

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 an aspect of the present disclosure, there is provided a use of a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in the manufacture of a medicament for treating cancer in an individual;

wherein the SIRP α 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) a PD-1 inhibitor, (b) an antimetabolite, and (c) a platinum-based chemotherapy agent;

wherein the cancer is head and neck squamous cell carcinoma (HNSCC), and

wherein the individual has not received prior treatment for HNSCC.

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

wherein the SIRP α 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-VEGF2 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.

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

wherein the SIRP α 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 medicament is to be administered to the individual in combination with a Bcl2 inhibitor.

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

wherein the SIRP α 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 medicament is to be administered to the individual in combination with a platinum-based chemotherapy agent.

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

wherein the SIRP α 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 medicament is to be administered to the individual in combination with (a) an anti-HER2 antibody, and (b) an anti-PD-L1 antibody.

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

wherein the SIRP α 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 medicament is to be administered to the individual in combination with an anti-TROP2 antibody.

[0008] Provided is a method of treating cancer in an individual, comprising administering to the individual an effective amount of: (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, and (b) a Bcl-2 inhibitor; wherein the SIRP α 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. In some embodimentexamples, the cancer is leukemia, multiple myeloma, or non-Hodgkin's lymphoma. In some embodimentexamples, the non-Hodgkin's lymphoma is diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), or follicular lymphoma (FL). In some embodimentexamples, the leukemia is acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Chronic myeloid leukemia (CML), acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS). In some embodimentexamples, the leukemia is acute lymphoblastic leukemia. In some embodimentexamples, the Bcl-2 inhibitor is venetoclax, ABT-737, navitoclax, BCL201, or AZD-0466. In some embodimentexamples, the Bcl-2 inhibitor is venetoclax.

[0009] Also provided is a method of treating cancer in an individual, comprising administering to the individual an effective amount of: (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, and (b) a platinum-based chemotherapy agent; wherein the SIRP α 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. In some [embodimentexamples](#), the cancer is a solid tumor. In some [embodimentexamples](#), the solid tumor is colon cancer, lung cancer, head and neck cancer, esophageal cancer, breast cancer, bladder cancer, ovarian cancer, cervical cancer, testicular cancer, endometrial cancer, liver cancer, gastric cancer, gastroesophageal junction cancer, brain tumor, mesothelioma, or neuroblastoma. In some [embodimentexamples](#), the colon cancer is colon carcinoma. In some [embodimentexamples](#), the platinum-based chemotherapy agent is carboplatin, cisplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin. In some [embodimentexamples](#), the platinum-based chemotherapy agent is cisplatin or carboplatin.

[0010] Also provided is a method of treating cancer in an individual, comprising administering to the individual an effective amount of: (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, (b) a PD-1 inhibitor, (c) an antimetabolite, and (d) a platinum-based chemotherapy agent; wherein the SIRP α 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 head and neck squamous cell carcinoma (HNSCC), and wherein the individual has not received prior treatment for HNSCC. In some [embodimentexamples](#), the polypeptide comprising the SIRP α D1 domain variant and the Fc domain variant is administered at a dose of 10 mg/kg once a week (qw). In some [embodimentexamples](#), the polypeptide comprising the SIRP α D1 domain variant and the Fc domain variant is administered at a dose of 15 mg/kg once a week (qw).

[0011] In some [embodimentexamples](#), the HNSCC is advanced and/or metastatic HNSCC. In some [embodimentexamples](#), the PD-1 inhibitor is an anti-PD-1 antibody, e.g., pembrolizumab, nivolumab, pidilizumab, cemiplimab, or BMS-936559. In some [embodimentexamples](#), the anti-PD-1 antibody is pembrolizumab. In some [embodimentexamples](#), the antimetabolite is 5-fluorouracil, 6-mercaptopurine, capecitabine, cytarabine, floxuridine, fludarabine, gemcitabine, hydroxycarbamide, methotrexate, pemetrexed, phototrexate. In some [embodimentexamples](#), the antimetabolite is 5-

fluorouracil. In some [embodimentexamples](#), the platinum-based chemotherapy agent is carboplatin, cisplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin. In some [embodimentexamples](#), the platinum-based chemotherapy agent is cisplatin or carboplatin.

[0012] In another [aspectexample](#), provided is a method of treating cancer in an individual, comprising administering to the individual an effective amount of: (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, (b) an anti-HER2 antibody, and (c) an anti-PD-L1 antibody (e.g., an anti-PD-L1 antagonist antibody); wherein the SIRP α 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. In some [embodimentexamples](#), the cancer is solid tumor. In some [embodimentexamples](#), the solid tumor is colon cancer, lung cancer, head and neck cancer, esophageal cancer, breast cancer, bladder cancer, ovarian cancer, cervical cancer, testicular cancer, endometrial cancer, liver cancer, gastric cancer, gastroesophageal junction cancer, brain tumor, mesothelioma, or neuroblastoma. In some [embodimentexamples](#), the solid tumor is HER2⁺ solid tumor. In some [embodimentexamples](#), the solid tumor is colon cancer (e.g., HER2⁺ colon cancer). In some [embodimentexamples](#), the anti-HER2 antibody is trastuzumab. In some [embodimentexamples](#), the anti-PD-L1 antibody is atezolizumab, avelumab, or durvalumab.

[0013] In some [embodimentexamples](#), provided is a method of treating cancer in an individual, comprising administering to the individual an effective amount of: (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, (b) an anti-HER2 antibody, (c) an anti-VEGF2 antibody, and (d) paclitaxel; wherein the SIRP α 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 [embodimentexamples](#), the gastric cancer or GEJ cancer is a HER2-overexpressing (e.g., HER2⁺) gastric cancer or a HER2-overexpressing GEJ cancer. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), the anti-HER2 antibody is trastuzumab. In some [embodimentexamples](#), the anti-VEGF antibody is ramucirumab. In some [embodimentexamples](#), the polypeptide comprising the SIRPα D1 domain variant and the Fc domain variant is administered at a dose of 10 mg/kg once a week (qw). In some [embodimentexamples](#), the polypeptide comprising the SIRPα D1 domain variant and the Fc domain variant is administered at a dose of 15 mg/kg once a week (qw).

[0014] Also 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, and (b) an anti-TROP2 antibody; 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. In some [embodimentexamples](#), the cancer is solid tumor, gastric cancer, nasopharyngeal cancer, gallbladder cancer, cervical cancer, extranodal NK/T cell lymphoma, lung cancer, laryngeal squamous cell cancer, colon cancer, Hilar Cholangiocarcinoma, pancreatic cancer, squamous cell carcinoma of the oral cavity, endometrioid endometrial carcinoma, or ovarian carcinoma.

[0015] In some [embodimentexamples](#) of any of the methods described herein, the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 85. In some [embodimentexample](#), the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), the Fc domain variant comprises the amino acid sequence of SEQ ID NO: 91. In some [embodimentexamples](#), the polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 136. In some [embodimentexamples](#),

the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 135. In some [embodimentexamples](#), the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant forms a homodimer. In some [embodimentexamples](#), the individual is a human.

[0016] In another [aspectexample](#), provided is a kit comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in a pharmaceutically acceptable carrier, for use in combination with a Bcl-2 inhibitor for treating cancer in an individual in need, wherein the SIRP α 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 SIRP α D1 domain variant and an Fc domain variant in combination with the Bcl-2 inhibitor to the individual in need thereof. In some [embodimentexamples](#), the cancer is leukemia, multiple myeloma, or non-Hodgkin's lymphoma. In some [embodimentexamples](#), the Bcl-2 inhibitor is venetoclax.

[0017] Also provided is a kit comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in a pharmaceutically acceptable carrier, for use in combination with a platinum-based chemotherapy agent for treating cancer in an individual in need thereof, wherein the SIRP α 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 SIRP α D1 domain variant and an Fc domain variant in combination with the chemotherapy agent to the individual in need thereof. In some [embodimentexamples](#), the cancer is solid tumor. In some [embodimentexamples](#), the solid tumor is colon cancer, colon carcinoma, lung cancer,

head and neck cancer, esophageal cancer, breast cancer, bladder cancer, ovarian cancer, cervical cancer, testicular cancer, endometrial cancer, liver cancer, gastric cancer, brain tumor, mesothelioma, or neuroblastoma. In some [embodimentexamples](#), the platinum-based chemotherapy agent is cisplatin or carboplatin.

[0018] In some [embodimentexamples](#), provided is a kit comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in a pharmaceutically acceptable carrier, for use in combination with a PD-1 inhibitor, an antimetabolite, and a platinum-based chemotherapy agent for treating cancer in an individual in need thereof, wherein the SIRP α 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 SIRP α D1 domain variant and an Fc domain variant in combination with the anti-PD-1 antibody, the antimetabolite, and the platinum-based chemotherapy agent to an individual with head and neck squamous cell carcinoma (HNSCC) who has not received prior treatment for HNSCC. In some [embodimentexamples](#), the PD-1 inhibitor is pembrolizumab. In some [embodimentexamples](#), the antimetabolite is 5-fluorouracil. In some [embodimentexamples](#), the platinum-based chemotherapy agent is cisplatin or carboplatin.

[0019] In some [embodimentexamples](#), provided is a kit comprising a polypeptide comprising a SIRP α 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 SIRP α 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 SIRP α 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 [embodimentexamples](#), the gastric cancer or GEJ cancer is HER2⁺ gastric cancer or HER2⁺ GEJ cancer. In some [embodimentexamples](#), the anti-HER2 antibody is trastuzumab. In some [embodimentexamples](#), the anti-VEGFR2 antibody is ramucirumab. In some [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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)

[0020] Also provided is a kit comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in a pharmaceutically acceptable carrier, for use in combination with an anti-TROP2 antibody for treating cancer in an individual in need thereof, wherein the SIRP α 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 SIRP α D1 domain variant and an Fc domain variant in combination with the anti-TROP2 antibody to the individual in need thereof. In some [embodimentexamples](#), the cancer is solid tumor, gastric cancer, nasopharyngeal cancer, gallbladder cancer, cervical cancer, extranodal NK/T cell lymphoma, lung cancer, laryngeal squamous cell cancer, colon cancer, Hilar

Cholangiocarcinoma, pancreatic cancer, squamous cell carcinoma of the oral cavity, endometrioid endometrial carcinoma, or ovarian carcinoma.

[0021] Also provided is a kit comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in a pharmaceutically acceptable carrier, for use in combination with an anti-HER2 antibody and an anti-PD-L1 antibody (e.g., an anti PD-L1 antagonist antibody) for treating cancer in an individual in need thereof, wherein the SIRP α 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 SIRP α D1 domain variant and an Fc domain variant in combination with the anti-HER2 antibody and the anti-PD-L1 antibody (e.g., an anti PD-L1 antagonist antibody) to the individual in need thereof. In some [embodimentexamples](#), the cancer is colon cancer. In some [embodimentexamples](#), the colon cancer is HER2⁺ colon cancer. In some [embodimentexamples](#), the anti-HER2 antibody is trastuzumab. In some [embodimentexamples](#), the anti-PD-L1 antibody is atezolizumab, avelumab, or durvalumab.

[0022] In some [embodimentexamples](#) of the kits, the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO: 85. In some [embodimentexamples](#), the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), the Fc domain variant comprises the amino acid sequence of SEQ ID NO: 91. In some [embodimentexamples](#), the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 136. In some [embodimentexamples](#), the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 135. In some [embodimentexamples](#), the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant forms a homodimer. In some [embodimentexamples](#), the individual is a human.

DESCRIPTION OF THE FIGURES

[0023] **FIG. 1A** provides tumor volumes (mm³) in NOD-SCID female mice injected with RS4;11 leukemia cells following treatment with Drug A, venetoclax, venetoclax/Drug A

CLAIMS

1. ~~A method of treating cancer in an individual, comprising administering to the individual an effective amount of: (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, and (b) a Bcl-2 inhibitor;~~
~~wherein the SIRP α 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.~~
2. ~~The method of claim 1, wherein the cancer is leukemia, multiple myeloma, or non-Hodgkin's lymphoma.~~
3. ~~The method of claim 2, wherein the non-Hodgkin's lymphoma is diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), or follicular lymphoma (FL).~~
4. ~~The method of claim 2, wherein the leukemia is acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Chronic myeloid leukemia (CML), acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS).~~
5. ~~The method of claim 4, wherein the leukemia is acute lymphoblastic leukemia.~~
6. ~~The method of any one of claims 1-5, wherein the Bcl-2 inhibitor is venetoclax, ABT-737, navitoclax, BCL201, or AZD-0466.~~
7. ~~The method of claim 6, wherein the Bcl-2 inhibitor is venetoclax.~~

8. ~~_____ A method of treating cancer in an individual, comprising administering to the individual an effective amount of: (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, and (b) a platinum-based chemotherapy agent;~~
~~_____ wherein the SIRP α 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.~~

9. ~~_____ The method of claim 8, wherein the cancer is a solid tumor.~~

10. ~~_____ The method of claim 9, wherein the solid tumor is colon cancer, lung cancer, head and neck cancer, esophageal cancer, breast cancer, bladder cancer, ovarian cancer, cervical cancer, testicular cancer, endometrial cancer, liver cancer, gastric cancer, gastroesophageal junction cancer, brain tumor, mesothelioma, or neuroblastoma.~~

11. ~~_____ The method of claim 9, wherein the colon cancer is colon carcinoma.~~

421. Use of a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in the manufacture of a medicament for ~~A method of treating cancer in an individual, comprising administering to the individual an effective amount of: (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, (b) a PD-1 inhibitor, (c) an antimetabolite, and (d) a platinum-based chemotherapy agent;~~

~~_____ wherein the SIRP α 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) a PD-1 inhibitor, (b) an antimetabolite, and (c) a platinum-based chemotherapy agent;

wherein the cancer is head and neck squamous cell carcinoma (HNSCC), and wherein the individual has not received prior treatment for HNSCC.

~~132.~~ The ~~method of use according to~~ claim ~~121~~, wherein the HNSCC is advanced and/or metastatic HNSCC.

~~143.~~ The ~~method of use according to~~ claim ~~121~~ or ~~132~~, wherein the PD-1 inhibitor is an anti-PD-1 antibody.

~~154.~~ The ~~method of use according to~~ claim ~~143~~, wherein the anti-PD-1 antibody is pembrolizumab, nivolumab, pidilizumab, cemiplimab, or BMS-936559.

~~165.~~ The ~~method of use according to~~ claim ~~154~~, wherein the anti-PD-1 antibody is pembrolizumab.

~~176.~~ The ~~method of use according to~~ any one of claims ~~121-165~~, wherein the antimetabolite is 5-fluorouracil, 6-mercaptopurine, capecitabine, cytarabine, floxuridine, fludarabine, gemcitabine, hydroxycarbamide, methotrexate, pemetrexed, phototrexate.

~~187.~~ The ~~method of use according to~~ claim ~~176~~, wherein the antimetabolite is 5-fluorouracil.

~~19.~~ ~~The method of any one of claims 8-18, wherein the platinum-based chemotherapy agent is carboplatin, cisplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin.~~

~~20. The method of claim 19, wherein the platinum-based chemotherapy agent is cisplatin.~~

~~21. The method of claim 19, wherein the platinum-based chemotherapy agent is carboplatin.~~

~~22. A method of treating cancer in an individual, comprising administering to the individual an effective amount of: (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, (b) an anti-HER2 antibody, and (c) an anti-PD-L1 antibody;~~

~~wherein the SIRP α 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.~~

~~23. The method of claim 22, wherein the cancer is solid tumor.~~

~~24. The method of claim 23, wherein the solid tumor is colon cancer, lung cancer, head and neck cancer, esophageal cancer, breast cancer, bladder cancer, ovarian cancer, cervical cancer, testicular cancer, endometrial cancer, liver cancer, gastric cancer, gastroesophageal junction cancer, brain tumor, mesothelioma, or neuroblastoma~~

~~25. The method of claim 23 or 24, wherein the solid tumor is HER2⁺ solid tumor.~~

~~26. The method of any one of claims 23-25, wherein the solid tumor is colon cancer.~~

~~27. The method of any one of claims 22-26, wherein the anti-HER2 antibody is trastuzumab.~~

~~28. The method of any one of claims 22-27, wherein the anti-PD-L1 antibody is atezolizumab, avelumab, or durvalumab.~~

~~298. Use of a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in the manufacture of a medicament for A method of treating cancer in an individual, comprising administering to the individual an effective amount of: (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, (b) an anti-HER2 antibody, (c) an anti-VEGF2 antibody, and (d) paclitaxel;~~

wherein the SIRP α 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-VEGF2 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.

~~309. The method of use according to claim 298, 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.~~

~~3110. The method of use according to claim 29-8 or 309, wherein the anti-HER2 antibody is trastuzumab.~~

~~3211. The method of use according to any one of claims 298-3110, wherein the anti-VEGF antibody is ramucirumab.~~

3312. The ~~method of use according to~~ any one of claims ~~298-3211~~, wherein the gastric cancer or the GEJ cancer is HER2⁺ gastric cancer or HER2⁺ GEJ cancer.

3413. The ~~method of use according to~~ any one of claims ~~1-12-21 and 29-33~~, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant is to be administered at a dose of 10 mg/kg once a week.

3514. The ~~method of use according to~~ any one of claims ~~1-12-21 and 29-33~~, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant is to be administered at a dose of 15 mg/kg once a week.

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

wherein the SIRP α 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 medicament is to be administered to the individual in combination with a Bcl2 inhibitor.

16. The use according to claim 15, wherein the cancer is leukemia, multiple myeloma, or non-Hodgkin's lymphoma.

17. The use according to claim 16, wherein the non-Hodgkin's lymphoma is diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), or follicular lymphoma (FL).

18. The use according to claim 17, wherein the leukemia is acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL),

Chronic myeloid leukemia (CML), acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS).

19. The use according to claim 18, wherein the leukemia is acute lymphoblastic leukemia.

20. The use according to any one of claims 15-19, wherein the Bcl-2 inhibitor is venetoclax, ABT-737, navitoclax, BCL201, or AZD-0466.

21. The use according to claim 20, wherein the Bcl-2 inhibitor is venetoclax.

22. Use of a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in the manufacture of a medicament for treating cancer in an individual;
wherein the SIRP α 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 medicament is to be administered to the individual in combination with a platinum-based chemotherapy agent.

23. The use according to claim 22, wherein the cancer is a solid tumor.

24. The use according to claim 23, wherein the solid tumor is colon cancer, lung cancer, head and neck cancer, esophageal cancer, breast cancer, bladder cancer, ovarian cancer, cervical cancer, testicular cancer, endometrial cancer, liver cancer, gastric cancer, gastroesophageal junction cancer, brain tumor, mesothelioma, or neuroblastoma.

25. The use according to claim 24, wherein the colon cancer is colon carcinoma.

26. The use according to any one of claims 1-7 and 22-25, wherein the platinum-based chemotherapy agent is carboplatin, cisplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin.

27. The use according to claim 26, wherein the platinum-based chemotherapy agent is cisplatin.

28. The use according to claim 26, wherein the platinum-based chemotherapy agent is carboplatin.

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

wherein the SIRP α 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 medicament is to be administered to the individual in combination with (a) an anti-HER2 antibody, and (b) an anti-PD-L1 antibody.

30. The use according to claim 29, wherein the cancer is solid tumor.

31. The use according to claim 30, wherein the solid tumor is colon cancer, lung cancer, head and neck cancer, esophageal cancer, breast cancer, bladder cancer, ovarian cancer, cervical cancer, testicular cancer, endometrial cancer, liver cancer, gastric cancer, gastroesophageal junction cancer, brain tumor, mesothelioma, or neuroblastoma.

32. The use according to claim 30 or 31, wherein the solid tumor is HER2⁺ solid tumor.

33. The use according to any one of claims 30-32, wherein the solid tumor is colon cancer.

34. The use according to any one of claims 30-33, wherein the anti-HER2 antibody is trastuzumab.

35. The use according to any one of claims 30-34, wherein the anti-PD-L1 antibody is atezolizumab, avelumab, or durvalumab.

36. Use of a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in the manufacture of a medicament for ~~A method of~~ treating cancer in an individual; comprising administering to the individual an effective amount of (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, and (b) an anti-TROP2 antibody;

wherein the SIRP α 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 medicament is to be administered to the individual in combination with an anti-TROP2 antibody.

37. The ~~method of~~use according to claim 36, wherein the cancer is solid tumor, gastric cancer, nasopharyngeal cancer, gallbladder cancer, cervical cancer, extranodal NK/T cell lymphoma, lung cancer, laryngeal squamous cell cancer, colon cancer, Hilar Cholangiocarcinoma, pancreatic cancer, squamous cell carcinoma of the oral cavity, endometrioid endometrial carcinoma, or ovarian carcinoma.

38. The use according to method of any one of claims 1-37, wherein the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO: 85.
39. The use according to method of any one of claims 1-37, wherein the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81.
40. The use according to method of any one of claims 1-39, 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.
41. The use according to method of claim 40, wherein the Fc domain variant comprises the amino acid sequence of SEQ ID NO: 91.
42. The use according to method of any one of claims 1-38 and 40-41, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 136.
43. The use according to method of any one of claims 1-37 and 39-41, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 135.
44. The use according to method of any one of claims 1-43, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant forms a homodimer.
45. The use according to method of any one of claims 1-44, wherein the individual is a human.
- ~~46. ——— A kit comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in a pharmaceutically acceptable carrier, for use in combination with a Bcl-2 inhibitor for treating cancer in an individual in need thereof,
——— wherein the SIRP α 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 SIRP α D1 domain variant and an Fc domain variant in combination with the Bcl-2 inhibitor to the individual in need thereof.~~

47. ~~—————The kit of claim 46 wherein the cancer is leukemia, multiple myeloma, or non-Hodgkin's lymphoma.~~

48. ~~—————The kit of claim 46 or 47 wherein the Bcl-2 inhibitor is venetoclax.~~

49. ~~—————A kit comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in a pharmaceutically acceptable carrier, for use in combination with a platinum-based chemotherapy agent for treating cancer in an individual in need thereof;~~

~~—————wherein the SIRP α 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 SIRP α D1 domain variant and an Fc domain variant in combination with the platinum-based chemotherapy agent to the individual in need thereof.~~

50. ~~—————The kit of claim 49, wherein the cancer is solid tumor.~~

~~51. The kit of claim 50, wherein the solid tumor is colon cancer, colon carcinoma, lung cancer, head and neck cancer, esophageal cancer, breast cancer, bladder cancer, ovarian cancer, cervical cancer, testicular cancer, endometrial cancer, liver cancer, gastric cancer, brain tumor, mesothelioma, or neuroblastoma.~~

~~52. A kit comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in a pharmaceutically acceptable carrier, for use in combination with a PD-1 inhibitor, an antimetabolite, and a platinum-based chemotherapy agent for treating cancer in an individual in need thereof,~~

~~wherein the SIRP α 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 SIRP α D1 domain variant and an Fc domain variant in combination with the PD-1 inhibitor, the antimetabolite, and the platinum-based chemotherapy agent to an individual with head and neck squamous cell carcinoma (HNSCC), who has not received prior treatment for HNSCC.~~

~~53. The kit of any one of claims 49-52, wherein the PD-1 inhibitor is pembrolizumab.~~

~~54. The kit of any one of claims 49-53, wherein the antimetabolite is 5-fluorouracil.~~

~~55. The kit of any one of claims 49-54, wherein the platinum-based chemotherapy agent is cisplatin or carboplatin.~~

56. ~~A kit comprising a polypeptide comprising a SIRP α 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 SIRP α 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 SIRP α 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 (GEJ) cancer who has received at least one prior treatment for gastric cancer or GEJ cancer.~~
57. ~~The kit of claim 56, wherein the gastric cancer or GEJ cancer is HER2⁺ gastric cancer or HER2⁺ GEJ cancer.~~
58. ~~The kit of claim 56 or 57, wherein the anti-HER2 antibody is trastuzumab.~~
59. ~~The kit of any one of claims 56-58, wherein the anti-VEGFR2 antibody is ramucirumab.~~
60. ~~The kit of any one of claims 56-59, wherein the individual 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.~~
61. ~~A kit comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in a pharmaceutically acceptable carrier, for use in combination with an anti-TROP2 antibody for treating cancer in an individual in need thereof;~~

~~wherein the SIRP α 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 SIRP α D1 domain variant and an Fc domain variant in combination with the anti-TROP2 antibody to the individual in need thereof.~~

62. ~~The kit of claim 61, wherein the cancer is solid tumor, gastric cancer, nasopharyngeal cancer, gallbladder cancer, cervical cancer, extranodal NK/T cell lymphoma, lung cancer, laryngeal squamous cell cancer, colon cancer, Hilar Cholangiocarcinoma, pancreatic cancer, squamous cell carcinoma of the oral cavity, endometrioid endometrial carcinoma, or ovarian carcinoma.~~

63. ~~A kit comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in a pharmaceutically acceptable carrier, for use in combination with an anti-HER2 antibody and an anti-PD-L1 antibody for treating cancer in an individual in need thereof,~~

~~wherein the SIRP α 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 SIRP α D1 domain variant and an Fc domain variant in combination with the anti-HER2 antibody and the anti-PD-L1 antibody to the individual in need thereof.~~

~~64. _____ The kit of claim 63, wherein the cancer is colon cancer.~~

~~65. _____ The kit of claim 64 wherein the colon cancer is HER2⁺ colon cancer.~~

~~66. _____ The kit of any one of claims 63-65, wherein the anti-HER2 antibody is trastuzumab.~~

~~67. _____ The kit of any one of claims 63-66, wherein the anti-PD-L1 antibody is atezolizumab, avelumab, or durvalumab.~~

~~68. _____ The kit of any one of claims 46-67, wherein the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO: 85.~~

~~69. _____ The kit of any one of claims 46-67, wherein the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81.~~

~~70. _____ The kit of any one of claims 46-69, 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.~~

~~71. _____ The kit of claim 70, wherein the Fc domain variant comprises the amino acid sequence of SEQ ID NO: 91.~~

~~72. _____ The kit of any one of claims 46-68 and 70-71, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 136.~~

~~73. _____ The kit of any one of claims 46-67 and 69-71, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 135.~~

~~74. The kit of any one of claims 46-73 wherein the polypeptide comprising a SIRP α -D1 domain variant and an Fc domain variant forms a homodimer.~~

~~75. The kit of any one of claims 46-74, wherein the individual is human.~~