adenocarcinoma. Long-lasting infections with human papillomavirus (HPV) type 16 and 18 cause most cases of cervical cancer. The standard for first-line therapy of cervical cancer was a platinum-based therapy plus a taxane-based therapy. Bevacizumab, an anti-VEGF antibody, was approved by the U.S. Food and Drug Administration for use in combination with chemotherapy for the treatment of cervical cancer, which had improved overall survival in clinical trials. First-line (1L) treatment for advanced cervical cancer is comprised of bevacizumab combined with paclitaxel plus a platinum (*e.g.*, cisplatin or carboplatin) or paclitaxel plus topotecan. Despite a 48% objective response rate (ORR) and a median overall survival (OS) of approximately 18 months, unfortunately almost all patients relapse after this 1L treatment. *See* Tewari *et al.*, 2014, *N Engl J Med.*, 370:734-743. For second-line (2L) treatment, no approved therapy is available and patients are often treated with single agent modalities including, but not limited to: pemetrexed, topotecan, docetaxel, nab-paclitaxel, vinorelbine and in some cases bevacizumab. A meta-analysis of single agent treatment demonstrates a modest response rate of only 10.9% (*i.e.*, 60 responders out of 552 patients) and median overall survivals (OS) of approximately 7 months. The five year relative survival for stage IV cervical cancer is only 15%, demonstrating a high need for improved therapy against cervical cancer.

[0009] There remains a need for combination therapies with an acceptable safety profile and high efficacy for the treatment of cancer, in particular for the treatment of cervical cancer. The present invention meets this need by providing methods of treating cancer, such as cervical cancer, with a combination of an anti-VEGF antibody, such as bevacizumab, and an anti-Tissue Factor (anti-TF) antibody-drug conjugate, such as *e.g.*, tisotumab vedotin.

[0010] All references cited herein, including patent applications, patent publications, and scientific literature, are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

SUMMARY

[0010a] In one aspect, the present disclosure refers to the use of an antibody-drug conjugate that binds to tissue factor (TF) in the manufacture of a first medicament and use of an anti-VEGF antibody or an antigen-binding fragment thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating cancer in a subject,

wherein the antibody-drug conjugate comprises an anti-TF antibody or an antigen-binding fragment thereof conjugated to auristatin.

[0010b] In another aspect, the disclosure refers to the use of an antibody-drug conjugate that binds to tissue factor (TF) in the manufacture of a medicament for use in combination therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with an anti-VEGF antibody or an antigen-binding fragment thereof, wherein the antibody-drug conjugate comprises an anti-TF antibody or an antigen-binding fragment thereof conjugated to auristatin.

[0010c] In another aspect, the disclosure refers to the use of an anti-VEGF antibody or an antigen-binding fragment thereof in the manufacture of a medicament for use in combination therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with 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 auristatin.

[0010d] In another aspect, the disclosure refers to a kit comprising:

(a) a dosage ranging from about 5 mg/kg to about 20 mg/kg of an anti-VEGF antibody or antigen-binding fragment thereof ;

(b) a dosage ranging from about 0.65 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 an auristatin or a functional analog thereof or a functional derivative thereof; and

(c) instructions for using the anti-VEGF antibody or antigen-binding fragment thereof and the antibody drug conjugate according to the use as dislosed herein.

[0011] Provided herein is a method of treating cervical cancer in a subject, the method comprising administering to the subject an anti-VEGF antibody or antigen-binding fragment thereof 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. In

CLAIMS

1. Use of an antibody-drug conjugate that binds to tissue factor (TF) in the manufacture of a first medicament and use of an anti-VEGF antibody or an antigen-binding fragment thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating cancer in a subject, wherein the antibody-drug conjugate comprises an anti-TF antibody or an antigen-binding fragment thereof conjugated to an auristatin or a functional analog thereof or a functional derivative thereof.

2. Use of an antibody-drug conjugate that binds to tissue factor (TF) in the manufacture of a medicament for use in combination therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with an anti-VEGF antibody or an antigen-binding fragment thereof, wherein the antibody-drug conjugate comprises an anti-TF antibody or an antigen-binding fragment thereof conjugated to an auristatin or a functional analog thereof or a functional derivative thereof.

3. Use of an anti-VEGF antibody or an antigen-binding fragment thereof in the manufacture of a medicament for use in combination therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with 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 an auristatin or a functional analog thereof or a functional derivative thereof.

4. The use of any one of claims1-3, wherein the antibody-drug conjugate is to be administered at a dose ranging from about 0.65 mg/kg to about 2.1 mg/kg.

5. The use of claim 4, wherein the antibody-drug conjugate is to be administered at a dose of about 0.65 mg/kg.

6. The use of claim 4, wherein the antibody-drug conjugate is to be administered at a dose of about 0.9 mg/kg.

7. The use of claim 4, wherein the antibody-drug conjugate is to be administered at a dose of about 1.2 mg/kg.

8. The use of claim 4, wherein the antibody-drug conjugate is to be administered at a dose of about 1.3 mg/kg.

9. The use of claim 4, wherein the antibody-drug conjugate is to be administered at a dose of about 2.0 mg/kg.

10. The use of any one of claims 1-9, wherein the antibody-drug conjugate is to be administered once about every 3 weeks.

11. The use of any one of claims 1-9, wherein the antibody-drug conjugate is to be administered once about every 1 week for 3 consecutive weeks followed by about a 1 week rest period without any administration of the antibody-drug conjugate so that each cycle time is about 28 days including the resting period.

12. The use of any one of claims 1-9, wherein the antibody-drug conjugate is to be administered on about days 1, 8, and 15 of about a 4-week cycle.

13. The use of any one of claims 1-12, wherein the anti-VEGF antibody or antigen-binding fragment thereof is to be administered at a dose ranging from about 5 mg/kg to about 20 mg/kg.

14. The use of any one of claims 1-13, wherein the anti-VEGF antibody or antigen-binding fragment thereof is to be administered at a dose of about 7.5 mg/kg.

15. The use of any one of claims 1-13, wherein the anti-VEGF antibody or antigen-binding fragment thereof is to be administered at a dose of about 15 mg/kg.

16. The use of any one of claims 1-15, wherein the anti-VEGF antibody or antigen-binding fragment thereof is to be administered once about every 3 weeks.

17. The use of any one of claims 1-16, wherein the antibody-drug conjugate is to be administered at least 30 minutes after the administration of the anti-VEGF antibody or antigen-binding fragment thereof.

18. The use of any one of claims 1-17, 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.

19. The use of any one of claims 1-17, 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.

20. The use of any one of claims 1-17, 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.

21. The use of any one of claims 18-20, wherein the one or more therapeutic agents is selected from the group consisting of a chemotherapeutic agent, bevacizumab, cisplatin, carboplatin, paclitaxel, topotecan, a combination of bevacizumab and paclitaxel, a combination of bevacizumab and cisplatin, a combination of bevacizumab and carboplatin, a combination of paclitaxel and topotecan, a combination of bevacizumab and topotecan, a combination of bevacizumab, cisplatin and paclitaxel, a combination of bevacizumab, carboplatin and paclitaxel, and a combination of bevacizumab, paclitaxel and topotecan.

22. The use of any one of claims 1-21, wherein the subject is not a candidate for curative therapy.

23. The use of claim 22, wherein curative therapy comprises radiotherapy and/or exenterative surgery.

24. The use of any one of claims 1-23, wherein the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma.

25. The use of any one of claims 1-24, wherein the cervical cancer is an advanced stage cervical cancer.

26. The use of claim 25, wherein the advanced stage cervical cancer is a stage 3 or stage 4 cervical cancer.

27. The use of claim 25 or claim 26, wherein the advanced stage cervical cancer is metastatic cervical cancer.

28. The use of any one of claims 1-27, wherein the cervical cancer is recurrent cervical cancer.

29. The use of any one of claims 1-28, 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.

30. The use 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 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 of the antibody-drug conjugate are defined by the IMGT numbering scheme.

31. The use of any one of claims 1-30, 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.

32. The use 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 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.

33. The use of any one of claims 1-32, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

34. The use of any one of claims 1-33, wherein the auristatin is a monomethyl auristatin.

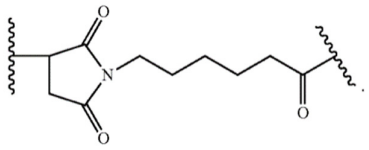
35. The use of any one of claims 34, wherein the monomethyl auristatin is monomethyl auristatin E (MMAE).

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

37. The use of claim 36, wherein the linker is a cleavable peptide linker.

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

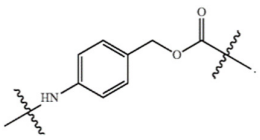
a) MC is:



,

b) vc is the dipeptide valine-citrulline, and

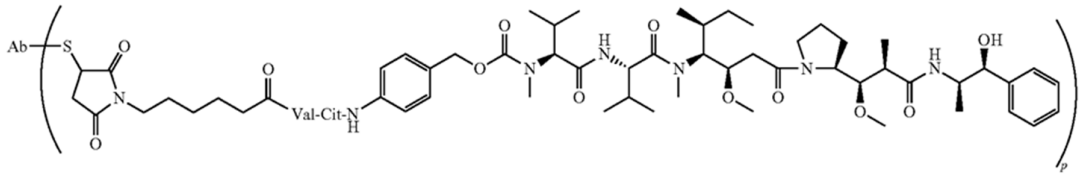
c) PAB is:



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39. The use of any one of claims 36-38, 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.

40. The use of claim 39, 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.

41. The use of claim 40, wherein the average value of p in a population of the antibody-drug conjugates is about 4.

42. The use of any one of claims 1-41, wherein the antibody-drug conjugate is tisotumab vedotin.

43. The use of any one of claims 1-42, wherein the route of administration for the antibody-drug conjugate is intravenous.

44. The use of any one of claims 1-43, wherein the anti-VEGF 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, wherein the CDRs of the anti-VEGF antibody or antigen-binding fragment thereof are defined by the Kabat numbering scheme.

45. The use of any one of claims 1-44, wherein the anti-VEGF 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.

46. The use of any one of claims 1-45, wherein the anti-VEGF 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.

47. The use of any one of claims 1-46, wherein the anti-VEGF 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.

48. The use of any one of claims 1-47, wherein the anti-VEGF antibody is bevacizumab.

49. The use of any one of claims 1-47, wherein the anti-VEGF antibody is a biosimilar of bevacizumab.

50. The use of claim 49, wherein the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, FKB238, BCD-021, BCD500, Krabeva, BI 695502, CT-P16, CHS-5217, DRZ_BZ, Cizumab, Bevax, ONS-1045, PF-06439535, HD204, Bevacirel, and SB8.

51. The use of claim 49, wherein the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel.

52. The use of any one of claims 1-51, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous or subcutaneous.

53. The use of claim 52, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous.

54. The use of any one of claims 1-53, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered sequentially.

55. The use of any one of claims 1-53, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered simultaneously.

56. The use of any one of claims 1-55, 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.

57. The use of any one of claims 1-56, wherein one or more therapeutic effects in the subject is improved after administration of the antibody-drug conjugate and the anti-VEGF antibody or antigen-binding fragment thereof relative to a baseline.

58. The use of claim 57, 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.

59. The use of any one of claims 1-58, 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-VEGF antibody or antigen-binding fragment thereof.

60. The use of any one of claims 1-59, 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%.

61. The use of any one of claims 1-60, 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-VEGF antibody or antigen-binding fragment thereof.

62. The use of any one of claims 1-61, 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-VEGF antibody or antigen-binding fragment thereof.

63. The use of any one of claims 1-62, 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-VEGF antibody or antigen-binding fragment thereof.

64. The use of any one of claims 1-63, 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.

65. The use of any one of claims 1-64, 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.

66. The use of claim 64 or claim 65, 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.

67. The use of any one of claims 64-66, wherein the one or more adverse events is a grade 3 or greater adverse event.

68. The use of any one of claims 64-66, wherein the one or more adverse events is a serious adverse event.

69. The use of claim 64 or claim 66, 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.

70. The use of any one of claims 1-69, wherein the subject is a human.

71. The use of any one of claims 1-70, wherein the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier.

72. The use of any one of claims 1-71, wherein the anti-VEGF antibody or antigen-binding fragment thereof is in a pharmaceutical composition comprising the anti-VEGF antibody or antigen-binding fragment thereof and a pharmaceutical acceptable carrier.

73. A kit comprising:

(a) a dosage ranging from about 5 mg/kg to about 20 mg/kg of an anti-VEGF antibody or antigen-binding fragment thereof ;

(b) a dosage ranging from about 0.65 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 an auristatin or a functional analog thereof or a functional derivative thereof; and

(c) instructions for using the anti-VEGF antibody or antigen-binding fragment thereof and the antibody drug conjugate according to the use of any one of claims 1-72.

74. The kit of claim 73, wherein the anti-VEGF antibody or antigen-binding fragment thereof is bevacizumab.

75. The kit of claim 73 or claim 74, wherein the antibody-drug conjugate is tisotumab vedotin.