

globocan(dot)iarc(dot)fr/Pages/fact_sheets_cancer(dot)aspx). There are estimated to be over 35,000 people living in the US with metastatic HNSCC, with over 50,000 newly incident cases at all stages diagnosed in 2019. Five-year survival is 84% for patients diagnosed with localized disease but decreases to only 39% for those diagnosed with metastatic disease. There is a need in the art for new treatments to provide additional therapeutic options and improve outcomes for such patients.

[0005] Tumor cells manipulate the myeloid compartment to evade the anti-tumor host immune response (Gabrilovich *et al.*, Nat Rev Immunol (2012) 12(4):253-68). For example, while CD47 expressed on the surface of normal cells binds SIRP α on macrophages and provides a “don’t eat me” signal, tumor cells have also been found to overexpress CD47 to evade the macrophage component of immune surveillance (Oldenborg, ISRN Hematol (2013) 614619).

[0006] Macrophage-mediated destruction of cancer cells requires both the disruption of "don't eat me" signals (*e.g.*, CD47- SIRP α) and the activation of "eat me" signals. Neither component alone is sufficient to trigger maximal phagocytic reaction against tumor cells. As described above, CD47 provides a fundamental “don’t eat me” signal through its interaction with SIRP α 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.

SUMMARY-OF-THE-INVENTION

[0008] Provided is a method of treating non-small cell lung cancer (NSCLC) 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-PD-1 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 individual is a human. In one aspect, the present disclosure refers to use of (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in the manufacture of a medicament for use in combinatorial therapy for treating non-small cell lung cancer (NSCLC) in an individual, wherein said medicament is to be administered in combination with (b) an anti-PD-1 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 individual is a human. In some **embodiment examples**, the NSCLC in the individual has progressed on a prior immune checkpoint inhibitor (CPI) therapy and/or has a PD-L1 tumor proportion score (TPS) of less than 50%.

[0009] Also provided is a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant for use in the manufacture of a medicament for treating NSCLC in an individual, wherein the medicament is for use (such as formulated for use) in combination with an anti-PD1 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 individual is a human. In some **embodiment examples**, the NSCLC in the individual has progressed on a prior immune checkpoint inhibitor (CPI) therapy and/or has a PD-L1 tumor proportion score (TPS) of less than 50%.

[0010] Also provided is a composition (such a pharmaceutical composition) comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant for use in combination with an anti-PD1 antibody for treating NSCLC in an individual (*e.g.*, for use in a method of treating NSCLC 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 individual is a human. In some **embodiment examples**, the NSCLC in the individual has progressed on a prior immune checkpoint inhibitor (CPI) therapy and/or has a PD-L1 tumor proportion score (TPS) of less than 50%.

[0011] In some [embodimentexamples](#), the prior CPI (immune checkpoint inhibitor therapy) comprised one or more agents selected from the group consisting of: nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, and cemiplimab. In some [embodimentexamples](#), the anti-PD-1 antibody blocks the interaction between PD-1 and PD-L1. In some [embodimentexamples](#), the anti-PD-1 antibody is pembrolizumab. In some [embodimentexamples](#), the pembrolizumab is administered to the individual at a dose of 200 mg every 3 weeks (Q3W) by intravenous (IV) infusion.

[0012] Also provided is a method of treating head and neck squamous cell carcinoma (HNSCC) 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-PD-1 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; wherein the HNSCC in the individual has progressed while on a prior platinum therapy or after the platinum therapy, and wherein the individual is a human. In one aspect, the present disclosure refers to use of (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in the manufacture of a medicament for use in combinatorial therapy for treating head and neck squamous cell carcinoma (HNSCC) in an individual, wherein said medicament is to be administered in combination with (b) an anti-PD-1 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 HNSCC in the individual has progressed while on a prior platinum therapy or after the prior platinum therapy, and wherein the individual is a human.

[0013] Also provided is a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant for use in the manufacture of a medicament for treating HNSCC in an individual, wherein the medicament is for use (such as formulated for use) in combination with an anti-PD1 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; wherein the HNSCC in the individual has progressed while on a prior platinum therapy or after the platinum therapy, and wherein the individual is a human.

[0014] Also provided is a composition (such a pharmaceutical composition) comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant for use in

combination with an anti-PD1 antibody for treating HNSCC in an individual (*e.g.*, for use in a method of treating HNSCC 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 HNSCC in the individual has progressed while on a prior platinum therapy or after the platinum therapy, and wherein the individual is a human.

[0015] In some [embodimentexamples](#), the individual with HNSCC received prior therapy with an immune checkpoint inhibitor (*e.g.*, an immune checkpoint inhibitor described herein). In some [embodimentexamples](#), such individual is considered to be / referred to as “checkpoint inhibitor experienced.” In some [embodimentexamples](#), the individual with HNSCC has not received prior therapy with an immune checkpoint inhibitor. In some [embodimentexamples](#), such individual is considered to be / referred to as “checkpoint inhibitor naïve.” In some [embodimentexample](#), the prior platinum therapy comprised one or more therapeutic agents selected from the group consisting of: cisplatin, carboplatin, and oxaliplatin. In some [embodimentexample](#), the anti-PD-1 antibody blocks the interaction between PD-1 and PD-L1. In some [embodimentexamples](#), the anti-PD-1 antibody is pembrolizumab. In some [embodimentexample](#), the pembrolizumab is administered (such as formulated for administration) to the individual at a dose of 200 mg every 3 weeks (Q3W) by intravenous (IV) infusion.

[0016] Provided is a method of treating HER2-positive gastric/gastroesophageal junction (GEJ) 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-HER2 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; wherein the gastric/GEJ cancer in the individual has progressed following a prior treatment with a fluoropyrimidine-based therapy and/or a prior treatment with an anti-HER2 antibody, and wherein the individual is a human. In one aspect, the present disclosure refers to use of (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in the manufacture of a medicament for use in combinatorial therapy for treating HER2-positive gastric/gastroesophageal junction (GEJ) cancer in an individual, wherein said medicament is to be administered in combination with (b) an anti-HER2 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 gastric/GEJ cancer in the individual has progressed following a prior treatment with a fluoropyrimidine-based therapy and/or a prior treatment with an anti-HER2 antibody, and wherein the individual is a human.

[0017] Also provided is a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant for use in the manufacture of a medicament for treating HER2-positive gastric/gastroesophageal junction (GEJ) cancer in an individual, wherein the medicament is for use (such as formulated for use) in combination with an anti-HER2 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; wherein the gastric/GEJ cancer in the individual has progressed following a prior treatment with a fluoropyrimidine-based therapy and/or a prior treatment with an anti-HER2 antibody, and wherein the individual is a human.

[0018] Also provided is a composition (such a pharmaceutical composition) comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant for use in combination with an anti-HER2 antibody for treating HER2-positive gastric/gastroesophageal junction (GEJ) cancer in an individual (*e.g.*, for use in a method of treating HER2-positive gastric/gastroesophageal junction (GEJ) 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 gastric/GEJ cancer in the individual has progressed following a prior treatment with a fluoropyrimidine-based therapy and/or a prior treatment with an anti-HER2 antibody, and wherein the individual is a human.

[0019] In some embodiment examples, the prior treatment with the fluoropyrimidine-based therapy or the prior treatment with the anti-HER2 antibody comprised one or more therapeutic agents selected from the group consisting of: trastuzumab, pertuzumab, 5-fluorouracil, capecitabine, margetuximab, and FOLFOX. In some embodiment examples, the anti-HER2 antibody is trastuzumab. In some embodiment examples, trastuzumab is administered (such as formulated for administration) to the individual at an initial dose of 8 mg/kg and at a dose of 6 mg/kg for each subsequent dose, and wherein trastuzumab is administered to the individual by IV infusion every 3 weeks (Q3W).

[0020] Provided is a method of treating aggressive non-Hodgkin lymphoma (NHL) 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-CD20 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; wherein the aggressive NHL in the individual is relapsed and/or refractory to a prior treatment for aggressive NHL and there is no available curative therapy, and wherein the individual is a human. In one aspect, the present disclosure refers to use of (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in the manufacture of a medicament for use in combinatorial therapy for treating aggressive non-Hodgkin lymphoma (NHL) in an individual, wherein said medicament is to be administered in combination with (b) an anti-CD20 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 aggressive NHL in the individual is relapsed and/or refractory to a prior treatment for aggressive NHL and there is no available curative therapy, and wherein the individual is a human.

[0021] Also provided is a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant for use in the manufacture of a medicament for treating aggressive non-Hodgkin lymphoma (NHL) in an individual, wherein the medicament is for use (such as formulated for use) in combination with an anti-CD20 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; wherein the aggressive NHL in the

individual is relapsed and/or refractory to a prior treatment for aggressive NHL and there is no available curative therapy, and wherein the individual is a human.

[0022] Also provided is a composition (such a pharmaceutical composition) comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant for use in combination with an anti-CD20 antibody for treating aggressive non-Hodgkin lymphoma (NHL) in an individual (*e.g.*, for use in a method of treating aggressive NHL), 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 aggressive NHL in the individual is relapsed and/or refractory to a prior treatment for aggressive NHL and there is no available curative therapy, and wherein the individual is a human.

[0023] In some embodimentexamples, the aggressive NHL is diffuse large B-cell lymphoma (DLBCL), *e.g.*, *de novo* DLBCL or transformed DLBCL. In some embodimentexamples, the prior treatment(s) for aggressive NHL comprised rituximab, cyclophosphamide, doxorubicin, vincristine, gemcitabine, lenalidomide, prednisone, prednisolone, etoposide, procarbazine, epirubicin, bendamustine, cisplatin, oxaliplatin, cytarabine, ifosfamide, carboplatin, dexamethasone, mesna, carmustine, melphalan, solumedrol, methyl-glyoxal-bis(guanylhyazone), thiotepa, methotrexate, ibrutinib, obinituzumab, tisagenlecleucel, axicabtagene, brentuximab vedotin, and combinations thereof. In some embodimentexamples, the anti-CD20 antibody is rituximab. In some embodimentexamples, the rituximab is administered (such as formulated for administration) to the individual at a dose of 375 mg/m² by IV infusion, wherein rituximab is administered (such as formulated for administration) to the individual once per week for four weeks and once per month thereafter.

[0024] Provided is a method of treating indolent lymphoma 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-CD20 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; wherein the indolent lymphoma in the individual is relapsed and/or refractory to a prior treatment for indolent lymphoma, and wherein the individual is a human. In one aspect, the present disclosure refers to use of (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant in the manufacture of a medicament for use in combinatorial therapy for treating indolent lymphoma in an individual, wherein said medicament is to be administered in combination with (b) an anti-CD20 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 indolent lymphoma in the individual is relapsed and/or refractory to a prior treatment for indolent lymphoma, and wherein the individual is a human.

[0025] Also provided is a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant for use in the manufacture of a medicament for treating indolent lymphoma in an individual, wherein the medicament is for use (such as formulated for use) in combination with an anti-CD20 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; wherein the indolent lymphoma in the individual is relapsed and/or refractory to a prior treatment for indolent lymphoma, and wherein the individual is a human.

[0026] Also provided is a composition (such a pharmaceutical composition) comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant for use in combination with an anti-CD20 antibody for treating indolent lymphoma in an individual (*e.g.*, for use in a method of treating indolent lymphoma 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 indolent lymphoma in the individual is relapsed and/or refractory to a prior treatment for indolent lymphoma, and wherein the individual is a human.

[0027] In some [embodimentexamples](#), the indolent lymphoma is an indolent non-Hodgkin lymphoma (NHL). In some [embodimentexamples](#), the indolent NHL is a marginal zone lymphoma or a follicular lymphoma. In some [embodimentexamples](#), the prior treatment for indolent lymphoma comprised rituximab, cyclophosphamide, doxorubicin, vincristine, gemcitabine, lenalidomide, prednisone, prednisolone, etoposide, procarbazine, epirubicin, bendamustine, cisplatin, oxaliplatin, cytarabine, ifosfamide, carboplatin, dexamethasone, mesna, carmustine, melphalan, solumedrol, methyl-glyoxal-bis(guanylhydrazone), thiotepa, methotrexate, ibrutinib, obinituzumab, tisagenlecleucel, axicabtagene, brentuximab vedotin, fludarabine mitoxantrone, everolimus, bortezomib, navitoclax, and combinations thereof. In some [embodimentexamples](#), the anti-CD20 antibody is rituximab. In some [embodimentexamples](#), the rituximab is administered (such as formulated for administration) to the individual at a dose of 375 mg/m² by IV infusion, wherein rituximab is administered (such as formulated for administration) to the individual once per week for four weeks and once per month thereafter. In some [embodimentexamples](#), the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant (such as the medicament manufactured using such polypeptide or a pharmaceutical composition comprising such polypeptide) is administered (such as formulated for administration) to the individual at a dose of 10 mg/kg or 15 mg/kg once per week (QW), *e.g.*, by IV infusion.

[0028] In some [embodimentexamples](#) of any of the methods herein, 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.

[0029] In some [embodimentexamples](#), the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant (such as the medicament manufactured using such polypeptide or a pharmaceutical composition comprising such polypeptide) is administered (such as formulated for administration) to the individual at a dose of 10 mg/kg once per week (QW). In some [embodimentexamples](#), the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant (or the medicament manufactured therefrom or the pharmaceutical composition comprising such

polypeptide) is administered (such as formulated for administration) to the individual by IV infusion.

[0030] Also provided is a kit comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant (such as the medicament manufactured using such polypeptide or a pharmaceutical composition comprising such polypeptide), for use in combination with pembrolizumab for treating non-small cell lung cancer (NSCLC) in an individual (e.g., human individual) in need thereof, according to a method described herein. In some **embodimentexamples**, the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 85; 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 one aspect, the present disclosure refers to 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 pembrolizumab for treating non-small cell lung cancer (NSCLC) 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 individual is human. In some **embodimentexamples**, the NSCLC in the individual has progressed on a prior immune checkpoint inhibitor (CPI) therapy and/or has a PD-L1 tumor proportion score (TPS) of less than 50%. In some **embodimentexamples**, the kit further comprises instructions for administering pembrolizumab at a dose of 200 mg every 3 weeks (Q3W) by IV infusion. In some **embodimentexamples**, the kit further comprises instructions for administering the polypeptide (e.g. fusion polypeptide) at a dose of 10 mg/kg once a week, e.g., by IV infusion.

[0031] Also provided is a kit comprising a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant (such as the medicament manufactured using such polypeptide or a pharmaceutical composition comprising such polypeptide) for use in combination with pembrolizumab for treating head and neck squamous cell carcinoma (HNSCC) in an individual (e.g., a human individual) in need thereof, according to a method described herein. In some **embodimentexamples**, the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 85; 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

the HNSCC in the individual has progressed while on a prior platinum therapy or after the platinum therapy. In one aspect, the present disclosure refers to 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 pembrolizumab for treating head and neck squamous cell carcinoma (HNSCC) in an individual in need thereof, 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 HNSCC in the individual has progressed while on a prior platinum therapy or after the platinum therapy, and wherein the individual is human. In some **embodimentexamples**, the individual received prior therapy with an immune checkpoint inhibitor. In some **embodimentexamples**, the individual has not received prior therapy with an immune checkpoint inhibitor. In some **embodimentexamples**, the kit further comprises instructions for administering pembrolizumab at a dose of 200 mg every 3 weeks (Q3W) by IV infusion. In some **embodimentexamples**, the kit further comprises instructions for administering the polypeptide (e.g. fusion polypeptide) at a dose of 10 mg/kg once a week, e.g., by IV infusion.

[0032] Also provided herein 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 trastuzumab for treating HER2-positive gastric/gastroesophageal junction (GEJ) cancer in an individual (e.g., a human individual) in need thereof, according to a method described herein. In some **embodimentexamples**, the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 85; 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 the HER2-positive gastric/GEJ cancer in the individual has progressed following a prior fluoropyrimidine-based therapy or a prior treatment with an anti-HER2 antibody. In one aspect, the present disclosure refers to 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 trastuzumab for treating HER2-positive gastric/gastroesophageal junction (GEJ) cancer in an individual in need thereof, 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 HER2-positive gastric/GEJ cancer in the individual has progressed following a prior fluoropyrimidine-based therapy or a prior treatment with an anti-HER2 antibody, and wherein the individual is human. In some **embodimentexamples**, the kit further comprises instructions for administering trastuzumab at an initial dose of 8 mg/kg and at a dose of 6 mg/kg for each subsequent dose, and wherein trastuzumab is administered to the individual by IV infusion every 3 weeks (Q3W). In some **embodimentexamples**, the kit further comprises instructions for administering the polypeptide (e.g. fusion polypeptide) at a dose of 10 mg/kg once a week, e.g., by IV infusion.

[0033] 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 rituximab for treating aggressive non-Hodgkin lymphoma (NHL) in an individual (e.g., a human individual) in need thereof, according to a method described herein. In some **embodimentexamples**, the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 85; 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 the aggressive NHL in the individual is relapsed and/or refractory to a prior treatment for aggressive NHL and there is no available curative therapy. In one aspect, the present disclosure refers to 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 rituximab for treating aggressive non-Hodgkin lymphoma (NHL) 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 aggressive NHL in the individual is relapsed and/or refractory to a prior treatment for aggressive NHL and there is no available curative therapy, and wherein the individual is human. In some **embodimentexamples**, the aggressive NHL is a diffuse large B-cell lymphoma (DLBCL), e.g., a *de novo* DLBCL or a transformed DLBCL. In some **embodimentexamples**, the aggressive NHL is a mantle cell lymphoma. In some **embodimentexamples**, the kit further comprises instructions for administering rituximab at a dose of 375 mg/m² by IV infusion, wherein rituximab is administered to the individual once per week for four weeks and once per month thereafter. In some **embodimentexamples**, the kit further comprises instructions for administering the polypeptide (e.g. fusion polypeptide) at a dose of 10 mg/kg or 15 mg/kg once a week, e.g., by IV infusion.

[0034] 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 rituximab for treating indolent lymphoma in an individual (e.g., a human individual) in need thereof, according to a method described herein. In some **embodimentexamples**, the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 85; 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 the indolent lymphoma in the individual is relapsed or refractory to a prior treatment for indolent lymphoma. In one aspect, the present disclosure refers to 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 rituximab for treating indolent lymphoma 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 indolent lymphoma in the individual is relapsed or refractory to a prior treatment for indolent lymphoma, and wherein the individual is human. In some **embodimentexamples**, the indolent lymphoma is an indolent non-Hodgkin lymphoma (NHL). In some **embodimentexamples**, the indolent NHL is a Marginal zone lymphoma or a follicular lymphoma. In some **embodimentexample**, the kit further comprises instructions for administering rituximab at a dose of 375 mg/m² by IV infusion, wherein rituximab is administered to the individual once per week for four weeks and once per month thereafter. In some **embodimentexamples**, the kit further comprises instructions for administering the polypeptide (e.g. fusion polypeptide) at a dose of 10 mg/kg or 15 mg/kg once a week, e.g., by IV infusion.

[0035] In some embodimentexamples of any 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, further comprising instructions for administering the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant (or the medicament manufactured therefrom or the pharmaceutical composition comprising such polypeptide) to the individual at a dose of 10 mg/kg once per week (QW). In some embodimentexamples, the kit comprises instructions for administering the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant (or the medicament manufactured therefrom or the pharmaceutical composition comprising such polypeptide) to the individual by IV infusion.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] **FIGs 1A-1B** depicts Drug A is a monomer (**FIG 1A**), and as a homodimer (**FIG 1B**). The SIRP α D1 domain variant selectively binds CD47 with picomolar binding affinity to block its interactions with SIRP α . The molecular weight of Drug A is half the size of a typical antibody, allowing twice the molar concentration to be delivered to tumors. The Fc domain is modified to eliminate binding to Fc gamma receptors to minimize toxicity. Drug A exhibits antibody-like pharmacokinetics.

[0037] **FIG 2** provides a schematic of the clinical study described in Example 1.

[0038] **FIGs 3A-3C** show the clinical activity of Drug A + trastuzumab in the HER2 positive gastric/GEJ cancer expansion cohort. **FIG 3A** provides the change in tumor size, shown as percent from baseline. ORR = overall response rate; DCR = disease control rate; mPFS = median progression-free; CI = confidence interval. The changes in tumor sizes shown as percent from baseline for each patient over the course of the study are provided in **FIG 3B**. For **FIGs 3A-3B**: patients who received at least one dose of Drug A in the expansion phase, had a baseline assessment, and at least one post-baseline disease assessment are included; the top dashed line indicates the threshold for objective progression; the bottom dashed line indicates the threshold for overall response. The duration of treatment for each enrolled patient who received at least one