

CLAIMS

WHAT IS CLAIMED IS:

1. ~~A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG-3) comprising one, two or three amino acid sequences selected from: (a) an amino acid sequence of SEQ ID NO: 5, (b) an amino acid sequence of SEQ ID NO: 6, and (c) an amino acid sequence of SEQ ID NO: 7.~~
2. ~~A polypeptide containing a heavy chain variable region comprising one, two or three CDRs selected from: (a) CDR H1 comprising an amino acid sequence of SEQ ID NO: 5, (b) CDR H2 comprising an amino acid sequence of SEQ ID NO: 6, and (c) CDR H3 comprising an amino acid sequence of SEQ ID NO: 7.~~
3. ~~A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG-3), wherein said polypeptide comprises a heavy chain variable region comprising:
a CDR H1 defined by an amino acid sequence at least 80%, 85% or 90% identical to SEQ ID NO: 5; and/or
a CDR H2 defined by an amino acid sequence at least 80%, 85% or 90% identical to SEQ ID NO: 6; and/or
a CDR H3 defined by an amino acid sequence at least 80%, 85% or 90% identical to SEQ ID NO: 7.~~
4. ~~The polypeptide of claim 3, wherein said polypeptide comprises:
a CDR H1 defined by an amino acid sequence at least 80%, 85% or 90% identical to SEQ ID NO: 5;
a CDR H2 defined by an amino acid sequence at least 80%, 85% or 90% identical to SEQ ID NO: 6; and
a CDR H3 defined by an amino acid sequence at least 80%, 85% or 90% identical to SEQ ID NO: 7.~~
5. ~~A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG-3) comprising one, two or three amino acid sequences selected from: (a) an amino acid sequence of SEQ ID NO: 8, (b) an amino acid sequence of SEQ ID NO: 9, and (c) an amino acid sequence of SEQ ID NO: 10.~~

- ~~6. A polypeptide containing a light chain variable region comprising one, two or three CDRs selected from: (a) CDR L1 comprising an amino acid sequence of SEQ ID NO: 8, (b) CDR L2 comprising an amino acid sequence of SEQ ID NO: 9, and (c) CDR L3 comprising an amino acid sequence of SEQ ID NO: 10.~~
- ~~7. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG-3), wherein said polypeptide comprises a light chain variable region comprising:~~
- ~~a CDR L1 defined by an amino acid sequence at least 80%, 85% or 90% identical to SEQ ID NO: 8; and/or~~
 - ~~a CDR L2 defined by an amino acid sequence at least 80%, 85% or 90% identical to SEQ ID NO: 9; and/or~~
 - ~~a CDR L3 defined by an amino acid sequence at least 80%, 85% or 90% identical to SEQ ID NO: 10.~~
- ~~8. The polypeptide of claim 7, comprising~~
- ~~a CDR L1 defined by an amino acid sequence at least 80%, 85% or 90% identical to SEQ ID NO: 8;~~
 - ~~a CDR L2 defined by an amino acid sequence at least 80%, 85% or 90% identical to SEQ ID NO: 9; and~~
 - ~~a CDR L3 defined by an amino acid sequence at least 80%, 85% or 90% identical to SEQ ID NO: 10.~~
- ~~9. A polypeptide that is capable of binding LAG-3, comprising~~
- ~~at least one amino acid sequence according to claim 1 or a heavy chain variable region of any one of claims 2-4;~~
 - ~~and~~
 - ~~at least one amino acid sequence according to claim 5 or a light chain variable region of any one of claims 6-8.~~
- ~~10. The polypeptide of any one of claims 1-9, wherein said polypeptide comprises:~~
- ~~a CDR H1 defined by SEQ ID NO: 5;~~
 - ~~a CDR H2 defined by SEQ ID NO: 6;~~
 - ~~a CDR H3 defined by SEQ ID NO: 7;~~
 - ~~a CDR L1 defined by SEQ ID NO: 8;~~
 - ~~a CDR L2 defined by SEQ ID NO: 9; and~~

- ~~a CDR-L3 defined by SEQ ID NO: 10.~~
- ~~11. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG-3),
comprising a heavy chain variable region amino acid sequence having at least 80%, 85%,
90%, 95%, or 98% sequence identity to SEQ ID NO: 3.~~
 - ~~12. The polypeptide of claim 11, comprising a heavy chain variable region amino acid
sequence defined by SEQ ID NO: 3.~~
 - ~~13. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG-3),
comprising a light chain variable region amino acid sequence having at least 80%, 85%,
90%, 95%, or 98% sequence identity to SEQ ID NO: 4.~~
 - ~~14. The polypeptide of claim 13, comprising a light chain variable region amino acid
sequence defined by SEQ ID NO: 4.~~
 - ~~15. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG-3),
comprising:
 a heavy chain variable region according to claim 11 or 12; and
 a light chain variable region according to claim 13 or 14.~~
 - ~~16. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG-3),
comprising a heavy chain polypeptide sequence having at least 80%, 85%, 90%, 95%, or
98% sequence identity to SEQ ID NO: 1 or SEQ ID NO: 21.~~
 - ~~17. The polypeptide of claim 16, comprising a heavy chain polypeptide sequence defined by
SEQ ID NO: 1.~~
 - ~~18. The polypeptide of claim 16, comprising a heavy chain polypeptide sequence defined by
SEQ ID NO: 21.~~
 - ~~19. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG-3),
comprising a light chain polypeptide sequence having at least 80%, 85%, 90%, 95%, or
98% sequence identity to SEQ ID NO: 2 or SEQ ID NO: 22.~~
 - ~~20. The polypeptide of claim 19, comprising a light chain polypeptide sequence defined by
SEQ ID NO: 2.~~

- ~~21. The polypeptide of claim 19, comprising a light chain polypeptide sequence defined by SEQ ID NO: 22.~~
- ~~22. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG 3), comprising:~~
- ~~a heavy chain polypeptide sequence according to any one of claims 16-18;~~
 - ~~and~~
 - ~~a light chain polypeptide sequence according to any one of claims 19-21.~~
- ~~23. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG 3), wherein the polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95%, or 98% sequence identity to SEQ ID NO: 1, SEQ ID NO:3, or SEQ ID NO:21.~~
- ~~24. A heavy chain polypeptide comprising an amino acid sequence having at least 80%, 85%, 90%, 95%, or 98% sequence identity to SEQ ID NO: 1, SEQ ID NO:3, or SEQ ID NO: 21.~~
- ~~25. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG 3), wherein the polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95%, or 98% sequence identity to SEQ ID NO: 2, SEQ ID NO: 4, or SEQ ID NO: 22.~~
- ~~26. A light chain polypeptide comprising an amino acid sequence having at least 80%, 85%, 90%, 95%, or 98% sequence identity to SEQ ID NO: 2, SEQ ID NO: 4, or SEQ ID NO: 22.~~
- ~~27. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG 3) comprising:~~
- ~~i) — an amino acid having at least 80%, 85%, 90%, 95%, or 98% sequence identity to SEQ ID NO: 1, SEQ ID NO:3, or SEQ ID NO: 21; and~~
 - ~~ii) — an amino acid having at least 80%, 85%, 90%, 95%, or 98% sequence identity to SEQ ID NO: 2, SEQ ID NO: 4, or SEQ ID NO: 22.~~
- ~~28. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG 3) comprising:~~

- i) ~~one, two or three amino acid sequences selected from:~~
- ~~(a) an amino acid sequence that is identical in sequence or contains between 1-5 amino acid substitutions as compared to SEQ ID NO: 5,~~
 - ~~(b) an amino acid sequence that is identical in sequence or contains between 1-5 amino acid substitutions as compared to SEQ ID NO: 6, and~~
 - ~~(c) an amino acid sequence that is identical in sequence or contains between 1-5 amino acid substitutions as compared to SEQ ID NO: 7;~~

and

- ii) ~~one, two or three amino acid sequences selected from:~~
- ~~(a) an amino acid sequence that is identical in sequence or contains between 1-5 amino acid substitutions as compared to SEQ ID NO: 8,~~
 - ~~(b) an amino acid sequence that is identical in sequence or contains between 1-5 amino acid substitutions as compared to SEQ ID NO: 9, and~~
 - ~~(c) an amino acid sequence that is identical in sequence or contains between 1-5 amino acid substitutions as compared to SEQ ID NO: 10.~~

29. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG-3) comprising:

- i) ~~one, two or three amino acid sequences selected from: (a) an amino acid sequence of SEQ ID NO: 5, (b) an amino acid sequence of SEQ ID NO: 6, and (c) an amino acid sequence of SEQ ID NO: 7; and~~
- ii) ~~one, two or three amino acid sequences selected from: (a) an amino acid sequence of SEQ ID NO: 8, (b) an amino acid sequence of SEQ ID NO: 9, and (c) an amino acid sequence of SEQ ID NO: 10.~~

30. The polypeptide of any one of claims 1-29, wherein the polypeptide comprises at least one disulfide bond formed by a first cysteine and a second cysteine; wherein:

- i) ~~the first cysteine is selected from residue 41, 115, 147, 160, 216, 239, 242, 274, 334, 380 and 438 of SEQ ID NO: 1, and the second cysteine is selected from residue 41, 115, 147, 160, 216, 239, 242, 274, 334, 380 and 438 of SEQ ID NO: 1~~
- ii) ~~the first cysteine is selected from residue 41, 115, 147, 160, 216, 239, 242, 274, 334, 380 and 438 of SEQ ID NO: 1, and the second cysteine is selected from residue 45, 115, 161, 221 and 241 of SEQ ID NO: 2; or~~
- iii) ~~the first cysteine is selected from residue 45, 115, 161, 221 and 241 of SEQ ID~~

NO: 2, and the second cysteine is selected from residue 45, 115, 161, 221 and 241 of SEQ ID NO: 2.

31. The polypeptide of any one of claims 1-30, wherein the polypeptide comprises at least one disulfide bond formed by a first cysteine and a second cysteine; wherein:
- i) — the first residue is residue 45 of SEQ ID NO: 2, and the second residue is residue 115 of SEQ ID NO: 2;
 - ii) — the first residue is residue 161 of SEQ ID NO: 2, and the second residue is residue 221 of SEQ ID NO: 2;
 - iii) — the first residue is residue 147 of SEQ ID NO: 1, and the second residue is residue 241 of SEQ ID NO: 2;
 - iv) — the first residue is residue 41 of SEQ ID NO: 1, and the second residue is residue 115 of SEQ ID NO: 1;
 - v) — the first residue is residue 160 of SEQ ID NO: 1, and the second residue is residue 216 of SEQ ID NO: 1;
 - vi) — the first residue is residue 239 of SEQ ID NO: 1, and the second residue is residue 242 of SEQ ID NO: 1;
 - vii) — the first residue is residue 274 of SEQ ID NO: 1, and the second residue is residue 334 of SEQ ID NO: 1; or
 - viii) the first residue is residue 380 of SEQ ID NO: 1, and the second residue is residue 438 of SEQ ID NO: 1.
32. The polypeptide of any one of claims 1-31, wherein the polypeptide contains at least one asparagine that is glycosylated.
33. A polypeptide that is capable of binding Lymphocyte Activation Gene 3 (LAG-3) comprising at least one asparagine that is glycosylated; wherein the polypeptide contains:
- i) — a heavy chain variable region comprising a CDR-H1 comprising an amino acid sequence of SEQ ID NO: 5, a CDR-H2 comprising an amino acid sequence of SEQ ID NO: 6, and a CDR-H3 comprising an amino acid sequence of SEQ ID NO: 7; and
 - ii) — a light chain variable region comprising a CDR-L1 comprising an amino acid sequence of SEQ ID NO: 8, a CDR-L2 comprising an amino acid sequence of SEQ ID NO: 9, and a CDR-L3 comprising an amino acid sequence of SEQ ID NO: 10.
34. The polypeptide of claim 33 wherein the polypeptide contains at least one disulfide bond formed by a first cysteine and a second cysteine; wherein:

- i) ~~the first cysteine is selected from residue 41, 115, 147, 160, 216, 239, 242, 274, 334, 380 and 438 of SEQ ID NO: 1, and the second cysteine is selected from residue 45, 115, 161, 221 and 241 of SEQ ID NO: 2;~~
- ii) ~~the first cysteine is selected from residue 41, 115, 147, 160, 216, 239, 242, 274, 334, 380 and 438 of SEQ ID NO: 1, and the second cysteine is selected from residue 41, 115, 147, 160, 216, 239, 242, 274, 334, 380 and 438 of SEQ ID NO: 1; or~~
- iii) ~~the first cysteine is selected from residue 45, 115, 161, 221 and 241 of SEQ ID NO: 2, and the second cysteine is selected from residue 45, 115, 161, 221 and 241 of SEQ ID NO: 2.~~

35. The polypeptide of claim 33 or 34, wherein the polypeptide comprises a heavy chain having at least 80%, 85%, 90%, 95%, or 98% sequence identity to SEQ ID NO: 3 and/or a light chain having at least 80%, 85%, 90%, 95%, or 98% sequence identity to SEQ ID NO: 4.

36. The polypeptide of any one of claims 33-35, wherein the polypeptide comprises a heavy chain having at least 80%, 85%, 90%, 95%, or 98% sequence identity to SEQ ID NO: 1 and/or a light chain having at least 80%, 85%, 90%, 95%, or 98% sequence identity to SEQ ID NO: 2.

37. The polypeptide of any one of claims 33-36, comprising a glycosylated asparagine on the heavy chain.

38. The polypeptide of claim 37, wherein the glycosylated asparagine is N291 of the heavy chain.

39. The polypeptide of any one of claims 1-38, wherein total N-linked oligosaccharides comprise G0F.

40. The polypeptide of any one of claims 1-39, wherein total N-linked oligosaccharides comprise G1F.

41. The polypeptide of any one of claims 1-40, wherein total N-linked oligosaccharides comprise G2F.

42. The polypeptide of any one of claims 1-41, wherein total N-linked oligosaccharides comprise Man-5.

43. The polypeptide of any one of claims 1-42, wherein total N-linked oligosaccharides comprise G0F and G1F.
44. The polypeptide of any one of claims 1-43, wherein total N-linked oligosaccharides comprise G0F, G1F, G2F, and Man-5.
45. The polypeptide of any one of claims 1-44, wherein the polypeptide binds Lymphocyte Activation Gene-3 (LAG-3) and/or inhibits the interaction between LAG-3 and MHC II.
46. The polypeptide of any one of claims 1-45, wherein the polypeptide activates T cells.
47. The polypeptide of claim 46, wherein the activation of T cells is assessed by an increase in production of IL-2.
48. The polypeptide of any one of claims 1-47, wherein the polypeptide is human or humanized.
49. An isolated nucleic acid sequence encoding the polypeptide of any one of claims 1-48.
50. The isolated nucleic acid of claim 49, wherein the isolated nucleic acid comprises a nucleic acid of SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 21, or SEQ ID NO: 22.
51. An isolated nucleic acid sequence comprising one, two or three nucleic acid sequences selected from: (a) a nucleic acid sequence of SEQ ID NO: 15, (b) a nucleic acid sequence of SEQ ID NO: 16, and (c) a nucleic acid sequence of SEQ ID NO: 17.
52. An isolated nucleic acid sequence comprising one, two or three nucleic acid sequences selected from: (a) a nucleic acid sequence of SEQ ID NO: 18, (b) a nucleic acid sequence of SEQ ID NO: 19, and (c) a nucleic acid sequence of SEQ ID NO: 20.
53. A vector comprising the isolated nucleic acid sequence of any one of claims 49-52.
54. An isolated cell comprising the vector of claim 53.
55. A composition comprising the polypeptide of any one of claims 1-48 the isolated nucleic acid of any one of claims 49-52, the vector of claim 53, or the isolated cell of claim 54.

56. The composition of claim 55, wherein the composition further comprises a pharmaceutically acceptable carrier.
57. An antibody agent comprising the polypeptide of any one of claims 1-48.
58. The antibody agent of claim 57, wherein the antibody agent binds to LAG-3 with a K_D between about 1 picomolar (pM) and about 100 micromolar (μ M).
59. A method of inducing an immune response in a mammal having a disorder that is responsive to Lymphocyte Activation Gene 3 (LAG-3) inhibition, comprising administering to said mammal an effective amount of an agent that is capable of inhibiting LAG-3 signaling (LAG-3 agent), whereupon the immune response is induced in the mammal, optionally wherein the LAG-3 agent is selected from the group consisting of: the polypeptide of any one of claims 1-48, the isolated nucleic acid of any one of claims 49-52, the vector of claim 53, the isolated cell of claim 54, the composition of claim 55 or 56, or the antibody agent of claim 57 or 58.
60. A method of inducing an immune response in a mammal having a disorder that is responsive to Lymphocyte Activation Gene 3 (LAG-3) inhibition, comprising administering to said mammal an effective amount of an agent that is capable of inhibiting LAG-3 signaling (LAG-3 agent), an effective amount of an agent that is capable of inhibiting programmed death 1 protein (PD-1) signaling (PD-1 agent), and an effective amount of an agent that is capable of inhibiting T cell immunoglobulin and mucin protein 3 (TIM-3) signaling (TIM-3 agent), whereupon the an immune response is induced in the mammal, optionally wherein the LAG-3 agent is selected from the group consisting of: the polypeptide of any one of claims 1-48, the isolated nucleic acid of any one of claims 49-52, the vector of claim 53, the isolated cell of claim 54, the composition of claim 55 or 56, or the antibody agent of claim 57 or 58.
61. A method of enhancing an immune response or increasing the activity of an immune cell in a mammal having a disorder that is responsive to Lymphocyte Activation Gene 3 (LAG-3) inhibition, comprising administering to said mammal an effective amount of an agent that is capable of inhibiting LAG-3 signaling (LAG-3 agent), whereupon the immune response is induced in the mammal, optionally wherein the LAG-3 agent is selected from the group consisting of: the polypeptide of any one of claims 1-48, the

isolated nucleic acid of any one of claims 49-52, the vector of claim 53, the isolated cell of claim 54, the composition of claim 55 or 56, or the antibody agent of claim 57 or 58.

62. A method of enhancing an immune response or increasing the activity of an immune cell in a mammal having a disorder that is responsive to Lymphocyte Activation Gene 3 (LAG-3) inhibition, comprising administering to said mammal an effective amount of an agent that is capable of inhibiting LAG-3 signaling (LAG-3 agent), an effective amount of an agent that is capable of inhibiting programmed death 1 protein (PD-1) signaling (PD-1 agent), and an effective amount of an agent that is capable of inhibiting T cell immunoglobulin and mucin protein 3 (TIM-3) signaling (TIM-3 agent), whereupon the immune response is induced in the mammal, optionally wherein the LAG-3 agent is selected from the group consisting of: the polypeptide of any one of claims 1-48, the isolated nucleic acid of any one of claims 49-52, the vector of claim 53, the isolated cell of claim 54, the composition of claim 55 or 56, or the antibody agent of claim 57 or 58.
63. The method of any one of claims 59-62, wherein the immune response is a humoral or cell mediated immune response.
64. The method of claim 63, wherein the immune response is a CD4 or CD8 T-cell response.
65. The method of claim 63, wherein the immune response is a B-cell response.
66. A method of treating a disorder in a mammal that is responsive to Lymphocyte Activation Gene 3 (LAG-3) inhibition, comprising administering an effective amount of an agent that is capable of inhibiting LAG-3 signaling (LAG-3 agent) to a mammal having a disorder that is responsive to LAG-3 inhibition, whereupon the disorder is treated in the mammal, optionally wherein the LAG-3 agent is selected from the group consisting of: the polypeptide of any one of claims 1-48, the isolated nucleic acid of any one of claims 49-52, the vector of claim 53, the isolated cell of claim 54, the composition of claim 55 or 56, or the antibody agent of claim 57 or 58.
67. A method of treating a disorder in a mammal that is responsive to Lymphocyte Activation Gene 3 (LAG-3) inhibition, comprising administering an effective amount of an agent that is capable of inhibiting LAG-3 signaling (LAG-3 agent), an effective amount of an agent that is capable of inhibiting programmed death 1 protein (PD-1) signaling (PD-1 agent), and an effective amount of an agent that is capable of inhibiting T cell

immunoglobulin and mucin protein 3 (TIM-3) signaling (TIM-3 agent) to a mammal having a disorder that is responsive to LAG-3 inhibition, whereupon the disorder is treated in the mammal, optionally wherein the LAG-3 agent is selected from the group consisting of: the polypeptide of any one of claims 1-48, the isolated nucleic acid of any one of claims 49-52, the vector of claim 53, the isolated cell of claim 54, the composition of claim 55 or 56, or the antibody agent of claim 57 or 58.

68. The method of any one of claims 59-67, wherein the disorder is cancer.

69. The method of claim 68, wherein the cancer is:

- i) — a cancer associated with a high tumor mutation burden (TMB);
- ii) — a cancer that is microsatellite stable (MSS);
- iii) — a cancer that is characterized by microsatellite instability;
- iv) — a cancer that has a high microsatellite instability status (MSI-H);
- v) — a cancer that has a low microsatellite instability status (MSI-L);
- vi) — a cancer associated with high TMB and MSI-H;
- vii) — a cancer associated with high TMB and MSI-L or MSS;
- viii) — a cancer that has a defective DNA mismatch repair system;
- ix) — a cancer that has a defect in a DNA mismatch repair gene;
- x) — a hypermutated cancer;
- xi) — a cancer comprising a mutation in polymerase delta (POLD);
- xii) — a cancer comprising a mutation in polymerase epsilon (POLE);
- xiii) — a cancer that has homologous recombination repair deficiency/homologous repair deficiency (“HRD”) or is characterized by a homologous recombination repair (HRR) gene mutation or deletion;

xiv) ~~adenocarcinoma, endometrial cancer, breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, testicular cancer, primary peritoneal cancer, colon cancer, colorectal cancer, small intestine cancer, squamous cell carcinoma of the anus, squamous cell carcinoma of the penis, squamous cell carcinoma of the cervix, squamous cell carcinoma of the vagina, squamous cell carcinoma of the vulva, soft tissue sarcoma, melanoma, renal cell carcinoma, lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous cell carcinoma of the lung, stomach cancer, bladder cancer, gall bladder cancer, liver cancer, thyroid cancer, laryngeal cancer, salivary gland cancer, esophageal cancer, head and neck cancer, squamous cell carcinoma of the head and neck, prostate cancer, pancreatic cancer, mesothelioma, Merkel cell carcinoma, sarcoma, glioblastoma, a hematological cancer, multiple myeloma, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma/primary mediastinal B-cell lymphoma, chronic myelogenous leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, non-Hodgkin's lymphoma, neuroblastoma, a CNS tumor, diffuse intrinsic pontine glioma (DIPG), Ewing's sarcoma, embryonal rhabdomyosarcoma, osteosarcoma, or Wilms tumor; or~~

xv) ~~a cancer of xiv), wherein the cancer is MSS or MSI-L, is characterized by microsatellite instability, is MSI-H, has high TMB, has high TMB and is MSS or MSI-L, has high TMB and is MSI-H, has a defective DNA mismatch repair system, has a defect in a DNA mismatch repair gene, is a hypermutated cancer, is an HRD or HRR cancer, comprises a mutation in polymerase delta (POLD), or comprises a mutation in polymerase epsilon (POLE).~~

70. ~~The method of claim 69, wherein the cancer is melanoma, renal cell carcinoma, lung cancer, bladder cancer, breast cancer, cervical cancer, colon cancer, gall bladder cancer, laryngeal cancer, liver cancer, thyroid cancer, stomach cancer, salivary gland cancer, prostate cancer, pancreatic cancer, endometrial cancer, ovarian cancer, or Merkel cell carcinoma.~~

71. ~~The method of claim 69, wherein the cancer is non-small cell lung cancer, endometrial cancer, renal cell carcinoma, cervical cancer, stomach cancer, colorectal cancer, or triple negative breast cancer (TNBC).~~

72. The method of claim 69, wherein the cancer is a cancer that has homologous recombination repair deficiency/homologous repair deficiency (“HRD”) or is characterized by a homologous recombination repair (HRR) gene mutation or deletion.
73. The method of claim 69, wherein the cancer is endometrial cancer, optionally MSI H or MSS/MSI L endometrial cancer.
74. The method of claim 69, wherein the cancer is a MSI H cancer comprising a mutation in POLE or POLD, optionally a MSI H non-endometrial cancer comprising a mutation in POLE or POLD.
75. The method of claim 69, wherein the cancer is breast cancer, optionally triple negative breast cancer (TNBC).
76. The method of claim 69, wherein the cancer is ovarian cancer, optionally epithelial ovarian cancer.
77. The method of claim 69, wherein the cancer is lung cancer, optionally non-small cell lung cancer.
78. The method of claim 69, wherein the cancer is melanoma.
79. The method of claim 69, wherein the cancer is colorectal cancer.
80. The method of claim 69, wherein the cancer is squamous cell carcinoma of the anus, squamous cell carcinoma of the penis, squamous cell carcinoma of the cervix, squamous cell carcinoma of the vagina, or squamous cell carcinoma of the vulva.
81. The method of claim 69, wherein the cancer is acute myeloid leukemia.
82. The method of claim 69, wherein the cancer is acute lymphoblastic leukemia.
83. The method of claim 69, wherein the cancer is non-Hodgkin’s lymphoma.
84. The method of claim 69, wherein the cancer is Hodgkin’s lymphoma.
85. The method of claim 69, wherein the cancer is neuroblastoma.
86. The method of claim 69, wherein the cancer is a CNS tumor.

- ~~87. The method of claim 69, wherein the cancer is diffuse intrinsic pontine glioma (DIPG).~~
- ~~88. The method of claim 69, wherein the cancer is Ewing's sarcoma.~~
- ~~89. The method of claim 69, wherein the cancer is embryonal rhabdomyosarcoma.~~
- ~~90. The method of claim 69, wherein the cancer is osteosarcoma.~~
- ~~91. The method of claim 69, wherein the cancer is Wilms tumor.~~
- ~~92. The method of claim 69, wherein the cancer is soft tissue sarcoma.~~
- ~~93. The method of claim 69, wherein the cancer is leiomyosarcoma.~~
- ~~94. The method of any one of claims 60, 62-65, and 67-68, wherein the cancer is large B-cell lymphoma, thymoma, acute myeloid leukemia, testicular tumor, lung adenocarcinoma, non-small cell lung cancer, kidney clear cell cancer, breast cancer, triple negative breast cancer (TNBC), non-triple negative breast cancer (non-TNBC), gastric cancer, lung squamous cell cancer, mesothelioma, pancreatic cancer, cervical cancer, head and neck cancer, melanoma, hepatocellular carcinoma, nasopharyngeal cancer, esophageal cancer, colon adenocarcinoma, colorectal cancer, rectum carcinoma, cholangiocarcinoma, uterine endometrial cancer, sarcoma, bladder cancer, thyroid carcinoma, kidney papillary cancer, glioblastoma multiforme, liver cancer, uterine carcinosarcoma, pheochromocytoma, lower grade glioma, kidney chromophobe, adrenocortical cancer, or uveal melanoma.~~
- ~~95. The method of any one of claims 59-67, wherein the disorder is an infectious disease.~~
- ~~96. The method of claim 95, wherein the infectious disease is caused by a virus or a bacterium.~~
- ~~97. The method of claim 96, wherein the virus is human immunodeficiency virus (HIV), respiratory syncytial virus (RSV), influenza virus, dengue virus, Epstein-Barr virus (EBV), human papillomavirus (HPV), hepatitis B virus (HBV), or hepatitis C virus (HCV), optionally wherein the cancer is virally infected head and neck cancer, cervical cancer, hepatocellular carcinoma, or nasopharyngeal cancer.~~
- ~~98. The method of any one of claims 59-67, wherein the disorder is an autoimmune disease.~~

99. ~~The method of claim 98, wherein the autoimmune disease is multiple sclerosis, type 1 diabetes mellitus, rheumatoid arthritis, scleroderma, Crohn's disease, psoriasis, systemic lupus erythematosus (SLE), or ulcerative colitis.~~
100. ~~—The method of any one of claims 59-99, wherein the method further comprises administering another therapeutic agent or treatment.~~
101. ~~—The method of claim 100, wherein the method further comprises administering one or more of surgery, a radiotherapy, a chemotherapy, an immunotherapy, an anti-angiogenic agent, or an anti-inflammatory.~~
102. ~~—The method of any one of the preceding claims, wherein the subject has been further administered or will be administered an immune checkpoint inhibitor, such that the mammal receives the agent that is capable of inhibiting LAG-3 signaling and the immune checkpoint inhibitor.~~
103. ~~—The method of claim 102, comprising further administering one, two, or three immune checkpoint inhibitors.~~
104. ~~—The method of claim 102 or 103, wherein an immune checkpoint inhibitor is an inhibitor of PD-1, TIM-3, CTLA-4, TIGIT, CEACAM, VISTA, BTLA, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM, KIR, A2aR, MHC class I, MHC class II, GALS, adenosine, TGFR, B7-H1, B7-H4 (VTCN1), OX-40, CD137, CD40, IDO, or CSF1R.~~
105. ~~—The method of claim 103 or 104, wherein the immune checkpoint inhibitor is an agent that inhibits programmed death 1 protein (PD-1) signaling, T cell immunoglobulin and mucin protein 3 (TIM-3), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), T cell immunoglobulin and ITIM domain (TIGIT), indoleamine 2,3-dioxygenase (IDO), or colony-stimulating factor 1 receptor (CSF1R).~~
106. ~~—The method of claim 105, wherein the immune checkpoint inhibitor is an agent that inhibits TIM-3.~~
107. ~~—The method of claim 106, wherein the agent that inhibits TIM-3 is a small molecule, a nucleic acid, a polypeptide (e.g. an antibody), a carbohydrate, a lipid, a metal, a toxin or a TIM-3 binding agent.~~

108. ~~The method of claim 107, wherein the agent that inhibits TIM-3 is a TIM-3 binding agent.~~
109. ~~The method of claim 108, wherein the TIM-3 binding agent is an antibody, an antibody conjugate, or an antigen-binding fragment thereof.~~
110. ~~The method of claim 109, wherein the TIM-3 binding agent is TSR-022.~~
111. ~~The method of claim 105, wherein the immune checkpoint inhibitor is an agent that inhibits PD-1.~~
112. ~~The method of claim 111, wherein the agent that inhibits PD-1 is a small molecule, a nucleic acid, a polypeptide (e.g. an antibody, a carbohydrate, a lipid, a metal, a toxin, or a PD-1 binding agent).~~
113. ~~The method of claim 112, wherein the agent that inhibits PD-1 is a PD-1 binding agent.~~
114. ~~The method of claim 113, wherein the PD-1 binding agent is an antibody, an antibody conjugate, or an antigen-binding fragment thereof.~~
115. ~~The method of claim 114, wherein the PD-1 binding agent is selected from the group consisting of: BGB-A317, BI-754091, IBI308, INC5HR-1210, JNJ-63723283, JS-001, MEDI-0680, MGA-012, nivolumab, PDR001, pembrolizumab, PF-06801591, REGN-2810, TSR-042, and derivatives thereof.~~
116. ~~The method of claim 115, wherein the PD-1 binding agent is TSR-042.~~
117. ~~The method of claim 111, wherein the agent that inhibits PD-1 is an anti-PD-L1/L2 agent.~~
118. ~~The method of claim 117, wherein the anti-PD-L1/L2 agent is an anti-PD-L1 antibody agent.~~
119. ~~The method of claim 118, wherein the anti-PD-L1 antibody agent is atezolizumab, avelumab, CX-072, durvalumab, FAZ053, LY3300054, PD-L1 millamolecule, or derivatives thereof.~~

120. ~~The method of claim 105, wherein the immune checkpoint inhibitor is a CTLA-4 inhibitor.~~
121. ~~The method of claim 120, wherein the CTLA-4 inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g. an antibody), a carbohydrate, a lipid, a metal, a toxin or a CTLA-4 binding agent.~~
122. ~~The method of claim 121, wherein the CTLA-4 binding agent is an antibody, an antibody conjugate, or an antigen binding fragment thereof.~~
123. ~~The method of claim 105, wherein the immune checkpoint inhibitor is a TIGIT inhibitor.~~
124. ~~The method of claim 123, wherein the TIGIT inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g. an antibody), a carbohydrate, a lipid, a metal, a toxin, or a TIGIT binding agent.~~
125. ~~The method of claim 124, wherein the TIGIT binding agent is an antibody, an antibody conjugate, or an antigen binding fragment thereof.~~
126. ~~The method of claim 105, wherein the immune checkpoint inhibitor is an IDO inhibitor.~~
127. ~~The method of claim 126, wherein the IDO inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g. an antibody), a carbohydrate, a lipid, a metal, a toxin, or a IDO binding agent.~~
128. ~~The method of claim 127, wherein the IDO binding agent is an antibody, an antibody conjugate, or an antigen binding fragment thereof.~~
129. ~~The method of claim 105, wherein the immune checkpoint inhibitor is a CSF1R inhibitor.~~
130. ~~The method of claim 129, wherein the CSF1R inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g. an antibody), a carbohydrate, a lipid, a metal, a toxin, or a CSF1R binding agent.~~

- ~~131. The method of claim 130, wherein the CSF1R binding agent is an antibody, an antibody conjugate, or an antigen binding fragment thereof.~~
- ~~132. The method of any one of claims 59-119, wherein the mammal has been administered or will be administered an agent that inhibits TIM-3 and an agent that inhibits PD-1 such that the mammal receives all three.~~
- ~~133. The method of any one of claims 59-105, 111-117, and 132, wherein the PD-1 agent or the agent that inhibits PD-1 is BGB-A317, BI-754091, IBI308, INC5HR-1210, JNJ-63723283, JS-001, MEDI-0680, MGA-012, nivolumab, PDR001, pembrolizumab, PF-06801591, REGN-2810, TSR-042, atezolizumab, avelumab, CX-072, durvalumab, FAZ053, LY3300054, PD-L1 millamolecule, or derivatives thereof.~~
- ~~134. The method of any one of claims 59-110, 132, and 133, wherein the TIM-3 agent and the agent that inhibits TIM-3 is MBG453, LY3321367, Sym023, TSR-022 or a derivative thereof.~~
- ~~135. The method of claim 132, wherein the mammal has been administered or will be administered an agent that inhibits TIM-3 that is TSR-022 and an agent that inhibits PD-1 that is TSR-042.~~
- ~~136. The method of any one of claims 59-105, 111-119 and 132-135, wherein the PD-1 agent or the agent that inhibits PD-1 is administered at a dose of about 500 mg/patient to about 1000 mg/patient.~~
- ~~137. The method of claim 136, wherein the PD-1 agent or the agent that inhibits PD-1 is administered at a dose of about 500 mg/patient.~~
- ~~138. The method of claim 136, wherein the PD-1 agent or the agent that inhibits PD-1 is administered at a dose of about 1000 mg/patient.~~
- ~~139. The method of any one of claims 136-138, wherein the PD-1 agent or the agent that inhibits PD-1 is administered to the patient once every three weeks.~~
- ~~140. The method of claim 139, wherein the PD-1 agent or the agent that inhibits PD-1 is administered for multiple cycles.~~

141. ~~_____ The method of claim 140, wherein the PD-1 agent or the agent that inhibits PD-1 is administered for 2, 3, 4, 5, 6, or more cycles.~~
142. ~~_____ The method of claim 141, wherein the PD-1 agent or the agent that inhibits PD-1 is administered for three, four, or five cycles.~~
143. ~~_____ The method of claim 141, wherein the PD-1 agent or the agent that inhibits PD-1 is administered for four cycles.~~
144. ~~_____ The method of claim 142, wherein after the third, fourth, or fifth cycle, the agent that inhibits PD-1 is administered at a higher dose once every 6 weeks or more.~~
145. ~~_____ The method of claim 144, wherein the PD-1 agent or the agent that inhibits PD-1 is administered at a higher dose once every 6 weeks.~~
146. ~~_____ The method of claim 144 or 145, wherein the PD-1 agent or the agent that inhibits PD-1 is administered at a first dose of about 500 mg/patient.~~
147. ~~_____ The method of any one of claims 144-146, wherein the PD-1 agent or the agent that inhibits PD-1 is administered at a higher dose of about 1000 mg.~~
148. ~~_____ The method of any one of claims 144-147, wherein the PD-1 agent or the agent that inhibits PD-1 is administered at a first dose of about 500 mg once every 3 weeks for 3, 4, or 5 cycles followed by a second dose of about 1000 mg once every 6 weeks or more.~~
149. ~~_____ The method of any one of claims 144-147, wherein the PD-1 agent or the agent that inhibits PD-1 is administered at a first dose of about 500 mg once every 3 weeks for 3 cycles followed by a second dose of about 1000 mg once every 6 weeks or more.~~
150. ~~_____ The method of any one of claims 144-147, wherein the PD-1 agent or the agent that inhibits PD-1 is administered at a first dose of about 500 mg once every 3 weeks for 4 cycles followed by a second dose of about 1000 mg once every 6 weeks or more.~~
151. ~~_____ The method of any one of claims 144-147, wherein the PD-1 agent or the agent that inhibits PD-1 is administered at a first dose of about 500 mg once every 3 weeks for 5 cycles followed by a second dose of about 1000 mg once every 6 weeks or more.~~

- ~~152. The method of claim 151, wherein the second dose of 1000 mg is administered once every 6 weeks.~~
- ~~153. The method of any one of claims 59-110 and 132-152, wherein the TIM-3 agent or the agent that inhibits TIM-3 is administered at a dose of about 1, 3 or 10 mg/kg.~~
- ~~154. The method of any one of claims 59-110 and 132-152, wherein the TIM-3 agent or the agent that inhibits TIM-3 is administered at a dose of about 100-1500 mg.~~
- ~~155. The method of claim 154, wherein the TIM-3 agent or the agent that inhibits TIM-3 is administered at a flat dose about 100 mg; a flat dose about 200 mg; a flat dose about 300 mg; a flat dose about 400 mg; a flat dose about 500 mg; a flat dose about 600 mg; a flat dose about 700 mg; a flat dose about 800 mg; a flat dose about 900 mg; a flat dose about 1000 mg; a flat dose about 1100 mg; a flat dose about 1200 mg; a flat dose about 1300 mg; a flat dose about 1400 mg; or a flat dose about 1500 mg.~~
- ~~156. The method of claim 154 or 155, wherein the dose is a flat dose of no more than about 1200 mg.~~
- ~~157. The method of claim 154 or 155, wherein the dose is a flat dose of no more than about 900 mg.~~
- ~~158. The method of claim 154 or 155, wherein the dose is a flat dose between about 100-500 mg.~~
- ~~159. The method of claim 154 or 155, wherein the dose is a flat dose between about 1000-1500 mg.~~
- ~~160. The method of any one of claims 153-159, wherein the TIM-3 agent or the agent that inhibits TIM-3 is administered at the administration interval of once a week, once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 5 weeks, or once every 6 weeks.~~
- ~~161. The method of claim 160, wherein the TIM-3 agent or the agent that inhibits TIM-3 is administered at the administration interval of once every 2 weeks.~~
- ~~162. The method of claim 160, wherein the TIM-3 agent or the agent that inhibits TIM-3 is administered at the administration interval of once every 3 weeks.~~

- ~~163. The method of any one of claims 153-162, wherein the TIM-3 agent or the agent that inhibits TIM-3 is administered for the period of at least 2, 4, 6, 8, 10, 12, 14, 16, 18, or 20 weeks.~~
- ~~164. The method of any one of claims 132-163, wherein the PD-1 agent or the agent that inhibits PD-1 is TSR-042 and is administered in an amount of about 500 mg every three weeks; and the TIM-3 agent or the agent that inhibits TIM-3 is TSR-022 and is administered in an amount of no more than about 1200 mg every three weeks.~~
- ~~165. The method of claim 164, wherein TSR-022 is administered in an amount of no more than about 900 mg every three weeks.~~
- ~~166. The method of any one of claims 132-165, wherein the PD-1 agent or the agent that inhibits PD-1 and/or the TIM-3 agent or the agent that inhibits TIM-3 is administered intravenously.~~
- ~~167. The method of any one of claims 132-166, wherein the agent that inhibits LAG-3, the agent that inhibits PD-1 and/or the agent that inhibits TIM-3 is administered at a reduced dose.~~
- ~~168. The method of any one of claims 59-167, wherein the mammal is resistant to treatment with an agent that inhibits PD-1.~~
- ~~169. The method of any one of claims 59-168, wherein the mammal is refractory to treatment with an agent that inhibits PD-1.~~
- ~~170. The method of anyone of claims 59-169, wherein the method sensitizes the mammal to treatment with an agent that inhibits PD-1.~~
- ~~171. The method of any one of claims 59-170, wherein the mammal has been administered or will be administered an agent that inhibits PARP, such that the mammal receives both.~~
- ~~172. The method of claim 171, wherein the agent that inhibits PARP is administered at a reduced dose.~~

173. ~~The method of claim 171 or 172, wherein the agent that inhibits PARP is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a carbohydrate, a lipid, a metal, or a toxin.~~
174. ~~The method of any one of claims 171-173 wherein the agent that inhibits PARP is selected from the group consisting of: ABT-767, AZD-2461, BGB-290, BGP-15, CEP-8983, CEP-9722, DR-2313, E7016, E7449, fluzoparib (SHR-3162), IMP-4297, INO1001, JPI-289, JPI-547, monoclonal antibody B3-LysPE40 conjugate, MP-124, niraparib (ZEJULA) (MK-4827), NU-1025, NU-1064, NU-1076, NU-1085, olaparib (AZD2281), ONO2231, PD-128763, R-503, R554, rucaparib (RUBRACA) (AG-014699, PF-01367338), SBP-101, SC-101914, simmiparib, talazoparib (BMN-673), veliparib (ABT-888), WW-46, 2-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-thiopyrano[4,3-d]pyrimidin-4-ol, and salts or derivatives thereof.~~
175. ~~The method of claim 174, wherein the agent that inhibits PARP is niraparib.~~
176. ~~The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 1 to about 5000 mg, about 1 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 50 mg, about 100 mg, about 200 mg, about 250 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 2000 mg, about 3000 mg, about 4000 mg, or about 5000 mg.~~
177. ~~The method of claim 176, wherein the method comprises administering the LAG-3 agent at a dose of about 20 mg, about 80 mg, about 240 mg, about 500 mg, about 720 mg, about 900 mg, about 1000 mg, about 1200 mg, about 1500 mg, about 1800 mg, about 2100 mg, about 2200 mg, or about 2500 mg.~~
178. ~~The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 0.01 mg/kg to about 100 mg/kg, about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 12 mg/kg, about 15 mg/kg, about 20 mg/kg, about~~

~~25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, or about 100 mg/kg of the mammal.~~

~~179. — The method of claim 178, wherein the method comprises administering the LAG-3 agent at a dose of about 1 mg/kg, about 3 mg/kg, about 10 mg/kg, about 12 mg/kg, about 15 mg/kg, about 20 mg/kg, or about 25 mg/kg.~~

~~180. — The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 1 mg/kg to about 30 mg/kg.~~

~~181. — The method of claim 180, wherein the method comprises administering the LAG-3 agent at a dose of about 1 mg/kg to about 10 mg/kg, about 1 mg/kg to about 25 mg/kg, or about 1 mg/kg to about 15 mg/kg.~~

~~182. — The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 20 mg, about 80 mg, about 240 mg, about 500 mg, about 720 mg, about 900 mg, or about 1000 mg, about 240-720 mg, about 240-1000 mg, or no more than about 1000 mg.~~

~~183. — The method of any one of claims 59-182, wherein the method comprises administering the LAG-3 agent every week, every two weeks, every three weeks, every four weeks, every five weeks, every six weeks, every seven weeks, or every eight weeks.~~

~~184. — The method of any one of claims 59-183, wherein the method comprises administering the LAG-3 agent every two weeks.~~

~~185. — The method of claim 184, wherein the method comprises administering the LAG-3 agent at a dose of about 20 mg, about 80 mg, about 240 mg, about 500 mg, about 720 mg, about 900 mg, about 1000 mg, or about 1500 mg every two weeks, or about 240-720 mg or about 240-1500 mg every two weeks.~~

~~186. — The method of any one of claims 59-183, wherein the method comprises administering the LAG-3 agent every three weeks.~~

- ~~187. The method of claim 186, wherein the method comprises administering the LAG-3 agent at a dose of about 20 mg, about 80 mg, about 240 mg, about 500 mg, about 720 mg, about 900 mg, about 1000 mg, about 1500 mg, about 1800 mg, about 2100 mg, about 2200 mg, or about 2500 mg every three weeks, or about 240-720 mg or about 240-2500 mg every three weeks.~~
- ~~188. The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 240-720 mg/patient.~~
- ~~189. The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 20 mg/patient.~~
- ~~190. The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 80 mg/patient.~~
- ~~191. The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 240 mg/patient.~~
- ~~192. The method of claim 191, wherein the method comprises administering the LAG-3 agent once every two weeks.~~
- ~~193. The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 500 mg/patient.~~
- ~~194. The method of claim 193, wherein the method comprises administering the LAG-3 agent once every two weeks.~~
- ~~195. The method of claim 193, wherein the method comprises administering the LAG-3 agent once every three weeks.~~
- ~~196. The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 720 mg/patient.~~
- ~~197. The method of claim 196, wherein the method comprises administering the LAG-3 agent once every two weeks.~~
- ~~198. The method of claim 196, wherein the method comprises administering the LAG-3 agent once every three weeks.~~

199. ~~—The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 900 mg/patient.~~
200. ~~—The method of claim 199, wherein the method comprises administering the LAG-3 agent once every two weeks.~~
201. ~~—The method of claim 199, wherein the method comprises administering the LAG-3 agent once every three weeks.~~
202. ~~—The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 1000 mg/patient.~~
203. ~~—The method of claim 202, wherein the method comprises administering the LAG-3 agent once every two weeks.~~
204. ~~—The method of claim 202, wherein the method comprises administering the LAG-3 agent once every three weeks.~~
205. ~~—The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of no more than about 1000 mg/patient.~~
206. ~~—The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 1500 mg/patient.~~
207. ~~—The method of claim 206, wherein the method comprises administering the LAG-3 agent once every two weeks.~~
208. ~~—The method of claim 206, wherein the method comprises administering the LAG-3 agent once every three weeks.~~
209. ~~—The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 1800 mg/patient.~~
210. ~~—The method of claim 209, wherein the method comprises administering the LAG-3 agent once every three weeks.~~
211. ~~—The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 2100 mg/patient.~~

212. ~~The method of claim 211, wherein the method comprises administering the LAG-3 agent once every three weeks.~~
213. ~~The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 2200 mg/patient.~~
214. ~~The method of claim 213, wherein the method comprises administering the LAG-3 agent once every three weeks.~~
215. ~~The method any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 2500 mg/patient.~~
216. ~~The method of claim 215, wherein the method comprises administering the LAG-3 agent once every three weeks.~~
217. ~~The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 3 mg/kg.~~
218. ~~The method of claim 217, wherein the method comprises administering the LAG-3 agent once every two weeks.~~
219. ~~The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 10 mg/kg.~~
220. ~~The method of claim 219, wherein the method comprises administering the LAG-3 agent once every two weeks.~~
221. ~~The method of claim 219, wherein the method comprises administering the LAG-3 agent once every three weeks.~~
222. ~~The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 12 mg/kg.~~
223. ~~The method of claim 222, wherein the method comprises administering the LAG-3 agent once every two weeks.~~
224. ~~The method of claim 222, wherein the method comprises administering the LAG-3 agent once every three weeks.~~

225. ~~The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 15 mg/kg.~~
226. ~~The method of claim 225, wherein the method comprises administering the LAG-3 agent once every two weeks.~~
227. ~~The method of claim 225, wherein the method comprises administering the LAG-3 agent once every three weeks.~~
228. ~~The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 20 mg/kg.~~
229. ~~The method of claim 228, wherein the method comprises administering the LAG-3 agent once every three weeks.~~
230. ~~The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 25 mg/kg.~~
231. ~~The method of claim 230, wherein the method comprises administering the LAG-3 agent once every three weeks.~~
232. ~~The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 3 mg/kg, about 10 mg/kg, about 12 mg/kg, or about 15 mg/kg every two weeks.~~
233. ~~The method of any one of claims 59-175, wherein the method comprises administering the LAG-3 agent at a dose of about 10 mg/kg, about 12 mg/kg, about 15 mg/kg, about 20 mg/kg, or about 25 mg/kg every three weeks.~~
234. ~~The method of any one of claims 59-233, wherein the LAG-3 agent is administered ocularly, oral, parenterally, topically, bronchially, buccally, intradermally, interdermally, transdermally, enterally, intra-arterially, intradermally, intragastrically, intramedullarily, intramuscular, intranasally, intraperitoneally, intrathecally, intravenously, intraventricular, within a specific organ (e.g., intrahepatically), mucosally, nasally, orally, rectally, subcutaneously, sublingually, topically, tracheally, vaginally, vitreally, or any combination thereof.~~

235. ~~—The method of any one of claims 59-234, wherein the LAG-3 agent is administered intravenously.~~
236. ~~—The method of any one of claims 59-235, wherein the mammal is human.~~
237. ~~—The method of any one of claims 59-236, wherein the mammal has previously been treated with one or more different cancer treatment modalities.~~
238. ~~—The method of claim 237, wherein the mammal has previously been treated with one or more of surgery, radiotherapy, chemotherapy, or immunotherapy.~~
239. ~~—The method of claim 237 or 238, wherein the mammal has been treated with one, two, three, four, or five lines of prior therapy.~~
240. ~~—The method of claim 239, wherein the prior therapy is a cytotoxic therapy.~~
241. ~~—The method of any one of claims 59-240, wherein the LAG-3 agent is a small molecule, a nucleic acid, a polypeptide, a carbohydrate, a lipid, a metal, or a toxin.~~
242. ~~—The method of claim 241, wherein the LAG-3 agent is a LAG-3 binding agent.~~
243. ~~—The method of claim 242, wherein the LAG-3 binding agent is an antibody, an antibody conjugate, or an antigen binding fragment thereof.~~
244. ~~—The method of any one of claims 59-240, wherein the LAG-3 agent is IMP321, relatlimab (BMS-986016), BI 754111, GSK2831781 (IMP-731), Novartis LAG525 (IMP701), REGN3767, MK-4280, MGD-013, GSK-2831781, FS-118, XmAb22841, INCAGN-2385, FS-18, ENUM-006, AVA-017, AM-0003, Avacta PD-L1/LAG-3 bispecific affamer, iOnetura anti-LAG-3 antibody, Arcus anti-LAG-3 antibody, or Sym022.~~
245. ~~—The method of any one of claims 59-240, wherein the LAG-3 agent is selected from the group consisting of: the polypeptide of any one of claims 1-48, the isolated nucleic acid of any one of claims 49-52, the vector of claim 53, the isolated cell of claim 54, the composition of claim 55 or 56, or the antibody agent of claim 57 or 58.~~
246. ~~—The method of claim 245, wherein the LAG-3 agent is a polypeptide comprising: a CDR-H1 defined by SEQ ID NO: 5;~~

~~a CDR H2 defined by SEQ ID NO: 6;~~
~~a CDR H3 defined by SEQ ID NO: 7;~~
~~a CDR L1 defined by SEQ ID NO: 8;~~
~~a CDR L2 defined by SEQ ID NO: 9; and~~
~~a CDR L3 defined by SEQ ID NO: 10.~~

247. ~~—The method of claim 245, wherein the LAG 3 agent is a polypeptide comprising:~~
~~a heavy chain variable region amino acid sequence having at least 80%, 85%, 90%,~~
~~95%, or 98% sequence identity to SEQ ID NO: 3; and~~
~~a light chain variable region amino acid sequence having at least 80%, 85%, 90%,~~
~~95%, or 98% sequence identity to SEQ ID NO: 4.~~

248. ~~—The method of claim 245 wherein the LAG 3 agent is a polypeptide comprising:~~
~~a heavy chain polypeptide sequence having at least 80%, 85%, 90%, 95%, or 98%~~
~~sequence identity to SEQ ID NO: 1 or SEQ ID NO: 21; and~~
~~a light chain polypeptide sequence having at least 80%, 85%, 90%, 95%, or 98%~~
~~sequence identity to SEQ ID NO: 2 or SEQ ID NO: 22.~~

249. ~~—A method of manufacturing the polypeptide of any one of claims 1-48, by~~
~~expressing a nucleic acid encoding the polypeptide in a host cell culture.~~

250. ~~—A method of manufacturing the composition of claim 55 or 56, by combining the~~
~~polypeptide with the pharmaceutically acceptable carrier and formulating for~~
~~administration to a subject.~~

251. ~~—The method of claim 250, wherein the step of formulating for administration~~
~~comprises formulating for parenteral delivery.~~

252. ~~—A method of inducing an immune response in a mammal having a disorder that is~~
~~responsive to Lymphocyte Activation Gene 3 (LAG 3) inhibition, comprising~~
~~administering to said mammal an effective amount of an agent that is capable of~~
~~inhibiting LAG 3 signaling (LAG 3 agent), an effective amount of an agent that is~~
~~capable of inhibiting programmed death 1 protein (PD 1) signaling (PD 1 agent), and an~~
~~effective amount of an agent that is capable of inhibiting T cell immunoglobulin and~~
~~mucin protein 3 (TIM 3) signaling (TIM 3 agent), whereupon the immune response is~~
~~induced in the mammal, wherein the LAG 3 agent is selected from the group consisting~~

of: the polypeptide of any one of claims 1-48, the isolated nucleic acid of any one of claims 49-52, the vector of claim 53, the isolated cell of claim 54, the composition of claim 55 or 56, or the antibody agent of claim 57 or 58, wherein the PD-1 agent is TSR-042, and wherein the TIM-3 agent is TSR-033.

253. ——— A method of enhancing an immune response or increasing the activity of an immune cell in a mammal having a disorder that is responsive to Lymphocyte Activation Gene-3 (LAG-3) inhibition, comprising administering to said mammal an effective amount of an agent that is capable of inhibiting LAG-3 signaling (LAG-3 agent), an effective amount of an agent that is capable of inhibiting programmed death 1 protein (PD-1) signaling (PD-1 agent), and an effective amount of an agent that is capable of inhibiting T cell immunoglobulin and mucin protein 3 (TIM-3) signaling (TIM-3 agent), whereupon the immune response is induced in the mammal, wherein the LAG-3 agent is selected from the group consisting of: the polypeptide of any one of claims 1-48, the isolated nucleic acid of any one of claims 49-52, the vector of claim 53, the isolated cell of claim 54, the composition of claim 55 or 56, or the antibody agent of claim 57 or 58, wherein the PD-1 agent is TSR-042, and wherein the TIM-3 agent is TSR-033.

254. A method of treating a disorder in a mammal that is responsive to Lymphocyte Activation Gene-3 (LAG-3) inhibition, comprising administering an effective amount of an agent that is capable of inhibiting LAG-3 signaling (LAG-3 agent), an effective amount of an agent that is capable of inhibiting programmed death 1 protein (PD-1) signaling (PD-1 agent), and an effective amount of an agent that is capable of inhibiting T cell immunoglobulin and mucin protein 3 (TIM-3) signaling (TIM-3 agent) to a mammal having a disorder that is responsive to LAG-3 inhibition, whereupon the disorder is treated in the mammal, wherein the LAG-3 agent is selected from the group consisting of: the polypeptide of any one of claims 1-48, the isolated nucleic acid of any one of claims 49-52, the vector of claim 53, the isolated cell of claim 54, the composition of claim 55 or 56, or the antibody agent of claim 57 or 58, wherein the PD-1 agent is TSR-042, and wherein the TIM-3 agent is TSR-033.

1. A polypeptide that is capable of binding Lymphocyte Activation Gene-3 (LAG-3) comprising: (a) an amino acid sequence of SEQ ID NO: 5, (b) an amino acid sequence of SEQ ID NO: 6, and (c) an amino acid sequence of SEQ ID NO: 7.

2. A polypeptide that is capable of binding Lymphocyte Activation Gene-3 (LAG-3) comprising: (a) an amino acid sequence of SEQ ID NO: 8, (b) an amino acid sequence of SEQ ID NO: 9, and (c) an amino acid sequence of SEQ ID NO: 10.
3. A polypeptide that is a Lymphocyte Activation Gene-3 (LAG-3) binding agent capable of binding LAG-3, wherein said polypeptide comprises
- a heavy chain variable region comprising:
- a CDR-H1 comprising an amino acid sequence at least 80% identical to SEQ ID NO: 5;
- a CDR-H2 comprising an amino acid sequence at least 90% identical to SEQ ID NO: 6;
- a CDR-H3 comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7;
- and
- a light chain variable region comprising:
- a CDR-L1 defined by an amino acid sequence at least 90% identical to SEQ ID NO: 8;
- a CDR-L2 defined by an amino acid sequence at least 90% identical to SEQ ID NO: 9; and
- a CDR-L3 defined by an amino acid sequence at least 85% identical to SEQ ID NO: 10.
4. A polypeptide that is capable of binding Lymphocyte Activation Gene-3 (LAG-3), comprising:
- a heavy chain polypeptide sequence according to SEQ ID NO: 1;
- and
- a light chain polypeptide sequence according to SEQ ID NO: 2.
5. A composition comprising the polypeptide of claim 3 and a pharmaceutically acceptable carrier.
6. Use of a pharmaceutically effective amount of the composition of claim 5 in the manufacture of a medicament for the treatment of cancer, wherein the pharmaceutically effective amount of the composition to a human in need thereof.

7. The use of claim 6, wherein the cancer is:

- i) a cancer associated with a high tumor mutation burden (TMB);
- ii) a cancer that is microsatellite stable (MSS),
- iii) a cancer that is characterized by microsatellite instability,
- iv) a cancer that has a high microsatellite instability status (MSI-H),
- v) a cancer that has a low microsatellite instability status (MSI-L),
- vi) a cancer associated with high TMB and MSI-H,
- vii) a cancer associated with high TMB and MSI-L or MSS,
- viii) a cancer that has a defective DNA mismatch repair system,
- ix) a cancer that has a defect in a DNA mismatch repair gene,
- x) a hypermutated cancer,
- xi) a cancer comprising a mutation in polymerase delta (POLD)
- xii) a cancer comprising a mutation in polymerase epsilon (POLE),
- xiii) a cancer that has homologous recombination repair deficiency/homologous repair deficiency (“HRD”) or is characterized by a homologous recombination repair (HRR) gene mutation or deletion;
- xiv) adenocarcinoma, endometrial cancer, breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, testicular cancer, primary peritoneal cancer, colon cancer, colorectal cancer, small intestine cancer, squamous cell carcinoma of the anus, squamous cell carcinoma of the penis, squamous cell carcinoma of the cervix, squamous cell carcinoma of the vagina, squamous cell carcinoma of the vulva, soft tissue sarcoma, melanoma, renal cell carcinoma, lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous cell carcinoma of the lung, stomach cancer, bladder cancer, gall bladder cancer, liver cancer, thyroid cancer, laryngeal cancer, salivary gland cancer, esophageal cancer, head and neck cancer, squamous cell carcinoma of the head and neck, prostate cancer, pancreatic cancer,

mesothelioma, Merkel cell carcinoma, sarcoma, glioblastoma, a hematological cancer, multiple myeloma, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma/primary mediastinal B-cell lymphoma, chronic myelogenous leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, non-Hodgkin's lymphoma, neuroblastoma, a CNS tumor, diffuse intrinsic pontine glioma (DIPG), Ewing's sarcoma, embryonal rhabdomyosarcoma, osteosarcoma, or Wilms tumor; or

xv) a cancer of xiv), wherein the cancer is MSS or MSI-L, is characterized by microsatellite instability, is MSI-H, has high TMB, has high TMB and is MSS or MSI-L, has high TMB and is MSI-H, has a defective DNA mismatch repair system, has a defect in a DNA mismatch repair gene, is a hypermutated cancer, is an HRD or HRR cancer, comprises a mutation in polymerase delta (POLD), or comprises a mutation in polymerase epsilon (POLE).

8. The use of claim 7, wherein the use further comprises another therapeutic agent or treatment to be administered.

9. The use of claim 8, wherein the use further comprises one or more of surgery, a radiotherapy, a chemotherapy, an immunotherapy, an anti-angiogenic agent, or an anti-inflammatory to be administered.

10. The use of claim 7, wherein the human has been further administered or will be administered an immune checkpoint inhibitor.

11. The use of claim 10, wherein an immune checkpoint inhibitor is an inhibitor of PD-1, TIM-3, CTLA-4, TIGIT, CEACAM, VISTA, BTLA, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM, KIR, A2aR, MHC class I, MHC class II, GALS, adenosine, TGFR, B7-H1, B7-H4 (VTCN1), OX-40, CD137, CD40, IDO, or CSF1R.

12. The use of claim 7, wherein the use comprises the LAG-3 binding agent to be administered at a dose of about 1 to about 5000 mg, about 1 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 50 mg, about 100 mg, about 200 mg, about 250 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 2000 mg, about 3000 mg, about 4000 mg, or about 5000 mg.

13. The use of claim 7, wherein the use comprises the LAG-3 binding agent to be administered every week, every two weeks, every three weeks, every four weeks, every five weeks, every six weeks, every seven weeks, or every eight weeks.
14. The use of claim 7, wherein the use comprises the LAG-3 binding agent to be administered at a dose of about 20 mg, about 80 mg, about 240 mg, about 500 mg, about 720 mg, about 900 mg, about 1000 mg, or about 1500 mg every two weeks, or about 240-720 mg or about 240-1500 mg every two weeks.
15. The use of claim 7, wherein the LAG-3 binding agent is to be administered parenterally, intravenously, or subcutaneously.
16. Use of an anti-LAG-3 antibody in the manufacture of a medicament for the treatment of cancer in a human, wherein the anti-LAG-3 antibody comprising a heavy chain at least 90% identical to SEQ ID NO: 1 and a light chain at least 90% identical to SEQ ID NO: 2, and wherein the anti-LAG-3 antibody is to be administered intravenously.
17. The use of claim 16, wherein the cancer is non-small cell lung cancer.
18. Use of an anti-LAG-3 antibody in the manufacture of a medicament for the treatment of cancer in a human, wherein the anti-LAG-3 antibody comprises:
- (i) a heavy chain variable region comprising:
 - a CDR-H1 comprising an amino acid sequence at least 80% identical to SEQ ID NO: 5;
 - a CDR-H2 comprising an amino acid sequence at least 90% identical to SEQ ID NO: 6; and
 - a CDR-H3 comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7; and
 - (ii) a light chain variable region comprising:
 - a CDR-L1 comprising an amino acid sequence at least 90% identical to SEQ ID NO: 8;
 - a CDR-L2 comprising an amino acid sequence at least 90% identical to SEQ ID NO: 9; and
 - a CDR-L3 comprising an amino acid sequence at least 85% identical to SEQ ID NO: 10.

and wherein the anti-LAG-3 antibody is to be administered intravenously.

19. The use of claim 18, wherein the cancer is non-small cell lung cancer.

20. The use of claim 18, wherein the method further comprises one or more checkpoint inhibitors to be administered.