

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating cancer in a subject, the method comprising administering to the subject a platinum-based agent 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 a monomethyl auristatin or a functional analog thereof or a functional derivative thereof.
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 platinum-based agent is administered at a dose between about AUC=4 and about AUC=6.
11. The method of claim 10, wherein the platinum-based agent is administered a dose of about AUC=5.
12. The method of claim 10, wherein the platinum-based agent is administered a dose of AUC=5.
13. The method of any one of claims 1-12, wherein the platinum-based agent is administered once about every 1 week, once about every 2 weeks, once about every 3 weeks or once about every 4 weeks.
14. The method of claim 13, wherein the platinum-based agent is administered once about every 3 weeks.
15. The method of claim 13, wherein the platinum-based agent is administered once every 3 weeks.
16. The method of any one of claims 1-15, wherein the cancer is bladder cancer.
17. The method of any one of claims 1-15, wherein the cancer is cervical cancer.
18. The method of claim 17, wherein the subject is not a candidate for curative therapy.
19. The method of claim 18, wherein curative therapy comprises radiotherapy and/or exenterative surgery.
20. The method of claim 17, wherein the subject has not received prior systemic therapy for the cervical cancer.
21. The method of any one of claims 17-20, wherein the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma.

22. The method of any one of claims 17-21, wherein the cervical cancer is an advanced stage cervical cancer.
23. The method of claim 22, wherein the advanced stage cervical cancer is a stage 3 or stage 4 cervical cancer.
24. The method of claim 22 or 23, wherein the advanced stage cervical cancer is metastatic cervical cancer.
25. The method of any one of claims 17-24, wherein the cervical cancer is recurrent cervical cancer.
26. The method of any one of claims 1-25, wherein the monomethyl auristatin is monomethyl auristatin E (MMAE).
27. The method of any one of claims 1-26, 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.
28. The method of any one of claims 1-27, wherein the anti-TF antibody or antigen-binding fragment thereof of the antibody-drug conjugate 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.

29. The method of any one of claims 1-28, 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 at least 85% identical to the amino acid sequence of SEQ ID NO:7 and a light chain variable region comprising an amino acid sequence at least 85% identical to the amino acid sequence of SEQ ID NO:8.

30. The method of any one of claims 1-29, 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.

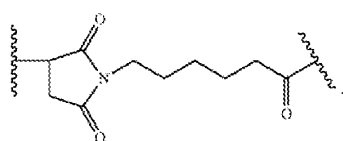
31. The method of any one of claims 1-30, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

32. The method of any one of claims 1-31, wherein the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the monomethyl auristatin.

33. The method of claim 32, wherein the linker is a cleavable peptide linker.

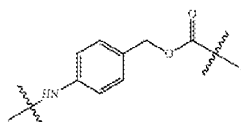
34. The method of claim 33, wherein the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

a) MC is:



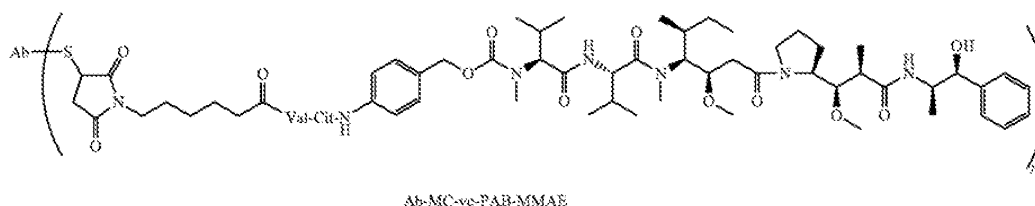
b) vc is the dipeptide valine-citrulline, and

c) PAB is:



35. The method of any one of claims 32-34, wherein the linker is attached to sulphydryl residues of the anti-TF antibody obtained by partial reduction or full reduction of the anti-TF antibody or antigen-binding fragment thereof.

36. The method of claim 35, 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.

37. The method of claim 36, wherein the average value of p in a population of the antibody-drug conjugates is about 4.

38. The method of any one of claims 1-37, wherein the antibody-drug conjugate is tisotumab vedotin.

39. The method of any one of claims 1-38, wherein the route of administration for the antibody-drug conjugate is intravenous.

40. The method of any one of claims 1-39, wherein the platinum-based agent is selected from the group consisting of carboplatin, cisplatin, oxaliplatin, and nedaplatin.

41. The method of any one of claims 1-39, wherein the platinum-based agent is carboplatin.

42. The method of any one of claims 1-39, wherein the platinum-based agent is cisplatin.

43. The method of any one of claims 1-42, wherein the route of administration for the platinum-based agent is intravenous.

44. The method of any one of claims 1-43, wherein the platinum-based agent and the antibody-drug conjugate are administered sequentially.
45. The method of any one of claims 1-43, wherein the platinum-based agent and the antibody-drug conjugate are administered simultaneously.
46. The method of any one of claims 1-45, 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 the cervical cancer cells express TF.
47. The method of any one of claims 1-46, wherein one or more therapeutic effects in the subject is improved after administration of the antibody-drug conjugate and the platinum-based agent relative to a baseline.
48. The method of claim 47, wherein the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cervical cancer, objective response rate, duration of response, time to response, progression free survival, and overall survival.
49. The method of any one of claims 1-48, wherein the size of a tumor derived from the cervical 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 cervical cancer before administration of the antibody-drug conjugate and the platinum-based agent.
50. The method of any one of claims 1-49, 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%.

51. The method of any one of claims 1-50, 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 platinum-based agent.

52. The method of any one of claims 1-51, 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 platinum-based agent.

53. The method of any one of claims 1-52, 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 platinum-based agent.

54. The method of any one of claims 1-53, 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.

55. The method of any one of claims 1-54, 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.

56. The method of claim 54 or claim 55, wherein the one or more adverse events is hemorrhage, nausea, alopecia, conjunctivitis, keratitis, conjunctival ulceration, mucositis, constipation, decreased appetite, diarrhea, vomiting, neutropenia, febrile neutropenia, decreased platelet count, or increased bleeding.
57. The method of claim 54 or claim 55, wherein the one or more adverse events is a grade 3 or greater adverse event.
58. The method of claim 54 or claim 55, wherein the one or more adverse events is a serious adverse event.
59. The method of claim 54 or claim 55, wherein the one or more adverse events is conjunctivitis and/or keratitis and the additional agent is a preservative-free lubricating eye drop, an ocular vasoconstrictor and/or a steroid eye drop.
60. The method of any one of claims 1-59, wherein the subject is a human.
61. The method of any one of claims 1-60, wherein the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier.
62. The method of any one of claims 1-61, wherein the platinum-based agent is in a pharmaceutical composition comprising the platinum-based agent and a pharmaceutical acceptable carrier.
63. A kit comprising:
- (a) a dosage ranging from about AUC=4 to about AUC=6 of a platinum-based agent;
 - (b) a dosage ranging from about 1.5 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 a monomethyl auristatin or a functional analog thereof or a functional derivative thereof; and

(c) instructions for using the platinum-based agent and the antibody drug conjugate according to the method of any one of claims 1-62.

64. The kit of claim 63, wherein the platinum-based agent is carboplatin.

65. The kit of claim 63 or claim 64, wherein the antibody-drug conjugate is tisotumab vedotin.

66. An antibody-drug conjugate that binds to TF for use in the method of any one of claims 1-62, wherein the antibody-drug conjugate is for administration, or to be administered in combination with a platinum-based agent, wherein the antibody-drug conjugate comprises an anti-TF antibody or an antigen-binding fragment thereof conjugated to a monomethyl auristatin or a functional analog thereof or a functional derivative thereof.

67. Use of an antibody-drug conjugate that binds to TF for the manufacture of a medicament for use in the method of any one of claims 1-62, wherein the medicament is for use in combination with a platinum-based agent, wherein the antibody-drug conjugate comprises an anti-TF antibody or an antigen-binding fragment thereof conjugated to a monomethyl auristatin or a functional analog thereof or a functional derivative thereof.

68. A platinum-based agent for use in the method of any one of claims 1-62, wherein the platinum-based agent is for administration, or to be administered in combination with an antibody-drug conjugate that binds to TF, wherein the antibody-drug conjugate comprises an anti-TF antibody or an antigen-binding fragment thereof conjugated to a monomethyl auristatin or a functional analog thereof or a functional derivative thereof.

69. Use of a platinum-based agent for the manufacture of a medicament for use in the method of any one of claims 1-62, wherein the medicament is for use in combination with an antibody-drug conjugate that binds to TF, wherein the antibody-drug conjugate comprises an anti-TF antibody or an antigen-binding fragment thereof conjugated to a monomethyl auristatin or a functional analog thereof or a functional derivative thereof.