SIRPα on macrophages. The pro-phagocytic "eat me" signal can be provided to the same macrophages by binding to their activating Fc gamma receptors. For example, the pro-phagocytic "eat me" signal can be provided by binding of anti-tumor antibodies to Fc receptors on macrophages.

[0007] All references cited herein, including patent applications, patent publications, and UniProtKB/Swiss-Prot Accession numbers are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

BRIEF SUMMARY

[0007a] In a first aspect of the present disclosure, there is provided a use of a polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant in the manufacture of a medicament for treating cancer in an individual;

wherein the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 85;

wherein the Fc domain variant is

(i) a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations, wherein numbering is according to the EU index of Kabat;

(ii) a human IgG2 Fc region comprising A330S, P331S, and N297A mutations, wherein numbering is according to the EU index of Kabat;

(iii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, and delG236 mutations, wherein numbering is according to the EU index of Kabat; or

(iv) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, delG236, and N297A mutations, wherein numbering is according to the EU index of Kabat;

wherein the medicament is to be administered to the individual in combination with (a) an anti-HER2 antibody, (b) an anti-VEGFR2 antibody, and (c) paclitaxel;

wherein the cancer is gastric cancer or gastroesophageal junction (GEJ) cancer, and

wherein the individual has received at least one prior therapy for the gastric or the GEJ cancer.

[0008] In some examples, provided is a method of treating cancer in an individual, comprising administering to the individual an effective amount of: (a) a polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant, (b) an anti-HER2 antibody, (c) an anti-VEGF2 antibody, and (d) paclitaxel; wherein the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 85; wherein the Fc domain variant is (i) a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations, wherein numbering is according to the EU index of Kabat; (ii) a human IgG2 Fc region comprising A330S, P331S, and N297A mutations, wherein numbering is according to the EU index of Kabat; (iii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, and delG236 mutations, wherein numbering is according to the EU index of Kabat; or (iv) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, delG236, and N297A mutations, wherein numbering is according to the EU index of Kabat, wherein the cancer is gastric cancer or gastroesophageal junction (GEJ) cancer, and wherein the individual has received at least one prior therapy for the gastric or the GEJ cancer. In some examples, the gastric cancer or GEJ cancer is a HER2-overexpressing (*e.g.*, $HER2^+$) gastric cancer or a HER2-overexpressing GEJ cancer. In some examples, the individual has received prior therapy with an anti-HER2 antibody, with an anti-HER2 antibody and a fluoropyrimidine, with an anti HER2 antibody and a platinum-based chemotherapy agent, or with a platinum-based chemotherapy agent. In some examples, individual has progressed during or after a treatment with an anti-HER2 antibody, an anti-HER2 antibody and a fluoropyrimidine, an anti HER2 antibody and a platinum-based chemotherapy agent, or a platinum-based chemotherapy agent. In some examples, the anti-

HER2 antibody is trastuzumab. In some examples, the anti-VEGF antibody is ramucirumab. In some examples, the polypeptide comprising the SIRPα D1 domain variant and the Fc domain variant is administered at a dose between about 10 to about 60 mg/kg once a week (qw), such as 10 mg/kg, 15 mg/kg, or 30 mg/kg once a week. In some examples, the polypeptide comprising the SIRPα D1 domain variant and the Fc domain variant is administered at a dose of 10 mg/kg, 15 mg/kg, or 30 mg/kg once every two weeks. In some examples, the trastuzumab is administered at an initial dose of 8 mg/kg followed by 6 mg/kg once every three weeks. In some examples, the trastuzumab is administered at an initial dose of 6 mg/kg followed by 4 mg/kg once every two weeks (*e.g.*, an initial dose of 6 mg/kg, followed by a 4 mg/kg dose two weeks after the initial 6 mg/kg dose, followed by a 4 mg/kg dose every two weeks after the first 4 mg/kg dose). In some examples, the paclitaxel is administered at a dose of 80 mg/m2 on days 1, 8, and 15 of a 28-day cycle. In some examples, among a population of patients receiving the treatment, the overall response rate (ORR) of the population is greater than 65%, 70%, 75%, 80%, 85%, 90%, or 95%.

[0009] In some examples, the polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant forms a homodimer. In some examples, the individual is a human.

[0010] In some examples, provided is a kit comprising a polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant in a pharmaceutically acceptable carrier, for use in combination with an anti-HER2 antibody, an anti-VEGFR2 antibody, and paclitaxel; wherein the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 85; wherein the Fc domain variant is (i) a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations, wherein numbering is according to the EU index of Kabat; (ii) a human IgG2 Fc region comprising A330S, P331S, and N297A mutations, wherein numbering is according to the EU index of Kabat; (iii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, and delG236 mutations, wherein numbering is according to the EU index of Kabat; or (iv) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, delG236, and N297A mutations, wherein numbering is according to the EU index of Kabat, and wherein the kit comprises instructions for administering the polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant in combination with the anti-HER2 antibody, the anti-VEGFR2 antibody, and the paclitaxel to an individual with gastric cancer or gastroesophageal junction (GEJ) cancer who has received at least one prior therapy for

the gastric or the GEJ cancer. In some examples, the gastric cancer or GEJ cancer is $HER2^+$ gastric cancer or $HER2^+$ GEJ cancer. In some examples, the anti-HER2 antibody is trastuzumab. In some examples, the anti-VEGFR2 antibody is ramucirumab. In some examples, the individual received prior therapy (or therapies) with an anti-HER2 antibody (*e.g.*, trastuzumab) and/or a fluoropyrimidine, and/or a platinum-based chemotherapeutic agent. In some examples, the gastric cancer or GEJ cancer in the individual progressed during or after prior therapy (or therapies) comprising anti-HER2 antibody (*e.g.*, trastuzumab) and/or a fluoropyrimidine, and/or a platinum-based chemotherapeutic agent. In some examples, the individual failed (*e.g.*, relapsed after or did not respond to) prior therapy (or therapies) comprising anti-HER2 antibody (*e.g.*, trastuzumab) and/or a fluoropyrimidine, and/or a platinum-based chemotherapeutic agent. In some examples, the prior therapy (or therapies) comprised an anti-HER2 antibody and a fluoropyrimidine (*e.g.*, administered during the same line of therapy or during different lines of therapy). In some examples, the prior therapy (or therapies) comprised an anti-HER2 antibody and a platinum-based chemotherapy agent (*e.g.*, administered during the same line of therapy or during different lines of therapy).

DESCRIPTION OF THE FIGURES

[0011] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0012] **FIG 1** provides the results of experiments that were performed to determine the effect of DRUG A in combination with (a) an anti-HER2 antibody, (b) an anti-PD-L1 antibody, or (c) an anti-HER2 antibody and an anti-PD-L1 on tumor growth in a MC38 m:h chimeric colon cancer model in mice.

[0013] **FIG 2A** provides a graph of the best % change in baseline measurable lesions in each patient in the study described in Example 2E.

[0014] **FIG 2B** provides a graph showing the % change in baseline measurable lesions in each patient in the study described in Example 2E as a function of time .

[0015] **FIG 3** shows the results of experiments that were performed to assess whether DRUG B enhances the anti-tumor activity of anti-mouse VEGFR-2 + paclitaxel doublet therapy in a CT26

CLAIMS

1. Use of a polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant in the manufacture of a medicament for treating cancer in an individual;

wherein the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 85;

wherein the Fc domain variant is

(i) a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations, wherein numbering is according to the EU index of Kabat;

(ii) a human IgG2 Fc region comprising A330S, P331S, and N297A mutations, wherein numbering is according to the EU index of Kabat;

(iii) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, and delG236 mutations, wherein numbering is according to the EU index of Kabat; or

(iv) a human IgG4 Fc region comprising S228P, E233P, F234V, L235A, delG236, and N297A mutations, wherein numbering is according to the EU index of Kabat;

wherein the medicament is to be administered to the individual in combination with (a) an anti-HER2 antibody, (b) an anti-VEGFR2 antibody, and (c) paclitaxel;

wherein the cancer is gastric cancer or gastroesophageal junction (GEJ) cancer, and

wherein the individual has received at least one prior therapy for the gastric or the GEJ cancer.

2. The use according to claim 1, wherein the individual has received prior therapy with an anti-HER2 antibody, with an anti-HER2 antibody and a fluoropyrimidine, or with an anti HER2 antibody and a platinum-based chemotherapy agent.

3. The use according to claim 1 or 2, wherein the anti-HER2 antibody is trastuzumab.

4. The use according to any one of claims 1-3, wherein the anti-VEGF antibody is ramucirumab.

5. The use according to any one of claims 1-4, wherein the gastric cancer or the GEJ cancer is $HER2^+$ gastric cancer or $HER2^+$ GEJ cancer.

6. The use according to any one of claims 1-5, wherein the polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant is to be administered at a dose of 10 mg/kg once a week.

7. The use according to any one of claims 1-5, wherein the polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant is to be administered at a dose of 15 mg/kg once a week.

8. The use according to any one of claims 1-5, wherein the polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant is to be administered at a dose of 30 mg/kg once every two weeks.

9. The use according to any one of claims 3-8, wherein the anti-HER2 antibody is trastuzumab and is to be administered at an initial dose of 6 mg/kg followed by 4 mg/kg once every two weeks.

10. The use according to any one of claims 4-9, wherein the anti-VEGFR2 antibody is ramicirumab and is to be administered at a dose of 8 mg/kg once every two weeks.

11. The use according to any one of claims 1-10, wherein the paclitaxel is to be administered at a dose of 80 mg/m2 on Days 1, 8, and 15 of every 28-day cycle.

12. The use according to any one of claims 1-11, wherein, among a population of patients receiving treatment, the overall response rate (ORR) of the population is greater than 65%.

13. The use according to any one of claims 1-12, wherein the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 85.

14. The use according to any one of claims 1-12, wherein the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81.

15. The use according to any one of claims 1-14, wherein the Fc domain variant is a human IgG1 Fc region comprising L234A, L235A, G237A, and N297A mutations, wherein numbering is according to the EU index of Kabat.

16. The use according to claim 15, wherein the Fc domain variant comprises the amino acid sequence of SEQ ID NO: 91.

17. The use according to any one of claims 1-13 and 15-16, wherein the polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 136.

18. The use according to any one of claims 1-12 and 14-16, wherein the polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 135.

19. The use according to any one of claims 1-18, wherein the polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant forms a homodimer.

20. The use according to any one of claims 1-19, wherein the individual is a human.