CLAIMS

What is claimed is:

1. A method of treating cancer in a patient comprising administering to the patient a dose of at least about 6 µg/kg/day to about 15 µg/kg per day of the fusion protein of SEQ ID NO: 1.

2. The method of claim 1, wherein the dose is 6 µg/kg/day, 8 µg/kg/day, 10 µg/kg/day, 12 µg/kg/day, 14 µg/kg/day, or 15 µg/kg/day.

3. The method of claim 1, wherein administration results in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in T regulatory (Treg) cells.

4. The method of claim 3, wherein the increase in circulating NK cells and CD8+ cells is at least 2 fold over baseline.

5. The method of claim 3, wherein the increase in circulating NK cells and CD8+ cells is greater relative to the increase in circulating Treg cells.

6. The method of claim 3, wherein an increase in circulating NK cells and CD8+ cells is greater relative to the increase in circulating Treg cells as compared to the increase in circulating NK cells and CD8+ cells relative to the increase in circulating Treg cells in a patient receiving high dose rhIL-2 treatment.

7. The method of claim 1, wherein the patient has an improved safety profile as compared to a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment.

8. The method of claim 7, wherein the patient has a lower risk of capillary leak syndrome or cytokine release syndrome.

9. The method of claim 1, resulting in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in circulating T regulatory (Treg) cells and wherein the increase in circulating NK cells and CD8+ cells relative to the increase in circulating T regulatory (Treg) is greater as compared to the increase in circulating NK cells and CD8+ cells relative to the increase in circulating T regulatory (Treg) in a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment and wherein the patient has a lower risk of capillary leak syndrome.

10. The method of claim 1, wherein the dose is administered by intravenous (I.V.) injection or infusion.

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

12. The method of claim 11, wherein the solid tumor is a carcinoma, sarcoma or lymphoma.

13. The method of claim 12, wherein the cancer being treated is renal cell carcinoma (RCC), melanoma, breast cancer, pancreatic cancer, prostate cancer, non-small cell lung cancer, liver cancer, colon and rectal cancer, bladder cancer, cervical cancer, thyroid cancer, esophageal cancer, oral cancer, mesothelioma, and non-melanoma skin cancer.

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

15. The method of claim 14, wherein the blood cancer is leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma and multiple myeloma.

16. The method of claim 1, wherein the fusion protein of SEQ ID NO: 1 is administered by intravenous injection or infusion at a dose of at least about 6 µg/kg to about 15 µg/kg per day as a once a day administration for about 1 day to about 5 days.

17. The method of claim 16, wherein the fusion protein is administered once a day for at least about 2 consecutive days.

18. The method of claim 16, wherein the fusion protein is administered once a day for at least about 3 consecutive days.

19. The method of claim 16, wherein the fusion protein is administered once a day for at least about 4 consecutive days.

20. The method of claim 16, wherein the fusion protein of SEQ ID NO: 1 is administered once a day for at least about 5 consecutive days.

21. The method of claim 16, wherein the fusion protein of SEQ D NO: 1 is administered once a day on non-consecutive days for no more than about 5 total non-consecutive of days of administration.

22. The method of claim 16, wherein the fusion protein is administered followed by a rest period of at least about 9 consecutive days.

23. The method of claim 22, wherein the rest period is at least about 16 consecutive days.

24. The method of claim 1, wherein the fusion protein of SEQ ID NO: 1 is administered in at least two courses of treatment, the first course of treatment comprising administration by intravenous injection or infusion at a dose of at least about 6 µg/kg to about 15 µg/kg per day for a period of about 1 to about 5 consecutive or non-consecutive days followed by a rest period of at least about 9 consecutive days followed by a second course of treatment comprising administering the fusion protein of SEQ ID NO: 1 by intravenous injection or infusion at a dose of at least about 6 µg/kg to about 15 µg/kg per day for a period of at least about 1 to at least about 5 consecutive or nonconsecutive days, followed by a rest period of at least about 9 consecutive days.

25. The method of claim 24, wherein administration of the fusion protein of SEQ ID NO: 1 for the first course of treatment and for the second course of treatment is for a period of 5 consecutive days or 5 non-consecutive days prior to a rest period of at least about 9 days.

26. The method of claim 25, wherein the rest period is at least about 16 days.

27. The method of claim 25, wherein the rest period during the first course of treatment is about 9 consecutive days and wherein the rest period for the second course of treatment is about 16 or more consecutive days.

28. The method of claim 24, wherein the second course of treatment begins at least about 24 hours or more after completion of the first course of treatment.

29. The method of claim 24, further comprising a third course of treatment following the second course of treatment.

30. The method of claim 29, wherein the third course of treatment begins within about 24 hours or more after completion of the second course of treatment.

31. The method of claim 29, further comprising a fourth course of treatment following the third course of treatment.

32. The method of claim 29, wherein the fourth course of treatment begins about 24 hours or more after completion of the third course of treatment.

33. The method of claim 32, wherein subsequent courses of treatment begin about 24 hours or more after completion of the prior course of treatment until the cancer is treated or until the patient is no longer benefitting from the treatment.

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

35. The method of claim 34, where the therapeutic agent is a PARP inhibitor, an immune checkpoint inhibitor a cytotoxic agent or a chemotherapeutic agent.

36. The method of claim 34, wherein the therapeutic agent is an immune checkpoint inhibitor.

37. The method of claim 36, wherein the immune checkpoint inhibitor inhibits the interaction of PD-1 and PD-L1.

38. The method of claim 37, wherein the immune checkpoint inhibitor is pembrolizumab.

39. The method of claim 38, wherein the fusion protein of SEQ ID NO: 1 is administered in at least two courses of treatment, the first course of treatment comprising administration by intravenous injection or infusion at a dose of at least about 6 µg/kg to about 15 µg/kg per day once a day for 1 to 5 days followed by a rest period of at least about 16 consecutive days followed by a second course of treatment comprising administering by intravenous injection or infusion at a dose of at least about 6 µg/kg to about 15 µg/kg per day for a period 1 to 5 consecutive days, followed by a rest period of at least about 16 consecutive days and wherein the pembrolizumab is co-administered once during the 1 to 5 days of administration during the first course and second course of treatment.

40. The method of claim 38, wherein the fusion protein is administered once a day for at least about 2 consecutive days.

41. The method of claim 38, wherein the fusion protein is administered once a day for at least about 3 consecutive days.

42. The method of claim 38, wherein the fusion protein is administered once a day for at least about 4 consecutive days.

43. The method of claim 39, wherein the fusion protein of SEQ ID NO: 1 is administered once a day for at least about 5 consecutive days.

44. The method of claim 39, wherein the fusion protein of SEQ D NO: 1 is administered once a day on non-consecutive days for no more than about 5 total non-consecutive of days of administration.

45. The method of claim 39, wherein the second course of treatment begins at least about 24 hours or more after completion of the first course of treatment.

46. The method of claim 39, further comprising a third course of treatment following the second course of treatment.

47. The method of claim 46, wherein the third course of treatment begins within about 24 hours or more after completion of the second course of treatment.

48. The method of claim 47, further comprising a fourth course of treatment following the third course of treatment.

49. The method of claim 48, wherein the fourth course of treatment begins about 24 hours or more after completion of the third course of treatment.

50. The method of claim 49, wherein subsequent courses of treatment begin about 24 hours or more after completion of the prior course of treatment and continue until the cancer is treated or until the patient is no longer benefitting from the treatment.

51. The method of claim 39, wherein the pembrolizumab is co-administered prior to, simultaneously with, or subsequent to, administration of the fusion protein of SEQ ID NO:1.

52. The method of claim 51, wherein the pembrolizumab is co-administered in a separate composition from the fusion protein of SEQ ID NO: 1.

53. The method of claim 38, wherein pembrolizumab is co-administered in an amount of 200 mg by I.V. injection or infusion.

54. The method of claim 53, wherein pembrolizumab is administered on the first day of administration of the fusion protein of SEQ ID NO: 1 during the first course of treatment.

55. The method of claim 54, wherein pembrolizumab is administered on the first day of administration of the fusion protein of SEQ ID NO: 1 during the second course of treatment.

56. The method of claim 50, wherein pembrolizumab is administered on the first day of administration of the fusion protein of SEQ ID NO: 1 during subsequent courses of treatment.

57. The method of any one of claims 34 to 56 resulting in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in T regulatory (Treg) cells.

58. The method of claim 57, wherein the dose dependent increase in circulating NK cells and CD8+ cells is greater than the non-dose dependent increase in Treg cells.

59. The method of claim 57, wherein the patient has an improved safety profile as compared to a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment.

60. The method of claim 59, wherein the patient has a lower risk of cytokine release syndrome as compared to a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment.

61. The method of claim 59, wherein the patient has a lower risk of capillary leak syndrome as compared to a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment.

62. A method of treating cancer in a patient comprising administering to the patient a dose of at least about 6 µg/kg to about 15 µg/kg per day of the fusion protein of SEQ ID NO: 1 wherein administration results in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in T regulatory (Treg) cells.

63. The method of claim 62, wherein the increase in circulating NK cells and CD8+ cells is at least 2 fold over baseline prior to administration of the fusion protein of SEQ ID NO: 1 to the patient.

64. The method of claim 62, wherein increase in circulating NK cells and CD8+ cells is greater relative to the increase in circulating Treg cells as compared to the increase in circulating NK cells and CD8+ cells relative to the increase in circulating Treg cells in a patient receiving high dose rhIL-2 treatment.

65. A method of treating cancer in a patient comprising administering to the patient a daily dose of at least about 6 µg/kg to about 15 µg/kg per day of the fusion protein of SEQ ID NO: 1 wherein the dose is administered once a day by intravenous injection or infusion for a period of 1 to about 5 consecutive or non-consecutive days followed by a rest period of at least about 9 consecutive days resulting in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in T regulatory (Treg) cells.

66. The method of claim 65, wherein the increase in circulating NK cells and CD8+ cells is at least 2 fold over baseline prior to administration of the fusion protein of SEQ ID NO: 1 to the patient.

67. The method of claim 65, wherein the increase in circulating NK cells and CD8+ cells is greater relative to the expansion of Treg cells as compared to the increase in circulating NK cells and CD8+ cells relative to the expansion of Treg cells in a patient receiving high dose rhIL-2 treatment.

68. A method of treating cancer in a patient comprising administering to the patient a dose of at least about 6 µg/kg to about 15 µg/kg per day of the fusion protein of SEQ ID NO: 1 wherein the dose is administered by intravenous injection or infusion for a period of 1 to about 5 consecutive or non-consecutive days followed by a rest period of at least about 9 consecutive days resulting in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in T regulatory (Treg) cells and wherein the patient has an improved safety

profile as compared to a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment.

69. A method of treating cancer in a patient comprising administering to the patient a dose of at least about 6 µg/kg to about 15 µg/kg per day of the fusion protein of SEQ ID NO: 1 wherein the dose is administered once a day by intravenous injection or infusion for 1 to about 5 consecutive or non-consecutive days followed by a rest period of at least about 9 consecutive days resulting in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in T regulatory (Treg) cells and wherein the patient has a lower risk of capillary leak syndrome as compared to a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment.

70. A method of treating cancer in a patient comprising administering to the patient a dose of at least about 6 µg/kg to about 15 µg/kg per day of the fusion protein of SEQ ID NO: 1 wherein the dose is administered by intravenous injection or infusion for 1 to about 5 consecutive days followed by a rest period of at least about 9 consecutive days resulting in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in T regulatory (Treg) cells and wherein the patient has a lower risk of cytokine release syndrome as compared to a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment.

71. A method of treating cancer in a patient comprising administering to the patient a dose of at least about 6 µg/kg to about 15 µg/kg per day of the fusion protein of SEQ ID NO: 1 wherein the dose is administered once a day by intravenous injection or infusion for 1 to about 5 consecutive or non-consecutive days followed by a rest period of at least about 9 consecutive days resulting in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in circulating T regulatory (Treg) cells and wherein the increase in circulating NK cells and CD8+ cells relative to the increase in circulating T regulatory (Treg) is greater as compared to the increase in circulating NK cells and CD8+ cells relative to the increase in circulating T regulatory (Treg) in a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment and wherein the patient has a lower risk of capillary leak syndrome.

72. A method of treating cancer in a patient comprising administering to the patient a daily dose of at least about 6 µg/kg to about 15 µg/kg of the fusion protein of SEQ ID NO: 1 resulting in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in circulating T regulatory (Treg) cells and wherein the increase in circulating NK cells and CD8+ cells relative to the increase in circulating T regulatory (Treg) is greater compared to the increase in circulating NK cells and CD8+ cells relative to the increase in circulating T regulatory (Treg) in a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment and wherein the patient has a lower risk of capillary leak syndrome as compared to a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment.

73. A method of treating cancer in a patient comprising administering to the patient a dose of at least about 40 µg/kg to about 70 µg/kg per day of the fusion protein of SEQ ID NO: 1 once weekly.

74. The method of claim 71, wherein the daily dose is about 50 µg/kg to about 60 µg/kg.

75. A method of treating cancer in a patient comprising administering to the patient a dose of at least about 50 µg/kg to about 60 µg/kg per day of the fusion protein of SEQ ID NO: 1 one day per week resulting in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in circulating T regulatory (Treg) cells and wherein the increase in circulating NK cells and CD8+ cells relative to the increase in circulating T regulatory (Treg) is greater compared to the increase in circulating NK cells and CD8+ cells relative to the increase in circulating T regulatory (Treg) in a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment and wherein the patient has a lower risk of capillary leak syndrome as compared to a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment.

76. A method of treating cancer in a patient comprising administering to the patient a dose of at least about 50 µg/kg to about 60 µg/kg per day of the fusion protein of SEQ ID NO: 1 wherein the dose is administered by intravenous injection or infusion one

day per week resulting in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in circulating T regulatory (Treg) cells and wherein the increase in circulating NK cells and CD8+ cells relative to the increase in circulating T regulatory (Treg) is greater compared to the increase in circulating NK cells and CD8+ cells relative to the increase in circulating T regulatory (Treg) in a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment and wherein the patient has a lower risk of capillary leak syndrome as compared to a patient receiving high dose recombinant human IL-2 (rhIL-2) treatment.

77. A pharmaceutical composition comprising about 0.4 to about 1 mg of the fusion protein of SEQ ID NO: 1.

78. A method of treating cancer in a patient comprising administering to the patient a daily dose of at least about 3 µg/kg to about 5.5 µg/kg of the fusion protein of SEQ ID NO: 1 wherein administration results in a dose dependent increase in circulating NK cells and CD8+ cells in a patient in the absence of a dose dependent increase in circulating T regulatory (Treg) cells and wherein the increase in circulating NK cells and CD8+ cells is greater relative to the increase in circulating T regulatory cells (Treg).

79. The method of claim 1, wherein the dose is a fixed dose based on a 60-70 kg human.

80. The method of claim 1, wherein the dose is a fixed dose and wherein the patient is a child.

81. The method of claim 80, wherein the child weighs about 15 kg to about 50 kg.

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

83. The method of claim 11, wherein the size of the solid tumor is reduced.

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

85. A method for treating cancer in a patient comprising intravenously administering to the patient a dose of at about 16 µg/kg/day to about 70 µg/kg/day of the fusion protein of SEQ ID NO: 1 or a corresponding fixed dose based on an about 60-70 kg adult or about 12 kg to 50 kg or more child.

86. The method of claim 85, wherein the dose is about 16 µg/kg/day to about 50 µg/kg/day of the fusion protein of SEQ ID NO: 1 or a corresponding fixed dose based on an about 60-70 kg adult or about 12 kg to 50 kg or more child.

87. The method of claim 85, wherein the corresponding fixed dose is about 5 µg to about 3 mg.

88. The method of claim 85, wherein the corresponding fixed dose is about 5 µg to about 2 mg.

89. The method of claim 85, wherein the fusion protein of SEQ ID NO: 1 is administered on non-consecutive days.

90. The method of claim 89, wherein the fusion protein of SEQ ID NO: 1 is administered once every 7 days, once every 14 days or once every 21 days of a treatment cycle.

91. The method of claim 89, wherein the fusion protein of SEQ ID NO: 1 is administered on days 1, 7, 14 and 21 of a treatment cycle.

92. The method of claim 89, wherein the fusion protein of SEQ ID NO: 1 is administered on days 1 and 14 of a treatment cycle.

93. The method of claim 89 wherein the fusion protein of SEQ ID NO: 1 is administered on days 1 and 21 of a treatment cycle.

94. The method of claim 1, wherein the mean fold change from baseline (FCB) in IFNγ present in a patient's peripheral blood, serum or plasma is at least about 2-fold.

95. The method of claim 1, wherein the mean fold change from baseline (FCB) in IFNγ present in a patient's peripheral blood, serum or plasma is at least about 3-fold.

96. The method of claim 1, wherein the mean fold change from baseline in IFNγ present in a patient's peripheral blood, serum or plasma is about 4-fold to about 5- fold.

97. The method of claim 96, wherein the mean fold change from baseline in IL-6 is less than 4-fold.

98. The method of claim 96, wherein the dose of the fusion protein of SEQ ID NO: 1 is about 6 µg/kg/day or about 8 µg/kg/day.

99. The method of claim 85, wherein the mean fold change from baseline (FCB) in IFNγ present in a patient's peripheral blood, serum or plasma is at least about 2-fold.

100. The method of claim 85, wherein the mean fold change from baseline (FCB) in IFNγ present in a patient's peripheral blood, serum or plasma is at least about 3-fold.

101. The method of claim 85, wherein the mean fold change from baseline in IFNγ present in a patient's peripheral blood, serum or plasma is about 4-fold to about 5- fold.

102. The method of claim 99 wherein the mean fold change from baseline in IL-6 is less than 4-fold.

103. The method of claim 99 wherein the dose of the fusion protein of SEQ ID NO: 1 is about 30 µg/kg/day or about 50 µg/kg/day.