

Oncol. 108:42-46; Homesley *et al.*, 2008, *Int. J. Clin. Oncol.* 13:62-65; McLachlan *et al.*, 2017, *Clin. Oncol.* (R. Coll. Radiol.) 29:153-160; Miller *et al.*, 2008, *Gynecol. Oncol.* 110:65-70; Monk *et al.*, 2009, *J. Clin. Oncol.* 27:1069-1074; Muggia *et al.*, 2004, *Gynecol. Oncol.* 92:639-643; Rose *et al.*, 2006, *Gynecol. Oncol.* 102:210-213; Santin *et al.*, 2011, *Gynecol. Oncol.* 122:495-500; Schilder *et al.*, 2005, *Gynecol. Oncol.* 96:103-107; and Torfs *et al.*, 2012, *Eur. J. Cancer.* 48:1332-1340. The five year relative survival for stage IV cervical cancer is only 15%, demonstrating a high need for improved therapy against cervical cancer.

[0010] 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 bladder cancer and cervical cancer. The present invention meets this need by providing methods of treating cancer, such as bladder cancer and cervical cancer, with a combination of a platinum-based agent and an anti-Tissue Factor (anti-TF) antibody-drug conjugate.

[0011] 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

[0012] In one aspect, the current disclosure refers to the use of an antibody-drug conjugate that binds to tissue factor (TF) and a platinum-based agent in the manufacture of a medicament for combination therapy to treat cancer in a subject, wherein the antibody-drug conjugate comprises an anti-TF antibody or an antigen-binding fragment thereof conjugated to a cytotoxic or cytostatic drug wherein the cytotoxic or cytostatic drug is an auristatin or a functional analog thereof or a functional derivative thereof. Provided herein is 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. In some examples, the antibody-drug conjugate is administered at a dose ranging from about 0.9 mg/kg to about 2.1 mg/kg. In some examples, the antibody-drug conjugate is administered at a dose of about 1.3 mg/kg. In some examples, the antibody-drug conjugate is administered at a dose of 1.3 mg/kg. In some examples, the antibody-drug conjugate is administered at a dose of about 2.0 mg/kg. In some examples, the antibody-drug conjugate is administered at a dose of 2.0 mg/kg. In some of any of the examples herein, the antibody-drug conjugate is administered once about every 1 week, once about every 2 weeks,

decreased appetite, diarrhea, vomiting, neutropenia, febrile neutropenia, decreased platelet count, or increased bleeding. In some of any of the examples herein, the one or more adverse events is a grade 3 or greater adverse event. In some of any of the examples herein, the one or more adverse events is a serious adverse event. In some of any of the examples herein, 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. In some of any of the examples herein, the subject is a human. In some of any of the examples herein, the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier. In some of any of the examples herein, the platinum-based agent is in a pharmaceutical composition comprising the platinum-based agent and a pharmaceutical acceptable carrier.

[0013] In another aspect, also provided herein is 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 cytotoxic or cytostatic drug, wherein the cytotoxic or cytostatic drug is 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 some of any of the examples herein. In some examples, the platinum-based agent is carboplatin. In some of any of the examples herein, the antibody-drug conjugate is tisotumab vedotin.

WHAT IS CLAIMED IS:

1. Use of an antibody-drug conjugate that binds to tissue factor (TF) and a platinum-based agent in the manufacture of a medicament for combination therapy to treat cancer in a subject, wherein the antibody-drug conjugate comprises an anti-TF antibody or an antigen-binding fragment thereof conjugated to a cytotoxic or cytostatic drug wherein the cytotoxic or cytostatic drug is an auristatin or a functional analog thereof or a functional derivative thereof.
2. The use of claim 1, wherein the antibody-drug conjugate is to be administered at a dose ranging from 0.9 mg/kg to 2.1 mg/kg.
3. The use of claim 2, wherein the antibody-drug conjugate is to be administered at a dose of about 1.3 mg/kg.
4. The use of claim 2, wherein the antibody-drug conjugate is to be administered at a dose of about 2.0 mg/kg.
5. The use of any one of claims 1-4, wherein the antibody-drug conjugate is to be administered once about every 1 week, once about every 2 weeks, once about every 3 weeks or once about every 4 weeks.
6. The use of claim 5, wherein the antibody-drug conjugate is to be administered once about every 3 weeks.
7. The use of any one of claims 1-6, wherein the platinum-based agent is to be administered at a dose between AUC=4 and AUC=6.
8. The use of claim 7, wherein the platinum-based agent is to be administered a dose of about AUC=5.
9. The use of any one of claims 1-8, wherein the platinum-based agent is to be administered once about every 1 week, once about every 2 weeks, once about every 3 weeks or once about every 4 weeks.

10. The use of claim 9, wherein the platinum-based agent is to be administered once about every 3 weeks.
11. The use of any one of claims 1-10, wherein the cancer is bladder cancer.
12. The use of any one of claims 1-10, wherein the cancer is cervical cancer.
13. The use of claim 12, wherein the subject is not a candidate for curative therapy.
14. The use of claim 13, wherein curative therapy comprises radiotherapy and/or exenterative surgery.
15. The use of claim 12, wherein the subject has not received prior systemic therapy for the cervical cancer.
16. The use of any one of claims 12-15, wherein the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma.
17. The use of any one of claims 12-16, wherein the cervical cancer is an advanced stage cervical cancer.
18. The use of claim 17, wherein the advanced stage cervical cancer is a stage 3 or stage 4 cervical cancer.
19. The use of claim 17 or 18, wherein the advanced stage cervical cancer is metastatic cervical cancer.
20. The use of any one of claims 12-19, wherein the cervical cancer is recurrent cervical cancer.
21. The use of any one of claims 1-20, wherein the auristatin is a monomethyl auristatin.

22. The use of claim 21, wherein the monomethyl auristatin is monomethyl auristatin E (MMAE).

23. The use of any one of claims 1-22, 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.

24. The use of any one of claims 1-23, 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.

25. The use of any one of claims 1-24, 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.

26. The use of any one of claims 1-25, 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.

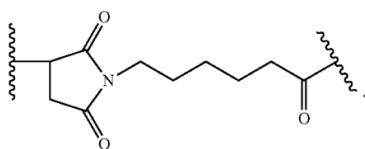
27. The use of any one of claims 1-26, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

28. The use of any one of claims 1-27, wherein the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the auristatin.

29. The use of claim 28, wherein the linker is a cleavable peptide linker.

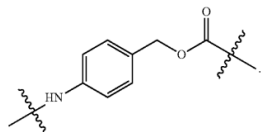
30. The use of claim 29, wherein the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

a) MC is:



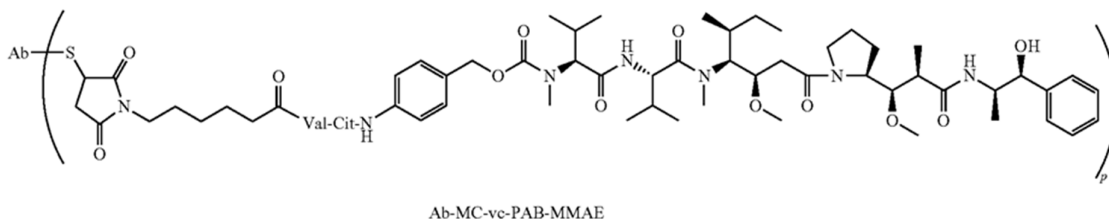
b) vc is the dipeptide valine-citrulline, and

c) PAB is:



31. The use of any one of claims 28-30, 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.

32. The use of claim 31, 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 sulphhydryl residue of the anti-TF antibody, and Ab designates the anti-TF antibody or antigen-binding fragment thereof.

33. The use of claim 32, wherein the average value of p in a population of the antibody-drug conjugates is about 4.

34. The use of any one of claims 1-33, wherein the antibody-drug conjugate is tisotumab vedotin.

35. The use of any one of claims 1-34, wherein the route of administration for the antibody-drug conjugate is intravenous.

36. The use of any one of claims 1-35, wherein the platinum-based agent is selected from the group consisting of carboplatin, cisplatin, oxaliplatin, and nedaplatin.

37. The use of any one of claims 1-36, wherein the platinum-based agent is carboplatin.

38. The use of any one of claims 1-36, wherein the platinum-based agent is cisplatin.

39. The use of any one of claims 1-38, wherein the route of administration for the platinum-based agent is intravenous.

40. The use of any one of claims 1-39, wherein the platinum-based agent and the antibody-drug conjugate are to be administered sequentially.

41. The use of any one of claims 1-39, wherein the platinum-based agent and the antibody-drug conjugate are to be administered simultaneously.

42. The use of any one of claims 1-41, 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.

43. The use of claim 42, wherein the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from cervical cancer, objective response rate, duration of response, time to response, progression free survival, and overall survival.

44. The use of any one of claims 1-10 or 12-43, wherein the cancer is cervical cancer, and wherein the size of a tumor derived from the cervical cancer is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at about 40%, at least 45%, at least 50%, at least 60%, at least 70%, or at least 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.

45. The use of any one of claims 1-44, wherein there is an objective response rate of at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, or at least 80%.

46. The use of any one of claims 1-45, 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.

47. The use of any one of claims 1-46, 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.

48. The use of any one of claims 1-47, 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.

49. The use of any one of claims 1-48, wherein the subject has one or more adverse events and wherein an additional therapeutic agent is to be administered to eliminate or reduce the severity of the one or more adverse events.

50. The use of any one of claims 1-49, wherein the subject is at risk of developing one or more adverse events and wherein an additional therapeutic agent is to be administered to prevent or reduce the severity of the one or more adverse events.

51. The use of claim 49 or claim 50, 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.

52. The use of claim 49 or claim 50, wherein the one or more adverse events is a grade 3 or greater adverse event.

53. The use of claim 49 or claim 50, wherein the one or more adverse events is a serious adverse event.

54. The use of claim 49 or claim 50, 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.

55. The use of any one of claims 1-54, wherein the subject is a human.

56. The use of any one of claims 1-55, wherein the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier.

57. The use of any one of claims 1-56, wherein the platinum-based agent is in a pharmaceutical composition comprising the platinum-based agent and a pharmaceutical acceptable carrier.

58. A kit comprising:

- (a) a dosage ranging from AUC=4 to AUC=6 of a platinum-based agent;
- (b) a dosage ranging from 1.5 mg/kg to 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 cytotoxic or cytostatic drug, wherein the cytotoxic or cytostatic drug is 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 use of any one of claims 1-57.

59. The kit of claim 58, wherein the platinum-based agent is carboplatin.

60. The kit of claim 58 or claim 59, wherein the antibody-drug conjugate is tisotumab vedotin.