CLAIMS

1. ~~A method of treating cancer in an individual, comprising administering to the individual an effective amount of:~~Use of (a) a fusion polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant~~, and~~ 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.

2. ~~A method of treating cancer in an individual, comprising administering to the individual an effective amount of:~~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.

3. The use~~method~~ of claim 1 or 2, wherein 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

wherein 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.

4. The use~~method~~ of claim 1 or 3, wherein the cancer is myelodysplastic syndrome (MDS) .

5. The usemethod of claim 4 wherein the MDS is higher risk MDS.

6. The usemethod of claim any one of claims 1 and 3-5, wherein the individual has received prior therapy for MDS.

7. The usemethod of any one of claims 1 and 3-5, wherein the individual has not received prior therapy for MDS.

8. The usemethod of any one of claims 1 and 3-7, wherein treatment comprises an induction phase and a maintenance phase, wherein the induction phase comprises administration ofadministering (a) the medicamentfusion polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant, and (b) the hypomethylating agent, and wherein the maintenance phase comprises administration ofadministering the medicament fusion polypeptide comprising a SIRPα D1 domain variant and an Fc domain variant without the hypomethylating agent.

9. The usemethod of claim 2 or 3, wherein the cancer is acute myeloid leukemia (AML).

10. The usemethod of claim 9, wherein the individual has one or more of the following characteristics:

(a) cytological or histologically confirmed diagnosis of relapsed/refractory or newly diagnosed AML;

(b) AML that is relapsed/refractory or that is previously untreated and not considered suitable for intensive induction therapy;

(c) AML that is relapsed/refractory after prior treatment with a HMA-based regimen;

(d) previously untreated AML and is not considered suitable candidate for intensive induction therapy; and

(e) adequate renal and liver function.

11. The usemethod of any one of claims 1-10, wherein 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.

12. The usemethod of claim 11, wherein the hypomethylating agent is azacitidine.

13. The usemethod of claim 12, wherein the azacitidine is to be administered to the individual in one or more 28-day cycles, and wherein the azacitidine is to be administered to the individual at a dose of 75 mg/m^2 daily for 7 days of every 28 day cycle.

14. The usemethod of claim 12, wherein the azacitidine is to be administered to the individual in one or more 28-day cycles, and wherein the azacitidine is to be 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 the azacitidine is to be administered to the individual at a dose of 75 mg/m^2 for 2 additional days.

15. The usemethod of any one of claims 12-14, wherein the azacitidine is to be administered intravenously or subcutaneously.

16. The usemethod of any one of claims 2-3 and 9-15, wherein the Bcl-2 inhibitor is venetoclax, ABT-737, navitoclax, BCL201, or AZD-0466.

17. The usemethod of claim 16, wherein the Bcl-2 inhibitor is venetoclax.

18. The usemethod of claim 17, wherein the venetoclax is to be 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.

19. The usemethod of claim 17, wherein the venetoclax is to be 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.

20. The usemethod of any one of claims 17-19, wherein the venetoclax is to be administered orally.

21. The usemethod of any one of claims 1-20, wherein the medicamentfusion polypeptide

is to be administered at a dose up to about 60 mg/kg.

22. The usemethod of claim 21, wherein the medicamentfusion polypeptide is to be administered at a dose of about 60 mg/kg once every four weeks (q4w).

23. A method of treating cancer in an individual, comprising administering to the individual an effective amount 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 medicamentfusion polypeptide is to be administered at a dose of up to about 60 mg/kg.

24. The usemethod of claim 23, wherein the medicamentfusion polypeptide is to be administered at a dose of about 60 mg/kg.

25. The usemethod of claim 24, wherein the medicamentfusion polypeptide is to be administered at a dose of about 60 mg/kg once every 4 weeks (q4w).

26. The usemethod of claim 23, wherein the medicamentfusion polypeptide is to be administered at a dose of about 45 mg/kg.

27. The usemethod of claim 26, wherein the medicamentfusion polypeptide is to be administered at a dose of about 45 mg/kg once every 3 weeks (q3w).

28. The usemethod of any one of claims 22-27, wherein 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

wherein 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.

29. The use~~method~~ of any one of claims 22-28, wherein the cancer is a hematological cancer.

30. The use~~method~~ of any one of claims 22-29 wherein the cancer is a solid tumor.

31. The use~~method~~ of any one of claims 1-30, wherein the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 85.

32. The use~~method~~ of any one of claims 1-30, wherein the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81.

33. The use~~method~~ of any one of claims 1-32, 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.

34. The use~~method~~ of claim 33, wherein the Fc domain variant comprises the amino acid sequence of SEQ ID NO: 91.

35. The use~~method~~ of any one of claims 1-31 and 33-34, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 136.

36. The use~~method~~ of any one of claims 1-30 and 32-34, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 135.

37. The use~~method~~ of any one of claims 1-36, wherein the fusion polypeptide forms a homodimer.

38. The use~~method~~ of any one of claims 1-37, wherein the medicament~~fusion polypeptide~~ is to be administered intravenously.

39. The use~~method~~ of any one of claims 1-38, wherein the individual is a human.

40. 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.

41. The kit of claim 40, wherein the cancer is myelodysplastic syndrome (MDS).

42. The kit of claim 41, wherein the MDS is higher risk MDS.

43. 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.

44. The kit of claim 43, wherein the cancer is acute myeloid leukemia (AML).

45. The kit of claim any one of claims 40-44, further comprising instructions for administering azacitidine by IV infusion or subcutaneously in one or more 28-day cycles, wherein the azacitidine is to be administered to the individual at a dose of 75 mg/m^2 daily for 7 days of each 28-day cycle.

46. The kit of any one of claims 40-44, further comprising instructions for administering azacitidine by IV infusion or subcutaneously in one or more 28-day cycles, wherein the azacitidine is to be 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 the azacitidine is to be administered to the individual at a dose of 75 mg/m^2 for 2 additional days.

47. The kit of any one of claims 43-46 further comprising 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.

48. The kit of any one of claims 43-46 further comprising 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.

49. The kit of any one of claims 40-48, wherein the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 85.

50. The kit of any one of claims 40-48, wherein the SIRPα D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81.

51. The kit of any one of claims 40-50, 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.

52. The kit of claim 51, wherein the Fc domain variant comprises the amino acid sequence of SEQ ID NO: 91.

53. The kit of any one of claims 40-49 and 51-52, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 136.

54. The kit of any one of claims 40-48 and 50-52, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 135.

55. The kit of any one of claims 40-54, wherein the fusion polypeptide forms a homodimer.

56. The kit of any one of claims 40-55, further comprising instructions for administering the fusion polypeptide to the individual at a dose of up to 60 mg/kg.

57. The kit of any one of claims 40-56, further comprising instructions for administering

the fusion polypeptide to the individual at a dose of 60 mg/kg once every four weeks (q4w).

58. The kit of any one of claims 40-57, further comprising instructions for administering the fusion polypeptide by IV infusion.