

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating cancer in a subject, the method comprising administering to the subject an antibody or an antigen-binding fragment thereof, wherein the antibody binds to Programmed Death-1 (PD-1) and inhibits PD-1 activity, and an antibody-drug conjugate that binds to tissue factor (TF), wherein the antibody-drug conjugate comprises an anti-TF antibody or an antigen-binding fragment thereof conjugated to monomethyl auristatin E, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:17;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO:18; and
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO:19; and

wherein the light chain variable region comprises:

- (i) a CDR-L1 comprising the amino acid sequence of SEQ ID NO:20;
- (ii) a CDR-L2 comprising the amino acid sequence of SEQ ID NO:21; and
- (iii) a CDR-L3 comprising the amino acid sequence of SEQ ID NO:22,

and wherein the anti-TF antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:1;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO:2; and
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO:3; and

wherein the light chain variable region comprises:

- (i) a CDR-L1 comprising the amino acid sequence of SEQ ID NO:4;
- (ii) a CDR-L2 comprising the amino acid sequence of SEQ ID NO:5; and
- (iii) a CDR-L3 comprising the amino acid sequence of SEQ ID NO:6, wherein the

CDRs of the anti-TF antibody or antigen-binding fragment thereof are defined by the IMGT numbering scheme.

2. The method of claim 1, wherein the antibody-drug conjugate is administered at a dose ranging from about 0.9 mg/kg to about 2.1 mg/kg.

3. The method claim 2, wherein the antibody-drug conjugate is administered at a dose of about 1.3 mg/kg.
4. The method claim 2, wherein the antibody-drug conjugate is administered at a dose of 1.3 mg/kg.
5. The method of claim 2, wherein the antibody-drug conjugate is administered at a dose of about 2.0 mg/kg.
6. The method of claim 2, wherein the antibody-drug conjugate is administered at a dose of 2.0 mg/kg.
7. The method of any one of claims 1-6, wherein the antibody-drug conjugate is administered once about every 1 week, once about every 2 weeks, once about every 3 weeks or once about every 4 weeks.
8. The method of claim 7, wherein the antibody-drug conjugate is administered once about every 3 weeks.
9. The method of claim 7, wherein the antibody-drug conjugate is administered once every 3 weeks.
10. The method of any one of claims 1-9, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is administered at a flat dose ranging from about 50 mg to about 500 mg.
11. The method of any one of claims 1-10, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is administered at a flat dose of about 200 mg.
12. The method of any one of claims 1-10, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is administered at a flat dose of 200 mg.

13. The method of any one of claims 1-10, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is administered at a flat dose of about 400 mg.
14. The method of any one of claims 1-10, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is administered at a flat dose of 400 mg.
15. The method of any one of claims 1-14, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is administered once about every 1 week, once about every 2 weeks, once about every 3 weeks, once about every 4 weeks, once about every 5 weeks, or once about every 6 weeks.
16. The method of claim 15, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is administered once about every 3 weeks.
17. The method of claim 15, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is administered once every 3 weeks.
18. The method of claim 15, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is administered once about every 6 weeks.
19. The method of claim 15, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is administered once every 6 weeks.
20. The method of any one of claims 1-19, wherein the cancer is breast cancer.
21. The method of claim 20, wherein the breast cancer is ER+/HER2- breast cancer or triple negative breast cancer.
22. The method of any one of claims 1-19, wherein the cancer is cervical cancer.
23. The method of claim 22, wherein the subject is not a candidate for curative therapy.
24. The method of claim 23, wherein curative therapy comprises radiotherapy and/or exenterative surgery.

25. The method of claim 24, wherein the subject has not received prior systemic therapy for the cervical cancer.
26. The method of any one of claims 22-25, wherein the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma.
27. The method of any one of claims 22-26, wherein the cervical cancer is an advanced stage cervical cancer.
28. The method of claim 27, wherein the advanced stage cervical cancer is a stage 3 or stage 4 cervical cancer.
29. The method of claim 27 or 28, wherein the advanced stage cervical cancer is metastatic cervical cancer.
30. The method of any one of claims 22-29, wherein the cervical cancer is recurrent cervical cancer.
31. The method of any one of claims 1-30, wherein the anti-TF antibody or antigen-binding fragment thereof of the antibody-drug conjugate is a monoclonal antibody or a monoclonal antigen-binding fragment thereof.
32. The method of any one of claims 1-31, wherein the anti-TF antibody or antigen-binding fragment thereof of the antibody-drug conjugate comprises a heavy chain variable region comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:7 and a light chain variable region comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:8.
33. The method of any one of claims 1-32, wherein the anti-TF antibody or antigen-binding fragment thereof of the antibody-drug conjugate comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:7 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:8.

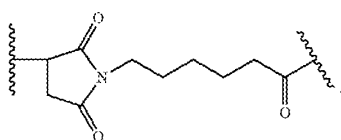
34. The method of any one of claims 1-33, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

35. The method of any one of claims 1-34, wherein the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the monomethyl auristatin E.

36. The method of claim 35, wherein the linker is a cleavable peptide linker.

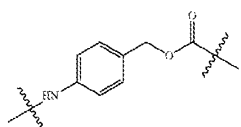
37. The method of claim 36, wherein the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

a) MC is:



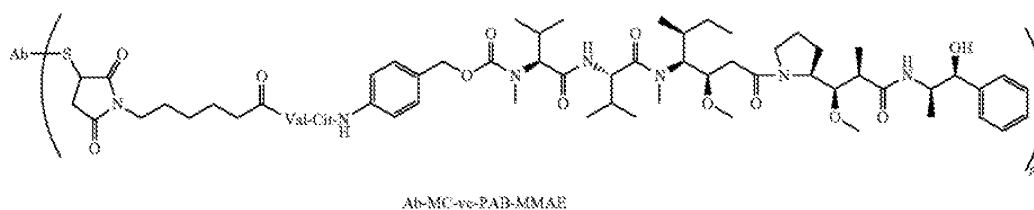
b) vc is the dipeptide valine-citrulline, and

c) PAB is:



38. The method of any one of claims 35-37, wherein the linker is attached to sulphydryl residues of the anti-TF antibody or antigen-binding fragment thereof obtained by partial reduction or full reduction of the anti-TF antibody or antigen-binding fragment thereof.

39. The method of claim 38, wherein the linker is attached to MMAE, wherein the antibody-drug conjugate has the following structure:



wherein p denotes a number from 1 to 8, S represents a sulphydryl residue of the anti-TF antibody, and Ab designates the anti-TF antibody or antigen-binding fragment thereof.

40. The method of claim 39, wherein the average value of p in a population of the antibody-drug conjugates is about 4.
41. The method of any one of claims 1-40, wherein the antibody-drug conjugate is tisotumab vedotin.
42. The method of any one of claims 1-41, wherein the route of administration for the antibody-drug conjugate is intravenous.
43. The method of any one of claims 1-42, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:31 and a light chain variable region comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:32.
44. The method of any one of claims 1-43, wherein the anti-PD-1 antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:31 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:32.
45. The method of any one of claims 1-44, wherein the anti-PD-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:33 and a light chain comprising the amino acid sequence of SEQ ID NO:34.
46. The method of any one of claims 1-45, wherein the anti-PD-1 antibody is pembrolizumab.

47. The method of any one of claims 1-46, wherein the route of administration for the anti-PD-1 antibody or antigen-binding fragment thereof is intravenous or subcutaneous.
48. The method any one of claims 1-46, wherein the route of administration for the anti-PD-1 antibody or antigen-binding fragment thereof is intravenous.
49. The method of any one of claims 1-46, wherein the route of administration for the anti-PD-1 antibody or antigen-binding fragment thereof is subcutaneous.
50. The method of any one of claims 1-49, wherein the anti-PD-1 antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered sequentially.
51. The method of any one of claims 1-49, wherein the anti-PD-1 antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered simultaneously.
52. The method of any one of claims 1-51, wherein at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of cancer cells from the subject express TF.
53. The method of any one of claims 1-52, wherein at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of cancer cells from the subject express PD-L1.
54. The method of any one of claims 1-53, wherein the subject has a tumor that expresses PD-L1 (TPS $\geq$ 1).

55. The method of any one of claims 1-53, wherein the subject has a tumor that has high PD-L1 expression ($TPS \geq 50$).
56. The method of any one of claims 1-53, wherein the subject has a tumor that expresses PD-L1 ($CPS \geq 1$).
57. The method of any one of claims 1-56, wherein a tumor derived from the cancer comprises one or more cells that express PD-L1, PD-L2, or both PD-L1 and PD-L2.
58. The method of any one of claims 1-57, wherein at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of T-cells from the subject express PD-1.
59. The method of any one of claims 1-58, wherein one or more therapeutic effects in the subject is improved after administration of the antibody-drug conjugate and the anti-PD-1 antibody or antigen-binding fragment thereof relative to a baseline.
60. The method of claim 59, wherein the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cancer, objective response rate, duration of response, time to response, progression free survival, and overall survival.
61. The method of any one of claims 1-60, wherein the size of a tumor derived from the cancer is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% relative to the size of the tumor derived from the cancer before administration of the antibody-drug conjugate and the anti-PD-1 antibody or antigen-binding fragment thereof.
62. The method of any one of claims 1-61, wherein the objective response rate is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at

least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%.

63. The method of any one of claims 1-62, wherein the subject exhibits progression-free survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the antibody-drug conjugate and the anti-PD-1 antibody or antigen-binding fragment thereof.

64. The method of any one of claims 1-63, wherein the subject exhibits overall survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the antibody-drug conjugate and the anti-PD-1 antibody or antigen-binding fragment thereof.

65. The method of any one of claims 1-64, wherein the duration of response to the antibody-drug conjugate is at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the antibody-drug conjugate and the anti-PD-1 antibody or antigen-binding fragment thereof.

66. The method of any one of claims 1-65, wherein the subject has one or more adverse events and is further administered an additional therapeutic agent to eliminate or reduce the severity of the one or more adverse events.

67. The method of any one of claims 1-66, wherein the subject is at risk of developing one or more adverse events and is further administered an additional therapeutic agent to prevent or reduce the severity of the one or more adverse events.
68. The method of claim 66 or claim 67, wherein the one or more adverse events is anemia, abdominal pain, hemorrhage, hyperthyroidism, hypothyroidism, hypokalemia, hyponatremia, epistaxis, fatigue, nausea, alopecia, conjunctivitis, keratitis, conjunctival ulceration, constipation, decreased appetite, diarrhea, vomiting, peripheral neuropathy, or general physical health deterioration.
69. The method of any one of claims 66-68, wherein the one or more adverse events is a grade 3 or greater adverse event.
70. The method of any one of claims 66-68, wherein the one or more adverse events is a serious adverse event.
71. The method of claim 66 or claim 67, wherein the one or more adverse events is conjunctivitis, conjunctival ulceration, and/or keratitis and the additional agent is a preservative-free lubricating eye drop, an ocular vasoconstrictor, antibiotic, and/or a steroid eye drop.
72. The method of any one of claims 1-71, wherein the subject is a human.
73. The method of any one of claims 1-72, wherein the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier.
74. The method of any one of claims 1-73, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is in a pharmaceutical composition comprising the anti-PD-1 antibody or antigen-binding fragment thereof and a pharmaceutical acceptable carrier.
75. A kit comprising:
- (a) a dosage ranging from about 50 mg to about 500 mg of an antibody or an antigen-binding fragment thereof, wherein the antibody binds to Programmed Death-1 (PD-1)

and inhibits PD-1 activity, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:17;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO:18; and
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO:19; and

wherein the light chain variable region comprises:

- (i) a CDR-L1 comprising the amino acid sequence of SEQ ID NO:20;
- (ii) a CDR-L2 comprising the amino acid sequence of SEQ ID NO:21; and
- (iii) a CDR-L3 comprising the amino acid sequence of SEQ ID NO:22;
- (b) a dosage ranging from about 0.9 mg/kg to about 2.1 mg/kg of an antibody-

drug conjugate that binds to tissue factor (TF), wherein the antibody-drug conjugate comprises an anti-TF antibody or an antigen-binding fragment thereof conjugated to monomethyl auristatin E, wherein the anti-TF antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises:

- (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:1;
- (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO:2; and
- (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO:3; and

wherein the light chain variable region comprises:

- (i) a CDR-L1 comprising the amino acid sequence of SEQ ID NO:4;
- (ii) a CDR-L2 comprising the amino acid sequence of SEQ ID NO:5; and
- (iii) a CDR-L3 comprising the amino acid sequence of SEQ ID NO:6, wherein the

CDRs of the anti-TF antibody or antigen-binding fragment thereof are defined by the IMGT numbering scheme; and

(c) instructions for use of the anti-PD-1 antibody or antigen-binding fragment thereof and the antibody drug conjugate according to the method of any one of claims 1-74.

76. The kit of claim 75, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is pembrolizumab.

77. The kit of claim 76, wherein the dose of the pembrolizumab is 200 mg.

78. The kit of claim 76, wherein the dose of the pembrolizumab is 400 mg.

79. The kit of any one of claims 75-78, wherein the antibody-drug conjugate is tisotumab vedotin.
80. The kit of claim 79, wherein the dose of the tisotumab vedotin is 1.3 mg/kg.
81. The kit of claim 79, wherein the dose of the tisotumab vedotin is 2.0 mg/kg.