

on the surface of cancer cells, and which can thereby mediate T-cell activation, simulation of an immune response and killing of cancer cells that express B7-H3. It is an object of this invention to identify such compositions and treatment regimens.

Summary:

[0021] The present disclosure is directed to combination therapy involving the administration of a first molecule that specifically binds to human B7-H3 (*i.e.*, a B7-H3-binding molecule) and a second molecule that specifically binds to human PD-1 (*i.e.*, a PD-1-binding molecule) to a subject for the treatment of cancer and inflammation. The disclosure also concerns pharmaceutical compositions that comprise a first molecule that specifically binds to human B7-H3 and a second molecule that specifically binds to human PD-1 that are capable of mediating, and more preferably enhancing, the activation of the immune system against cancer cells that are associated with a variety of human cancers. The disclosure also relates to the use of such pharmaceutical compositions to treat cancer and other diseases.

[0021a] In one aspect, there is provided use of (a) a molecule that specifically binds to B7-H3 in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the medicament is to be administered with (b) a molecule that specifically binds to PD-1.

[0022] The disclosure also provides a method of treating a cancer comprising administering to a subject in need thereof, a molecule that specifically binds to B7-H3, and a molecule that specifically binds to PD-1.

[0023] The disclosure particularly concerns embodiments of such uses and methods, wherein the molecule that specifically binds to B7-H3 is an anti-B7-H3 antibody or antigen-binding fragment thereof, and the molecule that specifically binds to PD-1 is an anti-PD-1 antibody, or an antigen-binding fragment thereof.

[0024] The disclosure particularly concerns the embodiment of such uses and methods wherein the anti-B7-H3 antibody, or antigen-binding fragment thereof:

- (a) competes for B7-H3 binding with BRCA84D, BRCA69D, PRCA157, or with an anti-B7-H3 antibody selected from **Table 5**; or
- (b) has the three heavy chain CDRs and the three light chain CDRs of BRCA84D, hBRCA84D (1.1), hBRCA84D (2.2), hBRCA84D-2, hBRCA69D (1.1), hBRCA (2.2), or the three heavy chain CDRs and the three light chain CDRs of an anti-B7-H3 selected from **Table 5**; or
- (c) has the heavy chain variable domain and the light chain variable domain of BRCA84D, hBRCA84D (1.1), hBRCA84D (2.2), hBRCA84D-2, hBRCA69D (1.1), hBRCA (2.2), or the heavy chain variable domain

and the light chain variable domain of an anti-B7-H3 selected from **Table 5**.

[0025] The disclosure particularly concerns the embodiment of such uses and methods wherein the anti-PD-1 antibody, or antigen-binding fragment thereof:

- (a) competes for PD-1 binding with nivolumab, pembrolizumab, pidilizumab, PD-1 mAb 3, PD-1 mAb 5, PD-1 mAb 6, PD-1 mAb7, PD-1 mAb 8, or with an anti-PD-1 antibody selected from **Table 6**; or
- (b) has the three heavy chain CDRs and the three light chain CDRs of nivolumab, pembrolizumab, pidilizumab, PD-1 mAb 3, PD-1 mAb 5, PD-1 mAb 6, PD-1 mAb7, PD-1 mAb 8, or the three heavy chain CDRs and the three light chain CDRs of an anti-PD-1 antibody selected from **Table 6**; or
- (c) has the heavy chain variable domain and the light chain variable domain of nivolumab, pembrolizumab, pidilizumab, PD-1 mAb 3, PD-1 mAb 5, PD-1 mAb 6, PD-1 mAb7, PD-1 mAb 8, or the heavy chain variable domain and the light chain variable domain of an anti-PD-1 antibody selected from **Table 6**.

[0026] The disclosure further concerns embodiments of such uses and methods wherein the anti-B7-H3 antibody, or antigen-binding fragment thereof, comprises an Fc Domain, and/or the anti-PD-1 antibody, or antigen-binding fragment thereof, comprises an Fc Domain. The disclosure further concerns the embodiments of such uses and methods wherein the anti-B7-H3 antibody or antigen-binding fragment thereof, comprises a variant Fc Domain having one, two, three, four, five or more modifications in the Fc Domain that enhances ADCC. The disclosure further concerns the embodiments of such uses and methods wherein the Fc Domain modifications that enhance(s) ADCC comprise any one, any two, any three, any four, or all five of the substitutions L235V, F243L, R292P, Y300L and P396L. The disclosure further concerns the embodiments of such uses and methods wherein the anti-PD-1 antibody or antigen-binding fragment thereof, comprises: (a) a variant Fc Domain having at least one modification in the Fc Domain that reduces or abolishes ADCC activity; or (b) an IgG4 Fc Domain. The disclosure further concerns the embodiments of such uses and methods wherein the Fc Domain modifications that reduce or abolish ADCC comprise the substitution of L234A; L235A; or L234A and L235A, preferably of an IgG1 Fc Domain.

[0027] The disclosure further concerns embodiments of such uses and methods, wherein the anti-B7-H3 antibody is hBRCA84D-2 and the anti-PD-1 antibody is nivolumab, pembrolizumab, pidilizumab, or PD-1 mAb 6-ISQ. The disclosure further concerns embodiments of such uses and methods, wherein the anti-B7-H3 antibody is hBRCA84D-2 and the anti-PD-1 antibody, or antigen-binding fragment thereof comprises the VH and VL of nivolumab, pembrolizumab, pidilizumab, PD-1 mAb 3, PD-1 mAb 5, PD-1 mAb 6, PD-1 mAb 7, PD-1 mAb 8, or an anti-PD-1 antibody selected from **Table 6**.

[0028] The disclosure additionally concerns embodiments of such uses and methods wherein the molecule that specifically binds to B7-H3 (particularly an anti-B7-H3 antibody) is administered at a dosage of 1-15 mg/kg body weight every week and the molecule that specifically binds to PD-1 (particularly an anti-PD-1 antibody) is administered at a fixed dosage of 200 mg every three weeks. The disclosure also concerns embodiments of such uses and methods wherein the molecule that specifically binds to B7-H3 (particularly an anti-B7-H3 antibody) is administered at a dosage of 1-15 mg/kg body weight every week and the molecule that specifically binds to PD-1 (particularly an anti-PD-1 antibody) is administered at a dosage of 1-10 mg/kg body weight every two or three weeks. The disclosure further concerns embodiments of such uses and methods wherein the molecule that specifically binds to B7-H3 (particularly an anti-B7-H3 antibody) is administered at a dosage of selected from 1 mg/kg, 3 mg/kg, 10 mg/kg and 15 mg/kg body weight every week and the molecule that specifically binds to PD-1 (particularly an anti-PD-1 antibody) is administered at a fixed dosage of 200 mg every three weeks. The disclosure further concerns embodiments of such uses and methods wherein the molecule that specifically binds to B7-H3 (particularly an anti-B7-H3 antibody) is administered at a dosage of selected from 1 mg/kg, 3 mg/kg, 10 mg/kg and 15 mg/kg body weight every week and the molecule that specifically binds to PD-1 (particularly an anti-PD-1 antibody) is administered at a dosage of selected from 1 mg/kg, 2 mg/kg, 3 mg/kg and 10 mg/kg body weight every two or three weeks. The disclosure particularly concerns embodiments of such uses and methods wherein the molecule that specifically binds to B7-H3 (particularly an anti-B7-H3 antibody) is administered at a dosage of selected from 3 mg/kg, 10 mg/kg and 15 mg/kg body weight every week and the molecule that specifically binds to PD-1 (particularly an anti-PD-1 antibody) is administered at a dosage of 2 mg/kg body weight every three weeks. The disclosure particularly concerns embodiments of such uses and methods wherein the molecule that specifically binds to B7-H3 (particularly an anti-B7-H3 antibody) is administered at a dosage of selected from 3 mg/kg, 10 mg/kg and 15 mg/kg body weight every week and the molecule that specifically binds to PD-1 (particularly an anti-

PD-1 antibody) is administered at a dosage of 3 mg/kg body weight every two weeks. The disclosure further concerns embodiments of such uses and methods wherein the molecule that specifically binds to B7-H3 (particularly an anti-B7-H3 antibody) and the molecule that specifically binds to PD-1 (particularly an anti-PD-1 antibody) are administered by IV infusion. The disclosure also concerns embodiments of such uses and methods wherein every two or three weeks the molecule that specifically binds to B7-H3 (particularly an anti-B7-H3 antibody) and the molecule that specifically binds to PD-1 (particularly an anti-PD-1 antibody) are administered with a 48-hour period.

[0029] The disclosure particularly concerns embodiments of such uses and methods wherein the cancer is a cancer in which B7-H3 is expressed. The disclosure further concerns embodiments of such uses and methods wherein the cancer is a squamous cell cancer of the head and neck (SCCHN), a bladder cancer, a breast cancer, a colorectal cancer, a gastric cancer, a glioblastoma, a kidney cancer, a lung cancer, a melanoma, an ovarian cancer, a pancreatic cancer, a pharyngeal cancer, a prostate cancer, a renal cell carcinoma, a small round blue cell tumor, a neuroblastoma, or a rhabdomyosarcoma, in which B7-H3 is expressed.

[0030] The disclosure additionally concerns embodiments of such uses and methods further comprising the step of administering a third therapeutic agent, particularly wherein the third therapeutic agent is an anti-angiogenic agent, an anti-neoplastic agent, a chemotherapeutic agent, or a cytotoxic agent

Detailed Description of the Invention:

[0031] The present invention is directed to a combination therapy involving the administration of a first molecule that specifically binds to human B7-H3 and a second molecule that specifically binds to human PD-1 to a subject for the treatment of cancer and/or inflammation. The invention also concerns pharmaceutical compositions that comprise a first molecule that specifically binds to human B7-H3 and a second molecule that specifically binds to human PD-1 that are capable of mediating, and more preferably enhancing, the activation of the immune system against cancer cells that are associated with any of a variety of human cancers. The invention also relates to the use of such pharmaceutical compositions to treat cancer and other diseases in recipient subjects.

What Is Claimed Is:

- Claim 1. Use of (a) a molecule that specifically binds to B7-H3 in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the medicament is to be administered with (b) a molecule that specifically binds to PD-1.
- Claim 2. The use of claim 1, wherein said molecule that specifically binds to B7-H3 is an anti-B7-H3 antibody or antigen-binding fragment thereof, and said molecule that specifically binds to PD-1 is an anti-PD-1 antibody, or an antigen-binding fragment thereof.
- Claim 3. The use of claim 2, wherein said anti-B7-H3 antibody, or antigen-binding fragment thereof:
- (a) competes for B7-H3 binding with BRCA84D, BRCA69D, PRCA157, or with an anti-B7-H3 antibody selected from **Table 5**; or
 - (b) has the three heavy chain CDRs and the three light chain CDRs of BRCA84D, hBRCA84D (1.1), hBRCA84D (2.2), hBRCA84D-2, hBRCA69D (1.1), hBRCA (2.2), or the three heavy chain CDRs and the three light chain CDRs of an anti-B7-H3 antibody selected from **Table 5**; or
 - (c) has the heavy chain variable domain and the light chain variable domain of BRCA84D, hBRCA84D (1.1), hBRCA84D (2.2), hBRCA84D-2, hBRCA69D (1.1), hBRCA (2.2), or the heavy chain variable domain and the light chain variable domain of an anti-B7-H3 antibody selected from **Table 5**.
- Claim 4. The use of any one of claims 2-3, wherein said anti-PD-1 antibody, or antigen-binding fragment thereof:
- (a) competes for PD-1 binding with nivolumab, pembrolizumab, pidilizumab, PD-1 mAb 3, PD-1 mAb 5, PD-1 mAb 6, PD-1 mAb7, PD-1 mAb 8, or with an anti-PD-1 antibody selected from Table 6; or
 - (b) has the three heavy chain CDRs and the three light chain CDRs of nivolumab, pembrolizumab, pidilizumab, PD-1 mAb 3, PD-1 mAb 5, PD-1 mAb 6, PD-1 mAb7, PD-1 mAb 8, or the three heavy chain CDRs

and the three light chain CDRs of an anti-PD-1 antibody selected from Table 6; or

- (c) has the heavy chain variable domain and the light chain variable domain of nivolumab, pembrolizumab, pidilizumab, PD-1 mAb 3, PD-1 mAb 5, PD-1 mAb 6, PD-1 mAb7, PD-1 mAb 8, or the heavy chain variable domain and the light chain variable domain of an anti-PD-1 antibody selected from Table 6.

Claim 5. The use of any one of claims 2-4, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof comprises an Fc Domain, and said anti-PD-1 antibody or antigen-binding fragment thereof comprises an Fc Domain.

Claim 6. The use of claim 5, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof, comprises a variant Fc Domain having at least one modification in the Fc Domain that enhances ADCC.

Claim 7. The use of claim 5 or 6, wherein said anti-PD-1 antibody or antigen-binding fragment thereof, comprises:

- (a) a variant Fc Domain having at least one modification in the Fc Domain that reduces or abolishes ADCC activity; or
- (b) an IgG4 Fc Domain.

Claim 8. The use of any one of claims 2-7, wherein said anti-B7-H3 antibody is hBRCA84D-2 and said anti-PD-1 antibody is nivolumab, pembrolizumab, pidilizumab, or PD-1 mAb 6-ISQ.

Claim 9. The use of any one of claims 2-8, wherein said anti-B7-H3 antibody is to be administered at a dosage of 1-15 mg/kg body weight every week, and said anti-PD-1 antibody is to be administered at a fixed dosage of 200 mg or at a dosage of 1-10 mg/kg body weight every two or three weeks.

Claim 10. The use of claim 9, wherein said anti-B7-H3 antibody is to be administered at a dosage of 1 mg/kg body weight, 3 mg/kg body weight, 10 mg/kg body weight or 15 mg/kg body weight every week.

- Claim 11. The use of claim 9 or 10, wherein said anti-B7-H3 antibody is to be administered at a dosage of 1 mg/kg body weight, 3 mg/kg body weight, 10 mg/kg body weight or 15 mg/kg body weight every week, and said anti-PD-1 antibody is to be administered at a dosage of 1 mg/kg body weight, 2 mg/kg body weight, 3 mg/kg body weight, or 10 mg/kg body weight every two or three weeks.
- Claim 12. The use of claim 10 or 11, wherein said anti-B7-H3 antibody is to be administered at a dosage of 3 mg/kg body weight, 10 mg/kg body weight, or 15 mg/kg body weight every week, and said anti-PD-1 antibody is to be administered at a dosage of 2 mg/kg body weight every three weeks.
- Claim 13. The use of claim 10 or 11, wherein said anti-B7-H3 antibody is to be administered at a dosage of 3 mg/kg body weight, 10 mg/kg body weight, or 15 mg/kg body weight every week, and said anti-PD-1 antibody is to be administered at a dosage of 3 mg/kg body weight every two weeks.
- Claim 14. The use of claim 10 or 11, wherein said anti-B7-H3 antibody is to be administered at a dosage of 3 mg/kg body weight, 10 mg/kg body weight, or 15 mg/kg body weight every week, and said anti-PD-1 antibody is to be administered at a dosage of 10 mg/kg body weight every two weeks.
- Claim 15. The use of any one of claims 1-11, wherein the anti-PD-1 antibody is to be administered every two weeks.
- Claim 16. The use of any one of claims 1-11, wherein the anti-PD-1 antibody is to be administered every three weeks.
- Claim 17. The use of any one of claims 2-16, wherein the anti-B7-H3 antibody and the anti-PD-1 antibody are to be administered by IV infusion.
- Claim 18. The use of any one of claims 1-12, 16 and 17, wherein every three weeks said anti-B7-H3 antibody and said anti-PD-1 antibody are to be administered within a 48-hour period.
- Claim 19. The use of any one of claims 2-11, 13-15 or 17, wherein every two weeks said anti-B7-H3 antibody and said anti-PD-1 antibody are to be administered within a 48-hour period.

- Claim 20. The use of any one of claims 1 to 19, wherein said cancer is a B7-H3-expressing cancer.
- Claim 21. The use of claim 20, wherein said B7-H3-expressing cancer is a squamous cell cancer of the head and neck (SCCHN), a bladder cancer, a breast cancer, a colorectal cancer, a gastric cancer, a glioblastoma, a kidney cancer, a lung cancer, a melanoma, an ovarian cancer, a pancreatic cancer, a pharyngeal cancer, a prostate cancer, a renal cell carcinoma, a small round blue cell tumor, a neuroblastoma, or a rhabdomyosarcoma, in which B7-H3 is expressed.
- Claim 22. The use of any one of claims 1 to 21, wherein said medicament is to be administered with a third therapeutic agent, wherein said third therapeutic agent is selected from the group consisting of an anti-angiogenic agent, an anti-neoplastic agent, a chemotherapeutic agent, and a cytotoxic agent.
- Claim 23. The use of any one of claims 2-22, wherein said anti-B7-H3 antibody is hBRCA84D-2.
- Claim 24. The use of any one of claims 2-23, wherein said anti-PD-1 antibody is pembrolizumab.
- Claim 25. The use of any one of claims 2-23, wherein said anti-PD-1 antibody is nivolumab.
- Claim 26. The use of any one of claims 2-23, wherein said anti-PD-1 antibody is pidilizumab.
- Claim 27. The use of any one of claims 2-23, wherein said anti-PD-1 antibody comprises the VH Domain and the VL Domain of PD-1 mAb 3.
- Claim 28. The use of any one of claims 2-23, wherein said anti-PD-1 antibody comprises the VH Domain and the VL Domain of PD-1 mAb 5.
- Claim 29. The use of any one of claims 2-23, wherein said anti-PD-1 antibody comprises the VH Domain and the VL Domain of PD-1 mAb 6.
- Claim 30. The use of claim 29, wherein said anti-PD-1 antibody is mAb 6 ISQ.

- Claim 31. The use of any one of claims 2-23, wherein said anti-PD-1 antibody comprises the VH and VL of PD-1 mAb 7.
- Claim 32. The use of any one of claims 2-23, wherein said anti-PD-1 antibody comprises the VH Domain and the VL Domain of PD-1 mAb 8.
- Claim 33. The use of any one of claims 2-23, wherein said anti-PD-1 antibody is selected from **Table 6**.