~~BRIEF~~ SUMMARY

[0010] In some ~~embodiment~~examples, provided is a method of treating cancer (e.g., myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)) in an individual, comprising administering to the individual an effective amount of: (a) a fusion polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant, and (b) a hypomethylating agent; wherein the C-terminus of the SIRPα D1 domain variant of the fusion polypeptide is linked to the N-terminus of the Fc-domain variant. In some ~~embodiment~~examples, provided is a method of treating cancer (e.g., AML) in an individual, comprising administering to the individual an effective amount of: (a) a fusion polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant, and (b) a hypomethylating agent; wherein the C-terminus of the SIRPα D1 domain variant of the fusion polypeptide is linked to the N-terminus of the Fc-domain variant. In one aspect, the present disclosure refers to use of (a) a fusion polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant in the manufacture of a medicament for use in combinatorial therapy for treating cancer in an individual, wherein said medicament is to be administered in combination with (b) a hypomethylating agent; wherein the C-terminus of the SIRPα D1 domain variant of the fusion polypeptide is linked to the N-terminus of the Fc-domain variant. In some ~~embodiment~~examples, the SIRPα D1 domain variant of the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 85; and the Fc domain variant of the fusion polypeptide 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 ~~embodiment~~examples, the cancer is myelodysplastic syndrome (MDS). In some ~~embodiment~~examples, the MDS is higher risk MDS. In some ~~embodiment~~examples, the individual has received prior therapy for MDS. In some ~~embodiment~~examples, the individual has not received prior therapy for MDS. In some ~~embodiment~~examples, treatment for MDS comprises an induction phase and a maintenance phase, wherein the induction phase comprises administering (a) the fusion polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant, and (b) the hypomethylating agent, and wherein the maintenance phase comprises administering the fusion polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant without the hypomethylating agent. In some ~~embodiment~~examples, the cancer is acute myeloid leukemia (AML). In some ~~embodiment~~examples, the fusion polypeptide is administered at a dose up to about 60 mg/kg. In some ~~embodiment~~examples, fusion polypeptide is administered at a dose of about 60 mg/kg once every four weeks (q4w). In some ~~embodiment~~examples, the cancer is acute myeloid leukemia (AML). In some ~~embodiment~~examples, the individual has subcytologically or histologically confirmed diagnosis of relapsed/refractory or newly diagnosed AML per WHO

2016 classification. In some ~~embodiment~~examples, the individual has AML that is relapsed/refractory or that is previously untreated in patients not considered suitable for intensive induction therapy. In some ~~embodiment~~examples, the individual has AML that is relapsed/refractory after prior treatment with a HMA-based regimen. In some ~~embodiment~~examples, the individual has previously untreated AML and is not considered a suitable candidate for intensive induction therapy. In some ~~embodiment~~examples, the individual has adequate renal and liver function. In some ~~embodiment~~examples, the individual is ≥18 years old. In some ~~embodiment~~examples, the individual has adequate performance status. In some ~~embodiment~~examples, the individual has not undergone prior allo-hematopoietic stem cell transplantation (HSCT). In some ~~embodiment~~examples, the individual is least 3 months post-HCST, without uncontrolled graft-versus-host disease (GVHD). In some ~~embodiment~~examples, the individual has not undergone prior allo-HSCT. In some ~~embodiment~~examples, the individual does not have newly diagnosed AML with favorable risk cytogenetics such as t(8;21), inv(16), or t(16;16) as per the National Comprehensive Cancer Network (NCCN) guidelines version 3, 2019 for AML. In some ~~embodiment~~examples, the individual does not have acute promyelocytic leukemia (APL). In some ~~embodiment~~examples, the individual has not undergone prior treatment with any anti-CD47 or anti-SIRPα (signal regulatory protein alpha) agent. In some ~~embodiment~~examples, the individual does not have known active viral infections, including hepatitis B and C, human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS) related illness, or sars-cov-2 (severe acute respiratory syndrome coronavirus 2). In some ~~embodiment~~examples, the fusion polypeptide is administered at a dose up to about 60 mg/kg. In some ~~embodiment~~examples, fusion polypeptide is administered at a dose of about 60 mg/kg once every four weeks (q4w).

[0011] In some ~~embodiment~~examples, the hypomethylating agent is azacitidine, decitabine, 5-fluoro-2′-deoxycytidine, zebularine, CP-4200, RG108, nanaomycin A, guadecitabine, RX-3117, EPI01, antroquinonol, CC-486, or ASTX727. In some ~~embodiment~~examples, the hypomethylating agent is azacitidine. In some ~~embodiment~~examples, the azacitidine is administered to the individual in one or more 28-day cycles, and wherein the azacitidine is administered to the individual at a dose of 75 mg/m^2 daily for 7 days of every 28 day cycle. In some ~~embodiment~~examples, the azacitidine is administered to the in one or more 28-day cycles, and wherein the azacitidine is administered to the individual during each 28-day cycle at a dose of 75 mg/m^2 daily for 5 days, followed by 2 days without azacitidine administration, and then administered to the individual at a dose of 75 mg/m^2 for 2 additional days. In some ~~embodiment~~examples, the azacitidine is administered intravenously or subcutaneously.

[0011a] In one aspect, the present disclosure refers to use of (a) a fusion polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant in the manufacture of a medicament for use in combinatorial therapy for treating cancer in an individual, wherein said medicament is to be administered in combination with (b) a hypomethylating agent, and (c) a Bcl-2 inhibitor; wherein the C-terminus of the SIRPα D1 domain variant of the fusion polypeptide is linked to the N-terminus of the Fc-domain variant.

[0012] In some ~~embodiment~~examples, the Bcl-2 inhibitor is venetoclax, ABT-737, navitoclax, BCL201, or AZD-0466. In some ~~embodiment~~examples, the Bcl-2 inhibitor is venetoclax. In some ~~embodiment~~examples, the venetoclax is administered at a dose of 100 mg on day 1, at a dose of 200 mg on day 2, and at a dose of 400 mg every day following day 2. In some ~~embodiment~~examples, the venetoclax is administered at a dose of 100 mg on day 1, at a dose of 200 mg on day 2, and at a dose of 400 mg on day 3, and at a dose of 600 mg every day following day 3. In some ~~embodiment~~examples, the venetoclax is administered orally.

[0013] In some ~~embodiment~~examples, provided is a method of treating cancer in an individual, comprising administering to the individual an effective amount of a fusion polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant, wherein the C-terminus of the SIRPα D1 domain variant is fused to the N-terminus of the Fc domain variant, and wherein the fusion polypeptide is administered at a dose of up to about 60 mg/kg. In one aspect, the present disclosure refers to use of a fusion polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant in the manufacture of a medicament for treating cancer in an individual, wherein the C-terminus of the SIRPα D1 domain variant is fused to the N-terminus of the Fc domain variant and wherein the medicament is to be administered at a dose of up to about 60 mg/kg. In some ~~embodiment~~examples, the fusion polypeptide is administered at a dose of about 60 mg/kg. In some ~~embodiment~~examples, wherein the fusion polypeptide is administered at a dose of about 60 mg/kg once every 4 weeks (q4w). In some ~~embodiment~~examples, the fusion polypeptide is administered at a dose of about 45 mg/kg. In some ~~embodiment~~examples, the fusion polypeptide is administered at a dose of about 45 mg/kg once every 3 weeks (q3w). In some ~~embodiment~~examples, the cancer is a hematological cancer. In some ~~embodiment~~examples, the cancer is a solid tumor.

[0014] In some ~~embodiment~~examples, the SIRPα D1 domain variant of the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 81 or SEQ ID NO: 85; and the Fc domain variant of the fusion polypeptide 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.

[0015] In some ~~embodiment~~examples of any of the methods provided herein, the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 85. In some ~~embodiment~~examples, the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the Fc domain variant comprises the amino acid sequence of SEQ ID NO: 91. In some ~~embodiment~~examples, the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 136. In some ~~embodiment~~examples, the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 135. In some ~~embodiment~~examples, the fusion polypeptide forms a homodimer. In some ~~embodiment~~examples, the fusion polypeptide is administered intravenously. In some ~~embodiment~~examples, the individual is a human.

[0016] In some ~~embodiment~~examples, provided is a kit comprising a fusion polypeptide in a pharmaceutically acceptable carrier, for use in combination with azacitidine for treating cancer in an individual in need thereof, wherein the fusion polypeptide comprises a SIRPα D1 domain variant and an Fc domain variant, wherein the C-terminus of the SIRPα D1 domain variant is fused to the N-terminus of the Fc domain variant, 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 individual is human. In one aspect, the present disclosure refers to a kit comprising a fusion polypeptide in a pharmaceutically acceptable carrier, for use in combination with azacitidine for treating cancer in an individual in need thereof, wherein the fusion polypeptide comprises a SIRPα D1 domain variant and an Fc domain variant, wherein the C-terminus of the SIRPα D1 domain variant is fused to the N-terminus of the Fc domain variant, 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 individual is human. In some ~~embodiment~~examples, the cancer is myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). In some ~~embodiment~~examples, the cancer is MDS. In some ~~embodiment~~examples, the MDS is higher risk MDS.

[0017] In some ~~embodiment~~examples, provided is a kit comprising a fusion polypeptide in a pharmaceutically acceptable carrier, for use in combination with azacitidine and venetoclax for treating cancer in an individual in need thereof, wherein the fusion polypeptide comprises a SIRPα D1 domain variant and an Fc domain variant, wherein the C-terminus of the SIRPα D1 domain variant is fused to the N-terminus of the Fc domain variant, 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 individual is human. In one aspect, the present disclosure refers to a kit comprising a fusion polypeptide in a pharmaceutically acceptable carrier, for use in combination with azacitidine and venetoclax for treating cancer in an individual in need thereof, wherein the fusion polypeptide comprises a SIRPα D1 domain variant and an Fc domain variant, wherein the C-terminus of the SIRPα D1 domain variant is fused to the N-terminus of the Fc domain variant, 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 individual is human. In some ~~embodiment~~examples, the cancer is AML.

[0018] In some ~~embodiment~~examples, the kit further comprises instructions for administering azacitidine by IV infusion or subcutaneously in one or more 28-day cycles, wherein the azacitidine is administered to the individual at a dose of 75 mg/m^2 daily for 7 days of each 28-day cycle. In some ~~embodiment~~examples, the kit further comprises instructions for administering azacitidine by IV infusion or subcutaneously in one or more 28-day cycles, wherein the azacitidine is administered to the individual during each 28 day cycle at a dose of 75 mg/m^2 daily for 5 days, followed by 2 days without azacitidine administration, and then administered to the individual at a dose of 75 mg/m^2 for 2 additional days.

[0019] In some ~~embodiment~~examples, the kit further comprises instructions for administering venetoclax orally at a dose of 100 mg on Day 1, 200 mg on Day 2, and 400 mg on every day following Day 2. In some ~~embodiment~~examples, the kit further comprises instructions for administering venetoclax orally at a dose of 100 mg on Day 1, 200 mg on Day 2, and 400 mg on Day 3, and 600 mg on every day following Day 3.

[0020] In some ~~embodiment~~examples of the kits, the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 85. In some ~~embodiment~~examples, the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81. In some ~~embodiment~~examples, 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 ~~embodiment~~examples, the Fc domain variant comprises the amino acid sequence of SEQ ID NO: 91. In some ~~embodiment~~examples, the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 136. In some ~~embodiment~~examples, the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 135. In some ~~embodiment~~examples, the fusion polypeptide forms a homodimer. In some ~~embodiment~~examples, the kit further comprises instructions for administering the fusion polypeptide to the individual at a dose of up to 60 mg/kg. In some ~~embodiment~~examples, the kit further comprises instructions for administering the fusion polypeptide to the individual at a dose of 60 mg/kg once every four weeks (q4w). In some ~~embodiment~~examples, the kit further comprises instructions for administering the fusion polypeptide by IV infusion.