simultaneously or sequentially. In another aspect, there is provided use of a PD-1 antagonist and a GITR agonist in the manufacture of a medicament for the treatment of an advanced stage tumor, wherein: a) the PD-1 antagonist is selected from the group consisting of BMS-936558, MK-3475, and MPDL3280A; and b) the GITR agonist is selected from the group consisting of: i. an antibody comprising: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81; ii. TRX518; and iii. TRX385.

CLAIMS

WHAT IS CLAIMED IS:

1. A combination of ~~method of treating a tumor in a patient comprising administering to the patient~~ a PD-1 antagonist and a GITR agonist for use in treating a tumor in a patient, wherein the PD-1 antagonist ~~agonist~~ and GITR agonist are administered simultaneously or sequentially.

2. The combination of the PD-1 antagonist and the GITR agonist ~~method~~ of claim 1, wherein

a. the PD-1 antagonist is an antibody or antigen binding fragment thereof, that binds PD-1 or PD-L1; and

b. the GITR agonist is an antibody or antigen binding fragment thereof, that binds GITR.

3. The combination of the PD-1 antagonist and the GITR agonist ~~method~~ of claim 2 wherein

a. the PD-1 antagonist is an antibody or antigen binding fragment thereof that binds to human PD-1 or human PD-L1; and

b. the GITR agonist is an antibody or antigen binding fragment thereof that binds to human GITR.

4. The combination of the PD-1 antagonist and the GITR agonist ~~method~~ of claim 3, wherein the antibody or binding fragment thereof is humanized or fully human.

5. The combination of the PD-1 antagonist and the GITR agonist ~~method~~ of claim 2, wherein

a. the PD-1 antagonist is selected from the group consisting of BMS-936558, MK-3475, and MPDL3280A; and

b. the GITR agonist is selected from the group consisting of:

i. an antibody comprising: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82; and CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81~~having at least one CDR of SEQ ID NOs: 1 - 66~~;

ii. TRX518; and

iii. TRX385.

6. The combination of the PD-1 antagonist and the GITR agonist ~~method~~ of claim 5, wherein the GITR agonist is an antibody comprising: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81; and the PD-1 antagonist is MK-3475~~having:~~

~~a) a heavy chain CDR1 of SEQ ID NOs: 1-11, CDR2 of SEQ ID NOs: 12-22, and CDR3 of SEQ ID NOs: 23-33; and/or~~

~~b) a light chain CDR1 of SEQ ID NOs: 34-44, CDR2 of SEQ ID NOs: 45-55, and CDR3 of SEQ ID NOs: 56-66~~.

7. The combination of the PD-1 antagonist and the GITR agonist ~~method~~ of claim 5, wherein the GITR agonist is an antibody comprising: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is N and amino acid 57 is N; and CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81; and the PD-1 antagonist is MK-3475~~having:~~

~~a) a variable heavy chain of SEQ ID NOs: 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, and 87; and/or~~

~~b) a variable light chain of SEQ ID NO: 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, and 88.~~.

8. The combination of the PD-1 antagonist and the GITR agonist ~~method~~ of claim 1, wherein the PD-1 antagonist and GITR agonist are to be administered concurrently at least one time.

9. The combination of the PD-1 antagonist and the GITR agonist ~~method~~ of claim 1, wherein the PD-1 antagonist and GITR agonist are to be administered concurrently at least 2 times.

10. The combination of the PD-1 antagonist and the GITR agonist ~~method~~ of claim 1, wherein the tumor is an advanced stage tumor.

11. The combination of the PD-1 antagonist and the GITR agonist ~~method~~ of claim 10, wherein the advanced stage tumor is selected from the group consisting of squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer, ~~such as~~ hepatic carcinoma, ~~and~~ hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma, ~~(such as~~ multiple myeloma~~)~~, salivary gland carcinoma, kidney cancer, ~~such as~~ renal cell carcinoma, ~~and~~ Wilms' tumors, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, and esophageal cancer.

12. A bispecific antibody or antigen binding fragment thereof for use in ~~method of~~ treating a tumor in a patient, wherein the ~~comprising administering to the patient a~~ bispecific antibody or antigen binding fragment thereof comprises, ~~comprising~~ a first arm that binds to PD-1 or PD-L1 and antagonizes PD-1 activity, and a second arm that binds to GITR and agonizes GITR activity.

13. The bispecific antibody or antigen binding fragment thereof ~~method~~ of claim 12, wherein

a. the first arm is selected from the group consisting of an antigen binding fragment from BMS-936558, MK-3475, and MPDL3280A~~; and~~

~~b. the second arm is selected from the group consisting of an antigen binding fragment from i. an antibody having at least one CDR of SEQ ID NO: 1 - 66 ; ii. TRX518; and iii. TRX385~~.

14. The bispecific antibody or antigen binding fragment thereof ~~method~~ of claim 13, wherein the second arm has:

a) a heavy chain comprising: CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81~~CDR1 of SEQ ID NOs: 1-11, CDR2 of SEQ ID NOs: 12-22, and CDR3 of SEQ ID NOs: 23-33~~; and~~/or~~

b) a light chain comprising: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is N and amino acid 57 is N~~CDR1 of SEQ ID NOs: 34-44, CDR2 of SEQ ID NOs: 45-55, and CDR3 of SEQ ID NOs: 56-66~~.

15. The bispecific antibody or antigen binding fragment thereof ~~method~~ of claim 13, wherein the second arm has:

a) a heavy chain comprising:

CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81;

and

b) a light chain comprising:

CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q

~~a) a variable heavy chain of SEQ ID NOs: 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, and 87; and/or~~

~~b) a variable light chain of SEQ ID NO: 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, and 88~~.

16. The bispecific antibody or antigen binding fragment thereof ~~method~~ of claim 12, wherein the tumor is an advanced stage tumor.

17. The bispecific antibody or antigen binding fragment thereof ~~method~~ of claim 16, wherein the advanced stage tumor is selected from the group consisting of squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer, ~~such as~~ hepatic carcinoma, ~~and~~ hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma, ~~(such as~~ multiple myeloma~~)~~, salivary gland carcinoma, kidney cancer, ~~such as~~ renal cell carcinoma, ~~and~~ Wilms' tumors, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, and esophageal cancer.

18. A pharmaceutical combination comprising a PD-1 antagonist and a GITR agonist, wherein:

a) the PD-1 antagonist is selected from the group consisting of BMS-936558, MK-3475, and MPDL3280A; and

b) the GITR agonist comprising: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and

CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81~~is selected from the group consisting of:~~

~~i. an antibody having at least one CDR of SEQ ID NOs: 1 - 66 ;~~

ii. TRX518; and

iii. TRX385.

19. Use of a PD-1 antagonist and a GITR agonist in the manufacture of a medicament for the treatment of a tumor in a patient, wherein the PD-1 antagonist and GITR agonist are for administration simultaneously or sequentially.

20. The use of claim 19, wherein

a. the PD-1 antagonist is an antibody or antigen binding fragment thereof, that binds PD-1 or PD-L1; and

b. the GITR agonist is an antibody or antigen binding fragment thereof, that binds GITR.

21. The use of claim 20 wherein

a. the PD-1 antagonist is an antibody or antigen binding fragment thereof that binds to human PD-1 or human PD-L1; and

b. the GITR agonist is an antibody or antigen binding fragment thereof that binds to human GITR.

22. The use of claim 21, wherein the antibody or binding fragment thereof is humanized or fully human.

23. The use of claim 20, wherein

a. the PD-1 antagonist is selected from the group consisting of BMS-936558, MK-3475, and MPDL3280A; and

b. the GITR agonist is selected from the group consisting of:

i. an antibody comprising: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82; and CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81;

ii. TRX518; and

iii. TRX385.

24. The use of claim 23, wherein the GITR agonist is an antibody comprising: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81; and the PD-1 antagonist is MK-3475.

25. The use of claim 23, wherein the GITR agonist is an antibody comprising: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is N and amino acid 57 is N; and CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81; and the PD-1 antagonist is MK-3475.

26. The use of claim 19, wherein the PD-1 antagonist and GITR agonist for administration concurrently at least one time.

27. The use of claim 19, wherein the PD-1 antagonist and GITR agonist are for administration concurrently at least 2 times.

28. The use of claim 19, wherein the tumor is an advanced stage tumor.

29. The use of claim 28, wherein the advanced stage tumor is selected from the group consisting of squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer, hepatic carcinoma, hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma, multiple myeloma, salivary gland carcinoma, kidney cancer, renal cell carcinoma, Wilms' tumors, basal cell carcinoma,

melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, and esophageal cancer.

~~19~~30. Use of a PD-1 antagonist and a GITR agonist in the manufacture of a medicament for the treatment of ~~to treat~~ an advanced stage tumor, wherein:

a) the PD-1 antagonist is selected from the group consisting of BMS-936558, MK-3475, and MPDL3280A; and

b) the GITR agonist is selected from the group consisting of:

i. an antibody comprising:

CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and

CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81~~having at least one CDR of SEQ ID NOs: 1 - 66~~;

ii. TRX518; and

iii. TRX385.