

CLAIMS

What is claimed is:

1. A method of treating cancer in a patient in need thereof, the method comprising:
 - 5 i) administering to the patient a therapeutically effective amount of a fusion protein of SEQ ID NO: 1, or a variant thereof that is at least 80% identical to SEQ ID NO: 1; and
 - ii) administering to the patient a therapeutically effective amount of an angiogenesis inhibitor selected from the group consisting of an antibody that binds specifically to VEGF or lenvatinib;
- 10 wherein step (i) is carried out before, after or simultaneously with step (ii).
2. The method of claim 1, wherein an effective amount of the fusion protein of SEQ ID NO: 1 is an amount effective to activate the IL-2 intermediate receptor, IL-2R $\beta\gamma$.
- 15 3. The method of claim 1, wherein the fusion protein of SEQ ID NO: 1 is administered by intravenous or subcutaneous injection.
4. The method of claim 1, wherein the angiogenesis inhibitor inhibits more than one receptor tyrosine kinase.
- 20 5. The method of claim 4, wherein the angiogenesis inhibitor inhibits one or more of the following receptor tyrosine kinases: vascular endothelial growth factor receptors types 1, 2, and 3; platelet derived growth factor receptors, types alpha and beta platelet derived growth factor receptors, and fibroblast growth factor receptors, types 1, 2, and 3.
- 25 8. The method of claim 1, wherein lenvatinib is administered orally.
9. The method of claim 1, wherein the combination of steps (i) and (ii) results in an increase in CD8⁺ T cells in the tumors and spleen of the patient as compared to administration of a
- 30 therapeutically effective amount of the fusion protein of SEQ ID NO: 1 as a monotherapy or

administration of a therapeutically effective amount of the angiogenesis inhibitor as a monotherapy.

10. The method of claim 9, wherein the increase in CD8⁺ T cells is at least 2-fold greater as compared to administration of a therapeutically effective amount of the fusion protein of SEQ ID NO: 1 as a monotherapy or administration of a therapeutically effective amount of the angiogenesis inhibitor as a monotherapy.
11. The method of claim 9, wherein there is no increase in CD4⁺ T regulatory (T_{regs}) cells or conventional CD4⁺ T cells in the patient.
12. The method of claim 9, wherein the combination of steps (i) and (ii) results in an increase in CD8⁺ T cells and dendritic cells in the tumors and spleen of the patient and a decrease in tumor associated macrophages in the patient as compared to administration of a therapeutically effective amount of the fusion protein of SEQ ID NO: 1 as a monotherapy or administration of a therapeutically effective amount of the angiogenesis inhibitor as a monotherapy.
13. The method of claim 1, wherein the combination of steps (i) and (ii) results in an increase CD8⁺ T cells in the tumors and spleen of the patient as compared to administration of a therapeutically effective amount of the fusion protein of SEQ ID NO: 1 as a monotherapy or administration of a therapeutically effective amount of the angiogenesis inhibitor as a monotherapy.
14. The method of claim 13, wherein the increase in CD8⁺ T cells is at least 2-fold greater as compared to administration of a therapeutically effective amount of the fusion protein of SEQ ID NO: 1 as a monotherapy or administration of a therapeutically effective amount of an angiogenesis inhibitor as a monotherapy.
15. The method of claim 13, wherein there is no increase in CD4⁺ T regulatory (T_{regs}) cells in the patient.

16. The method of claim 13, wherein the combination of steps (i) and (ii) results in an increase in CD8+ T cells and dendritic cells in the tumors and spleen of the patient and a decrease in tumor- associated macrophages in the patient as compared to administration of a therapeutically effective amount of the fusion protein of SEQ ID NO: 1 as a monotherapy or
5 administration of a therapeutically effective amount of the angiogenesis inhibitor as a monotherapy.

16. The method of claim 1, wherein the progression free survival of the patient is increased by at least about 10% as compared to administration of a therapeutically effective amount of the
10 fusion protein of SEQ ID NO: 1 as a monotherapy or administration of a therapeutically effective amount of the angiogenesis inhibitor as a monotherapy.

17. The method of claim 1, wherein the combination of steps (i) and (ii) results in greater expression of genes associated with cytotoxic immune cell function, T cell activation, and
15 antigen presentation as compared to administration of a therapeutically effective amount of the fusion protein of SEQ ID NO: 1 as a monotherapy or administration of a therapeutically effective amount of the angiogenesis inhibitor as a monotherapy.

18. The method of claim 1 wherein the combination of steps (i) and (ii) results in a decrease
20 in Esm1 expression, and increased expression of Type I interferon and Type II interferon-associated genes as compared to administration of a therapeutically effective amount of the fusion protein of SEQ ID NO: 1 as a monotherapy or administration of a therapeutically effective amount of the angiogenesis inhibitor as a monotherapy.

25 19. The method of claim 1, wherein the combination of steps (i) and (ii) results in changes in expression of a greater total number of genes as compared to administration of a therapeutically effective amount of the fusion protein of SEQ ID NO: 1 as a monotherapy or administration of a therapeutically effective amount of the angiogenesis inhibitor as a monotherapy.

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