

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 humanized anti-B7-H3 antibody or antigen-binding fragment thereof that specifically binds to B7-H3 expressed on the surface of a cancer cell in combination with an anti-PD-1 antibody, or an antigen-binding fragment thereof that specifically binds to PD-1 expressed on the surfaces of activated T-cells, B-cells, or monocytes in the manufacture of a medicament for treating a B7-H3-expressing cancer in a subject in need thereof, wherein said medicament comprises a pharmaceutical composition that comprises said humanized anti-B7-H3 antibody, or said antigen-binding fragment thereof, and a separate pharmaceutical composition that comprises said anti-PD-1 antibody, or said antigen-binding fragment thereof; wherein:

- (i) said humanized anti-B7-H3 antibody, and said antigen-binding fragment thereof, of said medicament comprises:
 - (1) a humanized light chain variable (VL) domain that comprises the amino acid sequences of the three complementarity determining regions (CDRs) of the light chain variable domain of anti-B7-H3 antibody BRCA84D:
 - CDR_{L1}: residues 24-34 of **SEQ ID NO:19**;
 - CDR_{L2}: residues 50-56 of **SEQ ID NO:19**; and
 - CDR_{L3}: residues 89-97 of **SEQ ID NO:19**; and

- (2) a humanized heavy chain variable (VH) domain that comprises the amino acid sequences of the three CDRs of the heavy chain variable domain of anti-B7-H3 antibody BRCA84D:
 - CDR_{H1}: residues 31-35 of **SEQ ID NO:20**;
 - CDR_{H2}: residues 50-66 of **SEQ ID NO:20**; and
 - CDR_{H3}: residues 99-111 of **SEQ ID NO:20**; and
- (ii) said anti-PD-1 antibody, and said antigen-binding fragment thereof, of said medicament comprises:
 - (a)
 - (1) a VL domain that comprises the three CDRs of the VL domain of anti-PD-1 antibody nivolumab:
 - CDR_{L1}: residues 24-34 of **SEQ ID NO:43**;
 - CDR_{L2}: residues 50-56 of **SEQ ID NO:43**; and
 - CDR_{L3}: residues 89-97 of **SEQ ID NO:43**; and
 - (2) a VH domain that comprises the three CDRs of the VH domain of anti-PD-1 antibody nivolumab:
 - CDR_{H1}: residues 31-35 of **SEQ ID NO:42**;
 - CDR_{H2}: residues 50-66 of **SEQ ID NO:42**; and
 - CDR_{H3}: residues 99-102 of **SEQ ID NO:42**;
 - or
 - (b)
 - (1) a VL domain that comprises the three CDRs of the VL domain of anti-PD-1 antibody pembrolizumab:
 - CDR_{L1}: residues 24-38 of **SEQ ID NO:45**;
 - CDR_{L2}: residues 54-60 of **SEQ ID NO:45**; and
 - CDR_{L3}: residues 93-101 of **SEQ ID NO:45**; and
 - (2) a VH domain that comprises the three CDRs of the VH domain of anti-PD-1 antibody pembrolizumab:
 - CDR_{H1}: residues 31-35 of **SEQ ID NO:44**;
 - CDR_{H2}: residues 50-66 of **SEQ ID NO:44**; and
 - CDR_{H3}: residues 99-109 of **SEQ ID NO:44**;
 - or
 - (c)
 - (1) a light chain domain that comprises the three CDRs of the light chain of anti-PD-1 antibody PD-1 mAb 6-ISQ:
 - CDR_{L1}: residues 24-38 of **SEQ ID NO:58**;
 - CDR_{L2}: residues 54-60 of **SEQ ID NO:58**; and
 - CDR_{L3}: residues 93-101 of **SEQ ID NO:58**; and
 wherein X₁ is S and X₂ is Q; and
 - (2) a heavy chain domain that comprises the VH Domain of PD-1 mAb 6 (**SEQ ID NO:52**), wherein X is I; and
- (iii)
 - (a) said humanized anti-B7-H3 antibody, or said antigen-binding fragment thereof, is to be administered weekly at a dosage of 1-15 mg/kg body weight; and
 - (b) said anti-PD-1 antibody, or said antigen-binding fragment thereof, is to be administered at:

- (1) a fixed dosage of between 50 mg and 500 mg every two or three weeks; or
- (2) a dosage of 1-10 mg/kg body weight every two or three weeks;

wherein said pharmaceutical composition that comprises said humanized anti-B7-H3 antibody, or said antigen-binding fragment thereof, and said separate pharmaceutical composition that comprises said anti-PD-1 antibody, or said antigen-binding fragment thereof are adapted to be administered concurrently or sequentially.

[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 examples 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 example 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

What Is Claimed Is:

Claim 1. Use of a humanized anti-B7-H3 antibody or antigen-binding fragment thereof that specifically binds to B7-H3 expressed on the surface of a cancer cell in combination with an anti-PD-1 antibody, or an antigen-binding fragment thereof that specifically binds to PD-1 expressed on the surfaces of activated T-cells, B-cells, or monocytes in the manufacture of a medicament for treating a B7-H3-expressing cancer in a subject in need thereof, wherein said medicament comprises a pharmaceutical composition that comprises said humanized anti-B7-H3 antibody, or said antigen-binding fragment thereof, and a separate pharmaceutical composition that comprises said anti-PD-1 antibody, or said antigen-binding fragment thereof; wherein:

(i) said humanized anti-B7-H3 antibody, and said antigen-binding fragment thereof, of said medicament comprises:

(1) a humanized light chain variable (VL) domain that comprises the amino acid sequences of the three complementarity determining regions (CDRs) of the light chain variable domain of anti-B7-H3 antibody BRCA84D:

CDR_{L1}: residues 24-34 of **SEQ ID NO:19**;

CDR_{L2}: residues 50-56 of **SEQ ID NO:19**; and

CDR_{L3}: residues 89-97 of **SEQ ID NO:19**; and

(2) a humanized heavy chain variable (VH) domain that comprises the amino acid sequences of the three CDRs of the heavy chain variable domain of anti-B7-H3 antibody BRCA84D:

CDR_{H1}: residues 31-35 of **SEQ ID NO:20**;

CDR_{H2}: residues 50-66 of **SEQ ID NO:20**; and

CDR_{H3}: residues 99-111 of **SEQ ID NO:20**; and

(ii) said anti-PD-1 antibody, and said antigen-binding fragment thereof, of said medicament comprises:

(a) (1) a VL domain that comprises the three CDRs of the VL domain of anti-PD-1 antibody nivolumab:

CDR_{L1}: residues 24-34 of **SEQ ID NO:43**;

CDR_{L2}: residues 50-56 of **SEQ ID NO:43**; and

CDR_L3: residues 89-97 of **SEQ ID NO:43**; and

- (2) a VH domain that comprises the three CDRs of the VH domain of anti-PD-1 antibody nivolumab:

CDR_H1: residues 31-35 of **SEQ ID NO:42**;

CDR_H2: residues 50-66 of **SEQ ID NO:42**; and

CDR_H3: residues 99-102 of **SEQ ID NO:42**;

or

- (b) (1) a VL domain that comprises the three CDRs of the VL domain of anti-PD-1 antibody pembrolizumab:

CDR_L1: residues 24-38 of **SEQ ID NO:45**;

CDR_L2: residues 54-60 of **SEQ ID NO:45**; and

CDR_L3: residues 93-101 of **SEQ ID NO:45**; and

- (2) a VH domain that comprises the three CDRs of the VH domain of anti-PD-1 antibody pembrolizumab:

CDR_H1: residues 31-35 of **SEQ ID NO:44**;

CDR_H2: residues 50-66 of **SEQ ID NO:44**; and

CDR_H3: residues 99-109 of **SEQ ID NO:44**;

or

- (c) (1) a light chain domain that comprises the three CDRs of the light chain of anti-PD-1 antibody PD-1 mAb 6-ISQ:

CDR_L1: residues 24-38 of **SEQ ID NO:58**;

CDR_L2: residues 54-60 of **SEQ ID NO:58**; and

CDR_L3: residues 93-101 of **SEQ ID NO:58**; and

wherein X₁ is S and X₂ is Q; and

- (2) a heavy chain domain that comprises the VH Domain of PD-1 mAb 6 (**SEQ ID NO:52**), wherein X is I; and

- (iii) (a) said humanized anti-B7-H3 antibody, or said antigen-binding fragment thereof, is to be administered weekly at a dosage of 1-15 mg/kg body weight; and

- (b) said anti-PD-1 antibody, or said antigen-binding fragment thereof, is to be administered at:

- (1) a fixed dosage of between 50 mg and 500 mg every two or three weeks; or

- (2) a dosage of 1-10 mg/kg body weight every two or three weeks;

wherein said pharmaceutical composition that comprises said humanized anti-B7-H3 antibody, or said antigen-binding fragment thereof, and said separate pharmaceutical composition that comprises said anti-PD-1 antibody, or said antigen-binding fragment thereof are adapted to be administered concurrently or sequentially.

Claim 2. The use of claim 1, wherein said anti-B7-H3 antibody, or antigen-binding fragment thereof comprises a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 28, 29 and 30, and a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 21, 22, 23, 24, 25 and 26.

Claim 3. The use of any one of claims 1-2, wherein said anti-PD-1 antibody, or antigen-binding fragment thereof comprises:

- (a) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:42, and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:43;
- (b) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:44, and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:45; or
- (c) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:52, and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:53.

Claim 4. The use of any one of claims 1-3, 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 5. The use of claim 4, 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 6. The use of claim 5, wherein said variant Fc Domain of said anti-B7-H3 antibody or antigen-binding fragment thereof comprises any one, any two, any three, any four, or all five of the substitutions L235V, F243L, R292P, Y300L, and P396L, wherein the numbering is according to the Kabat numbering scheme.
- Claim 7. The use of any one of claims 5-6, wherein said variant Fc Domain of said anti-B7-H3 antibody or antigen-binding fragment thereof comprises:
- (A) at least one substitution selected from the group consisting of F243L, R292P, Y300L, V305I, and P396L;
 - (B) at least two substitutions selected from the group consisting of:
 - (1) F243L and P396L;
 - (2) F243L and R292P; and
 - (3) R292P and V305I;
 - (C) at least three substitutions selected from the group consisting of:
 - (1) F243L, R292P and Y300L;
 - (2) F243L, R292P and V305I;
 - (3) F243L, R292P and P396L; and
 - (4) R292P, V305I and P396L;
 - (D) at least four substitutions selected from the group consisting of:
 - (1) F243L, R292P, Y300L and P396L; and
 - (2) F243L, R292P, V305I and P396L; or
 - (E) at least the five substitutions selected from the group consisting of:
 - (1) F243L, R292P, Y300L, V305I and P396L; and
 - (2) L235V, F243L, R292P, Y300L and P396L;
- wherein the numbering is according to the Kabat numbering scheme.
- Claim 8. The use of any one of claims 4-7, 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 9. The use of claim 8, wherein said variant Fc Domain of said anti-PD-1 antibody or antigen-binding fragment thereof comprises any one, any two, any

three, any four, or all five of the substitutions L234A, L235A, D265A, N297A, N297Q;

wherein the numbering is according to the Kabat numbering scheme.

Claim 10. The use of any one of claims 8-9, wherein said variant Fc Domain of said anti-PD-1 antibody or antigen-binding fragment thereof comprises the substitution:

(A) L234A, L235A;

(B) D265A;

(C) N297A; or

(D) N297Q;

wherein the numbering is according to the Kabat numbering scheme.

Claim 11. The use of any one of claims 1-10, wherein said anti-PD-1 antibody or antigen-binding fragment thereof is to be administered at a fixed dosage of between 50 mg and 500 mg every two or three weeks.

Claim 12. The use of claim 11, wherein said anti-PD-1 antibody or antigen-binding fragment thereof is to be administered at a fixed dosage of 300 mg every two or three weeks.

Claim 13. The use of claim 11, wherein said anti-PD-1 antibody or antigen-binding fragment thereof is to be administered at a fixed dosage of 200 mg every two or three weeks.

Claim 14. The use of any one of claims 1-10, wherein said anti-PD-1 antibody or antigen-binding fragment thereof is to be administered at a dosage of 1-10 mg/kg body weight every two or three weeks.

Claim 15. The use of any one of claims 1-14, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof 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.

Claim 16. The use of claim 15, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof is to be administered at a dosage of 15 mg/kg body weight.

- Claim 17. The use of claim 14, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof 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, and said anti-PD-1 antibody or antigen-binding fragment thereof is to be administered at a dosage of 1 mg/kg body weight, 2 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight, 6 mg/kg body weight, or 10 mg/kg body weight.
- Claim 18. The use of claim 17, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof is to be administered at a dosage of 3 mg/kg body weight, 10 mg/kg body weight, or 15 mg/kg body weight, and said anti-PD-1 antibody or antigen-binding fragment thereof is to be administered at a dosage of 5 mg/kg body weight.
- Claim 19. The use of claim 17, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof is to be administered at a dosage of 3 mg/kg body weight, 10 mg/kg body weight, or 15 mg/kg body weight, and said anti-PD-1 antibody or antigen-binding fragment thereof is to be administered at a dosage of 6 mg/kg body weight.
- Claim 20. The use of claim 17, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof is to be administered at a dosage of 3 mg/kg body weight, 10 mg/kg body weight, or 15 mg/kg body weight, and said anti-PD-1 antibody or antigen-binding fragment thereof is to be administered at a dosage of 10 mg/kg body weight.
- Claim 21. The use of any one of claims 1-20, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof is to be administered every week.
- Claim 22. The use of any one of claims 1-20, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof is to be administered every three weeks.
- Claim 23. The use of any one of claims 1-22, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is to be administered every two weeks.

- Claim 24. The use of any one of claims 1-22, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is to be administered every three weeks.
- Claim 25. The use of any one of claims 1-10, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof is to be administered at a dosage of 15 mg/kg body weight every three weeks, and said anti-PD-1 antibody or antigen-binding fragment thereof is to be administered at a fixed dosage of between 50 mg and 500 mg every three weeks.
- Claim 26. The use of claim 25, wherein said anti-PD-1 antibody or antigen-binding fragment thereof is to be administered at a fixed dosage of 300 mg every three weeks.
- Claim 27. The use of claim 25, wherein said anti-PD-1 antibody or antigen-binding fragment thereof is to be administered at a fixed dosage of 200 mg every three weeks.
- Claim 28. The use of any one of claims 1-10, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof is to be administered at a dosage of 15 mg/kg body weight every three weeks and said anti-PD-1 antibody or antigen-binding fragment thereof is to be administered at a dosage of 5 mg/kg body weight every three weeks.
- Claim 29. The use of any one of claims 1-28, wherein the anti-B7-H3 antibody or antigen-binding fragment thereof and the anti-PD-1 antibody or antigen-binding fragment thereof are to be administered by IV infusion.
- Claim 30. The use of any one of claims 1-20, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof and said anti-PD-1 antibody or antigen-binding fragment thereof are to be administered every three weeks and within a 48-hour period of each other.
- Claim 31. The use of any one of claims 1-20, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof and said anti-PD-1 antibody or antigen-binding fragment thereof are to be administered every two weeks and within a 48-hour period of each other.

- Claim 32. The use of any one of claims 1-31, wherein said B7-H3-expressing cancer is selected from the group consisting of: 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, and a rhabdomyosarcoma.
- Claim 33. The use of claim 32, wherein said B7-H3-expressing cancer is a squamous cell cancer of the head and neck (SCCHN).
- Claim 34. The use of any one of claims 1-33, wherein said anti-B7-H3 antibody or antigen-binding fragment thereof and said anti-PD-1 antibody or antigen-binding fragment thereof are to be administered in further combination with a third therapeutic agent selected from the group consisting of an anti-angiogenic agent, an anti-neoplastic agent, a chemotherapeutic agent, and a cytotoxic agent.
- Claim 35. The use of any one of claims 1-34, wherein said anti-B7-H3 antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:39, and a heavy chain comprising the amino acid sequence of SEQ ID NO:40.
- Claim 36. The use of any one of claims 1-35, wherein said anti-PD-1 antibody is pembrolizumab.
- Claim 37. The use of any one of claims 1-35, wherein said anti-PD-1 antibody is nivolumab.
- Claim 38. The use of any one of claims 1-35, wherein said anti-PD-1 antibody is pidilizumab.
- Claim 39. The use of any one of claims 1-35, wherein said anti-PD-1 antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:42 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:43.

- Claim 40. The use of any one of claims 1-35, wherein said anti-PD-1 antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:44 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:45.
- Claim 41. The use of any one of claims 1-35, wherein said anti-PD-1 antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:52 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:53.