cancer is only 15%, demonstrating a high need for improved methods of treating cervical cancer.

[0007] The present invention meets this need by providing highly specific and effective anti-TF antibody-drug conjugates, in particular for the use in the treatment of cervical cancer.

[0008] 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

[0009] Provided herein are methods of treating cervical cancer in a subject comprising administering to the subject an antibody-drug conjugate that binds to tissue factor (TF). In one aspect, the present disclosure refers to use of an antibody-drug conjugate that binds to tissue factor (TF) in the manufacture of a medicament for treating cervical cancer in a subject, 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 wherein the antibody-drug conjugate is to be administered at a dose ranging from about 1.5 mg/kg to about 2.1 mg/kg. In some examples, provided herein is a method of treating cervical 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 (e.g., a functional peptide analog) or a functional derivative thereof, and wherein the antibody-drug conjugate is administered at a dose ranging from about 1.5 mg/kg to about 2.1 mg/kg. In a further example, the dose is about 2.0 mg/kg. In some of any of the examples herein, the antibody-drug conjugate is administered once about every 1 week, 2 weeks, 3 weeks or 4 weeks. In some of any of the examples herein, the antibody-drug conjugate is administered once about every 3 weeks. In some of any of the examples herein, 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. In some of any of the examples herein, 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. In some of any of the examples herein, the subject has been previously treated with one or more therapeutic agents and has experienced disease

progression during the treatment, wherein the one or more therapeutic agents is not the antibody-drug conjugate. In some of any of the examples herein, the one or more therapeutic agents comprises a platinum-based therapeutic agent. In some of any of the examples herein, the one or more therapeutic agents is selected from the group consisting of: paclitaxel, cisplatin, carboplatin, topotecan, gemcitabine, fluorouracil, ixabepilone, imatinib mesylate, docetaxel, gefitinib, paclitaxel, pemetrexed, vinorelbine, doxil, cetuximab, pembrolizumab, nivolumab and bevacizumab. In some of any of the examples herein, the subject has experienced disease progression during or after treatment with: a) paclitaxel and cisplatin, b) paclitaxel and carboplatin, or c) paclitaxel and topotecan. In some of any of the examples herein, the subject has received treatment with bevacizumab. In some of any of the examples herein, the subject is ineligible for treatment with bevacizumab. In some of any of the examples herein, the subject is not a candidate for curative therapy. In some of any of the examples herein, the curative therapy comprises radiotherapy and/or exenterative surgery. In some of any of the examples herein, the subject did not respond to treatment with no more than two prior systemic treatment regimens. In some of any of the examples herein, the subject relapsed after treatment with no more than two prior systemic treatment regimens. In some of any of the examples herein, the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma. In some of any of the examples herein, the cervical cancer is an advanced stage cervical cancer, such as a stage 3 or stage 4 cervical cancer, such as metastatic cervical cancer. In some of any of the examples herein, the cervical cancer is recurrent cervical cancer. In some of any of the examples herein, the monomethyl auristatin is monomethyl auristatin E (MMAE). In some of any of the examples herein, 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. In some of any of the examples herein, 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:

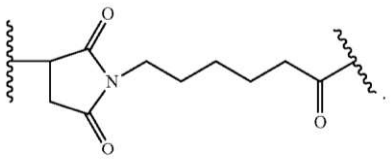
(i) a CDR-L1 comprising the amino acid sequence of SEQ ID NO:4;

(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.

In some of any of the examples herein, 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 about 85%, at least about 90%, or at least about 95% identical to the amino acid sequence of SEQ ID NO:7 and a light chain variable region comprising an amino acid sequence at least about 85%, at least about 90%, or at least about 95% identical to the amino acid sequence of SEQ ID NO:8. In some of any of the examples herein, 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. In some of any of the examples herein, the anti-TF antibody of the antibody-drug conjugate is tisotumab. In some of any of the examples herein, the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the monomethyl auristatin. In a further example, the linker is a cleavable peptide linker. In a further example, the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

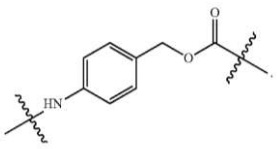
a) MC is:



,

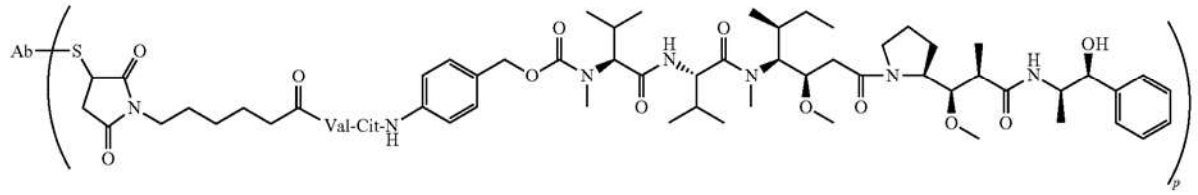
b) vc is the dipeptide valine-citrulline, and

c) PAB is:



.

[0010] In some of any of the examples herein, 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. In a further example, the linker is attached to 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. In a further example, the average value of p in a population of the antibody-drug conjugates is about 4. In some of any of the examples herein, the antibody-drug conjugate is tisotumab vedotin. In some of any of the examples herein, the route of administration for the antibody-drug conjugate is intravenous (*e.g.*, intravenous infusion). In some of any of the examples herein, 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. In some of any of the examples herein, one or more therapeutic effects in the subject is improved after administration of the antibody-drug conjugate relative to a baseline. In a further example, 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. In some of any of the examples herein, 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. In some of any of the examples herein, 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%. In some of any of the examples herein, 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. In some of any of the examples herein, 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. In some of any of the examples herein, 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. In some of any of the examples herein, 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. In some of any of the examples herein, 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. In some of any of the examples herein, 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. 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 antibody-drug conjugate is administered as a monotherapy. 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.

[0011] Also provided herein are articles of manufacture comprising an antibody-drug conjugate that binds to TF. In some examples, provided herein is an article of manufacture comprising: a) a medicament comprising an antibody-drug conjugate, 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 (e.g., a functional peptide analog) or a functional derivative thereof; and b) a package insert comprising instructions for administration of the medicament comprising the antibody-drug conjugate in a method of treating cervical cancer in a subject according to some of any of the examples herein. In a further example, the medicament comprising the antibody-drug conjugate is in a container selected from group consisting of: a vial, a syringe, and an infusion bag. In a further example, the container comprises the antibody-drug conjugate at a dosage amount from about 4 mg to about 500 mg. In a further example, the container comprises the antibody-drug conjugate at a dosage amount from about 20 mg to about 60 mg. In a further example, the container comprises the antibody-drug conjugate at a dosage amount of about 40 mg. In another further example, the container comprises the antibody-drug conjugate at a dosage amount of 40 mg. In another further example, the container comprises the antibody-drug conjugate at a concentration from about 5 mg/mL to about 15 mg/mL. In some of any of the examples herein, the medicament comprising the antibody-drug conjugate is a lyophilized powder. In a further example, the lyophilized powder is reconstituted with a suitable diluent resulting in a final concentration from about 5 mg/mL to about 15 mg/mL. In some of any of the examples herein, the medicament comprising the antibody-drug conjugate is for administration by intravenous infusion or injection. In a further example, the medicament comprising the antibody-drug conjugate is for administration by intravenous infusion.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0013] **FIG. 1** is a diagram showing the mechanism of action (MOA) of the antibody-drug conjugate tisotumab vedotin.

[0014] **FIG. 2** is a diagram showing the dose escalation study design for treatment of cancer patients with tisotumab vedotin. q3w indicates a treatment cycle is every three weeks.

[0015] **FIG. 3** is a graph showing the most common treatment-related adverse effects (AEs) occurring in ≥4 patients overall after treatment with tisotumab vedotin at all doses tested. N=27 indicates 27 patients.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of an antibody-drug conjugate that binds to tissue factor (TF) in the manufacture of a medicament for treating cervical cancer in a subject, 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 wherein the antibody-drug conjugate is to be administered at a dose ranging from about 1.5 mg/kg to about 2.1 mg/kg.

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

3. The use of claim 1 or claim 2, wherein the antibody-drug conjugate is to be administered once about every 1 week, 2 weeks, 3 weeks or 4 weeks.

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

5. The use of any one of claims 1-4, 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.

6. The use of any one of claims 1-4, 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.

7. The use of any one of claims 1-4, wherein the subject has been previously treated with one or more therapeutic agents and has experienced disease progression during treatment the, wherein the one or more therapeutic agents is not the antibody-drug conjugate.

8. The use of any one of claims 5-7, wherein the one or more therapeutic agents is a platinum-based therapeutic agent.

9. The use of any one of claims 5-7, wherein the one or more therapeutic agents is selected from the group consisting of: paclitaxel, cisplatin, carboplatin, topotecan, gemcitabine, fluorouracil, ixabepilone, imatinib mesylate, docetaxel, gefitinib, paclitaxel, pemetrexed, vinorelbine, doxil, cetuximab, pembrolizumab, nivolumab and bevacizumab.

10. The use of any one of claims 1-9, wherein the subject has experienced disease progression during or after treatment with:

a) paclitaxel and cisplatin,

b) paclitaxel and carboplatin, or

c) paclitaxel and topotecan.

11. The use of any one of claims 1-10, wherein the subject has received treatment with bevacizumab.

12. The use of any one of claims 1-10, wherein the subject is ineligible for treatment with bevacizumab.

13. The use of any one of claims 1-12, wherein the subject is not a candidate for curative therapy.

14. The use of claim 13, wherein the curative therapy comprises radiotherapy and/or exenterative surgery.

15. The use of any one of claims 1-14, wherein the subject did not respond to treatment with no more than two prior systemic treatment regimens.

16. The use of any one of claims 1-14, wherein the subject relapsed after treatment with no more than two prior systemic treatment regimens.

17. The use of any one of claims 1-16, wherein the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma.

18. The use of any one of claims 1-17, wherein the cervical cancer is an advanced stage cervical cancer, such as a stage 3 or stage 4 cervical cancer, such as metastatic cervical cancer.

19. The use of any one of claims 1-18, wherein the cervical cancer is recurrent cervical cancer.

20. The use of any one of claims 1-19, wherein the monomethyl auristatin is monomethyl auristatin E (MMAE).

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

22. The use of any one of claims 1-21, 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.

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 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.

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 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.

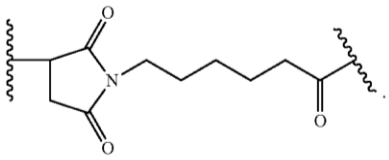
25. The use of any one of claims 1-24, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

26. The use of any one of claims 1-25, wherein the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the monomethyl auristatin.

27. The use of claim 26, wherein the linker is a cleavable peptide linker.

28. The use of claim 27, wherein the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

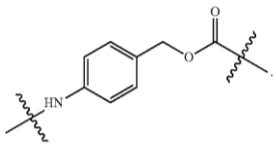
a) MC is:



,

b) vc is the dipeptide valine-citrulline, and

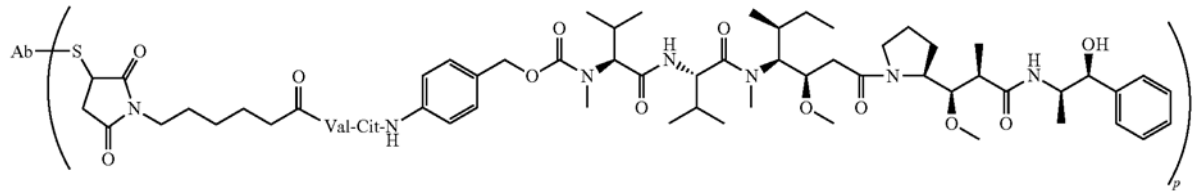
c) PAB is:



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29. The use of any one of claims 26-28, 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.

30. The use of claim 29, wherein the linker is attached to 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.

31. The use of claim 30, wherein the average value of p in a population of the antibody-drug conjugates is about 4.

32. The use of any one of claims 1-31, wherein the antibody-drug conjugate is tisotumab vedotin.

33. The use of any one of claims 1-32, wherein the route of administration for the antibody-drug conjugate is intravenous.

34. The use of any one of claims 1-33, 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.

35. The use of any one of claims 1-34, wherein one or more therapeutic effects in the subject is improved after administration of the antibody-drug conjugate relative to a baseline.

36. The use of claim 35, 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.

37. The use of any one of claims 1-36, 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.

38. The use of any one of claims 1-37, 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%.

39. The use of any one of claims 1-38, 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.

40. The use of any one of claims 1-39, 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.

41. The use of any one of claims 1-40, 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.

42. The use of any one of claims 1-41, wherein the subject has one or more adverse events and is further to be administered an additional therapeutic agent to eliminate or reduce the severity of the one or more adverse events.

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

44. The use of claim 42 or claim 43, 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.

45. The use of claim 42 or claim 43, wherein the one or more adverse events is a grade 3 or greater adverse event.

46. The use of claim 42 or claim 43, wherein the one or more adverse events is a serious adverse event.

47. The use of claim 42 or claim 43, 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.

48. The use of any one of claims 1-47, wherein the antibody-drug conjugate is to be administered as a monotherapy.

49. The use of any one of claims 1-48, wherein the subject is a human.

50. The use of any one of claims 1-49, wherein the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier.