

CLAIMS

What is claimed is:

- 5 1. ~~A method of treating cancer in a patient comprising periodically subcutaneously administering to the patient a dose of the fusion protein of SEQ ID NO: 1 wherein the periodic dosing is once every about 3 days to once every about 60 days.~~
- 10 2. ~~The method of claim 1, wherein the periodic dosing is once every about 3 days to once every about 21 days.~~
3. ~~The method of claim 1, wherein the periodic dosing is once every 3 days, once every 4 days, once every 7 days, once every 14 days or once every 21 days.~~
- 15 4. ~~The method of claim 1, wherein the dose is about 0.1 mgs to about 30 mgs of the fusion protein of SEQ ID NO: 1.~~
5. ~~The method of claim 1, wherein the dose is 1 mg, 3 mg, 6 mg, 10 mg, 15 mg, 20 mg or 30 mg.~~
- 20 6. ~~The method of claim 1, wherein the dose is about 0.1 mg to about 30 mg or about 1 µg/kg to about 500 µg/kg or a corresponding fixed dose based on an about 60 to about 70 kg adult or based on an about 12 kg to about 50 kg or more child.~~
- 25 7. ~~The method of claim 1, wherein periodic subcutaneous administration results in a greater increase in circulating CD8⁺ T cells as compared to daily subcutaneous administration.~~
8. ~~The method of claim 7, wherein the increase in circulating CD8⁺ T cells is at least 2 fold over baseline.~~

9. — The method of claim 7, wherein the ratio of increase of CD8+ T cells to CD4+ T regulatory cells (Tregs) is greater.

10. — The method of claim 1, wherein the cancer being treated is renal cell carcinoma (RCC), lymphomas, melanoma, hepatic cell carcinoma (HCC), non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), squamous cell carcinoma of the head and neck (SCCHN) breast cancer, pancreatic cancer, prostate cancer, colon and rectal cancer, bladder cancer, cervical cancer, thyroid cancer, esophageal cancer, oral cancer, mesothelioma, and non-melanoma skin cancer.

11. — The method of claim 1, wherein the patient has a lower risk of T cell exhaustion.

12. — The method of claim 1, wherein the patient has a lower risk of capillary leak syndrome (CLS) or cytokine release syndrome (CRS).

13. — The method of claim 1, wherein the patient has a lower risk of weight loss.

14. — The method of claim 1, further comprising co-administering to the patient a therapeutically effective amount of a therapeutic agent.

15. — The method of claim 14, where the therapeutic agent is a PARP inhibitor, an immune checkpoint protein inhibitor a cytotoxic agent or a chemotherapeutic agent.

16. — The method of claim 14, wherein the therapeutic agent is an immune checkpoint inhibitor.

17. — The method of claim 16, wherein the immune checkpoint inhibitor inhibits the interaction of PD-1 and PD-L1.

18. — The method of claim 16, wherein the immune checkpoint inhibitor is pembrolizumab.

19. — The method of claim 1, wherein the ratio of increase in IFN γ present in a patient's peripheral blood, serum or plasma resulting from subcutaneous administration is at least about 2 fold greater as compared to intravenous administration of an equivalent dose.

20. — The method of claim 1, wherein the ratio of increase in IFN γ present in a patient's peripheral blood, serum or plasma resulting from subcutaneous administration is at least about 5 fold greater as compared to intravenous administration of an equivalent dose.

21. — The method of claim 1, wherein the ratio of increase in IFN γ present in a patient's peripheral blood, serum or plasma when resulting from subcutaneous administration is about 2 fold to about 5 fold greater as compared to intravenous administration of an equivalent dose.

22. — The method of claim 1, wherein the ratio of increase in IL-6 present in a patient's peripheral blood, serum or plasma when resulting from subcutaneous administration is at least about 2 fold less as compared to intravenous administration of an equivalent dose.

23. — The method of claim 1, wherein the cancer being treated is a solid tumor.

24. — The method of claim 23, wherein the solid tumor is a carcinoma, sarcoma or lymphoma.

25. — The method of claim 1, wherein the cancer being treated is a blood cancer.

26. — The method of claim 25, wherein the blood cancer is leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma and multiple myeloma.

27. — ~~The method of claim 18, wherein the pembrolizumab is co-administered prior to, simultaneously with, or subsequent to, administration of the fusion protein of SEQ ID NO: 1.~~

28. — ~~The method of claim 27, wherein the pembrolizumab is co-administered in a separate composition from the fusion protein of SEQ ID NO: 1.~~

29. — ~~The method of claim 27, wherein pembrolizumab is administered in an amount of 200 mg by I.V. injection or infusion.~~

30. — ~~The method of claim 27, wherein pembrolizumab is administered on the first day of administration of the fusion protein of SEQ ID NO: 1.~~

31. — ~~The method of claim 27, wherein pembrolizumab is administered about once a week.~~

32. — ~~The method of claim 27, wherein pembrolizumab is administered about once every 3 weeks.~~

33. — ~~The method of claim 1, wherein the dose is provided as a pharmaceutical composition formulated for subcutaneous administration.~~

34. — ~~The method of claim 33, wherein the pharmaceutical composition is a stable aqueous solution ready for administration.~~

35. — ~~The method of claim 33, wherein the pharmaceutical composition is lyophilized.~~

36. — ~~The method of claim 35, wherein the pharmaceutical composition is reconstituted with a pharmaceutically acceptable vehicle suitable for injection.~~

37. — ~~The method of claim 33, wherein the dose comprises about 1 mg to about 30 mgs of the fusion protein of SEQ ID NO: 1.~~

38. — ~~The method of claim 33, wherein the dose comprises about 1 mg, 3 mg, 10 mg or 30 mg of the fusion protein of SEQ ID NO: 1.~~

39. — ~~A method of treating cancer in a patient comprising periodically subcutaneously administering to the patient a dose of a fusion protein having a sequence identity of at least 80% over a contiguous sequence of at least about 20 amino acids up to the full length of SEQ ID NO: 1 wherein the periodic dosing is once every about 3 days to once every about 60 days.~~

40. — ~~The method of claim 1, wherein periodic subcutaneous administration results in a greater ratio of CD8⁺ T cells to CD4⁺ T_{regs} as compared to daily subcutaneous administration.~~

41. — ~~The method of claim 7, wherein the increase in circulating CD8⁺ cells is at least 2-fold over baseline.~~

42. — ~~The method of claim 7, wherein the ratio of increase in circulating CD8⁺ cells is greater relative to the ratio of increase in circulating CD4⁺ Treg cells.~~

43. — ~~The method of claim 39, wherein the patient has a lower risk of T cell exhaustion.~~

44. — ~~The method of claim 39, wherein the patient has a lower risk of capillary leak syndrome (CLS) or cytokine release syndrome (CRS).~~

45. — ~~The method of claim 1, wherein the patient has a lower risk of weight loss.~~

46. — The method of claim 39, wherein the ratio of increase in IFN γ present in a patient's peripheral blood, serum or plasma resulting from subcutaneous administration is at least about 2 fold greater as compared to intravenous administration of an equivalent same dose.

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47. — The method of claim 39, wherein the ratio of increase in IFN γ present in a patient's peripheral blood, serum or plasma resulting from subcutaneous administration is at least about 5 fold greater as compared to intravenous administration of an equivalent dose.

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48. — The method of claim 39, wherein the ratio of increase in IFN γ present in a patient's peripheral blood, serum or plasma when resulting from subcutaneous administration is at least about 7 fold greater as compared to intravenous administration of an equivalent dose.

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49. — The method of claim 39, wherein the ratio of increase in IL-6 present in a patient's peripheral blood, serum or plasma when resulting from subcutaneous administration is at least about 2 fold less as compared to intravenous administration of an equivalent same dose.

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50. — The method of claim 49, wherein the ratio of increase in IL-6 present in a patient's peripheral blood, serum or plasma resulting from subcutaneous administration is less than the ratio of increase in IFN γ .

51. — The method of claim 1, wherein the cancer being treated is a solid tumor.

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52. — The method of claim 51, wherein the solid tumor is a carcinoma, sarcoma or lymphoma.

53. — The method of claim 1, wherein the cancer being treated is a blood cancer.

54. — ~~The method of claim 53, wherein the blood cancer is leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma and multiple myeloma.~~

55. — ~~The method of claim 51, wherein the size of the solid tumor is reduced.~~

56. — ~~The method of claim 1, further comprising repeating administration of the fusion protein of SEQ ID NO: 1 if the cancer reoccurs, or new cancer develops in the patient.~~

57. — ~~The method of claim 55, further comprising repeating administration of the fusion protein of SEQ ID NO: 1 if the tumor reoccurs, or new tumors develop in the patient.~~

58. — ~~The method of claim 1 wherein the method results in at least a partial response in the patient.~~

59. — ~~The method of claim 1, wherein the method results a mean fold change from baseline in IFN γ present in a patient's peripheral blood, serum or plasma is greater than the mean fold change from baseline in IL-6 present in a patient's peripheral blood, serum or plasma.~~

1. Use of the fusion protein of SEQ ID NO:1, or a fusion protein having a sequence identity of at least 80% over a contiguous sequence of the full length of SEQ ID NO: 1, in the manufacture of a medicament for reducing CD4+ regulatory T cells and increasing CD8+ memory T cells for treating cancer in a patient, wherein a dose of fusion protein is to be periodically subcutaneously administered to the patient, wherein the periodic dosing is once every about 3 days to once every about 60 days.

2. The use of claim 1, wherein:

the periodic dosing is once every about 3 days to once every about 21 days, optionally once every 3 days, once every 4 days, once every 7 days, once every 14 days or once every 21 days; and/or the dose is about 0.1 mgs to about 30 mgs of the fusion protein of SEQ ID NO: 1,

optionally 1 mg, 3 mg, 6 mg, 10 mg, 15 mg, 20 mg or 30 mg, or optionally about 0.1 mg to about 30 mg or about 1 µg/kg to about 500 µg/kg or a corresponding fixed dose based on an about 60 to about 70 kg adult or based on an about 12 kg to about 50 kg or more child.

5 3. The use of claim 1, wherein periodic subcutaneous administration results in a greater increase in circulating CD8+ T cells in the patient as compared to daily subcutaneous administration, optionally wherein:

the increase in circulating CD8+ T cells in the patient is at least 2-fold over baseline;

10 the ratio of increase of CD8+ T cells in the patient is greater than the ratio of increase in to CD4+T regulatory cells (Tregs); and/or

the ratio of increase in circulating CD8+ cells in the patient is greater than the ratio of increase in circulating CD4+ Treg cells.

15 4. The use of claim 1, wherein the cancer being treated is one or both of a solid tumor and a blood cancer, optionally wherein:

the solid tumor is a carcinoma, sarcoma or lymphoma;

the size of the solid tumor is reduced;

the blood cancer is leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma and multiple myeloma; and/or

20 the cancer being treated is renal cell carcinoma (RCC), lymphomas, melanoma, hepatic cell carcinoma (HCC), non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), squamous cell carcinoma of the head and neck (SCCHN) breast cancer, pancreatic cancer, prostate cancer, colon and rectal cancer, bladder cancer, cervical cancer, thyroid cancer, esophageal cancer, oral cancer, mesothelioma, and non-melanoma skin cancer.

25 5. The use of claim 1, wherein:

the patient has a lower risk of T cell exhaustion relative to daily subcutaneous or intravenous administration;

the patient has a lower risk of capillary leak syndrome (CLS) or cytokine release syndrome (CRS) relative to daily subcutaneous or intravenous administration; and/or
the patient has a lower risk of weight loss relative to daily subcutaneous or intravenous administration.

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6. The use of claim 1, wherein a therapeutically effective amount of a therapeutic agent is to be further co-administered to the patient, optionally wherein: the therapeutic agent is a PARP inhibitor, a cytotoxic agent, a chemotherapeutic agent, or an immune checkpoint protein inhibitor, optionally wherein the immune checkpoint inhibitor inhibits the interaction of PD-1 and PD-L1, optionally wherein the immune checkpoint inhibitor is pembrolizumab.

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7. The use of claim 1, wherein the ratio of increase in IFN γ present in a patient's peripheral blood, serum or plasma resulting from subcutaneous administration is at least about 2-fold greater, at least about 5-fold greater, or about 2 fold to about 5 fold greater, as compared to intravenous administration of an equivalent dose.

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8. The use of claim 1, wherein the ratio of increase in IL-6 present in a patient's peripheral blood, serum or plasma when resulting from subcutaneous administration is at least about 2-fold less as compared to intravenous administration of an equivalent dose.

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9. The use of claim 6, wherein the pembrolizumab is to be co-administered prior to, simultaneously with, or subsequent to, administration of the fusion protein of SEQ ID NO:1, optionally wherein:

the pembrolizumab is to be co-administered in a separate composition from the fusion protein of SEQ ID NO: 1;

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the pembrolizumab is to be administered in an amount of 200 mg by I.V. injection or infusion;

the pembrolizumab is to be administered on the first day of administration of the fusion protein of SEQ ID NO: 1;

and/or the pembrolizumab is to be administered about once a week or once every 3 weeks.

10. The use of claim 1, wherein the dose is provided as a pharmaceutical composition formulated for subcutaneous administration, optionally wherein:

the pharmaceutical composition is a stable aqueous solution ready for administration or the pharmaceutical composition is lyophilized, optionally wherein the lyophilized pharmaceutical composition is reconstituted with a pharmaceutically acceptable vehicle suitable for injection; and/or

the dose comprises about 1 mg to about 30 mg of the fusion protein of SEQ ID NO: 1, optionally 1 mg, 3 mg, 10 mg or 30 mg of the fusion protein of SEQ ID NO: 1.

11. The use of claim 1, wherein periodic subcutaneous administration results in a greater ratio of CD8+ T cells to CD4+T_{regs} in the patient as compared to daily subcutaneous administration.

12. The use of claim 8, wherein the ratio of increase in IL-6 present in a patient's peripheral blood, serum or plasma resulting from subcutaneous administration is less than the ratio of increase in IFN γ .

13. The use of claim 1, further comprising repeating administration of the fusion protein of SEQ ID NO: 1 if the cancer reoccurs, or a new cancer develops in the patient.

14. The use of claim 1 wherein the method results in at least a partial response in the patient.

15. The use of claim 1, wherein the method results a mean fold change from baseline in IFN γ present in a patient's peripheral blood, serum or plasma that is greater than the mean fold change from baseline in IL-6 present in a patient's peripheral blood, serum or plasma.