SUMMARY

[0010] In some 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 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 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 examples, the cancer is myelodysplastic syndrome (MDS). In some examples, the MDS is higher risk MDS. In some examples, the individual has received prior therapy for MDS. In some examples, the individual has not received prior therapy for MDS. In some 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 examples, the cancer is acute myeloid leukemia (AML). In some examples, the fusion polypeptide is administered at a dose up to about 60 mg/kg. In some examples, fusion polypeptide is administered at a dose of about 60 mg/kg once every four weeks (q4w). In some examples, the cancer is acute myeloid leukemia (AML). In some examples, the individual has subcytologically or histologically confirmed diagnosis of relapsed/refractory or newly diagnosed AML per WHO

2016 classification. In some 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 examples, the individual has AML that is relapsed/refractory after prior treatment with a HMA-based regimen. In some examples, the individual has previously untreated AML and is not considered a suitable candidate for intensive induction therapy. In some examples, the individual has adequate renal and liver function. In some examples, the individual is ≥18 years old. In some examples, the individual has adequate performance status. In some examples, the individual has not undergone prior allo-hematopoietic stem cell transplantation (HSCT). In some examples, the individual is least 3 months post-HCST, without uncontrolled graft-versus-host disease (GVHD). In some examples, the individual has not undergone prior allo-HSCT. In some 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 examples, the individual does not have acute promyelocytic leukemia (APL). In some examples, the individual has not undergone prior treatment with any anti-CD47 or anti-SIRPα (signal regulatory protein alpha) agent. In some 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 examples, the fusion polypeptide is administered at a dose up to about 60 mg/kg. In some examples, fusion polypeptide is administered at a dose of about 60 mg/kg once every four weeks (q4w).

[0011] In some 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 examples, the hypomethylating agent is azacitidine. In some 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 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 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 examples, the Bcl-2 inhibitor is venetoclax, ABT-737, navitoclax, BCL201, or AZD-0466. In some examples, the Bcl-2 inhibitor is venetoclax. In some 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 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 examples, the venetoclax is administered orally.

[0013] In some 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 examples, the fusion polypeptide is administered at a dose of about 60 mg/kg. In some examples, wherein the fusion polypeptide is administered at a dose of about 60 mg/kg once every 4 weeks (q4w). In some examples, the fusion polypeptide is administered at a dose of about 45 mg/kg. In some examples, the fusion polypeptide is administered at a dose of about 45 mg/kg once every 3 weeks (q3w). In some examples, the cancer is a hematological cancer. In some examples, the cancer is a solid tumor.

[0014] In some 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 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 examples, the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81. In some 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 examples, the Fc domain variant comprises the amino acid sequence of SEQ ID NO: 91. In some examples, the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 136. In some examples, the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 135. In some examples, the fusion polypeptide forms a homodimer. In some examples, the fusion polypeptide is administered intravenously. In some examples, the individual is a human.

[0016] In some 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 examples, the cancer is myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). In some examples, the cancer is MDS. In some examples, the MDS is higher risk MDS.

[0017] In some 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 examples, the cancer is AML.

[0018] In some 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 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 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 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 examples of the kits, the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 85. In some examples, the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81. In some 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 examples, the Fc domain variant comprises the amino acid sequence of SEQ ID NO: 91. In some examples, the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 136. In some examples, the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 135. In some examples, the fusion polypeptide forms a homodimer. In some 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 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 examples, the kit further comprises instructions for administering the fusion polypeptide by IV infusion.