CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating cancer in a subject, the method comprising administering to the subject 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, wherein the antibody-drug conjugate is administered at a dose ranging from about 1.5 mg/kg to about 2.1 mg/kg, and wherein the cancer is selected from the group consisting of colorectal cancer, non-small cell lung cancer, pancreatic cancer, head and neck cancer, bladder cancer, endometrial cancer, esophageal cancer and prostate cancer.

2. The method of claim 1, wherein the dose is about 2.0 mg/kg.

3. The method of claim 1, wherein the dose is 2.0 mg/kg.

4. The method of any one of claims 1-3, wherein the antibody-drug conjugate is administered once about every 1 week, 2 weeks, 3 weeks or 4 weeks.

5. The method of any one of claims 1-4, wherein the antibody-drug conjugate is administered once about every 3 weeks.

6. The method of any one of claims 1-5, wherein the subject has been previously treated with one or more therapeutic agents and did not respond to the treatment, wherein the one or more therapeutic agents is not the antibody-drug conjugate.

7. The method of any one of claims 1-5, wherein the subject has been previously treated with one or more therapeutic agents and relapsed after the treatment , wherein the one or more therapeutic agents is not the antibody-drug conjugate.

8. The method of any one of claims 1-5, wherein the subject has been previously treated with one or more therapeutic agents and has experienced disease progression during treatment, wherein the one or more therapeutic agents is not the antibody-drug conjugate.

9. The method of any one of claims 1-8, wherein the cancer is colorectal cancer.

10. The method of claim 9, wherein the subject received prior systemic therapy and experienced disease progression on or after the systemic therapy.

11. The method of claim 10, wherein the subject received 1, 2 or 3 rounds of prior systemic therapy.

12. The method of any one of claims 9-11, wherein the colorectal cancer is non-operable.

13. The method of any one of claims 9-12, wherein the subject has been previously treated with one or more agents selected from the group consisting of fluoropyrimidine, oxaliplatin, irinotecan and bevacizumab.

14. The method of any one of claims 9-13, wherein the subject has been previously treated with one or more agents selected from the group consisting of cetuximab, panitumab and a checkpoint inhibitor.

15. The method of any one of claims 1-8, wherein the cancer is non-small cell lung cancer.

16. The method of claim 15, wherein the non-small cell lung cancer is squamous cell carcinoma.

17. The method of claim 15 or claim 16, wherein the non-small cell lung cancer has predominant squamous histology.

18. The method of claim 17, wherein greater than 85% of the non-small cell lung cancer cells have squamous histology.

19. The method of embodiment 15, wherein the non-small cell lung cancer is adenocarcinoma.

20. The method of any one of claims 15-19, wherein the subject received prior systemic therapy and experienced disease progression on or after the systemic therapy.

21. The method of claim 20, wherein the subject received 1 or 2 rounds of prior systemic therapy.

22. The method of any one of claims 15-21, wherein the subject has been previously treated with one or more agents selected from the group consisting of a platinum-based therapy and a checkpoint inhibitor.

23. The method of any one of claims 1-8, wherein the cancer is pancreatic cancer.

24. The method of claim 23, wherein the pancreatic cancer is exocrine pancreatic adenocarcinoma.

25. The method of claim 23 or claim 24, wherein the pancreatic cancer has predominant adenocarcinoma histology.

26. The method of claim 25, wherein greater than 85% of the pancreatic cancer cells have adenocarcinoma histology.

27. The method of any one of claims 23-26, wherein the subject received prior systemic therapy and experienced disease progression on or after the systemic therapy.

28. The method of claim 27, wherein the subject received 1 round of prior systemic therapy.

29. The method of any one of claims 23-28, wherein the subject has been previously treated with one or more agents selected from the group consisting of gemcitabine and 5-fluorouracil.

30. The method of any one of claims 23-29, wherein the pancreatic cancer is not resectable.

31. The method of any one of claims 1-8, wherein the cancer is head and neck cancer.

32. The method of claim 31, wherein the head and neck cancer is squamous cell carcinoma.

33. The method of claim 31 or claim 32, wherein the subject received prior systemic therapy and experienced disease progression on or after the systemic therapy.

34. The method of claim 33, wherein, the subject received 1 or 2 rounds of prior systemic therapy.

35. The method of any one of claims 31-34, wherein the subject has been previously treated with one or more agents selected from the group consisting of a platinum-based therapy and a checkpoint inhibitor.

36. The method of any one of claims 31-35, wherein the subject has been previously treated with an anti-epithelial growth factor receptor therapy.

37. The method of any one of claims 1-8, wherein the cancer is bladder cancer.

38. The method of claim 37, wherein the subject received prior systemic therapy and experienced disease progression on or after the systemic therapy.

39. The method of claim 38, wherein the subject received 1, 2 or 3 rounds of prior systemic therapy.

40. The method of any one of claims 37-39, wherein the subject has been previously treated with a platinum-based therapy.

41. The method of any one of claims 37-40, wherein the subject has previously undergone surgery or radiation therapy for the bladder cancer.

42. The method of any one of claims 1-8, wherein the cancer is endometrial cancer.

43. The method of claim 42, wherein the subject received prior systemic therapy and experienced disease progression on or after the systemic therapy.

44. The method of claim 43, wherein the subject received 1, 2 or 3 rounds of prior systemic therapy.

45. The method of any one of claims 42-44, wherein the subject has been previously treated with one or more agents selected from the group consisting of a platinum-based therapy, hormone therapy, and a checkpoint inhibitor.

46. The method of any one of claims 42-45, wherein the subject has previously been treated with doxorubicin.

47. The method of any one of claims 42-46, wherein the subject has previously been treated with paclitaxel.

48. The method of any one of claims 42-47, wherein the subject has previously undergone surgery or radiation therapy for the endometrial cancer.

49. The method of any one of claims 1-8, wherein the cancer is esophageal cancer.

50. The method of claim 49, wherein the subject received prior systemic therapy and experienced disease progression on or after the systemic therapy.

51. The method of claim 50, wherein the subject received 1, 2 or 3 rounds of prior systemic therapy.

52. The method of any one of claims 49-51, wherein the subject has been previously treated with one or more agents selected from the group consisting of a platinum-based therapy and a checkpoint inhibitor.

53. The method of any one of claims 49-52, wherein the subject has been previously treated with one or more agents selected from the group consisting of ramucirumab, paclitaxel, 5-fluorouracil, docetaxel, irinotecan, capecitabine and trastuzumab.

54. The method of any one of claims 49-53, wherein the subject has previously undergone surgery, radiation therapy or endoscopic mucosal resection for the esophageal cancer.

55. The method of any one of claims 1-8, wherein the cancer is prostate cancer.

56. The method of claim 55, wherein the subject received prior systemic therapy and experienced disease progression on or after the systemic therapy.

57. The method of claim 56, wherein the subject received 1, 2 or 3 rounds of prior systemic therapy.

58. The method of any one of claims 55-57, wherein the prostate cancer is castration-resistant prostate cancer.

59. The method of any one of claims 55-58, wherein the subject experienced bone metastases.

60. The method of any one of claims 55-59, wherein the subject has been previously treated with one or more agents selected from the group consisting of androgen deprivation therapy, a luteinizing hormone-releasing hormone agonist, a luteinizing hormone-releasing hormone antagonist, a CYP17 inhibitor, and an anti-androgen.

61. The method of any one of claims 55-60, wherein the subject has been previously treated with one or more agents selected from the group consisting of docetaxel, prednisone and cabazitaxel.

62. The method of any one of claims 55-61, wherein the subject has previously undergone surgery or radiation therapy for the prostate cancer.

63. The method of any one of claims 1-62, wherein the cancer is an advanced stage cancer.

64. The method of claim 63, wherein the advanced stage cancer is a stage 3 or stage 4 cancer.

65. The method of claim 63 or 64, wherein the advanced stage cancer is metastatic cancer.

66. The method of any one of claims 1-65, wherein the cancer is recurrent cancer.

67. The method of any one of claims 1-66, wherein the subject received prior treatment with standard of care therapy for the cancer and failed the prior treatment.

68. The method of any one of claims 1-67, wherein the monomethyl auristatin is monomethyl auristatin E (MMAE).

69. The method of any one of claims 1-68, 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.

70. The method of any one of claims 1-69, 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.

71. The method of any one of claims 1-70, 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.

72. The method of any one of claims 1-71, 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.

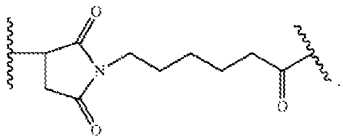
73. The method of any one of claims 1-72, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

74. The method of any one of claims 1-73, wherein the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the monomethyl auristatin.

75. The method of claim 74, wherein the linker is a cleavable peptide linker.

76. The method of claim 75, wherein the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

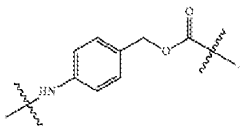
a) MC is:



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b) vc is the dipeptide valine-citrulline, and

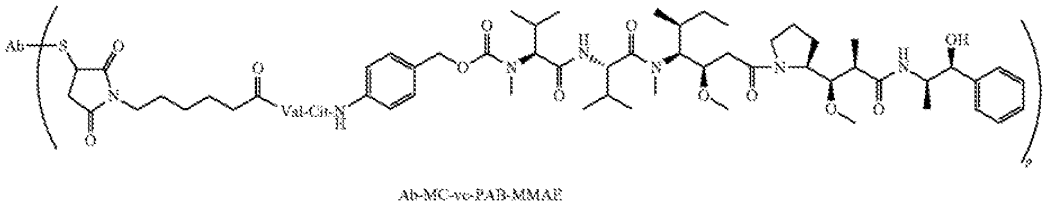
c) PAB is:



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77. The method of any one of claims 74-76, 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.

78. The method of claim 77, wherein the linker is attached to monomethyl auristatin E (MMAE), wherein the antibody-drug conjugate has the following structure:



Ab-MC-vc-PAB-MMAE

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.

79. The method of claim 78, wherein the average value of p in a population of the antibody-drug conjugates is about 4.

80. The method of any one of claims 1-79, wherein the antibody-drug conjugate is tisotumab vedotin.

81. The method of any one of claims 1-80, wherein the route of administration for the antibody-drug conjugate is intravenous.

82. The method of any one of claims 1-81, 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 cancer cells express TF.

83. The method of any one of claims 1-82, wherein one or more therapeutic effects in the subject is improved after administration of the antibody-drug conjugate relative to a baseline.

84. The method of claim 83, 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, overall survival and prostate specific antigen (PSA) level.

85. The method of any one of claims 55-62, wherein the subject exhibits a reduction in PSA level in a blood sample from the subject by at least about 5%, 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 PSA level in a blood sample obtained from the subject before administration of the antibody-drug conjugate.

86. The method of any one of claims 1-85, 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.

87. The method of any one of claims 1-86, 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%.

88. The method of any one of claims 1-87, 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.

89. The method of any one of claims 1-88, 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.

90. The method of any one of claims 1-89, 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.

91. The method of any one of claims 1-90, 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.

92. The method of any one of claims 1-90, 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.

93. The method of claim 91 or claim 92, wherein the one or more adverse events is anemia, abdominal pain, hypokalemia, hyponatremia, epistaxis, fatigue, nausea, alopecia, conjunctivitis, constipation, decreased appetite, diarrhea, vomiting, peripheral neuropathy, or general physical health deterioration.

94. The method of claim 91 or claim 92, wherein the one or more adverse events is a grade 3 or greater adverse event.

95. The method of claim 91 or claim 92, wherein the one or more adverse events is a serious adverse event.

96. The method of claim 91 or claim 92, 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.

97. The method of any one of claims 1-96, wherein the antibody-drug conjugate is administered as a monotherapy.

98. The method of any one of claims 1-97, wherein the subject is a human.

99. The method of any one of claims 1-98, wherein the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier.

100. A kit comprising:

(a) 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 a monomethyl auristatin or a functional analog thereof or a functional derivative thereof; and

(b) instructions for using the antibody drug conjugate according to the method of any one of claims 1-99.

101. Use of an antibody-drug conjugate that binds to tissue factor (TF) for the manufacture of a medicament for use in the method of any one of claims 1-99, 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.

102. An antibody-drug conjugate that binds to TF for use in the method of any one of claims 1-99, 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.