SUMMARY

[0017] In one aspect, the present disclosure refers to use of an antibody-drug conjugate that binds to tissue factor (TF) for the manufacture of a medicament for treating cancer in a human 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~~, wherein the antibody-drug conjugate is to be administered at a dose ranging from ~~about~~ 0.9 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~~,~~ and esophageal cancer ~~and prostate cancer~~. Provided herein are methods 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. 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, 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 treatment, wherein the one or more therapeutic agents is not the antibody-drug conjugate. In some of any of the examples herein, the cancer is colorectal cancer. In some of any of the examples herein, the subject received prior systemic therapy and experienced

CLAIMS

WHAT IS CLAIMED IS:

1. Use of an antibody-drug conjugate that binds to tissue factor (TF) for the manufacture of a medicament for treating cancer in a human 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~~, wherein the antibody-drug conjugate is to be administered at a dose ranging from ~~about~~ 0.9 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~~,~~ and esophageal cancer ~~and prostate cancer~~.

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

3. The use of any one of claims 1-2, 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 cancer is colorectal cancer.

5. The use of any one of claims 1-3, wherein the cancer is non-small cell lung cancer.

6. The use of any one of claims 1-3, wherein the cancer is pancreatic cancer.

7. The use of any one of claims 1-3, wherein the cancer is head and neck cancer.

8. The use of any one of claims 1-3, wherein the cancer is bladder cancer.

9. The use of any one of claims 1-3, wherein the cancer is endometrial cancer.

10. The use of any one of claims 1-3, wherein the cancer is esophageal cancer.

~~11. The use of any one of claims 1-3, wherein the cancer is prostate cancer.~~

~~12~~11. The use of any one of claims 1-~~11~~10, wherein the auristatin is a monomethyl auristatin.

~~13~~12. The use of ~~any one of~~ claim~~s~~ ~~12~~11, wherein the monomethyl auristatin is monomethyl auristatin E (MMAE).

~~14~~13. The use of any one of claims 1-~~13~~12, 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.

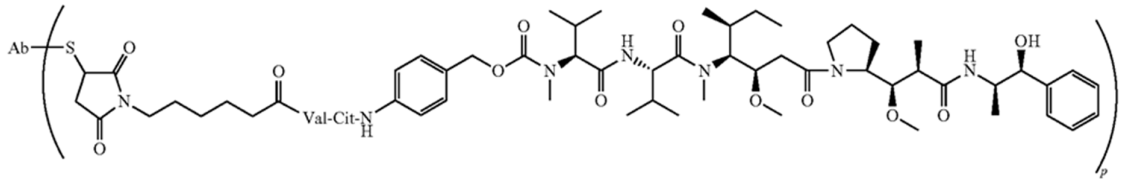
~~15~~14. The use of any one of claims 1-~~14~~13, wherein the anti-TF antibody or antigen-binding fragment thereof of the antibody-drug conjugate comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:7 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:8.

~~16~~15. The use of any one of claims 1-~~15~~14, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

~~17~~16. The use of any one of claims 1-~~16~~15, wherein the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the monomethyl auristatin.

~~18~~17. The use of claim ~~17~~16, 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.

~~19~~18. The use of any one of claims ~~17~~ 16 or ~~18~~17, 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.

~~20~~19. The use of any one of claims 1-~~19~~18, wherein the antibody-drug conjugate is tisotumab vedotin.

~~21~~20. The use of any one of claims 1-~~20~~19, 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.

~~22~~21. The use of any one of claims 1-~~21~~20, wherein one or more therapeutic effects in the subject is improved after administration of the antibody-drug conjugate relative to a baseline.

~~23~~22. The use of claim ~~22~~21, 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 ~~and prostate-specific antigen (PSA) level~~.

~~24~~23. The use of any one of claims 1-~~23~~22, 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.

~~25~~24. The use of any one of claims 1-~~24~~23, 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%.

~~26~~25. The use of any one of claims 1-~~25~~24, 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.

~~27~~26. The use of any one of claims 1-~~26~~25, 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.

~~28~~27. The use of any one of claims 1-~~27~~26, 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.

~~29~~28. The use of any one of claims 1-~~28~~27, wherein the subject has one or more adverse events and is to be further administered an additional therapeutic agent to eliminate or reduce the severity of the one or more adverse events.

~~30~~29. The use of claim ~~29~~28, 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.

~~31~~30. The use of claim ~~29~~ 28 or claim ~~30~~29, 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.

~~32~~31. The use of any one of claims 1-~~31~~30, wherein the antibody-drug conjugate is to be administered as a monotherapy.