

CLAIMS

1. 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; andwherein 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.
2. The use of claim 1, wherein 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.
3. The use of claim 1 or 2, wherein the anti-HER2 antibody is trastuzumab.
4. The use of claim 3, wherein trastuzumab is to be administered 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 to be administered to the individual by IV infusion every 3 weeks (Q3W).

~~15. A method of treating non-small cell lung cancer (NSCLC) in an individual, comprising administering to the individual an effective amount of~~Use of (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant,~~and 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.

~~26. The use~~method of claim ~~15~~, wherein the NSCLC in the individual has progressed on a prior checkpoint inhibitor (CPI) therapy and/or has a PD-L1 tumor proportion score (TPS) of less than 50%,

~~37. The use~~method of claim ~~26~~, wherein the prior checkpoint inhibitor therapy comprised one or more agents selected from the group consisting of: nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, and cemiplimab.

~~48. A method of treating head and neck squamous cell carcinoma (HNSCC) in an individual, comprising administering to the individual an effective amount of~~Use of (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant,~~and 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.

59. The ~~use method~~ of claim 48, wherein the individual has received prior therapy with an immune checkpoint inhibitor.

610. The ~~use method~~ of claim 48, wherein the individual has not received prior therapy with an immune checkpoint inhibitor.

711. The ~~use method~~ of any one of claims 4-68-10, wherein the prior platinum therapy comprised one or more therapeutic agents selected from the group consisting of: cisplatin, carboplatin, and oxaliplatin.

812. The ~~use method~~ of any one of claims 1-75-11, wherein the anti-PD-1 antibody is pembrolizumab.

913. The ~~use method~~ of claim 812, wherein pembrolizumab is to be administered to the individual at a dose of 200 mg every 3 weeks (Q3W) by intravenous (IV) infusion.

~~10.—A method of treating HER2-positive gastric/gastroesophageal junction (GEJ) cancer in an individual, comprising administering to the individual an effective amount~~Use of (a) a 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 HER2-positive gastric/gastroesophageal junction (GEJ) cancer in an individual, wherein said medicament is to be administered in combination with~~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; 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.~~

11. The use method of claim 10, wherein 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.

12. The use method of claim 10 or 11, wherein the anti-HER2 antibody is trastuzumab.

13. The use method of claim 12, wherein trastuzumab is to be administered 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 to be administered to the individual by IV infusion every 3 weeks (Q3W).

14. ~~A method of treating aggressive non-Hodgkin lymphoma (NHL) in an individual, comprising administering to the individual an effective amount~~ Use of (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, and 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.

15. The ~~use~~method of claim 14, wherein the aggressive NHL is a diffuse large B-cell lymphoma (DLBCL).

16. The ~~use~~method of claim 15, wherein the DLBCL is a *de novo* DLBCL or a transformed DLBCL.

17. The ~~use~~method of claim 14, wherein the aggressive NHL is a mantle cell lymphoma (MCL).

18. The ~~use~~method of any one of claims 14-17, wherein the prior treatment 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(guanylhydrazine), thiotepa, methotrexate, ibrutinib, obinituzumab, tisagenlecleucel, axicabtagene, brentuximab vedotin, and combinations thereof.

19. ~~A method of treating indolent lymphoma in an individual, comprising administering to the individual an effective amount~~Use of (a) a polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant, ~~and 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.

20. The usemethod of claim 19, wherein the indolent lymphoma is an indolent non-Hodgkin lymphoma (NHL).

21. The usemethod of claim 20, wherein the indolent NHL is a marginal zone lymphoma or a follicular lymphoma.

22. The usemethod of any one of claims 19-21, wherein the prior treatment for indolent lymphoma comprised 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; rituximab, obinituzumab, tisagenlecleucel, axicabtagene, brentuximab vedotin, fludarabine mitoxantrone, everolimus, bortezomib, navitoclax, and combinations thereof.

23. The usemethod of any one of claims 14-22, wherein the anti-CD20 antibody is rituximab.

24. The usemethod of claim 23, wherein rituximab is to be administered to the individual at a dose of 375 mg/m² by IV infusion, wherein rituximab is to be administered to the individual once per week for four weeks and once per month thereafter.

25. The ~~usemethod~~ of any one of claims 1-24, wherein the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO: 85.
26. The ~~usemethod~~ of any one of claims 1-24, wherein the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO~~L~~: 81.
27. The ~~usemethod~~ of any one of claims 1-26, 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.
28. The ~~usemethod~~ of claim 27, wherein the Fc domain variant comprises the amino acid sequence of SEQ ID NO: 91.
29. The ~~usemethod~~ of any one of claims 1-25 and 27-28, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 136.
30. The ~~usemethod~~ of any one of claims 1-24 and 26-28, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 135.
31. The ~~usemethod~~ of any one of claims 1-30, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant forms a homodimer.
32. The ~~usemethod~~ of any one of claims 1-31, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant is to be administered to the individual at a dose of 10 mg/kg once per week (QW).
33. The ~~usemethod~~ of any one of claims 14-31, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant is to be administered to the individual at a dose of 15 mg/kg once per week (QW).
34. The ~~usemethod~~ of claim 32 or 33, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant is to be administered to the individual by IV infusion.

35. 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.

36. The kit of claim 35, wherein the NSCLC in the individual has progressed on a prior checkpoint inhibitor (CPI) therapy and/or has a PD-L1 tumor proportion score (TPS) of less than 50%.

37. 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 head and neck squamous cell carcinoma (HNSCC) 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 HNSCC in the individual has progressed while on a prior platinum therapy or after the platinum therapy, and wherein the individual is human.

38. The kit of any one of claims 34-37, further comprising instructions for administering pembrolizumab at a dose of 200 mg every 3 weeks (Q3W) by IV infusion.

39. 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 trastuzumab for treating HER2-positive gastric/gastroesophageal junction (GEJ) cancer 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 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.

40. The kit of claim 39, further comprising 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).

41. 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.

42. The kit of claim 41 wherein the aggressive NHL is diffuse large B-cell lymphoma (DLBCL).

43. The kit of claim 42, wherein the DLBCL is a *de novo* DLBCL or a transformed DLBCL.

44. The kit of claim 41, wherein the aggressive NHL is a mantle cell lymphoma.

45. 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.
46. The kit of claim 45, wherein the indolent lymphoma is an indolent non-Hodgkin lymphoma (NHL).
47. The kit of claim 46, wherein the indolent NHL is a marginal zone lymphoma or a follicular lymphoma.
48. The kit of any one of claims 41-47, further comprising 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.
49. The kit of any one of claims 35-48, wherein the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO: 85.
50. The kit of any one of claims 35-48, wherein the SIRP α D1 domain variant comprises the amino acid sequence of SEQ ID NO: 81.
51. The kit of any one of claims 35-50, 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.
52. The kit of any one of claims 35-49 and 51, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 136.
53. The kit of any one of claims 35-48 and 50-51, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant comprises the amino acid sequence of SEQ ID NO: 135.

54. The kit of any one of claims 35-53, wherein the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant forms a homodimer.
55. The kit of any one of claims 35-54, further comprising instructions for administering the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant to the individual at a dose of 10 mg/kg once per week (QW).
56. The kit of any one of claims 41-54, further comprising instructions for administering the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant to the individual at a dose of 15 mg/kg once per week (QW).
57. The kit of claim 55 or 56, further comprising instructions for administering the polypeptide comprising a SIRP α D1 domain variant and an Fc domain variant to the individual by IV infusion.