

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 $\alpha$  D1 domain variant and an Fc domain variant in the manufacture of a medicament for treating cancer in an individual;

wherein the SIRP $\alpha$  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.

**[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 $\alpha$  D1 domain variant and an Fc domain variant, and (b) a Bcl-2 inhibitor; wherein the SIRP $\alpha$  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 examples, the cancer is leukemia, multiple myeloma, or non-Hodgkin's lymphoma. In some examples, the non-Hodgkin's lymphoma is diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), or follicular lymphoma (FL). In some examples, 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 examples, the leukemia is acute lymphoblastic leukemia. In some examples, the Bcl-2 inhibitor is venetoclax, ABT-737, navitoclax, BCL201, or AZD-0466. In some examples, 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 $\alpha$  D1 domain variant and an Fc domain variant, and (b) a platinum-based chemotherapy agent; wherein the SIRP $\alpha$  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