METHODS OF TREATING CANCER WITH A COMBINATION OF AN ANTI-VEGF ANTIBODY AND AN ANTI-TISSUE FACTOR ANTIBODY-DRUG CONJUGATE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/752,904 filed on October 30, 2018, the content of which is incorporated herein by reference in its entirety.

SUBMISSION OF SEQUENCE LISTING ON ASCII TEXT FILE

[0002] The content of the following submission on ASCII text file is incorporated herein by reference in its entirety: a computer readable form (CRF) of the Sequence Listing (file name: 761682001040SEQLIST.TXT, date recorded: October 14, 2019, size: 17 KB).

TECHNICAL FIELD

[0003] The present invention relates to methods of treating cancer, such as cervical cancer, with a combination of an anti-VEGF antibody and an anti-Tissue Factor (anti-TF) antibody-drug conjugate.

BACKGROUND

[0004] Tissue factor (TF), also called thromboplastin, factor III or CD142 is a protein present in subendothelial tissue, platelets, and leukocytes necessary for the initiation of thrombin formation from the zymogen prothrombin. Thrombin formation ultimately leads to the coagulation of blood. TF enables cells to initiate the blood coagulation cascades, and it functions as the high-affinity receptor for the coagulation factor VII (FVII), a serine protease. The resulting complex provides a catalytic event that is responsible for initiation of the coagulation protease cascades by specific limited proteolysis. Unlike the other cofactors of these protease cascades, which circulate as nonfunctional precursors, TF is a potent initiator that is fully functional when expressed on cell surfaces.

[0005] TF is the cell surface receptor for the serine protease factor VIIa (FVIIa). Binding of FVIIa to TF starts signaling processes inside the cell, said signaling function playing a role in angiogenesis. Whereas angiogenesis is a normal process in growth and development, as well as in wound healing, it is also a fundamental step in the transition of tumors from a dormant state to a malignant state. When cancer cells gain the ability to produce proteins that participate in angiogenesis (*i.e.*, angiogenic growth factors), these proteins are released by the tumor into nearby tissues, thereby stimulating new blood vessels to sprout from existing healthy blood vessels toward and into the tumor. Once new blood vessels enter the tumor, the tumor can rapidly expand its size and invade local tissue and organs. Through the new blood vessels, cancer cells may further escape into the circulation and lodge in other organs to form new tumors, also known as metastasis.

[0006] TF expression is observed in many types of cancer, including cervical cancer, and is associated with more aggressive disease. Furthermore, human TF also exists in a soluble alternatively-spliced form, asHTF. It has recently been found that asHTF promotes tumor growth (Hobbs *et al.*, 2007, *Thrombosis Res.* 120(2):S13-S21).

[0007] Angiogenesis inhibitors have emerged as an effective targeted therapy in the treatment of patients with many cancers. Bevacizumab, a neutralizing antibody against vascular endothelial growth factor, has been approved alone or in combination in a wide array of tumor types, at a variety of doses and schedules. Bevacizumab has demonstrated modest single-agent activity in heavily pretreated, recurrent cervical cancer. Efficacy observed in 49 patients treated with bevacizumab 15 mg/kg every 21 days, included an ORR of 10.9%, median duration of response 6.21 months, and a median PFS 3.4 months. The addition of bevacizumab 15 mg/kg 1Q3W to cisplatin/paclitaxel OR paclitaxel/topotecan led to significant improvements in overall survival, establishing these regimens as a standard of care treatment for patients with 1L recurrent or metastatic cervical cancer.

[0008] Cervical cancer poses a significant medical problem worldwide with an estimated incidence of more than 500,000 new cases and 250,000 deaths annually. *See* Tewari *et al.*, 2014, *N Engl J Med.*, 370:734-743. In the Europe Union, approximately 34,000 new cases of cervical cancer and 13,000 deaths occur annually. *See* Hillemanns *et al.*, 2016, *Oncol. Res. Treat.* 39:501-506. The main types of cervical cancer are squamous cell carcinoma and

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

[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

some embodiments, the antibody-drug conjugate is administered at a dose ranging from about 0.65 mg/kg to about 2.1 mg/kg. In some embodiments, the antibody-drug conjugate is administered at a dose of about 0.65 mg/kg. In some embodiments, the antibody-drug conjugate is administered at a dose of 0.65 mg/kg. In some embodiments, the antibody-drug conjugate is administered at a dose of about 0.9 mg/kg. In some embodiments, the antibody-drug conjugate is administered at a dose of 0.9 mg/kg. In some embodiments, the antibody-drug conjugate is administered at a dose of about 1.3 mg/kg. In some embodiments, the antibody-drug conjugate is administered at a dose of 1.3 mg/kg. In some embodiments, the antibody-drug conjugate is administered at a dose of about 2.0 mg/kg. In some embodiments, the antibody-drug conjugate is administered at a dose of 2.0 mg/kg. In some of any of the embodiments herein, the antibody-drug conjugate is administered once about every 3 weeks. In some of any of the embodiments herein, the antibody-drug conjugate is administered once every 3 weeks. In some of any of the embodiments herein, the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose ranging from about 5 mg/kg to about 20 mg/kg. In some of any of the embodiments herein, the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 7.5 mg/kg. In some of any of the embodiments herein, the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 7.5 mg/kg. In some of any of the embodiments herein, the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 15 mg/kg. In some of any of the embodiments herein, the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 15 mg/kg. In some of any of the embodiments herein, the anti-VEGF antibody or antigen-binding fragment thereof is administered once about every 3 weeks. In some of any of the embodiments herein, the anti-VEGF antibody or antigen-binding fragment thereof is administered once every 3 weeks. In some of any of the embodiments herein, the antibody-drug conjugate is administered at least 30 minutes after the administration of the anti-VEGF antibody or antigen-binding fragment thereof. In some of any of the embodiments 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 embodiments 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 embodiments 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 embodiments herein, 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. In some of any of the embodiments herein, the subject is not a candidate for curative therapy. In some embodiments, curative therapy comprises radiotherapy and/or exenterative surgery. In some of any of the embodiments herein, the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma. In some of any of the embodiments herein, the cervical cancer is an advanced stage cervical cancer. In some embodiments, the advanced stage cervical cancer is a stage 3 or stage 4 cervical cancer. In some of any of the embodiments herein, the advanced stage cervical cancer is metastatic cervical cancer. In some of any of the embodiments herein, the cervical cancer is recurrent cervical cancer. In some of any of the embodiments 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 embodiments 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:

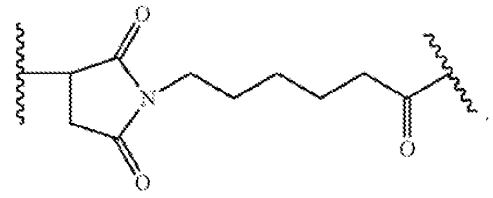
(i) a CDR-L1 comprising the amino acid sequence of SEQ ID NO:4;

(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 embodiments 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 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. In some of any of the embodiments 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 embodiments herein, the anti-TF antibody of the antibody-drug conjugate is tisotumab. In some of any of the embodiments herein, the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the monomethyl auristatin. In some embodiments, the linker is a cleavable peptide linker. In some embodiments, the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

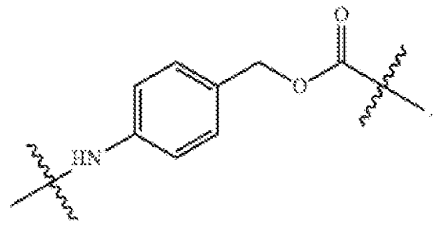
a) MC is:



,

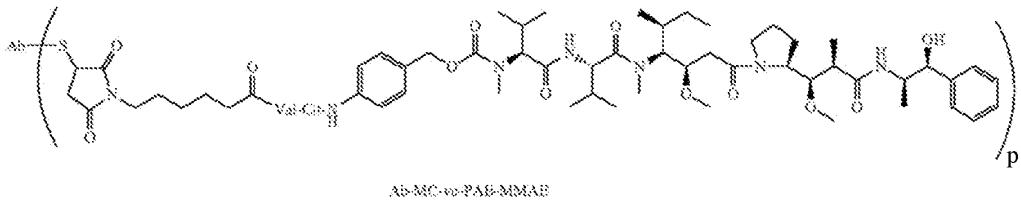
b) vc is the dipeptide valine-citrulline, and

c) PAB is:



. In some of any of the embodiments 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 some

embodiments, 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. In some embodiments, the average value of p in a population of the antibody-drug conjugates is about 4. In some of any of the embodiments herein, the antibody-drug conjugate is tisotumab vedotin. In some of any of the embodiments herein, the route of administration for the antibody-drug conjugate is intravenous. In some of any of the embodiments herein, 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. In some of any of the embodiments herein, 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. In some of any of the embodiments herein, 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. In some of any of the embodiments herein, 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. In some of any of the embodiments herein, the anti-VEGF antibody is bevacizumab. In some of any of the embodiments herein, the anti-VEGF antibody is a biosimilar of bevacizumab. In some of any of the embodiments herein, 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. In some of any of the embodiments herein, the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel. In some of any of the embodiments herein, the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous or subcutaneous. In some of any of the embodiments herein, the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous. In some of any of the embodiments herein, the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered sequentially. In some of any of the embodiments herein, the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered simultaneously. In some of any of the embodiments 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 cancer cells express TF. In some of any of the embodiments herein, 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. In some embodiments, 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. In some of any of the embodiments herein, 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. In some of any of the embodiments 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 embodiments 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 and the anti-VEGF antibody or antigen-binding fragment thereof. In some of any of the embodiments 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 and the anti-VEGF antibody or antigen-binding fragment thereof. In some of any of the embodiments 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 and the anti-VEGF antibody or antigen-binding fragment thereof. In some of any of the embodiments 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 embodiments 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 embodiments herein, 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. In some of any of the embodiments herein, the one or more adverse events is a grade 3 or greater adverse event. In some of any of the embodiments herein, 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. In some of any of the embodiments herein, the subject is a human. In some of any of the embodiments 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 embodiments herein, 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.

[0012] Also provided herein is 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 a monomethyl 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 some of any of the embodiments herein. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof is bevacizumab. In some of any of the embodiments herein, the antibody-drug conjugate is tisotumab vedotin.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1A-C is a series of graphs showing the anti-tumor activity of the combination of tisotumab vedotin and bevacizumab in a cervical cancer xenograft mouse model. Fig. 1A: Average tumor size in the mice after treatment with 4 mg/kg IgG1 control (open circle), 4 mg/kg

IgG1-MMAE control (closed circle), 2 mg/kg tisotumab vedotin (open square), 4 mg/kg tisotumab vedotin (closed square), 15 mg/kg bevacizumab (open diamond), 2 mg/kg tisotumab vedotin combined with 15 mg/kg bevacizumab (open triangle) or 4 mg/kg tisotumab vedotin combined with 15 mg/kg bevacizumab (closed triangle). Arrows indicate the day of treatment. Tumor burden was assessed by caliper measurements. Error bars indicate standard error of the mean. FIG. 1B: Average tumor size in mice at day 21 after first treatment with 4 mg/kg IgG1-MMAE control (closed circle), 2 mg/kg tisotumab vedotin (open square), 4 mg/kg tisotumab vedotin (closed square), 15 mg/kg bevacizumab (open diamond), 2 mg/kg tisotumab vedotin combined with 15 mg/kg bevacizumab (open triangle) or 4 mg/kg tisotumab vedotin combined with 15 mg/kg bevacizumab (closed triangle). FIG. 1C: Percent progression-free-survival with a tumor size cut-off at 500 mm^3 in mice treated with 4 mg/kg IgG1 control (open circle), 4 mg/kg IgG1-MMAE control (closed circle), 2 mg/kg tisotumab vedotin (open square), 4 mg/kg tisotumab vedotin (closed square), 15 mg/kg bevacizumab (open diamond), 2 mg/kg tisotumab vedotin combined with 15 mg/kg bevacizumab (open triangle) or 4 mg/kg tisotumab vedotin combined with 15 mg/kg bevacizumab (closed triangle).

[0014] FIG. 2A-C is a series of graphs showing the anti-tumor activity of the combination of tisotumab vedotin and bevacizumab in a cervical cancer xenograft mouse model. FIG. 2A: Average tumor size in the mice after treatment with 1 mg/kg IgG1 control (open circle), 1 mg/kg IgG1-MMAE control (closed circle), 0.5 mg/kg tisotumab vedotin (open square), 1 mg/kg tisotumab vedotin (closed square), 15 mg/kg bevacizumab (open diamond), 0.5 mg/kg tisotumab vedotin combined with 15 mg/kg bevacizumab (open triangle) or 1 mg/kg tisotumab vedotin combined with 15 mg/kg bevacizumab (closed triangle). Arrows indicate the day of treatment. Tumor burden was assessed by caliper measurements. Error bars indicate standard error of the mean. FIG. 2B: Average tumor size in mice at day 14 after first treatment with 1 mg/kg IgG1 control (open circle), 1 mg/kg IgG1-MMAE control (closed circle), 0.5 mg/kg tisotumab vedotin (open square), 1 mg/kg tisotumab vedotin (closed square), 15 mg/kg bevacizumab (open diamond), 0.5 mg/kg tisotumab vedotin combined with 15 mg/kg bevacizumab (open triangle) or 1 mg/kg tisotumab vedotin combined with 15 mg/kg bevacizumab (closed triangle). FIG. 2C: Percent progression-free survival with a tumor size cut-off at 1,000 mm^3 in mice treated with 1 mg/kg IgG1 control (open circle), 1 mg/kg IgG1-MMAE control (closed circle), 0.5 mg/kg tisotumab vedotin (open square), 1 mg/kg tisotumab vedotin (closed square), 15 mg/kg

bevacizumab (open diamond), 0.5 mg/kg tisotumab vedotin combined with 15 mg/kg bevacizumab (open triangle) or 1 mg/kg tisotumab vedotin combined with 15 mg/kg bevacizumab (closed triangle).

DETAILED DESCRIPTION

I. Definitions

[0015] In order that the present disclosure can be more readily understood, certain terms are first defined. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

[0016] The term "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0017] It is understood that aspects and embodiments of the invention described herein include “comprising,” “consisting,” and “consisting essentially of” aspects and embodiments.

[0018] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0019] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by

reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

[0020] The terms "tissue factor", "TF", "CD142", "tissue factor antigen", "TF antigen" and "CD142 antigen" are used interchangeably herein, and, unless specified otherwise, include any variants, isoforms and species homologs of human tissue factor which are naturally expressed by cells or are expressed on cells transfected with the tissue factor gene. In some embodiments, tissue factor comprises the amino acid sequence found under Genbank accession NP_001984.

[0021] The term "immunoglobulin" refers to a class of structurally related glycoproteins consisting of two pairs of polypeptide chains, one pair of light (L) low molecular weight chains and one pair of heavy (H) chains, all four inter-connected by disulfide bonds. The structure of immunoglobulins has been well characterized. See for instance Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N .Y. (1989)). Briefly, each heavy chain typically is comprised of a heavy chain variable region (abbreviated herein as V_H or VH) and a heavy chain constant region (C_H or CH). The heavy chain constant region typically is comprised of three domains, C_H1, C_H2, and C_H3. The heavy chains are generally inter-connected via disulfide bonds in the so-called “hinge region.” Each light chain typically is comprised of a light chain variable region (abbreviated herein as V_L or VL) and a light chain constant region (C_L or CL). The light chain constant region typically is comprised of one domain, C_L. The CL can be of κ (kappa) or λ (lambda) isotype. The terms “constant domain” and “constant region” are used interchangeably herein. An immunoglobulin can derive from any of the commonly known isotypes, including but not limited to IgA, secretory IgA, IgG, and IgM. IgG subclasses are also well known to those in the art and include but are not limited to human IgG1, IgG2, IgG3 and IgG4. "Isotype" refers to the antibody class or subclass (*e.g.*, IgM or IgG1) that is encoded by the heavy chain constant region genes.

[0022] The term “variable region” or “variable domain” refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable regions of the heavy chain and light chain (V_H and V_L, respectively) of a native antibody may be further subdivided into regions of hypervariability (or hypervariable regions, which may be hypervariable in sequence and/or form of structurally defined loops), also termed complementarity-determining regions (CDRs), interspersed with regions that are more

conserved, termed framework regions (FRs). The terms "complementarity determining regions" and "CDRs," synonymous with "hypervariable regions" or "HVRs" are known in the art to refer to non-contiguous sequences of amino acids within antibody variable regions, which confer antigen specificity and/or binding affinity. In general, there are three CDRs in each heavy chain variable region (CDR-H1, CDR-H2, CDR-H3) and three CDRs in each light chain variable region (CDR-L1, CDR-L2, CDR-L3). "Framework regions" and "FR" are known in the art to refer to the non-CDR portions of the variable regions of the heavy and light chains. In general, there are four FRs in each full-length heavy chain variable region (FR-H1, FR-H2, FR-H3, and FR-H4), and four FRs in each full-length light chain variable region (FR-L1, FR-L2, FR-L3, and FR-L4). Within each V_H and V_L, three CDRs and four FRs are typically arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4 (*See* also Chothia and Lesk *J. Mot. Biol.*, 195, 901-917 (1987)).

[0023] The term "antibody" (Ab) in the context of the present invention refers to an immunoglobulin molecule, a fragment of an immunoglobulin molecule, or a derivative of either thereof, which has the ability to specifically bind to an antigen under typical physiological conditions with a half-life of significant periods of time, such as at least about 30 min, at least about 45 min, at least about one hour (h), at least about two hours, at least about four hours, at least about eight hours, at least about 12 hours (h), about 24 hours or more, about 48 hours or more, about three, four, five, six, seven or more days, etc., or any other relevant functionally-defined period (such as a time sufficient to induce, promote, enhance, and/or modulate a physiological response associated with antibody binding to the antigen and/or time sufficient for the antibody to recruit an effector activity). The variable regions of the heavy and light chains of the immunoglobulin molecule contain a binding domain that interacts with an antigen. The constant regions of the antibodies (Abs) may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (such as effector cells) and components of the complement system such as C1q, the first component in the classical pathway of complement activation. An antibody may also be a bispecific antibody, diabody, multispecific antibody or similar molecule.

[0024] The term "monoclonal antibody" as used herein refers to a preparation of antibody molecules that are recombinantly produced with a single primary amino acid sequence. A monoclonal antibody composition displays a single binding specificity and affinity for a

particular epitope. Accordingly, the term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable and constant regions derived from human germline immunoglobulin sequences. The human monoclonal antibodies may be generated by a hybridoma which includes a B cell obtained from a transgenic or transchromosomal non-human animal, such as a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene, fused to an immortalized cell.

[0025] An "isolated antibody" refers to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that binds specifically to TF is substantially free of antibodies that bind specifically to antigens other than TF). An isolated antibody that binds specifically to TF can, however, have cross-reactivity to other antigens, such as TF molecules from different species. Moreover, an isolated antibody can be substantially free of other cellular material and/or chemicals. In one embodiment, an isolated antibody includes an antibody conjugate attached to another agent (*e.g.,* small molecule drug). In some embodiments, an isolated anti-TF antibody includes a conjugate of an anti-TF antibody with a small molecule drug (*e.g.,* MMAE or MMAF).

[0026] A "human antibody" (HuMAb) refers to an antibody having variable regions in which both the FRs and CDRs are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human antibodies of the disclosure can include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term "human antibody," as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. The terms "human antibodies" and "fully human antibodies" and are used synonymously.

[0027] The term “humanized antibody” as used herein, refers to a genetically engineered non-human antibody, which contains human antibody constant domains and non-human variable domains modified to contain a high level of sequence homology to human variable domains. This can be achieved by grafting of the six non-human antibody complementarity-determining regions (CDRs), which together form the antigen binding site, onto a homologous human

acceptor framework region (FR) (see WO92/22653 and EP0629240). In order to fully reconstitute the binding affinity and specificity of the parental antibody, the substitution of framework residues from the parental antibody (*i.e.* the non-human antibody) into the human framework regions (back-mutations) may be required. Structural homology modeling may help to identify the amino acid residues in the framework regions that are important for the binding properties of the antibody. Thus, a humanized antibody may comprise non-human CDR sequences, primarily human framework regions optionally comprising one or more amino acid back-mutations to the non-human amino acid sequence, and fully human constant regions. Optionally, additional amino acid modifications, which are not necessarily back-mutations, may be applied to obtain a humanized antibody with preferred characteristics, such as affinity and biochemical properties.

[0028] The term "chimeric antibody" as used herein, refers to an antibody wherein the variable region is derived from a non-human species (*e.g.* derived from rodents) and the constant region is derived from a different species, such as human. Chimeric antibodies may be generated by antibody engineering. "Antibody engineering" is a term used generic for different kinds of modifications of antibodies, and which is a well-known process for the skilled person. In particular, a chimeric antibody may be generated by using standard DNA techniques as described in Sambrook *et al.*, 1989, Molecular Cloning: A laboratory Manual, New York: Cold Spring Harbor Laboratory Press, Ch. 15. Thus, the chimeric antibody may be a genetically or an enzymatically engineered recombinant antibody. It is within the knowledge of the skilled person to generate a chimeric antibody, and thus, generation of the chimeric antibody according to the present invention may be performed by other methods than described herein. Chimeric monoclonal antibodies for therapeutic applications are developed to reduce antibody immunogenicity. They may typically contain non-human (*e.g.* murine) variable regions, which are specific for the antigen of interest, and human constant antibody heavy and light chain domains. The terms "variable region" or "variable domains" as used in the context of chimeric antibodies, refers to a region which comprises the CDRs and framework regions of both the heavy and light chains of the immunoglobulin.

[0029] An "anti-antigen antibody" refers to an antibody that binds to the antigen. For example, an anti-TF antibody is an antibody that binds to the antigen TF. In another example, an anti-VEGF antibody is an antibody that binds to the antigen VEGF.

[0030] An "antigen-binding portion" or antigen-binding fragment" of an antibody refers to one or more fragments of an antibody that retain the ability to bind specifically to the antigen bound by the whole antibody. Examples of antibody fragments (*e.g.*, antigen-binding fragment) include but are not limited to Fv, Fab, Fab', Fab'-SH, $F(ab')_2$; diabodies; linear antibodies; single-chain antibody molecules (*e.g.* scFv); and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

[0031] "Percent (%) sequence identity" with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For example, the % sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % sequence identity of A to B will not equal the % sequence identity of B to A.

[0032] As used herein, the terms "binding", "binds" or "specifically binds" in the context of the binding of an antibody to a pre-determined antigen typically is a binding with an affinity

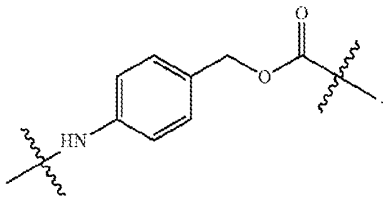
corresponding to a K_D of about 10^{-6} M or less, *e.g.* 10^{-7} M or less, such as about 10^{-8} M or less, such as about 10^{-9} M or less, about 10^{-10} M or less, or about 10^{-11} M or even less when determined by for instance BioLayer Interferometry (BLI) technology in a Octet HTX instrument using the antibody as the ligand and the antigen as the analyte, and wherein the antibody binds to the predetermined antigen with an affinity corresponding to a K_D that is at least ten-fold lower, such as at least 100-fold lower, for instance at least 1,000-fold lower, such as at least 10,000-fold lower, for instance at least 100,000-fold lower than its K_D of binding to a non-specific antigen (*e.g.*, BSA, casein) other than the predetermined antigen or a closely related antigen. The amount with which the K_D of binding is lower is dependent on the K_D of the antibody, so that when the K_D of the antibody is very low, then the amount with which the K_D of binding to the antigen is lower than the K_D of binding to a non-specific antigen may be at least 10,000-fold (that is, the antibody is highly specific).

[0033] The term "K_D" (M), as used herein, refers to the dissociation equilibrium constant of a particular antibody-antigen interaction. Affinity, as used herein, and K_D are inversely related, that is that higher affinity is intended to refer to lower K_D, and lower affinity is intended to refer to higher K_D.

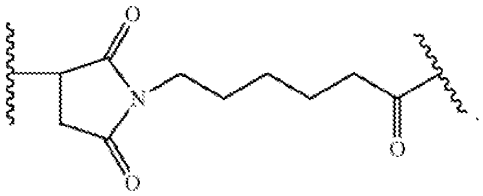
[0034] The term "ADC" refers to an antibody-drug conjugate, which in the context of the present invention refers to an anti-TF antibody, which is coupled to a drug moiety (*e.g.*, MMAE or MMAF) as described in the present application.

[0035] The abbreviations "vc" and "val-cit" refer to the dipeptide valine-citrulline.

[0036] The abbreviation "PAB" refers to the self-immolative spacer:



[0037] The abbreviation "MC" refers to the stretcher maleimidocaproyl:



[0038] The term “Ab-MC-vc-PAB-MMAE” refers to an antibody conjugated to the drug MMAE through a MC-vc-PAB linker.

[0039] A "cancer" refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. A "cancer" or "cancer tissue" can include a tumor. Unregulated cell division and growth results in the formation of malignant tumors that invade neighboring tissues and can also metastasize to distant parts of the body through the lymphatic system or bloodstream. Following metastasis, the distal tumors can be said to be "derived from" the pre-metastasis tumor. For example, a "tumor derived from" a cervical cancer refers to a tumor that is the result of a metastasized cervical cancer.

[0040] "Treatment" or "therapy" of a subject refers to any type of intervention or process performed on, or the administration of an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, slowing down, or preventing the onset, progression, development, severity, or recurrence of a symptom, complication, condition, or biochemical indicia associated with a disease. In some embodiments, the disease is cancer.

[0041] A "subject" includes any human or non-human animal. The term "non-human animal" includes, but is not limited to, vertebrates such as non-human primates, sheep, dogs, and rodents such as mice, rats, and guinea pigs. In some embodiments, the subject is a human. The terms "subject" and "patient" and “individual” are used interchangeably herein.

[0042] An “effective amount” or "therapeutically effective amount" or "therapeutically effective dosage" of a drug or therapeutic agent is any amount of the drug that, when used alone or in combination with another therapeutic agent, protects a subject against the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of

impairment or disability due to the disease affliction. The ability of a therapeutic agent to promote disease regression can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

[0043] By way of example for the treatment of tumors, a therapeutically effective amount of an anti-cancer agent inhibits cell growth or tumor growth by at least about 10%, by at least about 20%, by at least about 30%, by at least about 40%, by at least about 50%, by at least about 60%, by at least about 70%, or by at least about 80%, by at least about 90%, by at least about 95%, by at least about 96%, by at least about 97%, by at least about 98%, or by at least about 99% in a treated subject(s) (*e.g.*, one or more treated subjects) relative to an untreated subject(s) (*e.g.*, one or more untreated subjects). In some embodiments, a therapeutically effective amount of an anti-cancer agent inhibits cell growth or tumor growth by 100% in a treated subject(s) (*e.g.*, one or more treated subjects) relative to an untreated subject(s) (*e.g.*, one or more untreated subjects).

[0044] In other embodiments of the disclosure, tumor regression can be observed and continue for a period of at least about 20 days, at least about 30 days, at least about 40 days, at least about 50 days, or at least about 60 days.

[0045] A therapeutically effective amount of a drug (*e.g.*, anti-TF antibody-drug conjugate or anti-VEGF antibody) includes a "prophylactically effective amount," which is any amount of the drug that, when administered alone or in combination with an anti-cancer agent to a subject at risk of developing a cancer (*e.g.*, a subject having a pre-malignant condition) or of suffering a recurrence of cancer, inhibits the development or recurrence of the cancer. In some embodiments, the prophylactically effective amount prevents the development or recurrence of the cancer entirely. "Inhibiting" the development or recurrence of a cancer means either lessening the likelihood of the cancer's development or recurrence, or preventing the development or recurrence of the cancer entirely.

[0046] As used herein, "subtherapeutic dose" means a dose of a therapeutic compound (*e.g.*, an anti-TF antibody-drug conjugate or anti-VEGF antibody) that is lower than the usual or typical dose of the therapeutic compound when administered alone for the treatment of a hyperproliferative disease (*e.g.*, cancer).

[0047] An "immune-related response pattern" refers to a clinical response pattern often observed in cancer patients treated with immunotherapeutic agents that produce antitumor effects by inducing cancer-specific immune responses or by modifying native immune processes. This response pattern is characterized by a beneficial therapeutic effect that follows an initial increase in tumor burden or the appearance of new lesions, which in the evaluation of traditional chemotherapeutic agents would be classified as disease progression and would be synonymous with drug failure. Accordingly, proper evaluation of immunotherapeutic agents can require long-term monitoring of the effects of these agents on the target disease.

[0048] By way of example, an "anti-cancer agent" promotes cancer regression in a subject. In some embodiments, a therapeutically effective amount of the drug promotes cancer regression to the point of eliminating the cancer. "Promoting cancer regression" means that administering an effective amount of the drug, alone or in combination with an anti-cancer agent, results in a reduction in tumor growth or size, necrosis of the tumor, a decrease in severity of at least one disease symptom, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. In addition, the terms "effective" and "effectiveness" with regard to a treatment includes both pharmacological effectiveness and physiological safety. Pharmacological effectiveness refers to the ability of the drug to promote cancer regression in the patient. Physiological safety refers to the level of toxicity or other adverse physiological effects at the cellular, organ and/or organism level (adverse effects) resulting from administration of the drug.

[0049] "Sustained response" refers to the sustained effect on reducing tumor growth after cessation of a treatment. For example, the tumor size may remain to be the same or smaller as compared to the size at the beginning of the administration phase. In some embodiments, the sustained response has a duration that is at least the same as the treatment duration, or at least 1.5, 2.0, 2.5, or 3 times longer than the treatment duration.

[0050] As used herein, "complete response" or "CR" refers to disappearance of all target lesions; "partial response" or "PR" refers to at least a 30% decrease in the sum of the longest diameters (SLD) of target lesions, taking as reference the baseline SLD; and "stable disease" or "SD" refers to neither sufficient shrinkage of target lesions to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest SLD since the treatment started.

[0051] As used herein, "progression free survival" or "PFS" refers to the length of time during and after treatment during which the disease being treated (*e.g.*, cancer) does not get worse. Progression-free survival may include the amount of time patients have experienced a complete response or a partial response, as well as the amount of time patients have experienced stable disease.

[0052] As used herein, "overall response rate" or "ORR" refers to the sum of complete response (CR) rate and partial response (PR) rate.

[0053] As used herein, "overall survival" or "OS" refers to the percentage of individuals in a group who are likely to be alive after a particular duration of time.

[0054] The term "weight-based dose", as referred to herein, means that a dose administered to a subject is calculated based on the weight of the subject. For example, when a subject with 60 kg body weight requires 2.0 mg/kg of an anti-VEGF antibody or an anti-TF antibody-drug conjugate, one can calculate and use the appropriate amount of the anti-VEGF antibody or anti-TF antibody-drug conjugate (*i.e.*, 120 mg) for administration to said subject.

[0055] The use of the term "fixed dose" with regard to a method of the disclosure means that two or more different antibodies (*e.g.*, anti-VEGF antibody and anti-TF antibody-drug conjugate) are administered to a subject in particular (fixed) ratios with each other. In some embodiments, the fixed dose is based on the amount (*e.g.*, mg) of the antibodies. In certain embodiments, the fixed dose is based on the concentration (*e.g.*, mg/ml) of the antibodies. For example, a 3:1 ratio of an anti-VEGF antibody to an anti-TF antibody-drug conjugate administered to a subject can mean about 240 mg of the anti-VEGF antibody and about 80 mg of the anti-TF antibody-drug conjugate or about 3 mg/ml of the anti-VEGF antibody and about 1 mg/ml of the anti-TF antibody-drug conjugate are administered to the subject.

[0056] The use of the term "flat dose" with regard to the methods and dosages of the disclosure means a dose that is administered to a subject without regard for the weight or body surface area (BSA) of the subject. The flat dose is therefore not provided as a mg/kg dose, but rather as an absolute amount of the agent (*e.g.*, the anti-TF antibody-drug conjugate and/or anti-VEGF antibody). For example, a subject with 60 kg body weight and a subject with 100 kg body weight would receive the same dose of an antibody or an antibody-drug conjugate (*e.g.*, 240 mg of an anti-TF antibody-drug conjugate or *e.g.* 240 mg of an anti-VEGF antibody).

[0057] The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[0058] The phrase "pharmaceutically acceptable salt" as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound of the invention. Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate "mesylate", ethanesulfonate, benzenesulfonate, p-toluenesulfonate, pamoate (*i.e.*, 4,4'-methylene-bis -(2-hydroxy-3-naphthoate)) salts, alkali metal (*e.g.*, sodium and potassium) salts, alkaline earth metal (*e.g.*, magnesium) salts, and ammonium salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion.

[0059] "Administering" or "administration" refer to the physical introduction of a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Exemplary routes of administration for the anti-TF antibody-drug conjugate and/or anti-VEGF antibody include intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion (*e.g.,* intravenous infusion). The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as *in vivo* electroporation. A therapeutic agent can be administered via a non-parenteral route, or orally. Other non-parenteral routes include a topical, epidermal or

mucosal route of administration, for example, intranasally, vaginally, rectally, sublingually or topically. Administration can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[0060] The terms "baseline" or "baseline value" used interchangeably herein can refer to a measurement or characterization of a symptom before the administration of the therapy (*e.g.*, an anti-TF antibody-drug conjugate as described herein and/or an anti-VEGF antibody as described herein) or at the beginning of administration of the therapy. The baseline value can be compared to a reference value in order to determine the reduction or improvement of a symptom of a TF-associated disease and/or VEGF associated disease contemplated herein (*e.g.*, cervical cancer). The terms "reference" or "reference value" used interchangeably herein can refer to a measurement or characterization of a symptom after administration of the therapy (*e.g.*, an anti-TF antibody-drug conjugate as described herein and/or an anti-VEGF antibody as described herein). The reference value can be measured one or more times during a dosage regimen or treatment cycle or at the completion of the dosage regimen or treatment cycle. A "reference value" can be an absolute value; a relative value; a value that has an upper and/or lower limit; a range of values; an average value; a median value: a mean value; or a value as compared to a baseline value.

[0061] Similarly, a "baseline value" can be an absolute value; a relative value; a value that has an upper and/or lower limit; a range of values; an average value; a median value; a mean value; or a value as compared to a reference value. The reference value and/or baseline value can be obtained from one individual, from two different individuals or from a group of individuals (*e.g.*, a group of two, three, four, five or more individuals).

[0062] The term “monotherapy” as used herein means that the anti-TF antibody-drug conjugate or anti-VEGF antibody is the only anti-cancer agent administered to the subject during the treatment cycle. Other therapeutic agents, however, can be administered to the subject. For example, anti-inflammatory agents or other agents administered to a subject with cancer to treat symptoms associated with cancer, but not the underlying cancer itself, including, for example inflammation, pain, weight loss, and general malaise, can be administered during the period of monotherapy.

[0063] An "adverse event" (AE) as used herein is any unfavorable and generally unintended or undesirable sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a medical treatment. A medical treatment can have one or more associated AEs and each AE can have the same or different level of severity. Reference to methods capable of "altering adverse events" means a treatment regime that decreases the incidence and/or severity of one or more AEs associated with the use of a different treatment regime.

[0064] A “serious adverse event” or “SAE” as used herein is an adverse event that meets one of the following criteria:

- Is fatal or life-threatening (as used in the definition of a serious adverse event, “life-threatening” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, *i.e.*, defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Medical and scientific judgment must be exercised in deciding whether an AE is “medically significant”
- Requires inpatient hospitalization or prolongation of existing hospitalization, excluding the following: 1) routine treatment or monitoring of the underlying disease, not associated with any deterioration in condition; 2) elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent; and 3) social reasons and respite care in the absence of any deterioration in the patient’s general condition.

[0065] The use of the alternative (*e.g.*, "or") should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the indefinite articles "a" or "an" should be understood to refer to "one or more" of any recited or enumerated component.

[0066] The terms "about" or "comprising essentially of" refer to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, *i.e.*, the limitations of the measurement system. For example, "about" or "comprising essentially of" can mean within 1 or more than 1 standard deviation per the practice

in the art. Alternatively, "about" or "comprising essentially of" can mean a range of up to 20%. Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the application and claims, unless otherwise stated, the meaning of "about" or "comprising essentially of" should be assumed to be within an acceptable error range for that particular value or composition.

[0067] The terms "once about every week," "once about every two weeks," or any other similar dosing interval terms as used herein mean approximate numbers. "Once about every week" can include every seven days ± one day, *i.e.*, every six days to every eight days. "Once about every two weeks" can include every fourteen days ± two days, *i.e.*, every twelve days to every sixteen days. "Once about every three weeks" can include every twenty-one days ± three days, *i.e.*, every eighteen days to every twenty-four days. Similar approximations apply, for example, to once about every four weeks, once about every five weeks, once about every six weeks, and once about every twelve weeks. In some embodiments, a dosing interval of once about every six weeks or once about every twelve weeks means that the first dose can be administered any day in the first week, and then the next dose can be administered any day in the sixth or twelfth week, respectively. In other embodiments, a dosing interval of once about every six weeks or once about every twelve weeks means that the first dose is administered on a particular day of the first week (*e.g.*, Monday) and then the next dose is administered on the same day of the sixth or twelfth weeks (*i.e.*, Monday), respectively.

[0068] As described herein, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated.

[0069] Various aspects of the disclosure are described in further detail in the following subsections.

II. COMBINATION THERAPY

[0070] One aspect of the invention provides anti-TF antibody-drug conjugates that binds to TF for use in the treatment of cervical cancer wherein the antibody-drug conjugate is for administration, or 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 a monomethyl auristatin or a functional analog thereof or a functional derivative thereof. In some embodiments, the anti-TF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of tisotumab, or a biosimilar thereof. In some embodiments, the anti-TF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of tisotumab. In some embodiments, the anti-TF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of tisotumab, or a biosimilar thereof. In some embodiments, the anti-TF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of tisotumab. In some embodiments, the anti-TF antibody is tisotumab. In some embodiments, the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of bevacizumab, or a biosimilar thereof. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of bevacizumab. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of bevacizumab, or a biosimilar thereof. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of bevacizumab. In some embodiments, the anti-VEGF antibody is bevacizumab. In some embodiments, the cervical cancer is an advanced stage cervical cancer (*e.g.*, stage 3 cervical cancer or stage 4 cervical cancer or metastatic cervical cancer). In some embodiments, the advanced cervical cancer is a metastatic cancer. In some embodiments, the subject has relapsed, recurrent and/or metastatic cervical cancer.

[0071] In another aspect the present invention provides an anti-VEGF antibody or an antigen-binding fragment thereof for use in the treatment of cervical cancer wherein the anti-VEGF antibody or antigen-binding fragment thereof is for administration, or to be administered in combination with an antibody-drug conjugate that binds to 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 embodiments, the anti-TF antibody or antigen-binding fragment thereof comprises the

complementary determining regions (CDRs) of tisotumab, or a biosimilar thereof. In some embodiments, the anti-TF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of tisotumab. In some embodiments, the anti-TF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of tisotumab, or a biosimilar thereof. In some embodiments, the anti-TF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of tisotumab. In some embodiments, the anti-TF antibody is tisotumab. In some embodiments, the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of bevacizumab, or a biosimilar thereof. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of bevacizumab. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of bevacizumab, or a biosimilar thereof. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of bevacizumab. In some embodiments, the anti-VEGF antibody is bevacizumab. In some embodiments, the cervical cancer is an advanced stage cervical cancer (*e.g.*, stage 3 cervical cancer or stage 4 cervical cancer or metastatic cervical cancer). In some embodiments, the advanced cervical cancer is a metastatic cancer. In some embodiments, the subject has relapsed, recurrent and/or metastatic cervical cancer.

A. Anti-TF Antibody

[0072] Generally, anti-TF antibodies of the disclosure bind TF, *e.g.*, human TF, and exert cytostatic and cytotoxic effects on malignant cells, such as cervical cancer cells. Anti-TF antibodies of the disclosure are preferably monoclonal, and may be multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, and TF binding fragments of any of the above. In some embodiments, the anti-TF antibodies of the disclosure specifically bind TF. The immunoglobulin molecules of the disclosure can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

[0073] In certain embodiments of the disclosure, the anti-TF antibodies are antigen-binding fragments (*e.g.*, human antigen-binding fragments) as described herein and include, but are not limited to, Fab, Fab' and $F(ab')_2$, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a V_L or V_H domain. Antigen-binding fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, CH3 and CL domains. Also included in the present disclosure are antigen-binding fragments comprising any combination of variable region(s) with a hinge region, CH1, CH2, CH3 and CL domains. In some embodiments, the anti-TF antibodies or antigen-binding fragments thereof are human, murine (*e.g.*, mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camelid, horse, or chicken.

[0074] The anti-TF antibodies of the present disclosure may be monospecific, bispecific, trispecific or of greater multi specificity. Multispecific antibodies may be specific for different epitopes of TF or may be specific for both TF as well as for a heterologous protein. *See*, *e.g.*, PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, *et al.*, 1991, J. Immunol. 147:60 69; U.S. Pat. Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny *et al.*, 1992, J. Immunol. 148:1547 1553.

[0075] Anti-TF antibodies of the present disclosure may be described or specified in terms of the particular CDRs they comprise. The precise amino acid sequence boundaries of a given CDR or FR can be readily determined using any of a number of well-known schemes, including those described by Kabat *et al.* (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme); Al-Lazikani *et al.*, (1997) JMB 273,927-948 ("Chothia" numbering scheme); MacCallum *et al.*, J. Mol. Biol. 262:732-745 (1996), "Antibody-antigen interactions: Contact analysis and binding site topography," J. Mol. Biol. 262, 732-745." ("Contact" numbering scheme); Lefranc MP *et al.*, "IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains," Dev Comp Immunol, 2003 Jan;27(1):55-77 ("IMGT" numbering scheme); Honegger A and Plückthun A, "Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis tool," J Mol Biol, 2001 Jun 8;309(3):657-70, ("Aho" numbering scheme); and Martin *et al.*, "Modeling antibody hypervariable loops: a combined algorithm," PNAS, 1989, 86(23):9268-9272, ("AbM" numbering scheme). The boundaries of a given CDR may vary depending on the scheme used

for identification. In some embodiments, a "CDR" or "complementarity determining region," or individual specified CDRs (*e.g.*, CDR-H1, CDR-H2, CDR-H3), of a given antibody or region thereof (*e.g.*, variable region thereof) should be understood to encompass a (or the specific) CDR as defined by any of the aforementioned schemes. For example, where it is stated that a particular CDR (*e.g.*, a CDR-H3) contains the amino acid sequence of a corresponding CDR in a given V_H or V_L region amino acid sequence, it is understood that such a CDR has a sequence of the corresponding CDR (*e.g.*, CDR-H3) within the variable region, as defined by any of the aforementioned schemes. The scheme for identification of a particular CDR or CDRs may be specified, such as the CDR as defined by the Kabat, Chothia, AbM or IMGT method.

[0076] CDR sequences of the anti-TF antibodies of the anti-TF antibody-drug conjugates provided herein are according to the IMGT numbering scheme as described in Lefranc, M. P. *et al.*, Dev. Comp. Immunol., 2003, 27, 55-77.

[0077] In certain embodiments antibodies of the disclosure comprise one or more CDRs of the antibody 011. *See* WO 2011/157741 and WO 2010/066803. The disclosure encompasses an antibody or derivative thereof comprising a heavy or light chain variable domain, said variable domain comprising (a) a set of three CDRs, in which said set of CDRs are from monoclonal antibody 011, and (b) a set of four framework regions, in which said set of framework regions differs from the set of framework regions in monoclonal antibody 011, and in which said antibody or derivative thereof binds to TF. In some embodiments, said antibody or derivative thereof specifically binds to TF. In certain embodiments, the anti-TF antibody is 011. The antibody 011 is also known as tisotumab.

[0078] In one aspect, anti-TF antibodies that compete with tisotumab binding to TF are also provided herein. Anti-TF antibodies that bind to the same epitope as tisotumab are also provided herein.

[0079] In one aspect, provided herein is an anti-TF antibody comprising 1, 2, 3, 4, 5, or 6 of the CDR sequences of tisotumab.

[0080] In one aspect, provided herein is an anti-TF antibody comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (iii) CDR-H3 comprising the amino

acid sequence of SEQ ID NO:3; and/or wherein the light chain variable region comprises (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:4, (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:5, and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6, wherein the CDRs of the anti-TF antibody are defined by the IMGT numbering scheme.

[0081] An anti-TF antibody described herein may comprise any suitable framework variable domain sequence, provided that the antibody retains the ability to bind TF (*e.g.*, human TF). As used herein, heavy chain framework regions are designated "HC-FR1-FR4," and light chain framework regions are designated "LC-FR1-FR4." In some embodiments, the anti-TF antibody comprises a heavy chain variable domain framework sequence of SEQ ID NO:9, 10, 11, and 12 (HC-FR1, HC-FR2, HC-FR3, and HC-FR4, respectively). In some embodiments, the anti-TF antibody comprises a light chain variable domain framework sequence of SEQ ID NO:13, 14, 15, and 16 (LC-FR1, LC-FR2, LC-FR3, and LC-FR4, respectively).

[0082] In some embodiments of the anti-TF antibodies described herein, the heavy chain variable domain comprises the amino acid sequence of

EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSSISGSGDYT YYTDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSPWGYYLDSWGQGTLVT VSS (SEQ ID NO:7) and the light chain variable domain comprises the amino acid sequence of DIQMTQSPPSLSASAGDRVTITCRASQGISSRLAWYQQKPEKAPKSLIYAASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPYTFGQGTKLEIK (SEQ ID NO:8).

[0083] In some embodiments of the anti-TF antibodies described herein, the heavy chain CDR sequences comprise the following:

a) CDR-H1 (GFTFSNYA (SEQ ID NO:1));

b) CDR-H2 (ISGSGDYT (SEQ ID NO:2)); and

c) CDR-H3 (ARSPWGYYLDS (SEQ ID NO:3)).

[0084] In some embodiments of the anti-TF antibodies described herein, the heavy chain FR sequences comprise the following:

a) HC-FR1 (EVQLLESGGGLVQPGGSLRLSCAAS (SEQ ID NO:9));

b) HC-FR2 (MSWVRQAPGKGLEWVSS (SEQ ID NO:10));

c) HC-FR3 (YYTDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC (SEQ ID NO:11)); and

d) HC-FR4 (WGQGTLVTVSS (SEQ ID NO:12)).

[0085] In some embodiments of the anti-TF antibodies described herein, the light chain CDR sequences comprise the following:

a) CDR-L1 (QGISSR (SEQ ID NO:4));

b) CDR-L2 (AAS (SEQ ID NO:5)); and

c) CDR-L3 (QQYNSYPYT (SEQ ID NO:6)).

[0086] In some embodiments of the anti-TF antibodies described herein, the light chain FR sequences comprise the following:

a) LC-FR1 (DIQMTQSPPSLSASAGDRVTITCRAS (SEQ ID NO:13));

b) LC-FR2 (LAWYQQKPEKAPKSLIY (SEQ ID NO:14));

c) LC-FR3 (SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO:15)); and

d) LC-FR4 (FGQGTKLEIK (SEQ ID NO:16)).

[0087] In some embodiments, provided herein is an anti-TF antibody that binds to TF (*e.g.*, human TF), wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the antibody comprises:

(a) heavy chain variable domain comprising:

(1) an HC-FR1 comprising the amino acid sequence of SEQ ID NO:9;

(2) an CDR-H1 comprising the amino acid sequence of SEQ ID NO:1;

(3) an HC-FR2 comprising the amino acid sequence of SEQ ID NO:10;

(4) an CDR-H2 comprising the amino acid sequence of SEQ ID NO:2;

(5) an HC-FR3 comprising the amino acid sequence of SEQ ID NO:11;

(6) an CDR-H3 comprising the amino acid sequence of SEQ ID NO:3; and

(7) an HC-FR4 comprising the amino acid sequence of SEQ ID NO:12,

and/or

(b) a light chain variable domain comprising:

(1) an LC-FR1 comprising the amino acid sequence of SEQ ID NO:13;

(2) an CDR-L1 comprising the amino acid sequence of SEQ ID NO:4;
(3) an LC-FR2 comprising the amino acid sequence of SEQ ID NO:14;
(4) an CDR-L2 comprising the amino acid sequence of SEQ ID NO:5;
(5) an LC-FR3 comprising the amino acid sequence of SEQ ID NO:15;
(6) an CDR-L3 comprising the amino acid sequence of SEQ ID NO:6; and
(7) an LC-FR4 comprising the amino acid sequence of SEQ ID NO:16.

[0088] In one aspect, provided herein is an anti-TF antibody comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:7 or comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:8. In one aspect, provided herein is an anti-TF antibody comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:7 and comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:8.

[0089] In some embodiments, provided herein is an anti-TF antibody comprising a heavy chain variable domain comprising an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO:7. In certain embodiments, a heavy chain variable domain comprising an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO:7 contains substitutions (*e.g.*, conservative substitutions), insertions, or deletions relative to the reference sequence and retains the ability to bind to a TF (*e.g.*, human TF). In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:7. In certain embodiments, substitutions, insertions, or deletions (*e.g.*, 1, 2, 3, 4, or 5 amino acids) occur in regions outside the CDRs (*i.e.*, in the FRs). In some embodiments, the anti-TF antibody comprises a heavy chain variable domain sequence of SEQ ID NO:7 including post-translational modifications of that sequence. In a particular embodiment, the heavy chain variable domain comprises one, two or three CDRs selected from: (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3.

[0090] In some embodiments, provided herein is an anti-TF antibody comprising a light chain variable domain comprising an amino acid sequence having at least 85%, 86%, 87%, 88%,

89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO:8. In certain embodiments, a light chain variable domain comprising an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO:8 contains substitutions (*e.g.*, conservative substitutions), insertions, or deletions relative to the reference sequence and retains the ability to bind to a TF (*e.g.*, human TF). In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:8. In certain embodiments, substitutions, insertions, or deletions (*e.g.*, 1, 2, 3, 4, or 5 amino acids) occur in regions outside the CDRs (*i.e.,* in the FRs). In some embodiments, the anti-TF antibody comprises a light chain variable domain sequence of SEQ ID NO:8 including post-translational modifications of that sequence. In a particular embodiment, the light chain variable domain comprises one, two or three CDRs selected from: (a) CDR-L1 comprising the amino acid sequence of SEQ ID NO:4, (b) CDR-L2 comprising the amino acid sequence of SEQ ID NO:5, and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6.

[0091] In some embodiments, the anti-TF antibody comprises a heavy chain variable domain as in any of the embodiments provided above, and a light chain variable domain as in any of the embodiments provided above. In one embodiment, the antibody comprises the heavy chain variable domain sequence of SEQ ID NO:7 and the light chain variable domain sequence of SEQ ID NO:8, including post-translational modifications of those sequences.

[0092] In some embodiments, the anti-TF antibody of the anti-TF antibody-drug conjugate comprises: i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 2, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 3; and ii) a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6, wherein the CDRs of the anti-TF antibody are defined by the IMGT numbering scheme.

[0093] In some embodiments, the anti-TF antibody of the anti-TF antibody-drug conjugate comprises: i) an amino acid sequence having at least 85% sequence identity to a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7, and ii) an amino acid

sequence having at least 85% sequence identity to a light chain variable region comprising the amino acid sequence of SEQ ID NO: 8.

[0094] In some embodiments, the anti-TF antibody of the anti-TF antibody-drug conjugate is a monoclonal antibody.

[0095] In some embodiments, the anti-TF antibody of the anti-TF antibody-drug conjugate is tisotumab, which is also known as antibody 011 as described in WO 2011/157741 and WO 2010/066803.

[0096] Anti-TF antibodies of the present invention may also be described or specified in terms of their binding affinity to TF (*e.g.*, human TF). Preferred binding affinities include those with a dissociation constant or Kd less than 5 $x10^{-2}$ M, 10^{-2} M, $5x10^{-3}$ M, 10^{-3} M, $5x10^{-4}$ M, 10^{-4} M, $5x10^{-5}$ M, 10^{-5} M, $5x10^{-6}$ M, 10^{-6} M, $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8}M, $5x10^{-9}$ M, 10^{-9} M, $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, 10^{-13} M, $5x10^{-14}$ M, 10^{-14} M, $5x10^{-15}$ M, or 10^{-15} M.

[0097] There are five classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, having heavy chains designated α, δ, ε, γ and μ, respectively. The γ and α classes are further divided into subclasses *e.g.*, humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. IgG1 antibodies can exist in multiple polymorphic variants termed allotypes (reviewed in Jefferis and Lefranc 2009. *mAbs* Vol 1 Issue 4 1-7) any of which are suitable for use in some of the embodiments herein. Common allotypic variants in human populations are those designated by the letters a, f, n, z or combinations thereof. In any of the embodiments herein, the antibody may comprise a heavy chain Fc region comprising a human IgG Fc region. In further embodiments, the human IgG Fc region comprises a human IgG1.

[0098] The antibodies also include derivatives that are modified, *i.e.*, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from binding to TF or from exerting a cytostatic or cytotoxic effect on HD cells. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, *e.g.*, by glycosylation, acetylation, PEGylation, phosphylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation,

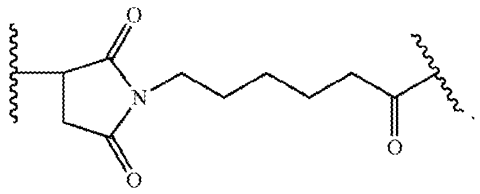
formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

B. Antibody-Drug Conjugate Structure

[0099] In some aspects, the anti-TF antibody-drug conjugates described herein comprise a linker between an anti-TF antibody or antigen-binding fragment thereof as described herein and a cytostatic or cytotoxic drug. In some embodiments the linker is a non-cleavable linker. In some embodiments the linker is a cleavable linker.

[0100] In some embodiments, the linker is a cleavable peptide linker comprising maleimido caproyl (MC), the dipeptide valine-citrulline (vc) and p-aminobenzylcarbamate (PAB). In some embodiments, the cleavable peptide linker has the formula: MC-vc-PAB-, wherein:

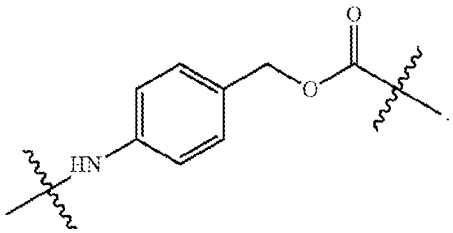
a) MC is:



,

b) vc is the dipeptide valine-citrulline, and

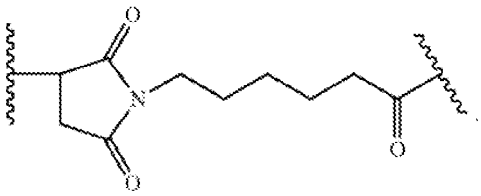
c) PAB is:



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[0101] In some embodiments, the linker is a cleavable peptide linker comprising maleimido caproyl (MC). In some embodiments, the cleavable peptide linker has the formula: MC-, wherein:

a) MC is:



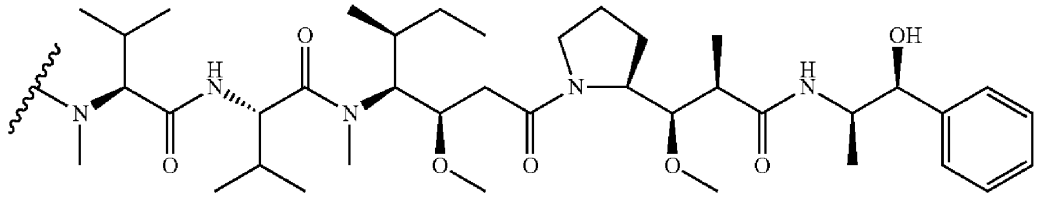
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[0102] In some embodiments, the linker is attached to sulphydryl residues of the anti-TF antibody or antigen-binding fragment thereof obtained by partial or full reduction of the anti-TF antibody or antigen-binding fragment thereof. In some embodiments, the linker is attached to sulphydryl residues of the anti-TF antibody or antigen-binding fragment thereof obtained by partial reduction of the anti-TF antibody or antigen-binding fragment thereof. In some embodiments, the linker is attached to sulphydryl residues of the anti-TF antibody or antigen-binding fragment thereof obtained by full reduction of the anti-TF antibody or antigen-binding fragment thereof.

[0103] In some aspects, the anti-TF antibody-drug conjugates described herein comprise a linker as described herein between an anti-TF antibody or antigen-binding fragment thereof as described herein and a cytostatic or cytotoxic drug. Auristatins have been shown to interfere with microtubule dynamics, GTP hydrolysis and nuclear and cellular division (*See* Woyke et al (2001) *Antimicrob. Agents and Chemother.* 45(12): 3580-3584) and have anti-cancer (*See* U.S. Patent Nos. 5663149) and antifungal activity (*See* Pettit *et al.*, (1998) *Antimicrob. Agents and Chemother.* 42: 2961-2965. For example, auristatin E can be reacted with para-acetyl benzoic acid or benzoylvaleric acid to produce AEB and AEVB, respectively. Other typical auristatin derivatives include AFP, MMAF (monomethyl auristatin F), and MMAE (monomethyl auristatin E). Suitable auristatins and auristatin analogs, derivatives and prodrugs, as well as suitable linkers for conjugation of auristatins to Abs, are described in, *e.g.*, U.S. Patent Nos. 5,635,483, 5,780,588 and 6,214,345 and in International patent application publications WO02088172,

WO2004010957, WO2005081711, WO2005084390, WO2006132670, WO03026577, WO200700860, WO207011968 and WO205082023. In some embodiments of the anti-TF antibody-drug conjugates described herein, the cytostatic or cytotoxic drug is an auristatin or a functional analog thereof (*e.g.*, functional peptide thereof) or a functional derivative thereof. In some embodiments, the auristatin is a monomethyl auristatin or a functional analog thereof (*e.g.*, functional peptide thereof) or a functional derivative thereof.

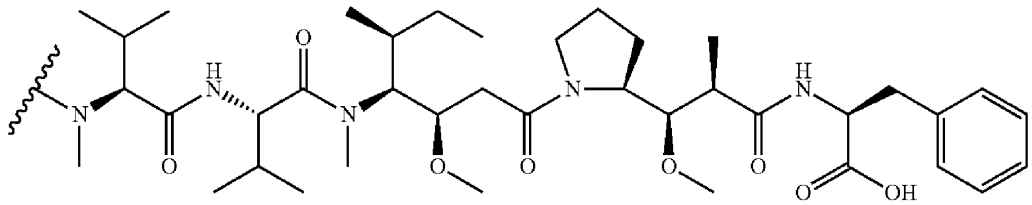
[0104] In one embodiment, the auristatin is monomethyl auristatin E (MMAE):



MMAE

wherein the wavy line indicates the attachment site for the linker.

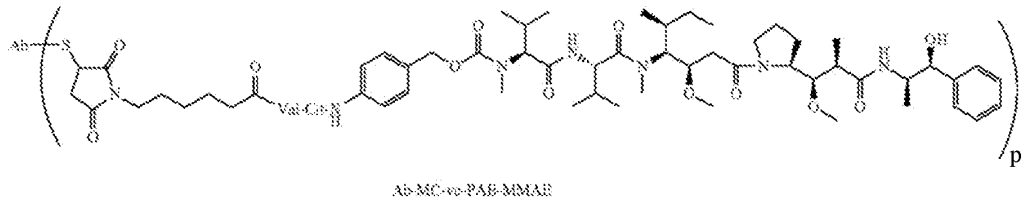
[0105] In one embodiment, the auristatin is monomethyl auristatin F (MMAF):



MMAF

wherein the wavy line indicates the attachment site for the linker.

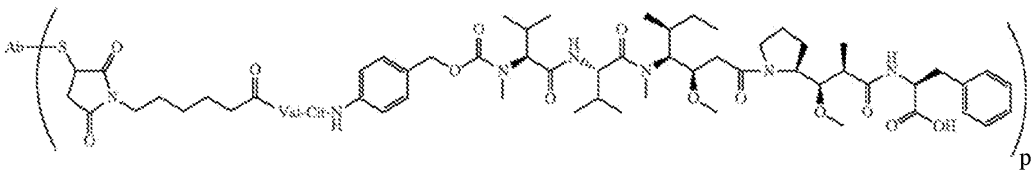
[0106] In one embodiment, the cleavable peptide linker has the formula: MC-vc-PAB-, and is attached to MMAE. The resulting linker-auristatin, MC-vc-PAB-MMAE is also designated vcMMAE. The vcMMAE drug linker moiety and conjugation methods are disclosed in WO2004010957, US7659241, US7829531 and US7851437. When vcMMAE is attached to an anti-TF antibody or antigen-binding fragment thereof as described herein, the resulting structure is:



Ab-MC-vc-PAB-MMAF

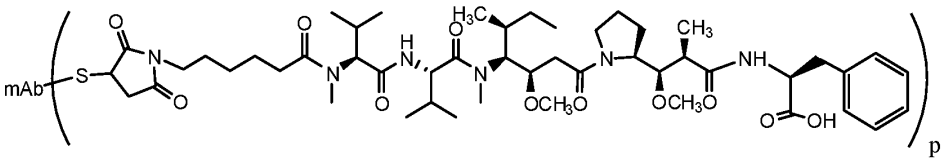
wherein p denotes a number from 1 to 8, *e.g.*, 1, 2, 3, 4, 5, 6, 7 or 8, *e.g.*, p may be from 3-5, S represents a sulphydryl residue of the anti-TF antibody and Ab designates an anti-TF antibody or antigen-binding fragment thereof as described herein. In one embodiment, the average value of p in a population of antibody-drug conjugates is about 4. In some embodiments, p is measured by hydrophobic interaction chromatography (HIC), for example by resolving drug-loaded species based on the increasing hydrophobicity with the least hydrophobic, unconjugated form eluting first and the most hydrophobic, 8-drug form eluting last with the area percentage of a peak representing the relative distribution of the particular drug-loaded antibody-drug conjugate species. *See* Ouyang, J., 2013, Antibody-Drug Conjugates, Methods in Molecular Biology (Methods and Protocols). In some embodiments, p is measured by reversed phase high-performance liquid chromatography (RP-HPLC), for example by first performing a reduction reaction to completely dissociate the heavy and light chains of the ADC, then separating the light and heavy chains and their corresponding drug-loaded forms on an RP column, where the percentage peak are from integration of the light chain and heavy chain peaks, combined with the assigned drug load for each peak, is used to calculate the weighted average drug to antibody ration. *See* Ouyang, J., 2013, Antibody-Drug Conjugates, Methods in Molecular Biology (Methods and Protocols).

[0107] In one embodiment, the cleavable peptide linker has the formula: MC-vc-PAB-, and is attached to MMAF. The resulting linker-auristatin, MC-vc-PAB-MMAF is also designated vcMMAF. In another embodiment, a non-cleavable linker MC is attached to MMAF. The resulting linker-auristatin MC-MMAF is also designated mcMMAF. Both the vcMMAF and mcMMAF drug linker moieties and conjugation methods are disclosed in WO2005081711 and US7498298.When vcMMAF or mcMMAF is attached to an anti-TF antibody or antigen-binding fragment thereof as described herein, the resulting structure is:



Ab-MC-vc-PAB-MMAF

or



mAb-MC-MMAF

wherein p denotes a number from 1 to 8, *e.g.*, 1, 2, 3, 4, 5, 6, 7 or 8, *e.g.*, p may be from 3-5, S represents a sulphydryl residue of the anti-TF antibody and Ab or mAb designates an anti-TF antibody or antigen-binding fragment thereof as described herein. In one embodiment, the average value of p in a population of antibody-drug conjugates is about 4. In some embodiments, p is measured by hydrophobic interaction chromatography (HIC), for example by resolving drug-loaded species based on the increasing hydrophobicity with the least hydrophobic, unconjugated form eluting first and the most hydrophobic, 8-drug form eluting last with the area percentage of a peak representing the relative distribution of the particular drug-loaded antibody-drug conjugate species. *See* Ouyang, J., 2013, Antibody-Drug Conjugates, Methods in Molecular Biology (Methods and Protocols). In some embodiments, p is measured by reversed phase high-performance liquid chromatography (RP-HPLC), for example by first performing a reduction reaction to completely dissociate the heavy and light chains of the ADC, then separating the light and heavy chains and their corresponding drug-loaded forms on an RP column, where the percentage peak are from integration of the light chain and heavy chain peaks, combined with the assigned drug load for each peak, is used to calculate the weighted average drug to antibody ration. *See* Ouyang, J., 2013, Antibody-Drug Conjugates, Methods in Molecular Biology (Methods and Protocols).

[0108] In one embodiment, the antibody-drug conjugate is tisotumab vedotin.

C. Anti-VEGF Antibody

[0109] Generally, anti-VEGF antibodies or antigen-binding fragments thereof of the disclosure bind to VEGF, *e.g.*, human VEGF. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of bevacizumab, or a biosimilar thereof. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of bevacizumab. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of bevacizumab, or a biosimilar thereof. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of bevacizumab. In some embodiments, the anti-VEGF antibody is bevacizumab. In some embodiments, 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. In some embodiments, the CDRs of the anti-VEGF antibody are delineated using the Kabat numbering scheme (Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NTH Publication No. 91-3242).

[0110] Anti-VEGF antibodies of the disclosure are preferably monoclonal, and may be multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, and VEGF binding fragments of any of the above. In some embodiments, an anti-VEGF antibody described herein binds specifically to VEGF (*e.g.*, human VEGF). The immunoglobulin molecules of the disclosure can

be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

[0111] In certain embodiments of the disclosure, the antibodies are antigen-binding fragments (*e.g.*, human antigen-binding fragments) as described herein and include, but are not limited to, Fab, Fab' and $F(ab')_2$, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a V_L or V_H domain. Antigen-binding fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, CH3 and CL domains. Also included in the present disclosure are antigen-binding fragments comprising any combination of variable region(s) with a hinge region, CH1, CH2, CH3 and CL domains. In some embodiments, the anti-VEGF antibodies or antigen-binding fragments thereof are human, murine (*e.g.*, mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camelid, horse, or chicken.

[0112] The anti-VEGF antibodies of the present disclosure may be monospecific, bispecific, trispecific or of greater multi specificity. Multispecific antibodies may be specific for different epitopes of VEGF or may be specific for both VEGF as well as for a heterologous protein. *See*, *e.g.*, PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, *et al.*, 1991, J. Immunol. 147:60 69; U.S. Pat. Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny *et al.*, 1992, J. Immunol. 148:1547 1553.

[0113] Anti-VEGF antibodies of the present disclosure may be described or specified in terms of the particular CDRs they comprise. The precise amino acid sequence boundaries of a given CDR or FR can be readily determined using any of a number of well-known schemes, including those described by Kabat *et al.* (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme); Al-Lazikani *et al.*, (1997) JMB 273,927-948 ("Chothia" numbering scheme); MacCallum *et al.*, J. Mol. Biol. 262:732-745 (1996), "Antibody-antigen interactions: Contact analysis and binding site topography," J. Mol. Biol. 262, 732-745." ("Contact" numbering scheme); Lefranc MP *et al.*, "IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains," Dev Comp Immunol, 2003 Jan;27(1):55-77 ("IMGT" numbering scheme); Honegger A and Plückthun A, "Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis

tool," J Mol Biol, 2001 Jun 8;309(3):657-70, ("Aho" numbering scheme); and Martin *et al.*, "Modeling antibody hypervariable loops: a combined algorithm," PNAS, 1989, 86(23):9268-9272, ("AbM" numbering scheme). The boundaries of a given CDR may vary depending on the scheme used for identification. In some embodiments, a "CDR" or "complementarity determining region," or individual specified CDRs (*e.g.*, CDR-H1, CDR-H2, CDR-H3), of a given antibody or region thereof (*e.g.*, variable region thereof) should be understood to encompass a (or the specific) CDR as defined by any of the aforementioned schemes. For example, where it is stated that a particular CDR (*e.g.*, a CDR-H3) contains the amino acid sequence of a corresponding CDR in a given V_H or V_L region amino acid sequence, it is understood that such a CDR has a sequence of the corresponding CDR (*e.g.*, CDR-H3) within the variable region, as defined by any of the aforementioned schemes. The scheme for identification of a particular CDR or CDRs may be specified, such as the CDR as defined by the Kabat, Chothia, AbM or IMGT method.

[0114] In some embodiments, the anti-VEGF antibodies of the present disclosure comprise the CDRs of the antibody bevacizumab, which is also known as A4.6.1. *See* U.S. Patent No. 6,884,879. In some embodiments, the CDRs of the antibody bevacizumab are delineated using the Kabat numbering scheme (Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NTH Publication No. 91-3242). The present disclosure encompasses an anti-VEGF antibody or derivative thereof comprising a heavy or light chain variable domain, said variable domain comprising (a) a set of three CDRs, in which said set of CDRs are from the monoclonal antibody bevacizumab, and (b) a set of four framework regions, in which said set of framework regions differs from the set of framework regions in the monoclonal antibody bevacizumab, and in which said anti-VEGF antibody or derivative thereof binds to VEGF. In certain embodiments, the anti-VEGF antibody is bevacizumab. The antibody bevacizumab is also known as AVASTIN®.

[0115] In one aspect, provided herein is an anti-VEGF antibody comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:17, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:18, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:19; and wherein the light chain variable region comprises (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:20, (ii) CDR-L2 comprising the amino

acid sequence of SEQ ID NO:21, and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:22. In some embodiments, the CDRs of the anti-VEGF antibody are delineated using the Kabat numbering scheme.

[0116] In one embodiment, an anti-VEGF antibody comprises a light chain variable domain comprising a framework sequence and hypervariable regions, wherein the framework sequence comprises the LC-FR1-LC-FR4 amino acid sequences of SEQ ID NO:27 (LC-FR1), SEQ ID NO:28 (LC-FR2), SEQ ID NO:29 (LC-FR3), and SEQ ID NO:30 (LC-FR4), respectively; the CDR-L1 comprises the amino acid sequence of SEQ ID NO:20; the CDR-L2 comprises the amino acid sequence of SEQ ID NO:21; and the CDR-L3 comprises the amino acid sequence of SEQ ID NO:22. In some embodiments, the CDRs of the anti-VEGF antibody are delineated using the Kabat numbering scheme.

[0117] In some embodiments of the anti-VEGF antibodies described herein, the heavy chain variable domain comprises the amino acid sequence of

EVQLVESGGGLVQPGGSLRLSCAASGYTFTNYGMNWVRQAPGKGLEWVGWINTYTGE PTYAADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYYGSSHWYFDVWG QGTLVTVSS (SEQ ID NO:31) and the light chain variable domain comprises the amino acid sequence of

DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKR (SEQ ID NO:32).

[0118] In some embodiments of the anti-VEGF antibodies described herein, the heavy chain CDR sequences comprise the following:

a) CDR-H1 (GYTFTNYGMN (SEQ ID NO:17));

b) CDR-H2 (WINTYTGEPTYAADFKR (SEQ ID NO:18)); and

c) CDR-H3 (YPHYYGSSHWYFDV (SEQ ID NO:19)). In some embodiments, the CDRs of the anti-VEGF antibody are delineated using the Kabat numbering scheme.

[0119] In some embodiments of the anti-VEGF antibodies described herein, the heavy chain FR sequences comprise the following:

a) HC-FR1 (EVQLVESGGGLVQPGGSLRLSCAAS (SEQ ID NO:23));

b) HC-FR2 (WVRQAPGKGLEWVG (SEQ ID NO:24));

c) HC-FR3 (RFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAK (SEQ ID NO:25)); and

d) HC-FR4 (WGQGTLVTVSS (SEQ ID NO:26)).

[0120] In some embodiments of the anti-VEGF antibodies described herein, the light chain CDR sequences comprise the following:

a) CDR-L1 (SASQDISNYLN (SEQ ID NO:20));

b) CDR-L2 (FTSSLHS (SEQ ID NO:21)); and

c) CDR-L3 (QQYSTVPWT (SEQ ID NO:22)). In some embodiments, the CDRs of the anti-VEGF antibody are delineated using the Kabat numbering scheme.

[0121] In some embodiments of the anti-VEGF antibodies described herein, the light chain FR sequences comprise the following:

a) LC-FR1 (DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO:27));

b) LC-FR2 (WYQQKPGKAPKVLIY (SEQ ID NO:28));

c) LC-FR3 (GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO:29)); and

d) LC-FR4 (FGQGTKVEIKR (SEQ ID NO:30)).

[0122] In some embodiments, provided herein is an anti-VEGF antibody that binds to VEGF (*e.g.*, human VEGF), wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the antibody comprises:

(a) heavy chain variable domain comprising:

(1) an HC-FR1 comprising the amino acid sequence of SEQ ID NO:23;

(2) an CDR-H1 comprising the amino acid sequence of SEQ ID NO:17;

(3) an HC-FR2 comprising the amino acid sequence of SEQ ID NO:24;

(4) an CDR-H2 comprising the amino acid sequence of SEQ ID NO:18;

(5) an HC-FR3 comprising the amino acid sequence of SEQ ID NO:25;

(6) an CDR-H3 comprising the amino acid sequence of SEQ ID NO:19; and

(7) an HC-FR4 comprising the amino acid sequence of SEQ ID NO:26,

and/or

(b) a light chain variable domain comprising:

(1) an LC-FR1 comprising the amino acid sequence of SEQ ID NO:27;

(2) an CDR-L1 comprising the amino acid sequence of SEQ ID NO:20;

(3) an LC-FR2 comprising the amino acid sequence of SEQ ID NO:28;

(4) an CDR-L2 comprising the amino acid sequence of SEQ ID NO:21;

(5) an LC-FR3 comprising the amino acid sequence of SEQ ID NO:29;

(6) an CDR-L3 comprising the amino acid sequence of SEQ ID NO:22; and

(7) an LC-FR4 comprising the amino acid sequence of SEQ ID NO:30. In some embodiments, the CDRs of the anti-VEGF antibody are delineated using the Kabat numbering scheme.

[0123] In one aspect, provided herein is an anti-VEGF antibody comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:31 or comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:32. In one aspect, provided herein is an anti-VEGF antibody comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:31 and comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:32.

[0124] In some embodiments, provided herein is an anti-VEGF antibody comprising a heavy chain variable domain comprising an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO:31. In certain embodiments, a heavy chain variable domain comprising an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO:31 contains substitutions (*e.g.*, conservative substitutions), insertions, or deletions relative to the reference sequence and retains the ability to bind to a VEGF (*e.g.*, human VEGF). In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:31. In certain embodiments, substitutions, insertions, or deletions (*e.g.*, 1, 2, 3, 4, or 5 amino acids) occur in regions outside the CDRs (*i.e.*, in the FRs). In some embodiments, the anti-VEGF antibody comprises a heavy chain variable domain sequence of SEQ ID NO:31 including post-translational modifications of that sequence. In a particular embodiment, the heavy chain variable domain comprises one, two or three CDRs selected from: (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:17, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:18, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:19. In some embodiments, the CDRs of the anti-VEGF antibody are delineated using the Kabat numbering scheme.

[0125] In some embodiments, provided herein is an anti-VEGF antibody comprising a light chain variable domain comprising an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO:32. In certain embodiments, a light chain variable domain comprising an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO:32 contains substitutions (*e.g.*, conservative substitutions), insertions, or deletions relative to the reference sequence and retains the ability to bind to a VEGF (*e.g.*, human VEGF). In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:32. In certain embodiments, substitutions, insertions, or deletions (*e.g.*, 1, 2, 3, 4, or 5 amino acids) occur in regions outside the CDR s (*i.e.*, in the FRs). In some embodiments, the anti-VEGF antibody comprises a light chain variable domain sequence of SEQ ID NO:32 including post-translational modifications of that sequence. In a particular embodiment, the light chain variable domain comprises one, two or three CDRs selected from: (a) CDR-L1 comprising the amino acid sequence of SEQ ID NO:20, (b) CDR-L2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-L3 comprising the amino acid sequence of SEQ ID NO:22. In some embodiments, the CDRs of the anti-VEGF antibody are delineated using the Kabat numbering scheme.

[0126] In some embodiments, the anti-VEGF antibody comprises a heavy chain variable domain as in any of the embodiments provided above, and a light chain variable domain as in any of the embodiments provided above. In one embodiment, the antibody comprises the heavy chain variable domain sequence of SEQ ID NO:31 and the light chain variable domain sequence of SEQ ID NO:32, including post-translational modifications of those sequences.

[0127] In some embodiments, the anti-VEGF antibody comprises: i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 17, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 18, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 19; and ii) a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 20, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 21, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 22. In some embodiments, the CDRs of the anti-VEGF antibody are delineated using the Kabat numbering scheme.

[0128] In some embodiments, the anti-VEGF antibody comprises: i) an amino acid sequence having at least 85% sequence identity to a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 31, and ii) an amino acid sequence having at least 85% sequence identity to a light chain variable region comprising the amino acid sequence of SEQ ID NO: 32.

[0129] In some embodiments of the anti-VEGF antibodies described herein, the heavy chain comprises the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGYTFTNYGMNWVRQAPGKGLEWVGWINTYTGE PTYAADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYYGSSHWYFDVWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:33) and the light chain comprises the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:34).

[0130] In some embodiments, the anti-VEGF antibody is a monoclonal antibody.

[0131] In some embodiments, the anti-VEGF antibody is bevacizumab, which is also known as AVASTIN® and antibody A.4.6.1, as described in U.S. Patent No. 6,884,879 and Presta et al., Cancer Res., 1997, 57:4593-4599.

[0132] In some embodiments, the anti-VEGF antibody is a biosimilar of bevacizumab. In some embodiments, the biosimilar of bevacizumab is selected from the group comprising bevacizumab-awwb (Amgen, USA), bevacizumab-bvzr (Pfizer, USA), FKB238 (AstraZeneca/Fujifilm Kyowa Kirin Biologics, USA/Japan), BCD-021 (Biocad, Russia), BCD500 (BIOCND, South Korea), Krabeva (Biocon, India), BI 695502 (Boehringer Ingelheim, Germany), CT-P16 (Celltrion, South Korea), CHS-5217 (Coherus, USA), DRZ_BZ (Dr Reddy's Laboratories, India), Cizumab (Hetero (Lupin), India), Bevax (mAbxience, Spain), ONS-1045

(Oncobiologics/Viropro, USA), PF-06439535 (Pfizer, USA), HD204 (Prestige Biopharma, Singapore), Bevacirel (Reliance Life Sciences/Lupin, India), and SB8 (Samsung Bioepis (Biogen/Samsung)/Merck, South Korea, USA). In some embodiments, 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. In some embodiments, the biosimilar of bevacizumab is selected from the group comprising bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel. In some embodiments, the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel. Bevacizumab-awwb is also known as Mvasi® and ABP 215. Bevacizumab-bvzr is also known as Zirabev®.

[0133] Anti-VEGF antibodies of the present invention may also be described or specified in terms of their binding affinity to VEGF (*e.g.*, human VEGF). Preferred binding affinities include those with a dissociation constant or Kd less than 5 $x10^{-2}$ M, 10^{-2} M, $5x10^{-3}$ M, 10^{-3} M, $5x10^{-4}$ M, 10^{-4} M, $5x10^{-5}$ M, 10^{-5} M, $5x10^{-6}$ M, 10^{-6} M, $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8}M, $5x10^{-9}$M, 10^{-9} M, $5x10^{-10}$M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, 10^{-13} M, $5x10^{-14}$ M, 10^{-14} M, $5x10^{-15}$ M, or 10^{-15} M.

[0134] There are five classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, having heavy chains designated α, δ, ε, γ and μ, respectively. The γ and α classes are further divided into subclasses *e.g.*, humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. IgG1 antibodies can exist in multiple polymorphic variants termed allotypes (reviewed in Jefferis and Lefranc 2009. *mAbs* Vol 1 Issue 4 1-7) any of which are suitable for use in some of the embodiments herein. Common allotypic variants in human populations are those designated by the letters a, f, n, z or combinations thereof. In any of the embodiments herein, the antibody may comprise a heavy chain Fc region comprising a human IgG Fc region. In further embodiments, the human IgG Fc region comprises a human IgG1.

[0135] The antibodies also include derivatives that are modified, *i.e.*, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from binding to VEGF. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, *e.g.*, by glycosylation,

acetylation, PEGylation, phosphylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

D. Nucleic acids, Host cells and Methods of Production

[0136] In some aspects, also provided herein are nucleic acids encoding an anti-TF antibody or antigen-binding fragment thereof as described herein or an anti-VEGF antibody or antigen-binding fragment thereof as described herein. Further provided herein are vectors comprising the nucleic acids encoding an anti-TF antibody or antigen-binding fragment thereof as described herein or an anti-VEGF antibody or antigen-binding fragment thereof as described herein. Further provided herein are host cells expressing the nucleic acids encoding an anti-TF antibody or antigen-binding fragment thereof as described herein or an anti-VEGF antibody or antigen-binding fragment thereof as described herein. Further provided herein are host cells comprising the vectors comprising the nucleic acids encoding an anti-TF antibody or antigen-binding fragment thereof as described herein or an anti-VEGF antibody or antigen-binding fragment thereof as described herein. Methods of producing an anti-TF antibody, linker and anti-TF antibody-drug conjugate are described in U.S. Pat. No. 9,168,314.

[0137] The anti-TF antibodies described herein or anti-VEGF antibodies described herein may be prepared by well-known recombinant techniques using well known expression vector systems and host cells. In one embodiment, the antibodies are prepared in a CHO cell using the GS expression vector system as disclosed in De la Cruz Edmunds *et al.*, 2006, *Molecular Biotechnology* 34; 179-190, EP216846, U.S. Pat. No. 5,981,216, WO 87/04462, EP323997, U.S. Pat. No. 5,591,639, U.S. Pat. No. 5,658,759, EP338841, U.S. Pat. No. 5,879,936, and U.S. Pat. No. 5,891,693.

[0138] After isolating and purifying the anti-TF antibodies from the cell media using well known techniques in the art, they are conjugated with an auristatin via a linker as described in U.S. Pat. No. 9,168,314.

[0139] Monoclonal anti-TF antibodies described herein or anti-VEGF antibodies described herein may *e.g.* be produced by the hybridoma method first described by Kohler *et al.*, *Nature*,

256, 495 (1975), or may be produced by recombinant DNA methods. Monoclonal antibodies may also be isolated from phage antibody libraries using the techniques described in, for example, Clackson *et al.*, *Nature*, 352, 624-628 (1991) and Marks *et al., JMol, Biol.*, 222(3):581-597 (1991). Monoclonal antibodies may be obtained from any suitable source. Thus, for example, monoclonal antibodies may be obtained from hybridomas prepared from murine splenic B cells obtained from mice immunized with an antigen of interest, for instance in form of cells expressing the antigen on the surface, or a nucleic acid encoding an antigen of interest. Monoclonal antibodies may also be obtained from hybridomas derived from antibody-expressing cells of immunized humans or non-human mammals such as rats, dogs, primates, etc.

[0140] In one embodiment, the antibody (*e.g.*, anti-TF antibody or anti-VEGF antibody) of the invention is a human antibody. Human monoclonal antibodies directed against TF or VEGF may be generated using transgenic or transchromosomal mice carrying parts of the human immune system rather than the mouse system. Such transgenic and transchromosomic mice include mice referred to herein as HuMAb mice and KM mice, respectively, and are collectively referred to herein as "transgenic mice".

[0141] The HuMAb mouse contains a human immunoglobulin gene minilocus that encodes unrearranged human heavy (μ and γ) and κ light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ and κ chain loci (Lonberg, N. *et al.*, *Nature*, 368, 856-859 (1994)). Accordingly, the mice exhibit reduced expression of mouse IgM or κ and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgG,κ monoclonal antibodies (Lonberg, N. *et al.* (1994), supra; reviewed in Lonberg, N. *Handbook of Experimental Pharmacology* 113, 49-101 (1994), Lonberg, N. and Huszar. D., *Intern. Rev. Immunol*, Vol. 13 65-93 (1995) and Harding, F. and Lonberg, *N. Ann, N.Y. Acad. Sci* 764:536-546 (1995)). The preparation of HuMAb mice is described in detail in Taylor, L. *et al.*, *Nucleic Acids Research.* 20:6287-6295 (1992), Chen, J. *et al.*, *International Immunology.* 5:647-656 (1993), Tuaillon at al., *J. Immunol*, 152:2912-2920 (1994), Taylor, L. *et al.*, *International Immunology,* 6:579-591 (1994), Fishwild, D. *et al.*, *Nature Biotechnology*, 14:845-851 (1996). *See* also U.S. Pat. No. 5,545,806, U.S. Pat. No. 5,569,825, U.S. Pat. No. 5,625,126, U.S. Pat. No. 5,633,425, U.S. Pat. No. 5,789,650, U.S. Pat. No. 5,877,397, U.S. Pat. No. 5,661,016, U.S. Pat. No. 5,814,318, U.S.

Pat. No. 5,874,299, U.S. Pat. No. 5,770,429, U.S. Pat. No. 5,545,807, WO 98/24884, WO 94/25585, WO 93/1227, WO 92/22645, WO 92/03918 and WO 01/09187.

[0142] The HCo7 mice have a JKD disruption in their endogenous light chain (kappa) genes (as described in Chen et al, *EMBO J.* 12:821-830 (1993)), a CMD disruption in their endogenous heavy chain genes (as described in Example 1 of WO 01/14424), a KCo5 human kappa light chain transgene (as described in Fishwild *et al.*, *Nature Biotechnology*, 14:845-851 (1996)), and a HCo7 human heavy chain transgene (as described in U.S. Pat. No. 5,770,429).

[0143] The HCo12 mice have a JKD disruption in their endogenous light chain (kappa) genes (as described in Chen *et al.*, *EMBO J.* 12:821-830 (1993)), a CMD disruption in their endogenous heavy chain genes (as described in Example 1 of WO 01/14424), a KCo5 human kappa light chain transgene (as described in Fishwild *et al.*, *Nature Biotechnology,* 14:845-851 (1996)), and a HCo12 human heavy chain transgene (as described in Example 2 of WO 01/14424).

[0144] The HCo17 transgenic mouse strain (see also US 2010/0077497) was generated by coinjection of the 80 kb insert of pHC2 (Taylor *et al.* (1994) *Int. Immunol.*, 6:579-591), the Kb insert of pVX6, and a ~460 kb yeast artificial chromosome fragment of the yIgH24 chromosome. This line was designated (HCo17) 25950. The (HCo17) 25950 line was then bred with mice comprising the CMD mutation (described in Example 1 of PCT Publication WO 01109187), the JKD mutation (Chen et al, (1993) *EMBO J.* 12:811-820), and the (KC05) 9272 transgene (Fishwild *et al.* (1996) *Nature Biotechnology*, 14:845-851). The resulting mice express human immunoglobulin heavy and kappa light chain trans genes in a background homozygous for disruption of the endogenous mouse heavy and kappa light chain loci.

[0145] The HCo20 transgenic mouse strain is the result of a co-injection of minilocus 30 heavy chain transgene pHC2, the germline variable region (Vh)-containing YAC yIgH10, and the minilocus construct pVx6 (described in WO09097006). The (HCo20) line was then bred with mice comprising the CMD mutation (described in Example 1 of PCT Publication WO 01/09187), the JKD mutation (Chen *et al.* (1993*) EMBO J.* 12:811-820), and the (KCO5) 9272 trans gene (Fishwild eta). (1996) *Nature Biotechnology,* 14:845-851). The resulting mice express human 10 immunoglobulin heavy and kappa light chain transgenes in a background homozygous for disruption of the endogenous mouse heavy and kappa light chain loci.

[0146] In order to generate HuMab mice with the salutary effects of the Balb/c strain, HuMab mice were crossed with KCO05 [MIK] (Balb) mice which were generated by backcrossing the KC05 strain (as described in Fishwild et (1996*) Nature Biotechnology*, 14:845-851) to wild-type Balb/c mice to generate mice as described in WO09097006. Using this crossing Balb/c hybrids were created for HCo12, HCo17, and HCo20 strains.

[0147] In the KM mouse strain, the endogenous mouse kappa light chain gene has been homozygously disrupted as described in Chen *et al.*, *EMBO J.* 12:811-820 (1993) and the endogenous mouse heavy chain gene has been homozygously disrupted as described in Example 1 of WO 01/09187, This mouse strain carries a human kappa light chain transgene, KCo5, as described in Fishwild *et al.*, *Nature Biotechnology*, 14:845-851 (1996). This mouse strain also carries a human heavy chain transchromosome composed of chromosome 14 fragment hCF (SC20) as described in WO 02/43478.

[0148] Splenocytes from these transgenic mice may be used to generate hybridomas that secrete human monoclonal antibodies according to well-known techniques, Human monoclonal or polyclonal antibodies of the present invention, or antibodies of the present invention originating from other species may also be generated transgenically through the generation of another non-human mammal or plant that is transgenic for the immunoglobulin heavy and light chain sequences of interest and production of the antibody in a recoverable form therefrom. In connection with the transgenic production in mammals, antibodies may be produced in, and recovered from, the milk of goats, cows, or other mammals. *See* for instance U.S. Pat. No. 5,827,690, U.S. Pat. No. 5,756,687, U.S. Pat. No. 5,750,172 and U.S. Pat. No. 5,741,957.

[0149] Further, human antibodies of the present invention or antibodies of the present invention from other species may be generated through display-type technologies, including, without limitation, phage display, retroviral display, ribosomal display, and other techniques, using techniques well known in the art and the resulting molecules may be subjected to additional maturation, such as affinity maturation, as such techniques are well known in the art (*See* for instance Hoogenboom *et al., J. Mol, Biol.* 227(2):381-388 (1992) (phage display), Vaughan *et al.*, *Nature Biotech*, 14:309 (1996) (phage display), Hanes and Plucthau, *PNAS USA* 94:4937-4942 (1997) (ribosomal display), Parmley and Smith, *Gene*, 73:305-318 (1988) (phage display), Scott, *TIBS.* 17:241-245 (1992), Cwirla *et al.*, *PNAS USA*, 87:6378-6382 (1990), Russel

et al., *Nucl. Acids Research*, 21:1081-4085 (1993), Hogenboom *et al.*, *Immunol, Reviews*, 130:43-68 (1992), Chiswell and McCafferty, TIBTECH, 10:80-84 (1992), and U.S. Pat. No. 5,733,743). If display technologies are utilized to produce antibodies that are not human, such antibodies may be humanized.

III. BINDING ASSAYS AND OTHER ASSAYS

[0150] In one aspect, an antibody of the invention is tested for its antigen binding activity, for example, by known methods such as Enzyme-Linked Immunosorbant Assay (ELISA), immunoblotting (*e.g.*, Western blotting), flow cytometry (*e.g.*, FACS™), immunohistochemistry, immunofluorescence, etc.

[0151] In another aspect, competition assays may be used to identify an antibody that competes with any one of the antibodies described herein for binding to TF (*e.g.*, tisotumab) or VEGF (*e.g.*, bevacizumab). Cross-competing antibodies can be readily identified based on their ability to cross-compete in standard TF or VEGF binding assays such as Biacore analysis, ELISA assays or flow cytometry (*See*, *e.g.*, WO 2013/173223). In certain embodiments, such a competing antibody binds to the same epitope (*e.g.*, a linear or a conformational epitope) that is bound by any one of the antibodies disclosed herein (*e.g.*, tisotumab or bevacizumab). Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris "Epitope Mapping Protocols," in Methods in Molecular Biology Vol. 66 (Humana Press, Totowa, NJ, 1996).

[0152] In an exemplary competition assay, immobilized VEGF is incubated in a solution comprising a first labeled antibody that binds to VEGF (*e.g.*, bevacizumab) and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to VEGF. The second antibody may be present in a hybridoma supernatant. As a control, immobilized VEGF is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to VEGF, excess unbound antibody is removed, and the amount of label associated with immobilized VEGF is measured. If the amount of label associated with immobilized VEGF is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for binding to VEGF. *See*, *e.g.*, Harlow *et al.* Antibodies: A Laboratory Manual. Ch.14 (Cold Spring Harbor

Laboratory, Cold Spring Harbor, NY, 1988). In some embodiments, an anti- VEGF antibody competes for binding to VEGF with another VEGF antibody (*e.g.*, bevacizumab) if the antibody blocks binding of the other antibody to VEGF in a competition assay by more than 20%, more than 25%, more than 30%, more than 35%, more than 40%, more than 45%, more than 50%, more than 55%, more than 60%, more than 65%, more than 70%, more than 75%, more than 80%, more than 85%, more than 90%, or more than 95%. In some embodiments, an anti-VEGF antibody does not compete for binding to VEGF with another VEGF antibody (*e.g.*, bevacizumab) if the antibody blocks binding of the other antibody to VEGF in a competition assay by less than 20%, less than 15%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1%. In some embodiments, the VEGF is human VEGF.

[0153] Similar competition assays can be performed to determine if an anti-TF antibody competes with tisotumab for binding to TF. In some embodiments, an anti-TF antibody competes for binding to TF with another TF antibody (*e.g.*, tisotumab) if the antibody blocks binding of the other antibody to TF in a competition assay by more than 20%, more than 25%, more than 30%, more than 35%, more than 40%, more than 45%, more than 50%, more than 55%, more than 60%, more than 65%, more than 70%, more than 75%, more than 80%, more than 85%, more than 90%, or more than 95%. In some embodiments, an anti-TF antibody does not compete for binding to TF with another TF antibody (*e.g.*, tisotumab) if the antibody blocks binding of the other antibody to TF in a competition assay by less than 20%, less than 15%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1%. In some embodiments, the TF is human TF.

IV. METHODS OF TREATMENT

A. Cervical Cancer

[0154] Cervical cancer remains to be one of the leading causes of cancer-related death in women despite advances in screening, diagnosis, prevention, and treatment. It accounts for ~4% of the total newly diagnosed cancer cases and 4% of the total cancer deaths. *See* Zhu *et al.*, 2016, *Drug Des. Devel. Ther.* 10:1885-1895. Cervical cancer is the 7th most common female cancer worldwide and the 16th most common cancer in the European Union. Depending on the stage at initial presentation, cervical cancer will recur in 25-61% of women. *See* Tempfer *et al.*,

2016, *Oncol. Res. Treat.* 39:525-533. In most cases, recurrent disease is diagnosed within 2 years of the initial treatment and may be observed in various sites. Chemotherapy is the standard treatment for these patients. *See* Zhu *et al.*, 2016, *Drug Des. Devel. Ther.* 10:1885-1895. The median overall survival exceeds one year now, however, the five year relative survival for stage IV cervical cancer is only 15%, demonstrating the high need for improved methods of treating cervical cancer.

[0155] The invention provides methods for treating cervical cancer in a subject with an anti-TF antibody-drug conjugate described herein and an anti-VEGF antibody described herein. In some embodiments, the anti-TF antibody-drug conjugate comprises the complementary determining regions (CDRs) of tisotumab vedotin, or a biosimilar thereof. In some embodiments, the anti-TF antibody-drug conjugate comprises the complementary determining regions (CDRs) of tisotumab vedotin. In some embodiments, the anti-TF antibody-drug conjugate comprises the heavy chain variable region and the light chain variable region of tisotumab vedotin, or a biosimilar thereof. In some embodiments, the anti-TF antibody-drug conjugate comprises the heavy chain variable region and the light chain variable region of tisotumab vedotin. In some embodiments, the anti-TF 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. In some embodiments, the CDRs of the anti- TF antibody-drug conjugate are delineated using the IMGT numbering scheme. In some embodiments, the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of bevacizumab, or a biosimilar thereof. In some

embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of bevacizumab. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of bevacizumab, or a biosimilar thereof. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of bevacizumab. In some embodiments, 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. In some embodiments, the CDRs of the anti-VEGF antibody are delineated using the Kabat numbering scheme. In one aspect, the anti-VEGF antibody is bevacizumab. In another aspect, the anti-VEGF antibody is a biosimilar of bevacizumab. In some embodiments, the biosimilar of bevacizumab is selected from the group comprising 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. In some embodiments, 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. In some embodiments, the biosimilar of bevacizumab is selected from the group comprising bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel. In some embodiments, the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel.

Bevacizumab-awwb is also known as Mvasi® and ABP 215. Bevacizumab-bvzr is also known as Zirabev®. In a particular embodiment, the subject is a human.

[0156] In another aspect the present invention provides an antibody-drug conjugate that binds to TF as described herein for use in the treatment of cervical cancer wherein the antibody-drug conjugate is for administration, or to be administered in combination with an anti-VEGF antibody or an antigen-binding fragment thereof as described herein. In some embodiments, the anti-TF antibody-drug conjugate comprises the complementary determining regions (CDRs) of tisotumab vedotin, or a biosimilar thereof. In some embodiments, the anti-TF antibody-drug conjugate comprises the complementary determining regions (CDRs) of tisotumab vedotin. In some embodiments, the anti-TF antibody-drug conjugate comprises the heavy chain variable region and the light chain variable region of tisotumab vedotin, or a biosimilar thereof. In some embodiments, the anti-TF antibody-drug conjugate comprises the heavy chain variable region and the light chain variable region of tisotumab vedotin. In some embodiments, the anti-TF 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. In some embodiments, the CDRs of the anti- TF antibody-drug conjugate are delineated using the IMGT numbering scheme. In some embodiments, the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the anti-VEGF antibody or the antigen-binding fragment thereof inhibits VEGF activity, and wherein the anti-VEGF antibody or an antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of bevacizumab, or a biosimilar thereof. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of bevacizumab. In some

embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of bevacizumab, or a biosimilar thereof. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of bevacizumab. In some embodiments, 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. In some embodiments, the CDRs of the anti-VEGF antibody are delineated using the Kabat numbering scheme. In one aspect, the anti-VEGF antibody is bevacizumab. In another aspect, the anti-VEGF antibody is a biosimilar of bevacizumab. In some embodiments, the biosimilar of bevacizumab is selected from the group comprising 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. In some embodiments, 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. In some embodiments, the biosimilar of bevacizumab is selected from the group comprising bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel. In some embodiments, the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel. Bevacizumab-awwb is also known as Mvasi® and ABP 215. Bevacizumab-bvzr is also known as Zirabev®. In a particular embodiment, the subject is a human.

[0157] In another aspect the present invention provides an anti-VEGF antibody or an antigen-binding fragment thereof as described herein for use in the treatment of cervical cancer wherein the anti-VEGF antibody is for administration, or to be administered in combination with an antibody-drug conjugate that binds to TF as described herein. In some embodiments, the anti-TF antibody-drug conjugate comprises the complementary determining regions (CDRs) of tisotumab vedotin, or a biosimilar thereof. In some embodiments, the anti-TF antibody-drug conjugate comprises the complementary determining regions (CDRs) of tisotumab vedotin. In some embodiments, the anti-TF antibody-drug conjugate comprises the heavy chain variable region and the light chain variable region of tisotumab vedotin, or a biosimilar thereof. In some embodiments, the anti-TF antibody-drug conjugate comprises the heavy chain variable region and the light chain variable region of tisotumab vedotin. In some embodiments, the anti-TF 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. In some embodiments, the CDRs of the anti- TF antibody-drug conjugate are delineated using the IMGT numbering scheme. In some embodiments, the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the anti-VEGF antibody or the antigen-binding fragment thereof inhibits VEGF activity, and wherein the anti-VEGF antibody or the antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of bevacizumab, or a biosimilar thereof. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of bevacizumab. In some embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of bevacizumab, or a biosimilar thereof. In some

embodiments, the anti-VEGF antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of bevacizumab. In some embodiments, 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. In some embodiments, the CDRs of the anti-VEGF antibody are delineated using the Kabat numbering scheme. In one aspect, the anti-VEGF antibody is bevacizumab. In another aspect, the anti-VEGF antibody is a biosimilar of bevacizumab. In some embodiments, the biosimilar of bevacizumab is selected from the group comprising 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. In some embodiments, 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. In some embodiments, the biosimilar of bevacizumab is selected from the group comprising bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel. In some embodiments, the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel. Bevacizumab-awwb is also known as Mvasi® and ABP 215. Bevacizumab-bvzr is also known as Zirabev®. In a particular embodiment, the subject is a human.

[0158] In some embodiments, the subject has been previously treated with chemotherapy and/or radiation therapy. In some embodiments, the subject is not a candidate for curative therapy. In some embodiments, the curative therapy is radiotherapy and/or exenterative therapy.

In some embodiments, the curative therapy is radiotherapy. In some embodiments, the curative therapy is exenterative therapy. In a particular embodiment, the subject is a human.

[0159] In some embodiments of the methods or uses or product for uses provided herein, the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma, a squamous cell carcinoma, a small cell carcinoma, a neuroendocrine tumor, a glassy cell carcinoma or a villoglandular adenocarcinoma. In some embodiments, the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma. In some embodiments, the cervical cancer is an adenocarcinoma. In some embodiments, the cervical cancer is an adenosquamous carcinoma. In some embodiments, the cervical cancer is a squamous cell carcinoma.

[0160] In some embodiments, 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 from the subject express TF. In some embodiments, at least 0.1%, at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 15%, 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% of the cervical cancer cells from the subject express TF. In some embodiments, the percentage of cells that express TF is determined using immunohistochemistry (IHC). In some embodiments, the percentage of cells that express TF is determined using flow cytometry. In some embodiments, the percentage of cells that express TF is determined using an enzyme-linked immunosorbent assay (ELISA).

[0161] In some embodiments of the methods or uses or product for uses provided herein, the cervical cancer is a stage 0, 1, 2, 3, or 4 cervical cancer. In some embodiments, the cervical cancer is a stage 0, 1A, 1B, 2A, 2B, 3A, 3B, 4A or 4B cervical cancer. In some embodiments, the cervical cancer is staged by the International Federation of Gynecology and Obstetrics (FIGO) staging system. In some embodiments, the staging is based on clinical examination. In some embodiments, in stage 0 cervical cancer the carcinoma is confined to the surface layer (cells lining) the cervix. In some embodiments, in stage 1 cervical cancer the carcinoma has grown deeper into the cervix but has not yet spread beyond it. In some embodiments, in stage

1A cervical cancer the invasive carcinoma can be diagnosed only by microscopy and the deepest invasion is less than 5 mm and the largest extension is less than 7 mm. In some embodiments, in stage 1B cervical cancer the lesions are clinically visible and are limited to the cervix uteri. In some embodiments, in stage 2 cervical cancer the cervical carcinoma has invaded beyond the uterus, but not to the pelvic wall or to the lower third of the vagina. In some embodiments, in stage 2A cervical cancer there is no parametrial invasion. In some embodiments, in stage 2B cervical cancer there is parametrial invasion. In some embodiments, in stage 3 cervical cancer the tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or non-functioning kidney. In some embodiments, in stage 3A cervical cancer the tumor involves the lower third of the vagina, with no extension to the pelvic wall. In some embodiments, in stage 3B cervical cancer extends to the pelvic wall and/or cause hydronephrosis or non-functioning kidney. In some embodiments, in stage 4 cervical cancer, the carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum. In some embodiments, in stage 4A cervical cancer the tumor has spread to adjacent organs. In some embodiments, in stage 4B cervical cancer the tumor has spread to distant organs. In some embodiments, the cervical cancer is an advanced stage cervical cancer. In some embodiments, the advanced stage cervical cancer is a grade 3 or grade 4 cervical cancer. In some embodiments, the advanced stage cervical cancer is metastatic cervical cancer. In some embodiments, the cervical cancer is metastatic and recurrent cervical cancer. In some embodiments, the cervical cancer is metastatic cervical cancer. In some embodiments, the cervical cancer is recurrent cervical cancer.

[0162] In some embodiments, the subject has been previously treated for the cervical cancer. In some embodiments, the subject has been previously treated with one or more therapeutic agents and did not respond to the treatment. In some embodiments, the subject has been previously treated with one or more therapeutic agents and relapsed after the treatment. In some embodiments, the subject has been previously treated with one or more therapeutic agents and experienced disease progression during treatment. In some embodiments, the one or more therapeutic agents is selected from the group consisting of a chemotherapeutic agent, pemetrexed, nab-paclitaxel, vinorelbine, 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. In some embodiments, the one or more therapeutic agents is a chemotherapeutic agent. In some embodiments, the one or more therapeutic agents is bevacizumab. In some embodiments, the one or more therapeutic agents is cisplatin, In some embodiments, the one or more therapeutic agents is carboplatin. In some embodiments, the one or more therapeutic agents is paclitaxel. In some embodiments, the one or more therapeutic agents is topotecan. In some embodiments, the one or more therapeutic agents is a combination of bevacizumab and paclitaxel. In some embodiments, the one or more therapeutic agents is a combination of bevacizumab and cisplatin. In some embodiments, the one or more therapeutic agents is a combination of bevacizumab and carboplatin. In some embodiments, the one or more therapeutic agents is a combination of paclitaxel and topotecan. In some embodiments, the one or more therapeutic agents is a combination of bevacizumab and topotecan. In some embodiments, the one or more therapeutic agents is a combination of bevacizumab, cisplatin and paclitaxel. In some embodiments, the one or more therapeutic agents is a combination of bevacizumab, carboplatin and paclitaxel. In some embodiments, the one or more therapeutic agents is a combination of bevacizumab, paclitaxel and topotecan. In some embodiments, the subject has been previously treated with chemotherapy and/or radiation therapy. In some embodiments, the subject did not respond to the treatment with chemotherapy and radiation therapy. In some embodiments, the subject received treatment for the cervical cancer with chemotherapy and did not respond to the chemotherapy. In some embodiments, the subject received treatment for the cervical cancer with irradiation and did not respond to the irradiation. In some embodiments, the subject relapsed after treatment with chemotherapy and radiation therapy. In some embodiments, the subject received treatment for the cervical cancer with chemotherapy and relapsed after treatment with the chemotherapy. In some embodiments, the subject received treatment for the cervical cancer with irradiation and relapsed after treatment with irradiation. In some embodiments, the subject experienced disease progression after treatment with chemotherapy and/or radiation therapy. In some embodiments, the subject received treatment for the cervical cancer with chemotherapy and experienced disease progression after treatment with the chemotherapy. In some embodiments, the subject received treatment for the cervical cancer with irradiation and experienced disease progression after

treatment with irradiation. In some embodiments, the subject is not a candidate for curative therapy. In some embodiments, the curative therapy is radiotherapy and/or exenterative therapy. In some embodiments, the curative therapy is radiotherapy. In some embodiments, the curative therapy is exenterative therapy. In a particular embodiment, the subject is a human.

B. Routes of Administration

[0163] An anti-VEGF antibody or antigen-binding fragment thereof described herein or anti-TF antibody-drug conjugate or antigen-binding fragment thereof described herein can be administered by any suitable route and mode. Suitable routes of administering antibodies and/or antibody-drug conjugate of the present invention are well known in the art and may be selected by those of ordinary skill in the art. In one embodiment, the anti-VEGF antibody described herein and/or anti-TF antibody-drug conjugate described herein are administered parenterally. Parenteral administration refers to modes of administration other than enteral and topical administration, usually by injection, and include epidermal, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, intratendinous, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, intracranial, intrathoracic, epidural and intrasternal injection and infusion. In some embodiments, the route of administration of an anti-TF antibody-drug conjugate or antigen-binding fragment described herein is intravenous injection or infusion. In some embodiments, the route of administration of an anti-TF antibody-drug conjugate or antigen-binding fragment described herein is intravenous infusion. In some embodiments, the route of administration of an anti-VEGF antibody or antigen-binding fragment described herein is intravenous injection or infusion. In some embodiments, the route of administration of an anti-VEGF antibody or antigen-binding fragment described herein is intravenous infusion.

C. Dosage and Frequency of Administration

[0164] In one aspect, the present invention provides for methods of treating a subject with cancer as described herein with a particular dose of an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein and an anti-VEGF antibody or antigen-binding fragment thereof as described herein, wherein the subject is administered the antibody-drug conjugate or antigen-binding fragment thereof as described herein and the anti-VEGF antibody or antigen-binding fragment thereof as described herein with particular frequencies.

[0165] In one embodiment of the methods or uses or product for uses provided herein, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose ranging from about 0.65 mg/kg to about 2.1 mg/kg of the subject's body weight. In certain embodiments, the dose is about 0.65 mg/kg, about 0.7 mg/kg, about 0.75 mg/kg, about 0.8 mg/kg, about 0.85 mg/kg, about 0.9 mg/kg, about 1.0 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, about 1.9 mg/kg, about 2.0 mg/kg or about 2.1 mg/kg. In one embodiment, the dose is about 0.65 mg/kg. In one embodiment, the dose is about 0.9 mg/kg. In one embodiment, the dose is about 1.3 mg/kg. In one embodiment, the dose is about 2.0 mg/kg. In certain embodiments, the dose is 0.65 mg/kg, 0.7 mg/kg, 0.75 mg/kg, 0.8 mg/kg, 0.85 mg/kg, 0.9 mg/kg, 1.0 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2.0 mg/kg or 2.1 mg/kg. In one embodiment, the dose is 0.65 mg/kg. In one embodiment, the dose is 0.9 mg/kg. In one embodiment, the dose is 1.3 mg/kg. In one embodiment, the dose is 2.0 mg/kg. In some embodiments, the dose is 0.65 mg/kg and the anti-TF antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is 0.9 mg/kg and the anti-TF antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is 1.3 mg/kg and the anti-TF antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is 2.0 mg/kg and the anti-TF antibody-drug conjugate is tisotumab vedotin. In some embodiments, for a subject weighing more than 100 kg, the dose of the anti-TF antibody-drug conjugate administered is the amount that would be administered if the subject weighed 100 kg. In some embodiments, for a subject weighing more than 100 kg, the dose of the anti-TF antibody-drug conjugate administered is 65 mg, 90 mg, 130 mg, or 200 mg.

[0166] In one embodiment of the methods or uses or product for uses provided herein, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject once about every 1 to 4 weeks. In certain embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered once about every 1 week, once about every 2 weeks, once about every 3 weeks or once about every 4 weeks. In one embodiment, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered once about every 3 weeks. In one embodiment, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered once every 3 weeks. In some embodiments, the dose is about

0.65 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 0.65 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 0.65 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 0.65 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 0.7 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 0.7 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 0.7 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 0.7 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 0.75 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 0.75 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 0.75 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 0.75 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 0.8 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 0.8 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 0.8 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 0.8 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 0.85 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 0.85 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 0.85 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 0.85 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 0.9 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 0.9 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 0.9 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 0.9 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 1.0 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 1.0 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 1.0 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 1.0 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 1.1 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 1.1 mg/kg and is

administered once about every 2 weeks. In some embodiments, the dose is about 1.1 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 1.1 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 1.2 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 1.2 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 1.2 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 1.2 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 1.3 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 1.3 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 1.3 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 1.3 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 1.4 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 1.4 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 1.4 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 1.4 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 1.5 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 1.5 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 1.5 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 1.5 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 1.6 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 1.6 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 1.6 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 1.6 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 1.7 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 1.7 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 1.7 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 1.7 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 1.8 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 1.8 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 1.8 mg/kg and is administered once about every

3 weeks. In some embodiments, the dose is about 1.8 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 1.9 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 1.9 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 1.9 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 1.9 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 2.0 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 2.0 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 2.0 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 2.0 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 2.1 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 2.1 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 2.1 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 2.1 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 0.65 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 0.65 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 0.65 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 0.65 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 0.7 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 0.7 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 0.7 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 0.7 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 0.75 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 0.75 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 0.75 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 0.75 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 0.8 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 0.8 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 0.8 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 0.8 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 0.85 mg/kg and is administered once about every 1 week. In some

embodiments, the dose is 0.85 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 0.85 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 0.85 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 0.9 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 0.9 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 0.9 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 0.9 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 1.0 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 1.0 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 1.0 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 1.0 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 1.1 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 1.1 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 1.1 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 1.1 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 1.2 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 1.2 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 1.2 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 1.2 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 1.3 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 1.3 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 1.3 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 1.3 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 1.4 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 1.4 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 1.4 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 1.4 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 1.5 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 1.5 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 1.5 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 1.5 mg/kg and is administered once about every 4 weeks. In some

embodiments, the dose is 1.6 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 1.6 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 1.6 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 1.6 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 1.7 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 1.7 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 1.7 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 1.7 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 1.8 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 1.8 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 1.8 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 1.8 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 1.9 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 1.9 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 1.9 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 1.9 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 2.0 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 2.0 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 2.0 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 2.0 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 2.1 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 2.1 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 2.1 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 2.1 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 2.0 mg/kg and is administered once about every 3 weeks (*e.g.*, ± 3 days). In some embodiments, the dose is 2.0 mg/kg and is administered once every 3 weeks. In some embodiments, the dose is 2.0 mg/kg and is administered once every 3 weeks and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is 2.0 mg/kg and is administered once every 3 weeks and the antibody-drug conjugate is tisotumab vedotin and the dose is decreased to 1.3 mg/kg if one or more adverse events occur. In some embodiments, the dose is 1.3 mg/kg and is administered once every 3 weeks. In some embodiments, the dose is 1.3

mg/kg and is administered once every 3 weeks and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is 1.3 mg/kg and is administered once every 3 weeks and the antibody-drug conjugate is tisotumab vedotin and the dose is decreased to 0.9 mg/kg if one or more adverse events occur. In some embodiments, the dose is about 0.9 mg/kg and is administered once about every week and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is 0.9 mg/kg and is administered once every week and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is about 0.9 mg/kg and is administered on about days 1, 8, and 15 of about a 4-week cycle and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is about 0.9 mg/kg and is administered on days 1, 8, and 15 of a 4-week cycle and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is 0.9 mg/kg and is administered on about days 1, 8, and 15 of about a 4-week cycle and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is 0.9 mg/kg and is administered on days 1, 8, and 15 of a 4-week cycle and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is 0.9 mg/kg and is administered on about days 1, 8, and 15 of about a 4-week cycle and the antibody drug conjugate is tisotumab vedotin and the dose is decreased to 0.65 mg/kg if one or more adverse events occur. In some embodiments, the dose is 0.9 mg/kg and is administered on days 1, 8, and 15 of a 4-week cycle and the antibody drug conjugate is tisotumab vedotin and the dose is decreased to 0.65 mg/kg if one or more adverse events occur. In some embodiments, the dose is about 0.65 mg/kg and is administered once about every week and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is 0.65 mg/kg and is administered once every week and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is 0.65 mg/kg and is administered on about days 1, 8, and 15 of about a 4-week cycle and the antibody drug conjugate is tisotumab vedotin. In some embodiments, the dose is 0.65 mg/kg and is administered on days 1, 8, and 15 of a 4-week cycle and the antibody drug conjugate is tisotumab vedotin. In some embodiments, the dose is about 1.2 mg/kg and is administered on about days 1, 8, and 15 of about a 4-week cycle and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is about 1.2 mg/kg and is administered on days 1, 8, and 15 of a 4-week cycle and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the dose is 1.2 mg/kg and is administered on about days 1, 8, and 15 of about a 4-week cycle and the antibody-drug conjugate is tisotumab vedotin. In some

embodiments, the dose is 1.2 mg/kg and is administered on days 1, 8, and 15 of a 4-week cycle and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, for a subject weighing more than 100 kg, the dose of the anti-TF antibody-drug conjugate administered is the amount that would be administered if the subject weighed 100 kg. In some embodiments, for a subject weighing more than 100 kg, the dose of the anti-TF antibody-drug conjugate administered is 65 mg, 90 mg, 130 mg, or 200 mg.

[0167] In one embodiment of the methods or uses or product for uses provided herein, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject once about every 1 week for 3 consecutive weeks followed by about a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is about 28 days including the resting period. In one embodiment of the methods or uses or product for uses provided herein, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject once every 1 week for 3 consecutive weeks followed by a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is 28 days including the resting period. Hereby, a dosing regimen is provided where the subject to be treated is dosed with a single weekly dose for three consecutive weeks followed by a resting week. This treatment schedule may also be referred to as a "dose-dense schedule" herein and is the same as "the 4-week (28 days) cycle" and "3Q4W". In one embodiment, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject on about days 1, 8, and 15 of about a 4-week cycle. In one embodiment, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject on days 1, 8, and 15 of a 4-week cycle. The present invention encompasses embodiments wherein the subject remains on the 3Q4W treatment cycle for at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more cycles. In another embodiment, the subject remains on the 3Q4W treatment cycle for between 2 and 48 cycles, such as between 2 and 36 cycles, such as between 2 and 24 cycles, such as between 2 and 15 cycles, such as between 2 and 12 cycles, such as 2 cycles, 3 cycles, 4 cycles, 5 cycles, 6 cycles, 7 cycles, 8 cycles, 9 cycles, 10 cycles, 11 cycles or 12 cycles wherein each cycle is 28 days as described above. In some embodiments, the subject remains on the 3Q4W treatment cycle for 12 cycles or more, such as 16 cycles or more, such as 24 cycles or more, such as 36 cycles or more.

In some embodiments, the 3Q4W treatment cycle is administered for no more than 3, no more than 4, no more than 5, or no more than 6 four-week treatment cycles. The number of treatment cycles suitable for any specific subject or group of subjects may be determined by a person of skill in the art, typically a physician. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of about 1.2 mg/kg once about every 1 week for 3 consecutive weeks followed by about a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is about 28 days including the resting period. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of about 1.2 mg/kg once every 1 week for 3 consecutive weeks followed by a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is 28 days including the resting period. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of about 1.2 mg/kg on about days 1, 8, and 15 of about a 4-week cycle. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of about 1.2 mg/kg on days 1, 8, and 15 of about a 4-week cycle. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of 1.2 mg/kg once about every 1 week for 3 consecutive weeks followed by about a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is about 28 days including the resting period. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of 1.2 mg/kg once every 1 week for 3 consecutive weeks followed by a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is 28 days including the resting period. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of 1.2 mg/kg on about days 1, 8, and 15 of about a 4-week cycle. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of 1.2 mg/kg on days 1, 8, and 15 of about a 4-week cycle. In some

embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of about 0.9 mg/kg once about every 1 week for 3 consecutive weeks followed by about a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is about 28 days including the resting period. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of about 0.9 mg/kg once every 1 week for 3 consecutive weeks followed by a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is 28 days including the resting period. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of about 0.9 mg/kg on about days 1, 8, and 15 of about a 4-week cycle. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of about 0.9 mg/kg on days 1, 8, and 15 of about a 4-week cycle. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of 0.9 mg/kg once about every 1 week for 3 consecutive weeks followed by about a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is about 28 days including the resting period. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of 0.9 mg/kg once every 1 week for 3 consecutive weeks followed by a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is 28 days including the resting period. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of 0.9 mg/kg on about days 1, 8, and 15 of about a 4-week cycle. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of 0.9 mg/kg on days 1, 8, and 15 of about a 4-week cycle. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of about 0.65 mg/kg once about every 1 week for 3 consecutive weeks followed by about a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so

that each cycle time is about 28 days including the resting period. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of about 0.65 mg/kg once every 1 week for 3 consecutive weeks followed by a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is 28 days including the resting period. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of about 0.65 mg/kg on about days 1, 8, and 15 of about a 4-week cycle. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of about 0.65 mg/kg on days 1, 8, and 15 of about a 4-week cycle. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of 0.65 mg/kg once about every 1 week for 3 consecutive weeks followed by about a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is about 28 days including the resting period. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of 0.65 mg/kg once every 1 week for 3 consecutive weeks followed by a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is 28 days including the resting period. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of 0.65 mg/kg on about days 1, 8, and 15 of about a 4-week cycle. In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a dose of 0.65 mg/kg on days 1, 8, and 15 of about a 4-week cycle. In some embodiments, the dose is 0.9 mg/kg and is administered on about days 1, 8, and 15 of about a 4-week cycle and the antibody drug conjugate is tisotumab vedotin. In some embodiments, the dose is 0.9 mg/kg and is administered on days 1, 8, and 15 of a 4-week cycle and the antibody drug conjugate is tisotumab vedotin. In some embodiments, the dose is 0.9 mg/kg and is administered on about days 1, 8, and 15 of about a 4-week cycle and the antibody drug conjugate is tisotumab vedotin and the dose is decreased to 0.65 mg/kg if one or more adverse events occur. In some embodiments, the dose is 0.9 mg/kg and is administered on days 1, 8, and 15 of a 4-week cycle and the antibody drug

conjugate is tisotumab vedotin and the dose is decreased to 0.65 mg/kg if one or more adverse events occur. In some embodiments, the dose is 1.2 mg/kg and is administered on about days 1, 8, and 15 of about a 4-week cycle and the antibody drug conjugate is tisotumab vedotin. In some embodiments, the dose is 1.2 mg/kg and is administered on days 1, 8, and 15 of a 4-week cycle and the antibody drug conjugate is tisotumab vedotin. In some embodiments, the dose is 0.65 mg/kg and is administered on about days 1, 8, and 15 of about a 4-week cycle and the antibody drug conjugate is tisotumab vedotin. In some embodiments, the dose is 0.65 mg/kg and is administered on days 1, 8, and 15 of a 4-week cycle and the antibody drug conjugate is tisotumab vedotin. In some embodiments, for a subject weighing more than 100 kg, the dose of the anti-TF antibody-drug conjugate administered is the amount that would be administered if the subject weighed 100 kg. In some embodiments, for a subject weighing more than 100 kg, the dose of the anti-TF antibody-drug conjugate administered is 65 mg, 90 mg, 130 mg, or 200 mg.

[0168] In one embodiment of the methods or uses or product for uses provided herein, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a flat dose ranging from about 50 mg to about 200 mg such as at a flat dose of about 50 mg or a flat dose of about 60 mg or a flat dose of about 70 mg or a flat dose of about 80 mg or a flat dose of about 90 mg or a flat dose of about 100 mg or a flat dose of about 110 mg or a flat dose of about 120 mg or a flat dose of about 130 mg or a flat dose of about 140 mg or a flat dose of about 150 mg or a flat dose of about 160 mg or a flat dose of about 170 mg or a flat dose of about 180 mg or a flat dose of about 190 mg or a flat dose of about 200 mg. In some embodiments, the flat dose is administered to the subject once about every 1 to 4 weeks. In certain embodiments, the flat dose is administered to the subject once about every 1 week, once about every 2 weeks, once about every 3 weeks or once about every 4 weeks. In some embodiments, the flat dose is administered to the subject once about every 3 weeks (*e.g.*, ± 3 days). In some embodiments, the flat dose is administered to the subject once every 3 weeks. In some embodiments, the flat dose is administered to the subject once every 3 weeks and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the flat does is administered to the subject once about every week (*e.g.*, ± 1 day). In some embodiments, the flat does is administered to the subject once every week. In some embodiments, the flat dose is administered to the subject once about every 1 week for 3 consecutive weeks followed by about a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or

antigen-binding fragment thereof so that each cycle time is about 28 days including the resting period. In some embodiments, the flat dose is administered to the subject once every 1 week for 3 consecutive weeks followed by a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is 28 days including the resting period. In some embodiments, the flat dose is administered to the subject on about days 1, 8, and 15 of about a 4-week cycle. In some embodiments, the flat dose is administered to the subject on days 1, 8, and 15 of a 4-week cycle. In some embodiments, the flat dose is administered to the subject on days 1, 8, and 15 of a 4-week cycle and the antibody-drug conjugate is tisotumab vedotin.

[0169] In one embodiment of the methods or uses or product for uses provided herein, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered to the subject at a flat dose ranging from 50 mg to 200 mg such as at a flat dose of 50 mg or a flat dose of 60 mg or a flat dose of 70 mg or a flat dose of 80 mg or a flat dose of 90 mg or a flat dose of 100 mg or a flat dose of 110 mg or a flat dose of 120 mg or a flat dose of 130 mg or a flat dose of 140 mg or a flat dose of 150 mg or a flat dose of 160 mg or a flat dose of 170 mg or a flat dose of 180 mg or a flat dose of 190 mg or a flat dose of 200 mg. In some embodiments, the flat dose is administered to the subject once about every 1 to 4 weeks. In certain embodiments, the flat dose is administered to the subject once about every 1 week, once about every 2 weeks, once about every 3 weeks or once about every 4 weeks. In some embodiments, the flat dose is administered to the subject once about every 3 weeks (*e.g.*, ± 3 days). In some embodiments, the flat dose is administered to the subject once every 3 weeks. In some embodiments, the flat dose is administered to the subject once every 3 weeks and the antibody-drug conjugate is tisotumab vedotin. In some embodiments, the flat does is administered to the subject once about every week (*e.g.*, ± 1 day). In some embodiments, the flat does is administered to the subject once every week. In some embodiments, the flat dose is administered to the subject once about every 1 week for 3 consecutive weeks followed by about a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is about 28 days including the resting period. In some embodiments, the flat dose is administered to the subject once every 1 week for 3 consecutive weeks followed by a 1 week rest period without any administration of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof so that each cycle time is 28 days

including the resting period. In some embodiments, the flat dose is administered to the subject on about days 1, 8, and 15 of about a 4-week cycle. In some embodiments, the flat dose is administered to the subject on days 1, 8, and 15 of a 4-week cycle. In some embodiments, the flat dose is administered to the subject on days 1, 8, and 15 of a 4-week cycle and the antibody-drug conjugate is tisotumab vedotin.

[0170] In one embodiment of the methods or uses or product for uses provided herein, an anti-VEGF antibody or antigen-binding fragment thereof as described herein is administered to the subject at a dose ranging from about 5 mg/kg to about 20 mg/kg of the subject's body weight. In certain embodiments, the dose is about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 7.5 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg or about 20 mg/kg. In one embodiment, the dose is about 7.5 mg/kg. In one embodiment, the dose is about 7.5 mg/kg and the anti-VEGF antibody is bevacizumab. In one embodiment, the dose is about 15 mg/kg and the anti-VEGF antibody is bevacizumab. In one embodiment, the dose is about 15 mg/kg. In certain embodiments, the dose is 5 mg/kg, 6 mg/kg, 7 mg/kg, 7.5 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg or 20 mg/kg. In one embodiment, the dose is 7.5 mg/kg. In one embodiment, the dose is 15 mg/kg. In one embodiment, the dose is 7.5 mg/kg and the anti-VEGF antibody is bevacizumab. In one embodiment, the dose is 15 mg/kg and the anti-VEGF antibody is bevacizumab.

[0171] In one embodiment of the methods or uses or product for uses provided herein, an anti-VEGF antibody or antigen-binding fragment thereof as described herein is administered to the subject once about every 1 to 4 weeks. In certain embodiments, an anti-VEGF antibody or antigen-binding fragment thereof as described herein is administered once about every 1 week, once about every 2 weeks, once about every 3 weeks or once about every 4 weeks. In one embodiment, an anti-VEGF antibody or antigen-binding fragment thereof as described herein is administered once about every 3 weeks. In one embodiment, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is administered once every 3 weeks. In some embodiments, the dose is about 5 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 5 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 5 mg/kg and is administered once about every 3

weeks. In some embodiments, the dose is about 5 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 6 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 6 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 6 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 6 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 7 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 7 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 7 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 7 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 7.5 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 7.5 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 7.5 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 7.5 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 8 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 8 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 8 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 8 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 9 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 9 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 9 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 9 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 10 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 10 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 10 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 10 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 11 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 11 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 11 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 11 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 12 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 12 mg/kg and is

administered once about every 2 weeks. In some embodiments, the dose is about 12 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 12 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 13 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 13 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 13 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 13 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 14 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 14 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 14 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 14 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 15 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 15 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 15 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 15 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 16 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 16 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 16 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 16 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 17 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 17 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 17 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 17 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 18 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 18 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 18 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 18 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 19 mg/kg and is administered once about every 1 week. In some embodiments, the dose is about 19 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 19 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 19 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is about 20 mg/kg and

is administered once about every 1 week. In some embodiments, the dose is about 20 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is about 20 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is about 20 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 5 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 5 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 5 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 5 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 6 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 6 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 6 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 6 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 7 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 7 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 7 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 7 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 7.5 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 7.5 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 7.5 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 7.5 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 8 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 8 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 8 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 8 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 9 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 9 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 9 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 9 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 10 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 10 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 10 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 10 mg/kg and is

administered once about every 4 weeks. In some embodiments, the dose is 11 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 11 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 11 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 11 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 12 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 12 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 12 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 12 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 13 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 13 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 13 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 13 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 14 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 14 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 14 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 14 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 15 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 15 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 15 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 15 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 16 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 16 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 16 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 16 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 17 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 17 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 17 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 17 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 18 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 18 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 18 mg/kg and is

administered once about every 3 weeks. In some embodiments, the dose is 18 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 19 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 19 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 19 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 19 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 20 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 20 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 20 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 20 mg/kg and is administered once about every 4 weeks. In some embodiments, the dose is 7.5 mg/kg and is administered once about every 3 weeks (*e.g.*, ± 3 days). In some embodiments, the dose is 7.5 mg/kg and is administered once every 3 weeks. In some embodiments, the dose is 7.5 mg/kg and is administered once every 3 weeks and the anti-VEGF antibody is bevacizumab. In some embodiments, the dose is 15 mg/kg and is administered once about every 3 weeks (*e.g.*, ± 3 days). In some embodiments, the dose is 15 mg/kg and is administered once every 3 weeks. In some embodiments, the dose is 15 mg/kg and is administered once every 3 weeks and the anti-VEGF antibody is bevacizumab.

[0172] In some embodiments of the methods or uses or product for uses provided herein, an anti-VEGF antibody or antigen-binding fragment thereof as described herein and an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein are administered to the subject at a fixed dose. In some embodiments, the fixed dose is based on the amount (*e.g.,* mg) of the antibodies. In certain embodiments, the fixed dose is based on the concentration (*e.g.,* mg/ml) of the antibodies. In some embodiments, the ratio of the amount (*e.g.,* mg) of the anti-VEGF antibody or antigen-binding fragment thereof as described herein to the amount (*e.g.,* mg) of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, about 1:15, about 1:20, about 1:30, about 1:40, about 1:50, about 1:60, about 1:70, about 1:80, about 1:90, about 1:100, about 1:120, about 1:140, about 1:160, about 1:180, about 1:200, about 200:1, about 180:1, about 160:1, about 140:1, about 120:1, about 100:1, about 90:1, about 80:1, about 70:1, about 60:1, about 50:1, about 40:1, about 30:1, about 20:1, about 15:1, about 10:1, about 9:1, about 8:1, about 7:1, about 6:1, about 5:1,

about 4:1, about 3:1, or about 2:1. In some embodiments, the ratio of the amount (*e.g.,* mg) of the anti-VEGF antibody or antigen-binding fragment thereof as described herein to the amount (*e.g.,* mg) of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, 1:30, 1:40, 1:50, 1:60, 1:70, 1:80, 1:90, 1:100, 1:120, 1:140, 1:160, 1:180, 1:200, 200:1, 180:1, 160:1, 140:1, 120:1, 100:1, 90:1, 80:1, 70:1, 60:1, 50:1, 40:1, 30:1, 20:1, 15:1, 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, or 2:1. In some embodiments, the ratio of the concentration (*e.g.,* mg/ml) of the anti-VEGF antibody or antigen-binding fragment thereof as described herein to the concentration (*e.g.,* mg/ml) of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, about 1:15, about 1:20, about 1:30, about 1:40, about 1:50, about 1:60, about 1:70, about 1:80, about 1:90, about 1:100, about 1:120, about 1:140, about 1:160, about 1:180, about 1:200, about 200:1, about 180:1, about 160:1, about 140:1, about 120:1, about 100:1, about 90:1, about 80:1, about 70:1, about 60:1, about 50:1, about 40:1, about 30:1, about 20:1, about 15:1, about 10:1, about 9:1, about 8:1, about 7:1, about 6:1, about 5:1, about 4:1, about 3:1, or about 2:1. In some embodiments, the ratio of the concentration (*e.g.,* mg/ml) of the anti-VEGF antibody or antigen-binding fragment thereof described herein to the concentration (*e.g.,* mg/ml) of the anti-TF antibody-drug conjugate or antigen-binding fragment thereof described herein is 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, 1:30, 1:40, 1:50, 1:60, 1:70, 1:80, 1:90, 1:100, 1:120, 1:140, 1:160, 1:180, 1:200, 200:1, 180:1, 160:1, 140:1, 120:1, 100:1, 90:1, 80:1, 70:1, 60:1, 50:1, 40:1, 30:1, 20:1, 15:1, 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, or 2:1.

[0173] In some embodiments, the dose of the anti-TF antibody-drug conjugate described herein is 2.0 mg/kg and is administered once about every 3 weeks (*e.g.,* ± 3 days) and the dose of the anti-VEGF antibody described herein is 15 mg/kg and is administered once about every 3 weeks (*e.g.,* ± 3 days). In some embodiments, the dose of the anti-TF antibody-drug conjugate described herein is 2.0 mg/kg and is administered once every 3 weeks and the dose of the anti-VEGF antibody described herein is 15 mg/kg and is administered once every 3 weeks. In some embodiments, the dose of the anti-TF antibody-drug conjugate is 2.0 mg/kg and is administered once every 3 weeks and the antibody-drug conjugate is tisotumab vedotin and the dose of the

anti- VEGF antibody is 15 mg/kg and is administered once every 3 weeks and the anti- VEGF antibody is bevacizumab.

[0174] In some embodiments, the dose of the anti-TF antibody-drug conjugate described herein is 1.3 mg/kg and is administered once about every 3 weeks (*e.g.*, ± 3 days) and the dose of the anti-VEGF antibody described herein is 7.5 mg/kg and is administered once about every 3 weeks (*e.g.*, ± 3 days). In some embodiments, the dose of the anti-TF antibody-drug conjugate described herein is 1.3 mg/kg and is administered once every 3 weeks and the dose of the anti-VEGF antibody described herein is 7.5 mg/kg and is administered once every 3 weeks. In some embodiments, the dose of the anti-TF antibody-drug conjugate is 1.3 mg/kg and is administered once every 3 weeks and the antibody-drug conjugate is tisotumab vedotin and the dose of the anti-VEGF antibody is 7.5 mg and is administered once every 3 weeks and the anti-VEGF antibody is bevacizumab.

[0175] In some embodiments, the dose of the anti-TF antibody-drug conjugate described herein is 1.3 mg/kg and is administered once about every 3 weeks (*e.g.*, ± 3 days) and the dose of the anti-VEGF antibody described herein is 15 mg/kg and is administered once about every 3 weeks (*e.g.*, ± 3 days). In some embodiments, the dose of the anti-TF antibody-drug conjugate described herein is 1.3 mg/kg and is administered once every 3 weeks and the dose of the anti-VEGF antibody described herein is 15 mg/kg and is administered once every 3 weeks. In some embodiments, the dose of the anti-TF antibody-drug conjugate is 1.3 mg/kg and is administered once every 3 weeks and the antibody-drug conjugate is tisotumab vedotin and the dose of the anti-VEGF antibody is 15 mg and is administered once every 3 weeks and the anti-VEGF antibody is bevacizumab.

[0176] In some embodiments, an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein and an anti-VEGF antibody or antigen-binding fragment thereof as described herein are coadministered. In some embodiments the coadministration is simultaneous or sequential. In some embodiments, an anti-TF antibody-drug conjugate as described herein is administered simultaneously with an anti-VEGF antibody as described herein. In some embodiments, simultaneous means that the anti-TF antibody-drug conjugate as described herein and the anti-VEGF antibody as described herein are administered to the subject less than about one hour apart, such as less than about 30 minutes apart, less than about 15

minutes apart, less than about 10 minutes apart or less than about 5 minutes apart. In some embodiments, simultaneous means that the anti-TF antibody-drug conjugate as described herein and the anti-VEGF antibody as described herein are administered to the subject less than one hour apart, such as less than 30 minutes apart, less than 15 minutes apart, less than 10 minutes apart or less than 5 minutes apart. In some embodiments, an anti-TF antibody-drug conjugate as described herein is administered sequentially with an anti-VEGF antibody as described herein. In some embodiments, sequential administration means that the anti-TF antibody-drug conjugate as described herein and the anti-VEGF antibody as described herein are administered a least 1 hour apart, at least 2 hours apart, at least 3 hours apart, at least 4 hours apart, at least 5 hours apart, at least 6 hours apart, at least 7 hours apart, at least 8 hours apart, at least 9 hours apart, at least 10 hours apart, at least 11 hours apart, at least 12 hours apart, at least 13 hours apart, at least 14 hours apart, at least 15 hours apart, at least 16 hours apart, at least 17 hours apart, at least 18 hours apart, at least 19 hours apart, at least 20 hours apart, at least 21 hours apart, at least 22 hours apart, at least 23 hours apart, at least 24 hours apart, at least 2 days apart, at least 3 days apart, at least 4 days apart, at least 5 days apart, at least 5 days apart, at least 7 days apart, at least 2 weeks apart, at least 3 weeks apart or at least 4 weeks apart.

[0177] In some embodiments, a method of treatment or use described herein further comprises the administration of one or more additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are administered simultaneously with an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein, such as tisotumab vedotin, and an anti-VEGF antibody or antigen-binding fragment thereof as described herein, such as bevacizumab. In some embodiments, the one or more additional therapeutic agents and an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein and an anti-VEGF antibody or antigen-binding fragment thereof as described herein are administered sequentially.

D. Treatment Outcome

[0178] In one aspect, a method of treating cancer with an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein and an anti-VEGF antibody or antigen-binding fragment thereof as described herein results in an improvement in one or more therapeutic effects in the subject after administration of the antibody-drug conjugate relative to a

baseline. In some embodiments, the one or more therapeutic effects is the size of the tumor derived from the cancer (*e.g.*, cervical cancer), the objective response rate, the duration of response, the time to response, progression free survival, overall survival, or any combination thereof. In one embodiment, the one or more therapeutic effects is the size of the tumor derived from the cancer. In one embodiment, the one or more therapeutic effects is decreased tumor size. In one embodiment, the one or more therapeutic effects is stable disease. In one embodiment, the one or more therapeutic effects is partial response. In one embodiment, the one or more therapeutic effects is complete response. In one embodiment, the one or more therapeutic effects is the objective response rate. In one embodiment, the one or more therapeutic effects is the duration of response. In one embodiment, the one or more therapeutic effects is the time to response. In one embodiment, the one or more therapeutic effects is progression free survival. In one embodiment, the one or more therapeutic effects is overall survival. In one embodiment, the one or more therapeutic effects is cancer regression.

[0179] In one embodiment of the methods or uses or product for uses provided herein, response to treatment with an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein and an anti-VEGF antibody or antigen-binding fragment thereof as described herein may include the following criteria (RECIST Criteria 1.1):

	Category	Criteria
Based on target lesions	Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
	Partial Response (PR)	≥ 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum of LDs.
	Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of LDs while in trial.
	Progressive Disease (PD)	≥ 20% (and ≥ 5 mm) increase in the sum of the LDs of target lesions, taking as reference the smallest sum of the target LDs recorded while in trial or the appearance of one or more new lesions.
Based on non-target lesions	CR	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

	SD	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
	PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

[0180] In one embodiment of the methods or uses or product for uses provided herein, the effectiveness of treatment with an anti-TF antibody-drug conjugate or antigen-binding fragment thereof described herein and an anti-VEGF antibody or antigen-binding fragment thereof described herein is assessed by measuring the objective response rate. In some embodiments, the objective response rate is the proportion of patients with tumor size reduction of a predefined amount and for a minimum period of time. In some embodiments the objective response rate is based upon RECIST v1.1. In one embodiment, 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 one embodiment, the objective response rate is at least about 20%-80%. In one embodiment, the objective response rate is at least about 30%-80%. In one embodiment, the objective response rate is at least about 40%-80%. In one embodiment, the objective response rate is at least about 50%-80%. In one embodiment, the objective response rate is at least about 60%-80%. In one embodiment, the objective response rate is at least about 70%-80%. In one embodiment, the objective response rate is at least about 80%. In one embodiment, the objective response rate is at least about 85%. In one embodiment, the objective response rate is at least about 90%. In one embodiment, the objective response rate is at least about 95%. In one embodiment, the objective response rate is at least about 98%. In one embodiment, the objective response rate is at least about 99%. In one embodiment, the objective response rate is 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%. In one embodiment, the objective response rate is at least 20%-80%. In one embodiment, the objective response rate is at least 30%-80%. In one embodiment, the objective response rate is at least 40%-80%. In one embodiment, the objective response rate is at least 50%-80%. In one embodiment, the objective response rate is at least 60%-80%. In one embodiment, the objective response rate is at least 70%-80%. In one embodiment, the objective response rate is at least 80%. In one embodiment, the objective response rate is at least 85%. In one embodiment, the

objective response rate is at least 90%. In one embodiment, the objective response rate is at least 95%. In one embodiment, the objective response rate is at least 98%. In one embodiment, the objective response rate is at least 99%. In one embodiment, the objective response rate is 100%.

[0181] In one embodiment of the methods or uses or product for uses provided herein, response to treatment with an anti-TF antibody-drug conjugate or antigen-binding fragment thereof described herein and an anti-VEGF antibody or antigen-binding fragment thereof described herein is assessed by measuring the size of a tumor derived from the cancer (*e.g.*, cervical cancer). In one embodiment, 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 anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 10%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 20%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 30%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 40%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 50%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 60%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 70%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 85%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 90%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 95%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 98%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least about 99%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 10%, at least 15%, 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% relative to the size of the tumor derived from the cancer before administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In one

embodiment, the size of a tumor derived from the cancer is reduced by at least 10%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 20%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 30%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 40%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 50%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 60%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 70%-80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 80%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 85%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 90%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 95%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 98%. In one embodiment, the size of a tumor derived from the cancer is reduced by at least 99%.In one embodiment, the size of a tumor derived from the cancer is reduced by 100%. In one embodiment, the size of a tumor derived from the cancer is measured by magnetic resonance imaging (MRI). In one embodiment, the size of a tumor derived from the cancer is measured by computed tomography (CT). In some embodiments, the size of a tumor derived from a cervical cancer is measured by pelvic examination. *See* Choi *et al.*, 2008, *J. Gynecol. Oncol.* 19(3):205. In some embodiments, the size of the tumor derived from the cancer is reduced relative to the size of the tumor before administration of the anti-TF antibody drug conjugate described herein and the anti-VEGF antibody described herein. In some embodiments, the size of the tumor derived from the cancer is reduced relative to the size of the tumor before administration of the anti-TF antibody drug conjugate described herein. In some embodiments, the size of the tumor derived from the cancer is reduced relative to the size of the tumor before administration of the anti-VEGF antibody described herein.

[0182] In one embodiment of the methods or uses or product for uses provided described herein, response to treatment with an antibody-drug conjugate or antigen-binding fragment thereof described herein, such as *e.g.*, tisotumab vedotin, and an anti-VEGF antibody or antigen-binding fragment thereof described herein, such as *e.g.*, bevacizumab, promotes regression of a tumor derived from the cancer (*e.g.*, cervical cancer). In one embodiment, a tumor derived from the cancer regresses 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 anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein. In one embodiment, a tumor derived from the cancer regresses by at least about 10% to about 80%. In one embodiment, a tumor derived from the cancer regresses by at least about 20% to about 80%. In one embodiment, a tumor derived from the cancer regresses by at least about 30% to about 80%. In one embodiment, a tumor derived from the cancer regresses by at least about 40% to about 80%. In one embodiment, a tumor derived from the cancer regresses by at least about 50% to about 80%. In one embodiment, a tumor derived from the cancer regresses by at least about 60% to about 80%. In one embodiment, a tumor derived from the cancer regresses by at least about 70% to about 80%. In one embodiment, a tumor derived from the cancer regresses by at least about 80%. In one embodiment, a tumor derived from the cancer regresses by at least about 85%. In one embodiment, a tumor derived from the cancer regresses by at least about 90%. In one embodiment, a tumor derived from the cancer regresses by at least about 95%. In one embodiment, a tumor derived from the cancer regresses by at least about 98%. In one embodiment, a tumor derived from the cancer regresses by at least about 99%. In one embodiment, a tumor derived from the cancer regresses by at least 10%, at least 15%, 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% relative to the size of the tumor derived from the cancer before administration of the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein. In one embodiment, a tumor derived from the cancer regresses by at least 10% to 80%. In one embodiment, a tumor derived from the cancer regresses by at least 20% to 80%. In one embodiment, a tumor derived from the cancer regresses by at least 30% to 80%. In one embodiment, a tumor derived from the cancer regresses by at least 40% to 80%. In one embodiment, a tumor derived from the cancer regresses by at least 50% to 80%. In one embodiment, a tumor derived from the cancer regresses by at least 60% to 80%. In one embodiment, a tumor derived from the cancer regresses by at least 70% to 80%. In one embodiment, a tumor derived from the cancer regresses by at least 80%. In one embodiment, a tumor derived from the cancer regresses by at least 85%. In one embodiment, a tumor derived from the cancer regresses by at least 90%. In one embodiment, a tumor derived from the cancer

regresses by at least 95%. In one embodiment, a tumor derived from the cancer regresses by at least 98%. In one embodiment, a tumor derived from the cancer regresses by at least 99%. In one embodiment, a tumor derived from the cancer regresses by 100%. In one embodiment, regression of a tumor is determined by measuring the size of the tumor by magnetic resonance imaging (MRI). In one embodiment, regression of a tumor is determined by measuring the size of the tumor by computed tomography (CT). In some embodiments, regression of a tumor is determined by measuring the size of the tumor by pelvic examination. *See* Choi *et al.*, 2008, *J. Gynecol. Oncol.* 19(3):205. In some embodiments, the tumor derived from the cancer regresses relative to the size of the tumor before administration of the anti-TF antibody drug conjugate described herein and the anti-VEGF antibody described herein. In some embodiments, the tumor derived from the cancer regresses relative to the size of the tumor before administration of the anti-TF antibody drug conjugate described herein. In some embodiments, the tumor derived from the cancer regresses relative to the size of the tumor before administration of the anti-VEGF antibody described herein.

[0183] In one embodiment of the methods or uses or product for uses described herein, response to treatment with an anti-TF antibody-drug conjugate or antigen-binding fragment thereof described herein and an anti-VEGF antibody or antigen-binding fragment thereof described herein is assessed by measuring the time of progression free survival after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, 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 anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits progression-free survival of at least about 6 months after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits progression-free survival of at least about one year after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject

exhibits progression-free survival of at least about two years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits progression-free survival of at least about three years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits progression-free survival of at least about four years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits progression-free survival of at least about five years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits progression-free survival of at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least eighteen months, at least two years, at least three years, at least four years, or at least five years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits progression-free survival of at least 6 months after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits progression-free survival of at least one year after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits progression-free survival of at least two years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits progression-free survival of at least three years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits progression-free survival of at least four years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits progression-free survival of at least five years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, response to treatment is assessed by measuring the time of progression free survival after administration of the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein. In

some embodiments, response to treatment is assessed by measuring the time of progression free survival after administration of the anti-TF antibody-drug conjugate described herein. In some embodiments, response to treatment is assessed by measuring the time of progression free survival after administration of the anti-VEGF antibody described herein.

[0184] In one embodiment of the methods or uses or product for uses described herein, response to treatment with an anti-TF antibody-drug conjugate or antigen-binding fragment thereof described herein and an anti-VEGF antibody or antigen-binding fragment thereof described herein is assessed by measuring the time of overall survival after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, 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 anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least about 6 months after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least about one year after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least about two years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least about three years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least about four years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least about five years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6

months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least about 12 months, at least eighteen months, at least two years, at least three years, at least four years, or at least five years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least 6 months after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least one year after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least two years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least three years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least four years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the subject exhibits overall survival of at least five years after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, response to treatment is assessed by measuring the time of overall survival after administration of the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein. In some embodiments, response to treatment is assessed by measuring the time of overall survival after administration of the anti-TF antibody-drug conjugate described herein. In some embodiments, response to treatment is assessed by measuring the time of overall survival after administration of the anti-VEGF antibody described herein.

[0185] In one embodiment of the methods or uses or product for uses described herein, response to treatment with an anti-TF antibody-drug conjugate or antigen-binding fragment thereof described herein and an anti-VEGF antibody or antigen-binding fragment thereof described herein is assessed by measuring the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein after administration of the anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate

described herein and the anti-VEGF antibody described herein 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 anti-TF antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least about 6 months after administration of the antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least about one year after administration of the antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least about two years after administration of the antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least about three years after administration of the antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least about four years after administration of the antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least about five years after administration of the antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least eighteen months, at least two years, at least three years, at least four years, or at least five years after administration of the anti-TF antibody-drug conjugate

described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least 6 months after administration of the antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least one year after administration of the antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least two years after administration of the antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least three years after administration of the antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least four years after administration of the antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response to the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein is at least five years after administration of the antibody-drug conjugate described herein and/or the anti-VEGF antibody described herein. In some embodiments, the duration of response is measured after administration of the anti-TF antibody drug conjugate described herein and the anti-VEGF antibody described herein. In some embodiments, the duration of response is measured after administration of the anti-TF antibody drug conjugate described herein. In some embodiments, the duration of response is measured after administration of the anti-VEGF antibody described herein.

E. Adverse Events

[0186] In one aspect, a method of treating cancer (*e.g.*, cervical cancer) with an anti-TF antibody-drug conjugates or antigen-binding fragments thereof described herein and an anti-VEGF antibody or antigen-binding fragment thereof described herein results in the subject developing one or more adverse events. In some embodiments, the subject is administered an additional therapeutic agent to eliminate or reduce the severity of the adverse event. In some embodiments, the one or more adverse events the subject develops 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, or any combination thereof. In some embodiments, the one or more adverse events is a grade 1 or greater adverse event. In some embodiments, the one or more adverse events is a grade 2 or greater adverse event. In some embodiments, the one or more adverse events is a grade 3 or greater adverse event. In some embodiments, the one or more adverse events is a grade 1 adverse event. In some embodiments, the one or more adverse events is a grade 2 adverse event. In some embodiments, the one or more adverse events is a grade 3 adverse event. In some embodiments, the one or more adverse events is a grade 4 adverse event. In some embodiments, the one or more adverse events is a serious adverse event. In some embodiments, the one or more adverse events is conjunctivitis, conjunctival ulceration, and/or keratitis and the additional therapeutic agent is a preservative-free lubricating eye drop, an ocular vasoconstrictor, antibiotic, a steroid eye drop, or any combination thereof. In some embodiments, the one or more adverse events is conjunctivitis, conjunctival ulceration, and keratitis and the additional therapeutic agent is a preservative-free lubricating eye drop, an ocular vasoconstrictor, antibiotic, a steroid eye drop, or any combination thereof. In some embodiments, the one or more adverse events is conjunctivitis and keratitis and the additional therapeutic agent is a preservative-free lubricating eye drop, an ocular vasoconstrictor, antibiotic, a steroid eye drop, or any combination thereof. In some embodiments, the one or more adverse events is conjunctivitis and the additional therapeutic agent is a preservative-free lubricating eye drop, an ocular vasoconstrictor, antibiotic, a steroid eye drop, or any combination thereof. In some embodiments, the one or more adverse events is keratitis and the additional therapeutic agent is a preservative-free lubricating eye drop, an ocular vasoconstrictor, antibiotic, a steroid eye drop, or any combination thereof. In some of any of the embodiments herein, the subject is administered a treatment with the additional therapeutic agent to eliminate or reduce the severity of the adverse event (*e.g.*, conjunctivitis, conjunctival ulceration, and/or keratitis). In some embodiments, the treatment is eye cooling pads (*e.g.* THERA PEARL Eye Mask or similar). In some embodiments, the one or more adverse events is a recurrent infusion related reaction and the additional therapeutic agent is an antihistamine, acetaminophen and/or a corticosteroid. In some embodiments, the one or more adverse events is neutropenia and the additional therapeutic agent is growth factor support (G-CSF). In some

embodiments, the one or more adverse events is hyperthyroidism and the additional agent is a non-selective beta-blockers (*e.g.*, propranolol) or thionamides. In some embodiments, the one or more adverse events is hypothyroidism and the additional agent is a thyroid replacement hormone (*e.g.*, levothyroxine or liothyroinine).

[0187] In one aspect, the subject treated with an anti-TF antibody-drug conjugates or antigen-binding fragments thereof described herein and an anti-VEGF antibody or antigen-binding fragment thereof described herein is at risk of developing one or more adverse events. In some embodiments, the subject is administered an additional therapeutic agent to prevent the development of the adverse event or to reduce the severity of the adverse event. In some embodiments, the one or more adverse events the subject is at risk of developing 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, or any combination thereof. In some embodiments, the one or more adverse events is a grade 1 or greater adverse event. In some embodiments, the one or more adverse events is a grade 2 or greater adverse event. In some embodiments, the one or more adverse events is a grade 3 or greater adverse event. In some embodiments, the one or more adverse events is a grade 1 adverse event. In some embodiments, the one or more adverse events is a grade 2 adverse event. In some embodiments, the one or more adverse events is a grade 3 adverse event. In some embodiments, the one or more adverse events is a grade 4 adverse event. In some embodiments, the one or more adverse events is a serious adverse event. In some embodiments, 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, a steroid eye drop, or any combination thereof. In some embodiments, the one or more adverse events is conjunctivitis and keratitis and the additional agent is a preservative-free lubricating eye drop, an ocular vasoconstrictor, antibiotic, a steroid eye drop, or any combination thereof. In some embodiments, the one or more adverse events is conjunctivitis and the additional agent is a preservative-free lubricating eye drop, an ocular vasoconstrictor, antibiotic, a steroid eye drop, or any combination thereof. In some embodiments, the one or more adverse events is keratitis and the additional agent is a preservative-free lubricating eye drop, an ocular vasoconstrictor, antibiotic, a steroid eye drop, or any combination thereof. In some of any of the embodiments

herein, the subject is administered a treatment with the additional therapeutic agent to prevent the development of the adverse event or to reduce the severity of the adverse event (*e.g.*, conjunctivitis, conjunctival ulceration, and/or keratitis). In some embodiments, the treatment is eye cooling pads (*e.g.* THERA PEARL Eye Mask or similar). In some embodiments, the one or more adverse events is a recurrent infusion related reaction and the additional agent is an antihistamine, acetaminophen and/or a corticosteroid. In some embodiments, the one or more adverse events is neutropenia and the additional agent is growth factor support (G-CSF). In some embodiments, the one or more adverse events is hyperthyroidism and the additional agent is a non-selective beta-blockers (*e.g.*, propranolol) or thionamides. In some embodiments, the one or more adverse events is hypothyroidism and the additional agent is a thyroid replacement hormone (*e.g.*, levothyroxine or liothyroinine).

V. COMPOSITIONS

[0188] In some aspects, also provided herein are compositions (*e.g.*, pharmaceutical compositions and therapeutic formulations) comprising any of the anti-TF antibody-drug conjugates or antigen-binding fragments thereof described herein and/or the anti-VEGF antibody or antigen-binding fragments thereof described herein.

[0189] Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (Remington: The Science and Practice of Pharmacy, 20th Ed., Lippincott Williams & Wiklins, Pub., Gennaro Ed., Philadelphia, Pa. 2000).

[0190] Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers, antioxidants including ascorbic acid, methionine, Vitamin E, sodium metabisulfite; preservatives, isotonicifiers, stabilizers, metal complexes (*e.g.* Zn-protein complexes); chelating agents such as EDTA and/or non-ionic surfactants.

[0191] Buffers can be used to control the pH in a range which optimizes the therapeutic effectiveness, especially if stability is pH dependent. Buffers can be present at concentrations ranging from about 50 mM to about 250 mM. Suitable buffering agents for use with the present invention include both organic and inorganic acids and salts thereof. For example, citrate,

phosphate, succinate, tartrate, fumarate, gluconate, oxalate, lactate, acetate. Additionally, buffers may be comprised of histidine and trimethylamine salts such as Tris.

[0192] Preservatives can be added to prevent microbial growth, and are typically present in a range from about 0.2%- 1.0% (w/v). Suitable preservatives for use with the present invention include octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium halides (*e.g.*, chloride, bromide, iodide), benzethonium chloride; thimerosal, phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol, 3-pentanol, and m-cresol.

[0193] Tonicity agents, sometimes known as "stabilizers" can be present to adjust or maintain the tonicity of liquid in a composition. When used with large, charged biomolecules such as proteins and antibodies, they are often termed "stabilizers" because they can interact with the charged groups of the amino acid side chains, thereby lessening the potential for inter and intramolecular interactions. Tonicity agents can be present in any amount between about 0.1% to about 25% by weight or between about 1% to about 5% by weight, taking into account the relative amounts of the other ingredients. In some embodiments, tonicity agents include polyhydric sugar alcohols, trihydric or higher sugar alcohols, such as glycerin, erythritol, arabitol, xylitol, sorbitol and mannitol.

[0194] Additional excipients include agents which can serve as one or more of the following: (1) bulking agents, (2) solubility enhancers, (3) stabilizers and (4) and agents preventing denaturation or adherence to the container wall. Such excipients include: polyhydric sugar alcohols (enumerated above); amino acids such as alanine, glycine, glutamine, asparagine, histidine, arginine, lysine, ornithine, leucine, 2-phenylalanine, glutamic acid, threonine, etc.; organic sugars or sugar alcohols such as sucrose, lactose, lactitol, trehalose, stachyose, mannose, sorbose, xylose, ribose, ribitol, myoinisitose, myoinisitol, galactose, galactitol, glycerol, cyclitols (*e.g.*, inositol), polyethylene glycol; sulfur containing reducing agents, such as urea, glutathione, thioctic acid, sodium thioglycolate, thioglycerol, a-monothioglycerol and sodium thio sulfate; low molecular weight proteins such as human serum albumin, bovine serum albumin, gelatin or other immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; monosaccharides (*e.g.*, xylose, mannose, fructose, glucose; disaccharides (*e.g.*, lactose, maltose, sucrose); trisaccharides such as raffinose; and polysaccharides such as dextrin or dextran.

[0195] Non-ionic surfactants or detergents (also known as "wetting agents") can be present to help solubilize the therapeutic agent as well as to protect the therapeutic protein against agitation-induced aggregation, which also permits the formulation to be exposed to shear surface stress without causing denaturation of the active therapeutic protein or antibody. Non-ionic surfactants are present in a range of about 0.05 mg/ml to about 1.0 mg/ml or about 0.07 mg/ml to about 0.2 mg/ml. In some embodiments, non-ionic surfactants are present in a range of about 0.001% to about 0.1% w/v or about 0.01% to about 0.1% w/v or about 0.01% to about 0.025% w/v.

[0196] Suitable non-ionic surfactants include polysorbates (20, 40, 60, 65, 80, etc.), polyoxamers (184, 188, etc.), PLURONIC® polyols, TRITON®, polyoxyethylene sorbitan monoethers (TWEEN®-20, TWEEN®-80, etc.), lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, sucrose fatty acid ester, methyl celluose and carboxymethyl cellulose. Anionic detergents that can be used include sodium lauryl sulfate, dioctyle sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents include benzalkonium chloride or benzethonium chloride.

[0197] Formulations comprising an anti-TF antibody-conjugate described herein for use in methods of treatment provided herein are described in WO2015/075201. In some embodiments, an anti-TF antibody-drug conjugate described herein is in a formulation comprising the anti-TF antibody drug conjugate, histidine, sucrose, and D-mannitol, wherein the formulation has a pH of about 6.0. In some embodiments, an anti-TF antibody-drug conjugate described herein is in a formulation comprising the anti-TF antibody drug conjugate at a concentration of about 10 mg/ml, histidine at a concentration of about 30 mM, sucrose at a concentration of about 88 mM, D-mannitol at a concentration of about 165 mM, wherein the formulation has a pH of about 6.0. In some embodiments, an anti-TF antibody-drug conjugate described herein is in a formulation comprising the anti-TF antibody drug conjugate at a concentration of 10 mg/ml, histidine at a concentration of 30 mM, sucrose at a concentration of 88 mM, D-mannitol at a concentration of 165 mM, wherein the formulation has a pH of 6.0. In some embodiments, the formulation comprises tisotumab vedotin at a concentration of 10 mg/ml, histidine at a concentration of 30 mM, sucrose at a concentration of 88 mM, D-mannitol at a concentration of 165 mM, wherein the formulation has a pH of 6.0.

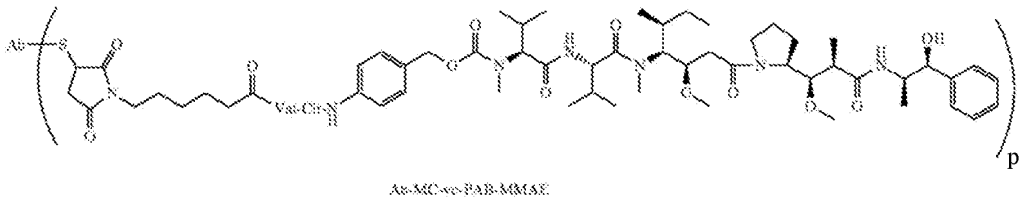
[0198] In some embodiments provided herein, a formulation comprising the anti-TF antibody-conjugate described herein does not comprise a surfactant (*i.e.*, is free of surfactant).

[0199] In order for the formulations to be used for in vivo administration, they must be sterile. The formulation may be rendered sterile by filtration through sterile filtration membranes. The therapeutic compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0200] The route of administration is in accordance with known and accepted methods, such as by single or multiple bolus or infusion over a long period of time in a suitable manner, *e.g.*, injection or infusion by subcutaneous, intravenous, intraperitoneal, intramuscular, intraarterial, intralesional or intraarticular routes, topical administration, inhalation or by sustained release or extended-release means.

[0201] The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise a cytotoxic agent, cytokine or growth inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[0202] The invention provides compositions comprising a population of anti-TF antibody-drug conjugates or antigen-binding fragments thereof as described herein for use in a method of treating cervical cancer as described herein. In some aspects, provided herein are compositions comprising a population of antibody-drug conjugates, wherein the antibody-drug conjugates comprise a linker attached to MMAE, wherein the antibody-drug conjugate has the following structure:



Ab-MC-vc-PAB-MMAE

[0203] wherein p denotes a number from 1 to 8, *e.g.*, 1, 2, 3, 4, 5, 6, 7 or 8, S represents a sulphydryl residue of the anti-TF antibody or antigen-binding fragment thereof, and Ab designates the anti-TF antibody or antigen-binding fragment thereof as described herein, such as tisotumab. In some embodiments, p denotes a number from 3 to 5. In some embodiments, the average value of p in the composition is about 4. In some embodiments, the population is a mixed population of antibody-drug conjugates in which p varies from 1 to 8 for each antibody-drug conjugate. In some embodiments, the population is a homogenous population of antibody-drug conjugates with each antibody-drug conjugate having the same value for p.

[0204] In some embodiments, a composition comprising an anti-TF antibody-drug conjugate or antigen-binding fragment thereof as described herein is coadministered with a composition comprising an anti-VEGF antibody or antigen-binding fragment thereof as described herein. In some embodiments the coadministration is simultaneous or sequential. In some embodiments, the anti-TF antibody-drug conjugate as described herein is administered simultaneously with the anti-VEGF antibody as described herein. In some embodiments, simultaneous means that the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein are administered to the subject less than about one hour apart, such as less than about 30 minutes apart, less than about 15 minutes apart, less than about 10 minutes apart or less than about 5 minutes apart. In some embodiments, simultaneous means that the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein are administered to the subject less than one hour apart, such as less than 30 minutes apart, less than 15 minutes apart, less than 10 minutes apart or less than 5 minutes apart. In some embodiments, the anti-TF antibody-drug conjugate described herein is administered sequentially with the anti-VEGF antibody described herein. In some embodiments, sequential administration means that the anti-TF antibody-drug conjugate described herein and the anti-VEGF antibody described herein are administered a least 1 hour apart, at least 2 hours apart, at least 3 hours apart, , at least 4 hours apart, at least 5 hours apart, at least 6 hours apart, at least 7 hours apart, at least 8 hours apart, at least 9 hours apart, at least 10 hours apart, at least 11 hours apart, at least 12 hours apart, at least 13 hours apart, at least 14 hours apart, at least 15 hours apart, at least 16 hours apart, at least 17 hours apart, at least 18 hours apart, at least 19 hours apart, at least 20 hours apart, at least 21 hours apart, at least 22 hours apart, at least 23 hours apart, at least 24 hours apart, at least 2 days apart, at least 3 days apart, at least 4 days apart, at least 5 days apart, at least 5 days apart, at least

7 days apart, at least 2 weeks apart, at least 3 weeks apart or at least 4 weeks apart. In some embodiments, the anti-TF antibody-drug conjugate described herein is administered after the administration of the anti-VEGF antibody described herein. In some embodiments, the anti-TF antibody-drug conjugate described herein is administered at least 30 minutes after the administration of the anti-VEGF antibody described herein. In some embodiments, the anti-TF antibody-drug conjugate described herein is administered 30 minutes after the administration of the anti-VEGF antibody described herein. In some embodiments, the anti-TF antibody-drug conjugate described herein is administered about 30 minutes to about 3 hours after the administration of the anti-VEGF antibody described herein. In some embodiments, the anti-TF antibody-drug conjugate described herein is administered about 30 minutes to about 2 hours after the administration of the anti-VEGF antibody described herein. In some embodiments, the anti-TF antibody-drug conjugate described herein is administered about 30 minutes to about 60 minutes after the administration of the anti-VEGF antibody described herein. In some embodiments, the anti-TF antibody-drug conjugate described herein is administered 30 minutes to 3 hours after the administration of the anti-VEGF antibody described herein. In some embodiments, the anti-TF antibody-drug conjugate described herein is administered 30 minutes to 2 hours after the administration of the anti-VEGF antibody described herein. In some embodiments, the anti-TF antibody-drug conjugate described herein is administered 30 minutes to 60 minutes after the administration of the anti-VEGF antibody described herein. In some embodiments, a composition comprising an ant-TF antibody-drug conjugate as described herein and/or an anti-VEGF antibody as described herein is coadministered with one or more therapeutic agents to eliminate or reduce the severity of one or more adverse events. In some embodiments, a composition comprising an anti-TF antibody-drug conjugate as described herein and/or an anti-VEGF antibody as described herein is coadministered with one or more therapeutic agents to prevent the development of the adverse event or to reduce the severity of the adverse event.

[0205] In some embodiments, a composition comprising an anti-TF antibody-drug conjugate as described herein and/or anti-VEGF antibody as described herein is coadministered with one or additional therapeutic agents. In some embodiments the coadministration is simultaneous or sequential. In some embodiments, the anti-TF antibody-drug conjugate as described herein and/or anti-VEGF antibody as described herein is administered simultaneously with the one or

more additional therapeutic agents. In some embodiments, simultaneous means that the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein and the one or more therapeutic agents are administered to the subject less than about one hour apart, such as less than about 30 minutes apart, less than about 15 minutes apart, less than about 10 minutes apart or less than about 5 minutes apart. In some embodiments, simultaneous means that the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein and the one or more therapeutic agents are administered to the subject less than one hour apart, such as less than 30 minutes apart, less than 15 minutes apart, less than 10 minutes apart or less than 5 minutes apart. In some embodiments, the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein is administered sequentially with the one or more additional therapeutic agents. In some embodiments, sequential administration means that the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein and the one or more additional therapeutic agents are administered a least 1 hour apart, at least 2 hours apart, at least 3 hours apart, , at least 4 hours apart, at least 5 hours apart, at least 6 hours apart, at least 7 hours apart, at least 8 hours apart, at least 9 hours apart, at least 10 hours apart, at least 11 hours apart, at least 12 hours apart, at least 13 hours apart, at least 14 hours apart, at least 15 hours apart, at least 16 hours apart, at least 17 hours apart, at least 18 hours apart, at least 19 hours apart, at least 20 hours apart, at least 21 hours apart, at least 22 hours apart, at least 23 hours apart, at least 24 hours apart, at least 2 days apart, at least 3 days apart, at least 4 days apart, at least 5 days apart, at least 5 days apart, at least 7 days apart, at least 2 weeks apart, at least 3 weeks apart or at least 4 weeks apart.

[0206] In some embodiments, a composition comprising an anti-TF antibody-drug conjugate as described herein and/or anti-VEGF antibody as described herein is coadministered with one or more therapeutic agents to eliminate or reduce the severity of one or more adverse events. In some embodiments the coadministration is simultaneous or sequential. In some embodiments, the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein is administered simultaneously with the one or more therapeutic agents to eliminate or reduce the severity of one or more adverse events. In some embodiments, simultaneous means that the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein and the one or more therapeutic agents to eliminate or reduce the severity of one or more adverse events are administered to the subject less than about one hour apart, such as less than

about 30 minutes apart, less than about 15 minutes apart, less than about 10 minutes apart or less than about 5 minutes apart. In some embodiments, simultaneous means that the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein and the one or more therapeutic agents to eliminate or reduce the severity of one or more adverse events are administered to the subject less than one hour apart, such as less than 30 minutes apart, less than 15 minutes apart, less than 10 minutes apart or less than 5 minutes apart. In some embodiments, the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein is administered sequentially with the one or more therapeutic agents to eliminate or reduce the severity of one or more adverse events. In some embodiments, sequential administration means that the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein and the one or more additional therapeutic agents are administered a least 1 hour apart, at least 2 hours apart, at least 3 hours apart, , at least 4 hours apart, at least 5 hours apart, at least 6 hours apart, at least 7 hours apart, at least 8 hours apart, at least 9 hours apart, at least 10 hours apart, at least 11 hours apart, at least 12 hours apart, at least 13 hours apart, at least 14 hours apart, at least 15 hours apart, at least 16 hours apart, at least 17 hours apart, at least 18 hours apart, at least 19 hours apart, at least 20 hours apart, at least 21 hours apart, at least 22 hours apart, at least 23 hours apart, at least 24 hours apart, at least 2 days apart, at least 3 days apart, at least 4 days apart, at least 5 days apart, at least 5 days apart, at least 7 days apart, at least 2 weeks apart, at least 3 weeks apart or at least 4 weeks apart. In some embodiments, the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein is administered prior to the one or more therapeutic agents to eliminate or reduce the severity of one or more adverse events. In some embodiments, the one or more therapeutic agents to eliminate or reduce the severity of one or more adverse events is administered prior to the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein.

VI. ARTICLES OF MANUFACTURE AND KITS

[0207] In another aspect, an article of manufacture or kit is provided which comprises an anti-TF antibody-drug conjugate described herein and/or an anti-VEGF antibody described herein. The article of manufacture or kit may further comprise instructions for use of the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein in the methods of the invention. Thus, in certain embodiments, the article of manufacture or kit

comprises instructions for the use of an anti-TF antibody-drug conjugate described herein and/or an anti-VEGF antibody described herein in methods for treating cancer (*e.g.*, cervical cancer) in a subject comprising administering to the subject an effective amount of an anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein. In some embodiments, the cancer is cervical cancer. In some embodiments, the cervical cancer is advanced stage cervical cancer. In some embodiments, the advanced stage cervical cancer is metastatic cervical cancer. In some embodiments, the advanced stage cervical cancer is a stage 3 or stage 4 cervical cancer. In some embodiments, the cervical cancer is metastatic cancer and recurrent cancer. In some embodiments the cervical cancer is recurrent cancer. In some embodiments, the subject is not a candidate for curative therapy. In some embodiments, the subject is a human.

[0208] The article of manufacture or kit may further comprise a container. Suitable containers include, for example, bottles, vials (*e.g.*, dual chamber vials), syringes (such as single or dual chamber syringes) and test tubes. In some embodiments, the container is a vial. The container may be formed from a variety of materials such as glass or plastic. The container holds the formulation.

[0209] The article of manufacture or kit may further comprise a label or a package insert, which is on or associated with the container, may indicate directions for reconstitution and/or use of the formulation. The label or package insert may further indicate that the formulation is useful or intended for subcutaneous, intravenous (*e.g.*, intravenous infusion), or other modes of administration for treating cancer in a subject such as cervical cancer described herein (*e.g.*, advanced cervical cancer such as grade 3 or grade 4 or metastatic cervical cancer). The container holding the formulation may be a single-use vial or a multi-use vial, which allows for repeat administrations of the reconstituted formulation. The article of manufacture or kit may further comprise a second container comprising a suitable diluent. The article of manufacture or kit may further include other materials desirable from a commercial, therapeutic, and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

[0210] The article of manufacture or kit herein optionally further comprises a container comprising a second medicament, wherein the anti-TF antibody-drug conjugate is a first

medicament, and which article or kit further comprises instructions on the label or package insert for treating the subject with the second medicament, in an effective amount. In some embodiments, the second medicament is an anti-VEGF antibody as described herein. In some embodiments, the label or package insert indicates that the first and second medicaments are to be administered sequentially or simultaneously, as described herein.

[0211] The article of manufacture or kit herein optionally further comprises a container comprising a third medicament, wherein the third medicament is for eliminating or reducing the severity of one or more adverse events, wherein the anti-TF antibody-drug conjugate described herein is a first medicament, the anti-VEGF antibody described herein is a second medicament, and which article or kit further comprises instructions on the label or package insert for treating the subject with the third medicament, in an effective amount. In some embodiments, the label or package insert indicates that the first, second and third medicaments are to be administered sequentially or simultaneously, as described herein, for example wherein the label or package insert indicates that the anti-TF antibody-drug conjugate described herein is to be administered first, followed by administration of the anti-VEGF antibody described herein, followed by administration of the third medicament.

[0212] In some embodiments, the anti-TF antibody-drug conjugate described herein and/or anti-VEGF antibody described herein is present in the container as a lyophilized powder. In some embodiments, the lyophilized powder is in a hermetically sealed container, such as a vial, an ampoule or sachette, indicating the quantity of the active agent. Where the pharmaceutical is administered by injection, an ampoule of sterile water for injection or saline can be, for example, provided, optionally as part of the kit, so that the ingredients can be mixed prior to administration. Such kits can further include, if desired, one or more of various conventional pharmaceutical components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Printed instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components can also be included in the kit.

VII. EXEMPLARY EMBODIMENTS

[0213] Among the embodiments provided herein are:

1. 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.
2. The method of embodiment 1, wherein the antibody-drug conjugate is administered at a dose ranging from about 0.65 mg/kg to about 2.1 mg/kg.
3. The method of embodiment 2, wherein the antibody-drug conjugate is administered at a dose of about 0.65 mg/kg.
4. The method of embodiment 2, wherein the antibody-drug conjugate is administered at a dose of 0.65 mg/kg.
5. The method of embodiment 2, wherein the antibody-drug conjugate is administered at a dose of about 0.9 mg/kg.
6. The method of embodiment 2, wherein the antibody-drug conjugate is administered at a dose of 0.9 mg/kg.
7. The method of embodiment 2, wherein the antibody-drug conjugate is administered at a dose of about 1.3 mg/kg.
8. The method of embodiment 2, wherein the antibody-drug conjugate is administered at a dose of 1.3 mg/kg.
9. The method of embodiment 2, wherein the antibody-drug conjugate is administered at a dose of about 2.0 mg/kg.
10. The method of embodiment 2, wherein the antibody-drug conjugate is administered at a dose of 2.0 mg/kg.
11. The method of any one of embodiments 1-10, wherein the antibody-drug conjugate is administered once about every 3 weeks.
12. The method of any one of embodiments 1-10, wherein the antibody-drug conjugate is administered once every 3 weeks.
13. The method of any one of embodiments 1-12, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose ranging from about 5 mg/kg to about 20 mg/kg.

14. The method of any one of embodiments 1-13, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 7.5 mg/kg.
15. The method of any one of embodiments 1-13, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 7.5 mg/kg.
16. The method of any one of embodiments 1-13, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 15 mg/kg.
17. The method of any one of embodiments 1-13, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 15 mg/kg.
18. The method of any one of embodiments 1-17, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered once about every 3 weeks.
19. The method of any one of embodiments 1-17, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered once every 3 weeks.
20. The method of any one of embodiments 1-19, wherein the antibody-drug conjugate is administered at least 30 minutes after the administration of the anti-VEGF antibody or antigen-binding fragment thereof.
21. The method of any one of embodiments 1-20, 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.
22. The method of any one of embodiments 1-20, 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.
23. The method of any one of embodiments 1-20, 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.
24. The method of any one of embodiments 21-23, 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.

25. The method of any one of embodiments 1-24, wherein the subject is not a candidate for curative therapy.

26. The method of embodiment 25, wherein curative therapy comprises radiotherapy and/or exenterative surgery.

27. The method of any one of embodiments 1-26, wherein the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma.

28. The method of any one of embodiments 1-27, wherein the cervical cancer is an advanced stage cervical cancer.

29. The method of embodiment 28, wherein the advanced stage cervical cancer is a stage 3 or stage 4 cervical cancer.

30. The method of embodiment 28 or embodiment 29, wherein the advanced stage cervical cancer is metastatic cervical cancer.

31. The method of any one of embodiments 1-30, wherein the cervical cancer is recurrent cervical cancer.

32. The method of any one of embodiments 1-31, 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.

33. The method of any one of embodiments 1-32, 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.

34. The method of any one of embodiments 1-33, 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.

35. The method of any one of embodiments 1-34, 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.

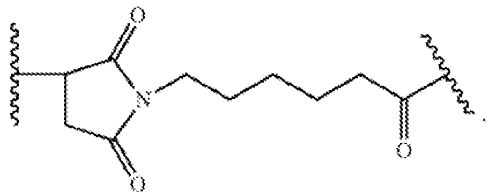
36. The method of any one of embodiments 1-35, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

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

38. The method of embodiment 37, wherein the linker is a cleavable peptide linker.

39. The method of embodiment 38, wherein the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

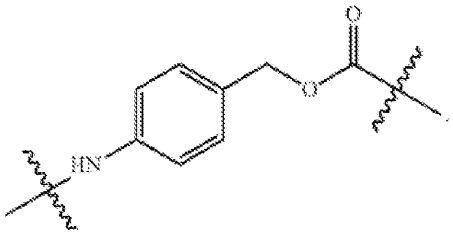
a) MC is:



,

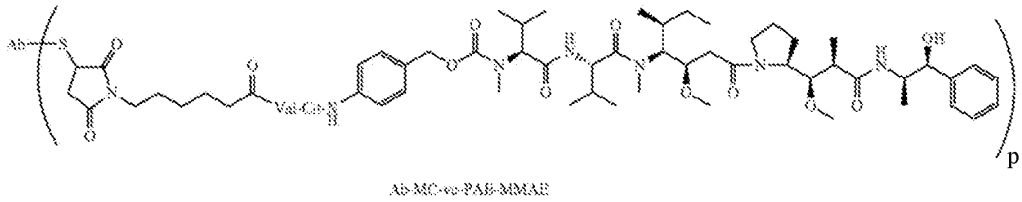
b) vc is the dipeptide valine-citrulline, and

c) PAB is:



40. The method of any one of embodiments 37-39, 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.

41. The method of embodiment 40, 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.

42. The method of embodiment 41, wherein the average value of p in a population of the antibody-drug conjugates is about 4.

43. The method of any one of embodiments 1-42, wherein the antibody-drug conjugate is tisotumab vedotin.

44. The method of any one of embodiments 1-43, wherein the route of administration for the antibody-drug conjugate is intravenous.

45. The method of any one of embodiments 1-44, 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.

46. The method of any one of embodiments 1-45, 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.

47. The method of any one of embodiments 1-46, 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.

48. The method of any one of embodiments 1-47, 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.

49. The method of any one of embodiments 1-48, wherein the anti-VEGF antibody is bevacizumab.

50. The method of any one of embodiments 1-48, wherein the anti-VEGF antibody is a biosimilar of bevacizumab.

51. The method of embodiment 50, 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.

52. The method of embodiment 50, wherein the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel.

53. The method of any one of embodiments 1-52, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous or subcutaneous.
54. The method of embodiment 53, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous.
55. The method of any one of embodiments 1-54, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered sequentially.
56. The method of any one of embodiments 1-54, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered simultaneously.
57. The method of any one of embodiments 1-56, 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.
58. The method of any one of embodiments 1-57, 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.
59. The method of embodiment 58, 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.
60. The method of any one of embodiments 1-59, 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.
61. The method of any one of embodiments 1-60, 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%.

62. The method of any one of embodiments 1-61, 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.

63. The method of any one of embodiments 1-62, 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.

64. The method of any one of embodiments 1-63, 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.

65. The method of any one of embodiments 1-64, 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.

66. The method of any one of embodiments 1-65, 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.

67. The method of embodiment 65 or embodiment 66, 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.

68. The method of any one of embodiments 65-67, wherein the one or more adverse events is a grade 3 or greater adverse event.

69. The method of any one of embodiments 65-67, wherein the one or more adverse events is a serious adverse event.

70. The method of embodiment 65 or embodiment 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.

71. The method of any one of embodiments 1-70, wherein the subject is a human.

72. The method of any one of embodiments 1-71, wherein the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier.

73. The method of any one of embodiments 1-72, 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.

74. 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 a monomethyl 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 method of any one of embodiments 1-73.

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

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

77. An antibody-drug conjugate that binds to tissue factor (TF) for use in the treatment of cervical cancer in a subject, wherein the antibody-drug conjugate is for administration, or to be administered in combination with an anti-VEGF antibody or antigen-binding fragment thereof, 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.

78. The antibody-drug conjugate for use of embodiment 77, wherein the antibody-drug conjugate is administered at a dose ranging from about 0.65 mg/kg to about 2.1 mg/kg.

79. The antibody-drug conjugate for use of embodiment 78, wherein the antibody-drug conjugate is administered at a dose of about 0.65 mg/kg.

80. The antibody-drug conjugate for use of embodiment 78, wherein the antibody-drug conjugate is administered at a dose of 0.65 mg/kg.

81. The antibody-drug conjugate for use of embodiment 78, wherein the antibody-drug conjugate is administered at a dose of about 0.9 mg/kg.

82. The antibody-drug conjugate for use of embodiment 78, wherein the antibody-drug conjugate is administered at a dose of 0.9 mg/kg.

83. The antibody-drug conjugate for use of embodiment 78, wherein the antibody-drug conjugate is administered at a dose of about 1.3 mg/kg.

84. The antibody-drug conjugate for use of embodiment 78, wherein the antibody-drug conjugate is administered at a dose of 1.3 mg/kg.

85. The antibody-drug conjugate for use of embodiment 78, wherein the antibody-drug conjugate is administered at a dose of about 2.0 mg/kg.

86. The antibody-drug conjugate for use of embodiment 78, wherein the antibody-drug conjugate is administered at a dose of 2.0 mg/kg.

87. The antibody-drug conjugate for use of any one of embodiments 77-86, wherein the antibody-drug conjugate is administered once about every 3 weeks.

88. The antibody-drug conjugate for use of any one of embodiments 77-86, wherein the antibody-drug conjugate is administered once every 3 weeks.

89. The antibody-drug conjugate for use of any one of embodiments 77-88, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose ranging from about 5 mg/kg to about 20 mg/kg.

90. The antibody-drug conjugate for use of any one of embodiments 77-89, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 7.5 mg/kg.

91. The antibody-drug conjugate for use of any one of embodiments 77-89, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 7.5 mg/kg.

92. The antibody-drug conjugate for use of any one of embodiments 77-89, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 15 mg/kg.

93. The antibody-drug conjugate for use of any one of embodiments 77-89, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 15 mg/kg.

94. The antibody-drug conjugate for use of any one of embodiments 77-93, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered once about every 3 weeks.

95. The antibody-drug conjugate for use of any one of embodiments 77-93, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered once every 3 weeks.

96. The antibody-drug conjugate for use of any one of embodiments 77-95, wherein the antibody-drug conjugate is administered at least 30 minutes after the administration of the anti-VEGF antibody or antigen-binding fragment thereof.

97. The antibody-drug conjugate for use of any one of embodiments 77-96, 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.

98. The antibody-drug conjugate for use of any one of embodiments 77-96, 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.

99. The antibody-drug conjugate for use of any one of embodiments 77-96, 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.

100. The antibody-drug conjugate for use of any one of embodiments 97-99, 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.

101. The antibody-drug conjugate for use of any one of embodiments 77-100, wherein the subject is not a candidate for curative therapy.

102. The antibody-drug conjugate for use of embodiment 101, wherein curative therapy comprises radiotherapy and/or exenterative surgery.

103. The antibody-drug conjugate for use of any one of embodiments 77-102, wherein the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma.

104. The antibody-drug conjugate for use of any one of embodiments 77-103, wherein the cervical cancer is an advanced stage cervical cancer.

105. The antibody-drug conjugate for use of embodiment 104, wherein the advanced stage cervical cancer is a stage 3 or stage 4 cervical cancer.

106. The antibody-drug conjugate for use of embodiment 104 or embodiment 105, wherein the advanced stage cervical cancer is metastatic cervical cancer.

107. The antibody-drug conjugate for use of any one of embodiments 77-106, wherein the cervical cancer is recurrent cervical cancer.

108. The antibody-drug conjugate for use of any one of embodiments 77-107, 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.

109. The antibody-drug conjugate for use of any one of embodiments 77-108, 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.

110. The antibody-drug conjugate for use of any one of embodiments 77-109, 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.

111. The antibody-drug conjugate for use of any one of embodiments 77-110, 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.

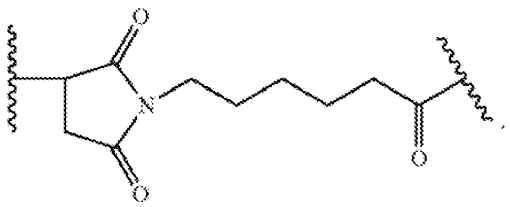
112. The antibody-drug conjugate for use of any one of embodiments 77-111, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

113. The antibody-drug conjugate for use of any one of embodiments 77-112, wherein the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the monomethyl auristatin.

114. The antibody-drug conjugate for use of embodiment 113, wherein the linker is a cleavable peptide linker.

115. The antibody-drug conjugate for use of embodiment 114, wherein the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

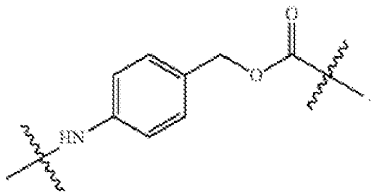
a) MC is:



,

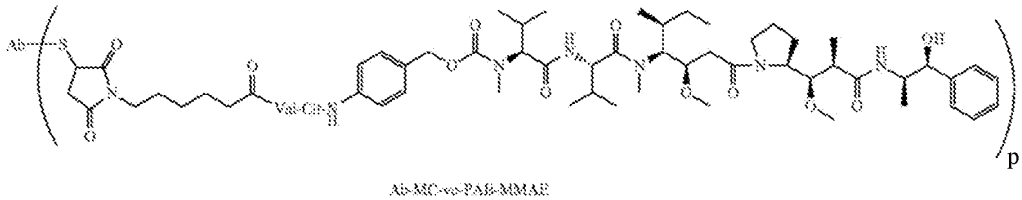
b) vc is the dipeptide valine-citrulline, and

c) PAB is:



116. The antibody-drug conjugate for use of any one of embodiments 113-115, 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.

117. The antibody-drug conjugate for use of embodiment 116, 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.

118. The antibody-drug conjugate for use of embodiment 117, wherein the average value of p in a population of the antibody-drug conjugates is about 4.

119. The antibody-drug conjugate for use of any one of embodiments 77-118, wherein the antibody-drug conjugate is tisotumab vedotin.

120. The antibody-drug conjugate for use of any one of embodiments 77-119, wherein the route of administration for the antibody-drug conjugate is intravenous.

121. The antibody-drug conjugate for use of any one of embodiments 77-120, 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.

122. The antibody-drug conjugate for use of any one of embodiments 77-121, 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.

123. The antibody-drug conjugate for use of any one of embodiments 77-122, 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.

124. The antibody-drug conjugate for use of any one of embodiments 77-123, 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.

125. The antibody-drug conjugate for use of any one of embodiments 77-124, wherein the anti-VEGF antibody is bevacizumab.

126. The antibody-drug conjugate for use of any one of embodiments 77-124, wherein the anti-VEGF antibody is a biosimilar of bevacizumab.

127. The antibody-drug conjugate for use of embodiment 126, 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.

128. The antibody-drug conjugate for use of embodiment 126, wherein the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel.

129. The antibody-drug conjugate for use of any one of embodiments 77-128, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous or subcutaneous.

130. The antibody-drug conjugate for use of embodiment 129, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous.

131. The antibody-drug conjugate for use of any one of embodiments 77-130, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered sequentially.

132. The antibody-drug conjugate for use of any one of embodiments 77-130, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered simultaneously.

133. The antibody-drug conjugate for use of any one of embodiments 77-132, 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.

134. The antibody-drug conjugate for use of any one of embodiments 77-133, 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.

135. The antibody-drug conjugate for use of embodiment 134, 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.

136. The antibody-drug conjugate for use of any one of embodiments 77-135, 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.

137. The antibody-drug conjugate for use of any one of embodiments 77-136, 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%.

138. The antibody-drug conjugate for use of any one of embodiments 77-137, 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.

139. The antibody-drug conjugate for use of any one of embodiments 77-138, 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.

140. The antibody-drug conjugate for use of any one of embodiments 77-139, 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.

141. The antibody-drug conjugate for use of any one of embodiments 77-140, 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.

142. The antibody-drug conjugate for use of any one of embodiments 77-141, 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.
143. The antibody-drug conjugate for use of embodiment 141 or embodiment 142, 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.
144. The antibody-drug conjugate for use of any one of embodiments 141-143, wherein the one or more adverse events is a grade 3 or greater adverse event.
145. The antibody-drug conjugate for use of any one of embodiments 141-143, wherein the one or more adverse events is a serious adverse event.
146. The antibody-drug conjugate for use of embodiment 141 or embodiment 142, 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.
147. The antibody-drug conjugate for use of any one of embodiments 77-146, wherein the subject is a human.
148. The antibody-drug conjugate for use of any one of embodiments 77-147, wherein the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier.
149. The antibody-drug conjugate for use of any one of embodiments 77-148, 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.
150. Use of an antibody-drug conjugate that binds to tissue factor (TF) for the manufacture of a medicament for treating cervical cancer in a subject, wherein the medicament is for use in combination with an anti-VEGF antibody or antigen-binding fragment thereof, 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.

151. The use of embodiment 150, wherein the antibody-drug conjugate is administered at a dose ranging from about 0.65 mg/kg to about 2.1 mg/kg.

152. The use of embodiment 151, wherein the antibody-drug conjugate is administered at a dose of about 0.65 mg/kg.

153. The use of embodiment 151, wherein the antibody-drug conjugate is administered at a dose of 0.65 mg/kg.

154. The use of embodiment 151, wherein the antibody-drug conjugate is administered at a dose of about 0.9 mg/kg.

155. The use of embodiment 151, wherein the antibody-drug conjugate is administered at a dose of 0.9 mg/kg.

156. The use of embodiment 151, wherein the antibody-drug conjugate is administered at a dose of about 1.3 mg/kg.

157. The use of embodiment 151, wherein the antibody-drug conjugate is administered at a dose of 1.3 mg/kg.

158. The use of embodiment 151, wherein the antibody-drug conjugate is administered at a dose of about 2.0 mg/kg.

159. The use of embodiment 151, wherein the antibody-drug conjugate is administered at a dose of 2.0 mg/kg.

160. The use of any one of embodiments 150-159, wherein the antibody-drug conjugate is administered once about every 3 weeks.

161. The use of any one of embodiments 150-159, wherein the antibody-drug conjugate is administered once every 3 weeks.

162. The use of any one of embodiments 150-161, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose ranging from about 5 mg/kg to about 20 mg/kg.

163. The use of any one of embodiments 150-162, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 7.5 mg/kg.

164. The use of any one of embodiments 150-162, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 7.5 mg/kg.

165. The use of any one of embodiments 150-162, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 15 mg/kg.

166. The use of any one of embodiments 150-162, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 15 mg/kg.

167. The use of any one of embodiments 150-166, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered once about every 3 weeks.

168. The use of any one of embodiments 150-166, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered once every 3 weeks.

169. The use of any one of embodiments 150-168, wherein the antibody-drug conjugate is administered at least 30 minutes after the administration of the anti-VEGF antibody or antigen-binding fragment thereof.

170. The use of any one of embodiments 150-169, 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.

171. The use of any one of embodiments 150-169, 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.

172. The use of any one of embodiments 150-169, 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.

173. The use of any one of embodiments 170-172, 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.

174. The use of any one of embodiments 150-173, wherein the subject is not a candidate for curative therapy.

175. The use of embodiment 174, wherein curative therapy comprises radiotherapy and/or exenterative surgery.

176. The use of any one of embodiments 150-175, wherein the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma.

177. The use of any one of embodiments 150-176, wherein the cervical cancer is an advanced stage cervical cancer.

178. The use of embodiment 177, wherein the advanced stage cervical cancer is a stage 3 or stage 4 cervical cancer.

179. The use of embodiment 177 or embodiment 178, wherein the advanced stage cervical cancer is metastatic cervical cancer.

180. The use of any one of embodiments 150-179, wherein the cervical cancer is recurrent cervical cancer.

181. The use of any one of embodiments 150-180, 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.

182. The use of any one of embodiments 150-181, 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.

183. The use of any one of embodiments 150-182, 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.

184. The use of any one of embodiments 150-183, 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.

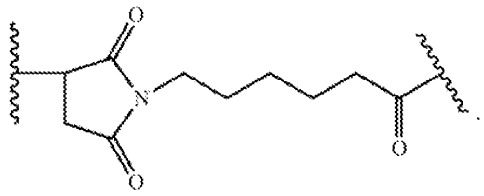
185. The use of any one of embodiments 150-184, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

186. The use of any one of embodiments 150-185, wherein the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the monomethyl auristatin.

187. The use of embodiment 186, wherein the linker is a cleavable peptide linker.

188. The use of embodiment 187, wherein the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

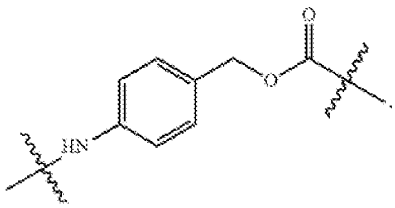
a) MC is:



,

b) vc is the dipeptide valine-citrulline, and

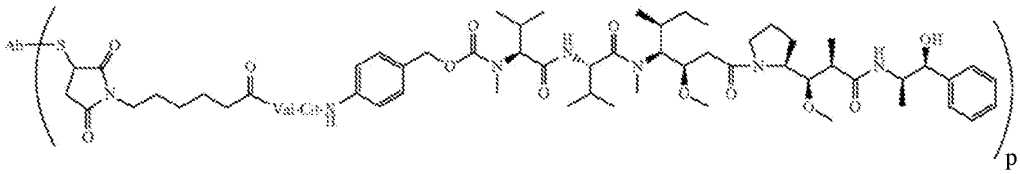
c) PAB is:



.

189. The use of any one of embodiments 186-188, 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.

190. The use of embodiment 189, 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.

191. The use of embodiment 190, wherein the average value of p in a population of the antibody-drug conjugates is about 4.

192. The use of any one of embodiments 150-191, wherein the antibody-drug conjugate is tisotumab vedotin.

193. The use of any one of embodiments 150-192, wherein the route of administration for the antibody-drug conjugate is intravenous.

194. The use of any one of embodiments 150-193, 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.

195. The use of any one of embodiments 150-194, 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.

196. The use of any one of embodiments 150-195, 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.

197. The use of any one of embodiments 150-196, 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.

198. The use of any one of embodiments 150-197, wherein the anti-VEGF antibody is bevacizumab.

199. The use of any one of embodiments 150-197, wherein the anti-VEGF antibody is a biosimilar of bevacizumab.

200. The use of embodiment 199, 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.

201. The use of embodiment 199, wherein the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel.

202. The use of any one of embodiments 150-201, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous or subcutaneous.

203. The use of embodiment 202, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous.

204. The use of any one of embodiments 150-203, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered sequentially.

205. The use of any one of embodiments 150-203, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered simultaneously.

206. The use of any one of embodiments 150-205, 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.

207. The use of any one of embodiments 150-206, 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.

208. The use of embodiment 207, 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.

209. The use of any one of embodiments 150-208, 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.

210. The use of any one of embodiments 150-209, 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%.

211. The use of any one of embodiments 150-210, 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.

212. The use of any one of embodiments 150-211, 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.

213. The use of any one of embodiments 150-212, 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.

214. The use of any one of embodiments 150-213, 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.

215. The use of any one of embodiments 150-214, 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.

216. The use of embodiment 214 or embodiment 215, 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.

217. The use of any one of embodiments 214-216, wherein the one or more adverse events is a grade 3 or greater adverse event.

218. The use of any one of embodiments 214-216, wherein the one or more adverse events is a serious adverse event.

219. The use of embodiment 214 or embodiment 215, 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.

220. The use of any one of embodiments 150-219, wherein the subject is a human.

221. The use of any one of embodiments 150-220, wherein the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier.

222. The use of any one of embodiments 150-221, 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.

223. An anti-VEGF antibody or antigen-binding fragment thereof for use in the treatment of cervical cancer in a subject, wherein the anti-VEGF antibody or antigen-binding fragment thereof is for administration, or 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 a monomethyl auristatin or a functional analog thereof or a functional derivative thereof.

224. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 223, wherein the antibody-drug conjugate is administered at a dose ranging from about 0.65 mg/kg to about 2.1 mg/kg.

225. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 224, wherein the antibody-drug conjugate is administered at a dose of about 0.65 mg/kg.

226. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 224, wherein the antibody-drug conjugate is administered at a dose of 0.65 mg/kg.

227. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 224, wherein the antibody-drug conjugate is administered at a dose of about 0.9 mg/kg.

228. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 224, wherein the antibody-drug conjugate is administered at a dose of 0.9 mg/kg.

229. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 224, wherein the antibody-drug conjugate is administered at a dose of about 1.3 mg/kg.

230. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 224, wherein the antibody-drug conjugate is administered at a dose of 1.3 mg/kg.

231. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 224, wherein the antibody-drug conjugate is administered at a dose of about 2.0 mg/kg.

232. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 224, wherein the antibody-drug conjugate is administered at a dose of 2.0 mg/kg.

233. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-232, wherein the antibody-drug conjugate is administered once about every 3 weeks.

234. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-232, wherein the antibody-drug conjugate is administered once every 3 weeks.
235. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-234, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose ranging from about 5 mg/kg to about 20 mg/kg.
236. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-235, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 7.5 mg/kg.
237. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-235, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 7.5 mg/kg.
238. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-235, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 15 mg/kg.
239. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-235, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 15 mg/kg.
240. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-239, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered once about every 3 weeks.
241. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-239, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered once every 3 weeks.
242. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-241, wherein the antibody-drug conjugate is administered at least 30 minutes after the administration of the anti-VEGF antibody or antigen-binding fragment thereof.
243. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-242, 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.

244. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-242, 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.

245. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-242, 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.

246. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 243-245, 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.

247. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-246, wherein the subject is not a candidate for curative therapy.

248. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 247, wherein curative therapy comprises radiotherapy and/or exenterative surgery.

249. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-248, wherein the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma.

250. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-249, wherein the cervical cancer is an advanced stage cervical cancer.

251. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 250, wherein the advanced stage cervical cancer is a stage 3 or stage 4 cervical cancer.

252. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 250 or embodiment 251, wherein the advanced stage cervical cancer is metastatic cervical cancer.

253. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-252, wherein the cervical cancer is recurrent cervical cancer.

254. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-253, 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.

255. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-254, 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.

256. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-255, 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.

257. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-256, 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.

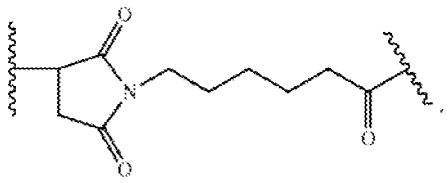
258. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-257, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

259. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-258, wherein the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the monomethyl auristatin.

260. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 259, wherein the linker is a cleavable peptide linker.

261. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 260, wherein the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

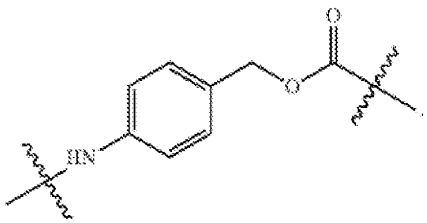
a) MC is:



,

b) vc is the dipeptide valine-citrulline, and

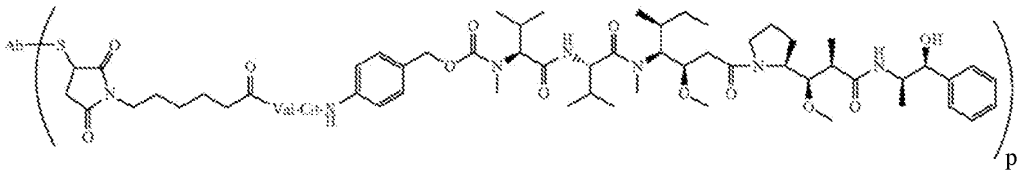
c) PAB is:



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262. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 259-261, 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.

263. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 262, 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.

264. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 263, wherein the average value of p in a population of the antibody-drug conjugates is about 4.

265. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-264, wherein the antibody-drug conjugate is tisotumab vedotin.

266. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-265, wherein the route of administration for the antibody-drug conjugate is intravenous.

267. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-266, 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.

268. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-267, 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.

269. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-268, 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.

270. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-269, 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.

271. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-270, wherein the anti-VEGF antibody is bevacizumab.

272. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-270, wherein the anti-VEGF antibody is a biosimilar of bevacizumab.

273. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 272, 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.

274. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 272, wherein the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel.

275. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-274, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous or subcutaneous.

276. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 275, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous.

277. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 2223-276, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered sequentially.

278. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-276, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered simultaneously.

279. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-278, 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.

280. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-279, 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.

281. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 280, 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.

282. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-281, 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.

283. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-282, 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%.

284. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-283, 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.

285. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-284, 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.

286. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-285, 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.

287. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-286, 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.

288. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-287, 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.

289. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 287 or embodiment 288, 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.

290. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 287-289, wherein the one or more adverse events is a grade 3 or greater adverse event.

291. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 287-289, wherein the one or more adverse events is a serious adverse event.

292. The anti-VEGF antibody or antigen-binding fragment thereof for use of embodiment 287 or embodiment 288, 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.

293. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-292, wherein the subject is a human.

294. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-293, wherein the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier.

295. The anti-VEGF antibody or antigen-binding fragment thereof for use of any one of embodiments 223-294, 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.

296. Use of an anti-VEGF antibody or antigen-binding fragment thereof for the manufacture of a medicament for treating cervical cancer in a subject, wherein the medicament is for use 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 a monomethyl auristatin or a functional analog thereof or a functional derivative thereof.

297. The use of embodiment 296, wherein the antibody-drug conjugate is administered at a dose ranging from about 0.65 mg/kg to about 2.1 mg/kg.

298. The use of embodiment 297, wherein the antibody-drug conjugate is administered at a dose of about 0.65 mg/kg.

299. The use of embodiment 297, wherein the antibody-drug conjugate is administered at a dose of 0.65 mg/kg.

300. The use of embodiment 297, wherein the antibody-drug conjugate is administered at a dose of about 0.9 mg/kg.

301. The use of embodiment 297, wherein the antibody-drug conjugate is administered at a dose of 0.9 mg/kg.

302. The use of embodiment 297, wherein the antibody-drug conjugate is administered at a dose of about 1.3 mg/kg.

303. The use of embodiment 297, wherein the antibody-drug conjugate is administered at a dose of 1.3 mg/kg.

304. The use of embodiment 297, wherein the antibody-drug conjugate is administered at a dose of about 2.0 mg/kg.

305. The use of embodiment 297, wherein the antibody-drug conjugate is administered at a dose of 2.0 mg/kg.

306. The use of any one of embodiments 296-305, wherein the antibody-drug conjugate is administered once about every 3 weeks.

307. The use of any one of embodiments 296-305, wherein the antibody-drug conjugate is administered once every 3 weeks.

308. The use of any one of embodiments 296-307, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose ranging from about 5 mg/kg to about 20 mg/kg.

309. The use of any one of embodiments 296-308, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 7.5 mg/kg.

310. The use of any one of embodiments 296-308, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 7.5 mg/kg.

311. The use of any one of embodiments 296-308, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 15 mg/kg.

312. The use of any one of embodiments 296-308, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 15 mg/kg.

313. The use of any one of embodiments 296-312, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered once about every 3 weeks.

314. The use of any one of embodiments 296-312, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered once every 3 weeks.

315. The use of any one of embodiments 296-314, wherein the antibody-drug conjugate is administered at least 30 minutes after the administration of the anti-VEGF antibody or antigen-binding fragment thereof.

316. The use of any one of embodiments 296-315, 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.

317. The use of any one of embodiments 296-315, 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.

318. The use of any one of embodiments 296-315, 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.

319. The use of any one of embodiments 316-318, 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.

320. The use of any one of embodiments 296-319, wherein the subject is not a candidate for curative therapy.

321. The use of embodiment 320, wherein curative therapy comprises radiotherapy and/or exenterative surgery.

322. The use of any one of embodiments 296-321, wherein the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma.

323. The use of any one of embodiments 296-322, wherein the cervical cancer is an advanced stage cervical cancer.

324. The use of embodiment 323, wherein the advanced stage cervical cancer is a stage 3 or stage 4 cervical cancer.

325. The use of embodiment 323 or embodiment 324, wherein the advanced stage cervical cancer is metastatic cervical cancer.

326. The use of any one of embodiments 296-325, wherein the cervical cancer is recurrent cervical cancer.

327. The use of any one of embodiments 296-326, 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.

328. The use of any one of embodiments 296-327, 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.

329. The use of any one of embodiments 296-328, 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.

330. The use of any one of embodiments 296-319, 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.

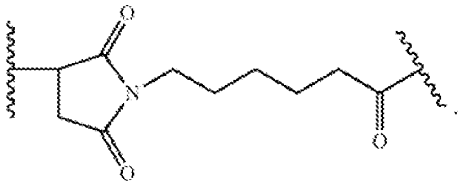
331. The use of any one of embodiments 296-330, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

332. The use of any one of embodiments 296-331, wherein the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the monomethyl auristatin.

333. The use of embodiment 332, wherein the linker is a cleavable peptide linker.

334. The use of embodiment 333, wherein the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

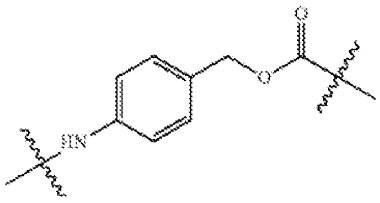
a) MC is:



,

b) vc is the dipeptide valine-citrulline, and

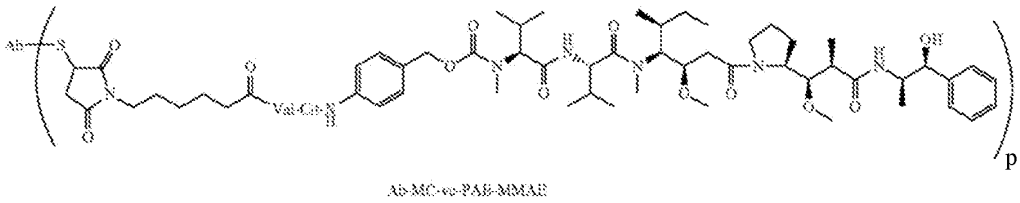
c) PAB is:



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335. The use of any one of embodiments 332-334, 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.

336. The use of embodiment 3335, 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.

337. The use of embodiment 336, wherein the average value of p in a population of the antibody-drug conjugates is about 4.

338. The use of any one of embodiments 296-337, wherein the antibody-drug conjugate is tisotumab vedotin.

339. The use of any one of embodiments 296-338, wherein the route of administration for the antibody-drug conjugate is intravenous.

340. The use of any one of embodiments 296-339, 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.

341. The use of any one of embodiments 296-340, 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.

342. The use of any one of embodiments 296-341, 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.

343. The use of any one of embodiments 296-342, 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.

344. The use of any one of embodiments 296-343, wherein the anti-VEGF antibody is bevacizumab.

345. The use of any one of embodiments 296-343, wherein the anti-VEGF antibody is a biosimilar of bevacizumab.

346. The use of embodiment 345, 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.

347. The use of embodiment 345, wherein the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel.

348. The use of any one of embodiments 296-347, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous or subcutaneous.

349. The use of embodiment 348, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous.

350. The use of any one of embodiments 296-349, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered sequentially.

351. The use of any one of embodiments 296-349, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered simultaneously.

352. The use of any one of embodiments 296-351, 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.

353. The use of any one of embodiments 296-352, 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.

354. The use of embodiment 353, 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.

355. The use of any one of embodiments 296-354, 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.

356. The use of any one of embodiments 296-355, 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%.

357. The use of any one of embodiments 296-356, 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.

358. The use of any one of embodiments 296-357, 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.

359. The use of any one of embodiments 296-358, 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.

360. The use of any one of embodiments 296-359, 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.

361. The use of any one of embodiments 296-360, 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.

362. The use of embodiment 360 or embodiment 361, 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.

363. The use of any one of embodiments 360-362, wherein the one or more adverse events is a grade 3 or greater adverse event.

364. The use of any one of embodiments 360-362, wherein the one or more adverse events is a serious adverse event.

365. The use of embodiment 360 or embodiment 361, 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.

366. The use of any one of embodiments 296-365, wherein the subject is a human.

367. The use of any one of embodiments 296-366, wherein the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier.

368. The use of any one of embodiments 296-367, 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.

[0214] The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention. It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

EXAMPLES

Example 1: Anti-tumor activity of tisotumab vedotin in combination bevacizumab in a cervical cancer mouse model

[0215] Bevacizumab, an anti-angiogenic antibody specific for vascular endothelial growth factor (VEGF), is used for the treatment of stage IVB, recurrent or persistent cervical carcinoma. *See* Bizzarri et al. Expert Opin. Biol. Ther. (2016). The combination of tisotumab vedotin with bevacizumab was evaluated herein for the treatment of cervical cancer in a preclinical model. The *in vivo* anti-tumor efficacy of tisotumab vedotin in combination with bevacizumab was evaluated in a patient-derived xenograft (PDX) mouse model in female BALB/c nude mice (Crown Bioscience [Taicang] Inc.). Xenografts were derived from tumor specimens from cancer patients. Tumor fragments were obtained from xenografts in serial passage in BALB/c nude mice. Tumors were cut into fragments of 2-4 mm diameter and placed in phosphate-buffered saline (PBS) until subcutaneous implantation. A cervical carcinoma PDX model (HuPrime® cervical xenograft model CV2320; Crown Bioscience Inc.) was used in this experiment. Tumor size was determined by caliper measurement at least two times a week and tumor volume was calculated as 0.5 x length x width^2. When tumors reached a mean volume of 155 mm^3, mice were randomized in 7 groups (10 mice per treatment group). The day of randomization was designated day 0. Mice were treated with the following by intravenous injections: 1) tisotumab vedotin alone at a dose level of 2 mg/kg or 4 mg/kg, provided on day 0, day 7, day 14 and day 21; 2) bevacizumab (Roche, lot no. H0158B02) alone at a dose of 15 mg/kg, provided on day 0, day 7, day 14 and day 21; 3) tisotumab vedotin at a dose level of 2 mg/kg or 4 mg/kg, provided on day

0, day 7, day 14 and day 21 in combination with bevacizumab at a dose of 15 mg/kg, provided on day 0, day 7, day 14 and day 21; 4) IgG1 isotype control at a dose of 4 mg/kg provided on day 0, day 7, day 14 and day 21; or 5) IgG1-MMAE control at a dose of 4 mg/kg provided on day 0, day 7, day 14 and day 21. Mice were observed for clinical signs of illness. Mice were housed in individually ventilated (IVC) cages, up to a maximum of five mice per cage and identified by ear tags. To determine whether there were statistically significant differences between tumor volumes in control and treatment groups, tumor volumes in the treatment groups were compared with those in the control group (*e.g.*, treatment groups vs IgG1-MMAE control) and combination treatment groups were compared with groups treated with either of the compounds alone, using Mann-Whitney analysis at the last day that all groups were intact, *i.e.*, day 21 and day 32, respectively. For progression-free survival time (tumor size cut-off 500 mm^3) analysis, Mantel-Cox analysis was performed on Kaplan-Meier plots.

[0216] Treatment with 4 mg/kg tisotumab vedotin in combination with 15 mg/kg bevacizumab efficiently enhanced anti-tumor activity and progression-free survival time (tumor size cut-off 500 mm^3) as compared to tisotumab vedotin alone or bevacizumab alone, in a mouse PDX model for cervical cancer (FIG. 1A-C, Table 1). Treatment with 4 mg/kg tisotumab vedotin in combination with 15 mg/kg bevacizumab clearly outperformed all other monotherapies and combinations in enhancing progression-free survival time (tumor size cut-off 500 mm^3) (FIG. 1C).

[0217] Treatment with 2 mg/kg or 4 mg/kg tisotumab vedotin alone did not significantly inhibit tumor growth, compared to IgG1-MMAE control (FIG. 1A-C, Table 1). Treatment with bevacizumab alone at a dose of 15 mg/kg efficiently inhibited tumor growth and enhanced progression-free survival time (tumor size cut-off 500 mm^3) (FIG.1A-C, Table 1).

Table 1. Statistical analysis

Treatment	Average tumor volume	Percentage of mice with tumor volume < 500 mm^3
	Mann-Whitney P value[1]	Mantel-Cox P value

Tisotumab vedotin, 2 mg/kg vs IgG1-MMAE, 4 mg/kg	0.4359	0.266
Tisotumab vedotin, 4 mg/kg vs IgG1-MMAE, 4 mg/kg	0.6842	0.583
Bevacizumab, 15 mg/kg vs IgG1-MMAE, 4 mg/kg	0.0068	0.014
Tisotumab vedotin, 2 mg/kg + bevacizumab, 15 mg/kg vs IgG1-MMAE, 4 mg/kg	0.0003	0.000
Tisotumab vedotin, 4 mg/kg + bevacizumab, 15 mg/kg vs IgG1-MMAE, 4 mg/kg	0.0003	0.000
Tisotumab vedotin, 2 mg/kg + bevacizumab, 15 mg/kg vs tisotumab vedotin, 2 mg/kg	0.0002	0.000
Tisotumab vedotin, 2 mg/kg + bevacizumab, 15 mg/kg vs bevacizumab, 15 mg/kg	0.0524	0.514
Tisotumab vedotin, 4 mg/kg + bevacizumab, 15 mg/kg vs tisotumab vedotin, 4 mg/kg	0.0002	0.000
Tisotumab vedotin, 4 mg/kg + bevacizumab, 15 mg/kg vs bevacizumab, 15 mg/kg	0.0288	0.018

[1]Statistical analysis was performed on day 21 data (treatment vs IgG1-MMAE control) or day 32 data (combination treatment vs monotherapy)

Example 2: Anti-tumor activity of tisotumab vedotin in combination bevacizumab in a cervical cancer mouse model

[0218] Bevacizumab, an anti-angiogenic antibody specific for vascular endothelial growth factor (VEGF), is used for the treatment of stage IVB, recurrent or persistent cervical carcinoma. *See* Bizzarri et al. Expert Opin. Biol. Ther. (2016). The combination of tisotumab vedotin with bevacizumab was evaluated herein for the treatment of cervical cancer in a preclinical model. The *in vivo* anti-tumor efficacy of tisotumab vedotin in combination with bevacizumab was evaluated in a patient-derived xenograft (PDX) mouse model in female BALB/c nude mice (Crown Bioscience [Taicang] Inc.). Xenografts were derived from tumor specimens from cancer patients. Tumor fragments were obtained from xenografts in serial passage in BALB/c nude mice. Tumors were cut into fragments of 2-3 mm diameter and placed in phosphate-buffered saline (PBS) until subcutaneous implantation. A cervical carcinoma PDX model (HuPrime® cervical xenograft model CV1802; Crown Bioscience Inc.) was used in this experiment. Tumor size was determined by caliper measurement at least two times a week and tumor volume was

calculated as 0.5 x length x width^2. When tumors reached a mean volume of 170 mm^3, mice were randomized in 7 groups (10 mice per treatment group). The day of randomization was designated day 0. Mice were treated with the following by intravenous injections: 1) tisotumab vedotin alone at a dose level of 0.5 mg/kg or 1 mg/kg, provided on day 0, day 7, day 14 and day 21; 2) bevacizumab (Roche, lot no. H0158B02) alone at a dose of 15 mg/kg, provided on day 0, day 7, day 14 and day 21; 3) tisotumab vedotin at a dose level of 0.5 mg/kg or 1 mg/kg, provided on day 0, day 7, day 14 and day 21 in combination with bevacizumab at a dose of 15 mg/kg, provided on day 0, day 7, day 14 and day 21; 4) IgG1 isotype control at a dose of 1 mg/kg provided on day 0, day 7, day 14 and day 21; or 5) IgG1-MMAE control at a dose of 1 mg/kg provided on day 0, day 7, day 14 and day 21. Mice were observed for clinical signs of illness. Mice were housed in individually ventilated (IVC) cages, up to a maximum of five mice per cage and identified by ear tags. To determine whether there were statistically significant differences between tumor volumes in control and treatment groups, tumor volumes in the treatment groups were compared with those in the control group (*e.g.*, treatment groups vs IgG1-MMAE control) and combination treatment groups were compared with groups treated with either of the compounds alone, using Mann-Whitney analysis at the last day that all groups were intact, *i.e.*, day 14 and day 25, respectively. For progression-free survival (tumor size cut-off 1,000 mm^3) analysis, Mantel-Cox analysis was performed on Kaplan-Meier plots.

[0219] Treatment with either 0.5 mg/kg or 1 mg/kg tisotumab vedotin alone or treatment with 15 mg/kg bevacizumab alone efficiently inhibited tumor growth and enhanced progression-free survival time (tumor size cut-off 1,000 mm^3) in a mouse PDX model for cervical cancer (FIG. 2A-C, Table 2). Treatment with 0.5 mg/kg or 1 mg/kg tisotumab vedotin in combination with 15 mg/kg bevacizumab significantly enhanced progression-free survival time (tumor size cut-off 1,000 mm^3), as compared to either treatment alone (FIG. 2C, Table 2) and was more efficient than treatment with bevacizumab alone in inhibiting tumor growth (FIG. 2A, FIG. 2B and Table 2). Strikingly, in the group treated with 0.5 mg/kg or 1 mg/kg tisotumab vedotin in combination with 15 mg/kg bevacizumab, 2 and 8 out of 10 mice, respectively, did not show tumors larger than 1,000 mm^3 until the last day of the experiment (day 81, FIG. 2C).

Table 2. Statistical analysis

SUBSTITUTE SHEET (RULE 26)

Treatment	Average tumor volume	Percentage of mice with tumor volume < 1,000 mm^3
	Mann-Whitney P value[1]	Mantel-Cox P value
Tisotumab vedotin, 0.5 mg/kg vs IgG1-MMAE, 1 mg/kg	< 0.0001	0.000
Tisotumab vedotin, 1 mg/kg vs IgG1-MMAE, 1 mg/kg	< 0.0001	0.000
Bevacizumab, 15 mg/kg vs IgG1-MMAE, 1 mg/kg	< 0.0001	0.000
Tisotumab vedotin, 0.5 mg/kg + bevacizumab, 15 mg/kg vs IgG1-MMAE, 1 mg/kg	< 0.0001	0.000
Tisotumab vedotin, 1 mg/kg + bevacizumab, 15 mg/kg vs IgG1-MMAE, 1 mg/kg	< 0.0001	0.000
Tisotumab vedotin, 0.5 mg/kg + bevacizumab, 15 mg/kg vs tisotumab vedotin, 0.5 mg/kg	0.6842	0.026
Tisotumab vedotin, 0.5 mg/kg + bevacizumab, 15 mg/kg vs bevacizumab, 15 mg/kg	0.0288	0.033
Tisotumab vedotin, 1 mg/kg + bevacizumab, 15 mg/kg vs tisotumab vedotin, 1 mg/kg	0.2176	0.000
Tisotumab vedotin, 1 mg/kg + bevacizumab, 15 mg/kg vs bevacizumab, 15 mg/kg	< 0.0001	0.000

[1]Statistical analysis was performed on day 14 data (treatment vs IgG1-MMAE control) or day 25 data (combination treatment vs monotherapy)

Example 3: A phase I/II clinical study of tisotumab vedotin in combination with an anti-VEGF antibody in recurrent or Stage IVB cervical cancer

[0220] This is an open label, multi-center trial of tisotumab vedotin in combination with bevacizumab in subjects with recurrent or stage IVB cervical cancer. The efficacy, safety and tolerability of tisotumab vedotin in combination with the anti-VEGF antibody bevacizumab in subjects with recurrent or Stage IVB cervical cancer is evaluated herein.

Methods

[0221] This is an open label, multi-center trial of tisotumab vedotin in combination with bevacizumab in subjects with recurrent or stage IVB cervical cancer. This trial will occur in cervical cancer subjects who have progressed during, after standard of care therapy, are intolerant, or ineligible to receive standard of care treatments. The trial will be conducted by escalating doses of both tisotumab vedotin and bevacizumab. Subjects are allocated to one of three treatment groups. Eligible subjects are treated with (1) tisotumab vedotin 1.3 mg/kg 1Q3W + bevacizumab 7.5 mg/kg 1Q3W, (2) tisotumab vedotin 1.3 mg/kg 1Q3W + bevacizumab 15 mg/kg 1Q3W, or (3) tisotumab vedotin 2.0 mg/kg 1Q3W + bevacizumab 1.5 mg/kg 1Q3W. Treatment cycles occur every 21 days (±3 days). All treatment components are administered intravenously. Subjects are treated until unacceptable toxicity, withdrawal of consent, or initial evidence of radiographic progression. Subjects enrolled in the trial are ≥18 years. The duration of the trial is approximately 7 years. Inclusion criteria and exclusion criteria for subjects enrolled in the trial are shown in Table 3.

Table 3. List of inclusion and exclusion criteria

<table>
<tr><td>Inclusion Criteria</td><td>

Must have squamous, adenosquamous, or adenocarcinoma of the cervix and progressed on or after standard of care treatments or are ineligible or intolerant to standard of care for recurrent or stage IVB cervical cancer.
Must have baseline measurable disease per RECIST v1.1

Note: Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

Must be at least 18 years of age on the day of signing informed consent.
Must demonstrate acceptable screening laboratory values:

<table>
<tr><th>Lab Test</th><th>Value</th></tr>
<tr><td colspan="2">Renal Function</td></tr>
<tr><td>Calculated (Cockcroft-Gault) Glomerular Filtration Rate (GFR)</td><td>> 50 mL/min</td></tr>
<tr><td colspan="2">Liver Function</td></tr>
<tr><td>Alanine aminotransferase (ALT)</td><td>≤ 2.5 × Upper Limit of Normal (ULN) (if liver tumor/metastases are present, then ≤ 5 × ULN is allowed)</td></tr>
<tr><td>Aspartate aminotransferase (AST)</td><td>≤ 2.5 × Upper Limit of Normal (ULN) (if liver tumor/metastases are present, then ≤ 5 × ULN is allowed)</td></tr>
<tr><td>Bilirubin</td><td>≤ 1.5 × ULN unless direct bilirubin ≤ institutional ULN, except in subjects diagnosed with Gilbert's syndrome, direct bilirubin ≤ 2 × ULN</td></tr>
</table>
</td></tr>
</table>

Hematological status*	
Absolute neutrophil count (ANC)	≥ 1500/μL (1.5 X 10^9/L)
Hemoglobin	≥ 5.6 mmol/L (9.0 g/dL) *Acceptable hematologic status must be met without erythropoietin administration and packed red blood cell (pRBC) transfusion within 2 weeks of C1D1.
Platelet count	≥100 X10^9/L
Coagulation status (Subjects not on anticoagulant therapy)	
Activated partial thromboplastin time (aPTT)	≤ 1.25 × ULN For subjects recieving unfractionated heparin: aPTT ≤ 1.5-2.0 ×ULN
International normalized ratio (INR)	≤ 1.2
Coagulation status **(Anticoagulant therapy within 2 weeks of the first dose of study medication is prohibited)** (Subjects on anticoagulant therapy)**	
Activated partial thromboplastin time (aPTT)	≤ 1.25 X ULN
INR	Subjects on anti-coagulants that require laboratory assessments for dose titration (warfarin or other Vitamin K dependent anticoagulant agents) must be on a steady dose (no active titration) for ≥ 4 weeks prior to first planned dose of tisotumab vedotin and must have an INR ≤ 2.5 within 5 days prior to cycle 1 day 1. Subjects on anti-coagulants that do not require laboratory assessments for dose titration must have an INR of ≤ 1.2. Subjects DO NOT need to be on a stable dose for ≥ 4 weeks prior to first planned dose of tisotumab vedotin.
**Note: Concurrent chronic use of prophylactic acetylsalicylic acid (ASA) (*e.g.*, aspirin) is prohibited for subjects on any type of anti-coagulation therapy.	

- Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Have a life expectancy of ≥ 3 months.
- Is not pregnant, breastfeeding, or expecting to conceive children within the projected duration of the trial and for at least 6 months after the last trial treatment administration and at least one of the following conditions applies:
    - Not a woman of childbearing potential (WOCBP).
    - A WOCBP must agree to use adequate contraception during and for 6 months after the last dose of trial treatment

	administration. Adequate contraception for women is defined as highly effective methods of contraception. Two highly effective methods of contraception must be used in countries where this is required. • Must be able to provide a fresh biopsy from a lesion not previously irradiated. For those subjects for whom fresh biopsies cannot be obtained (*e.g.*, inaccessible tumor or for safety concerns) may submit an archived biopsy in place of the fresh biopsy. *Note: Aspirates are not acceptable.* • Must have recovered from all AEs due to previous systemic therapies to ≤ grade 1. *Subjects with ≤ grade 2 neuropathy may be eligible.* • Must be willing and able to adhere to the prohibitions and restrictions specified in this protocol. • Must sign an informed consent form (ICF) indicating the trial subject understands the purpose of and the procedures required for the trial and are willing to participate in the trial.
Exclusion Criteria	• Has clinically relevant bilateral hydronephrosis which cannot be alleviated by ureteral stents or percutaneous drainage**.** • Has clinical signs or symptoms of gastrointestinal obstruction and requires parenteral hydration and/or nutrition. Post-operative obstructions within 4 weeks of abdominal surgery are permitted**.** • Has clinically significant bleeding issues or risks: o Known past or current coagulation defects leading to an increased risk of bleeding; o Diffuse alveolar hemorrhage from vasculitis; o Known bleeding diathesis; o Ongoing major bleeding; o Trauma with increased risk of life-threatening bleeding; o History of severe head trauma or intracranial surgery within 8 weeks of trial entry; o Tumor invasion into a blood vessel that would place the subject at risk for hemorrhage; o Prior history (within 3 month) or current evidence of hemoptysis (1/2 teaspoon or more)**;** Recent (within 4 weeks of first dose of trial treatment) clinically significant gastrointestinal or vaginal bleeding requiring PRBC transfusion**;**

	○ Recent (within 4 weeks of first dose of trial treatment) evidence of wound healing complications that require medical intervention. • Has an active ocular surface disease at baseline. Subjects with prior history of cicatricial conjunctivitis are ineligible. • Has a prior history of Steven Johnson syndrome. • Has cardiovascular issues or risk: ○ Clinically significant cardiac disease including unstable angina, acute myocardial infarction within 6 months of the first dose of trial treatment, or prior history of immunotherapy related myocarditis; ○ Any medical history of congestive heart failure (Grade III or IV as classified by the New York Heart Association); ○ Any medical history of decreased cardiac ejection fraction of < 45%; ○ A marked baseline prolongation of QT/QTc interval (*e.g.*, repeated demonstration of a QTc interval > 450 msec); ○ A complete left bundle branch block (defined as a QRS interval ≥ 120 msec in left bundle branch block form) or an incomplete left bundle branch block. • Has a history of uncontrolled clinically significant hypertension. • Has known past or current malignancy other than inclusion diagnosis, except for: non-invasive basal cell or squamous cell skin carcinoma; non-invasive, superficial bladder cancer, and any cancer with a CR of > 5 years. • Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, (*i.e.*, without evidence of progression) for at least 28 days by repeat imaging (note that the repeat imaging should be performed during trial screening). Subjects should be clinically stable, and should not require steroid treatment for at least 14 days prior to first dose of trial treatment. • Has had prior therapy that meets any of the following criteria: ○ Any prior treatment with MMAE-derived drugs. ○ Has received radiotherapy within 7 days of the start of trial treatment. Subjects must have recovered from all clinically significant radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.

	○ Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks (28 days) prior to the first dose of trial treatment. *Note: Subjects must have recovered from all AEs due to previous therapies to ≤ grade 1 or baseline. Subjects with ≤ grade 2 neuropathy may be eligible.* ○ Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (*e.g.*, CTLA-4, OX40, CD137) AND was discontinued from treatment due to a grade 3 or higher AE of special interest (AESI). ○ Has received a live vaccine within 30 days prior to the first dose of trial treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (*e.g.*, FluMist®) are live attenuated vaccines and are not allowed. • Has had major or minor surgery within 4 weeks (28 days) of the first dose of trial treatment. Subjects must have recovered adequately from the toxicity and/or complications from the intervention prior to starting trial treatment. Subjects who have planned major surgery during the treatment period must also be excluded from the trial. • Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. • Is currently participating in or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of trial treatment. *Note: Subjects who have entered the follow-up phase of an investigational trial may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.* • Has an ongoing significant, uncontrolled medical condition; clinically significant active viral, bacterial or fungal infection requiring IV or oral (PO) treatment with antimicrobial therapy ending less than 7 days prior to first trial treatment administration.

	• *Note: This criterion does not apply to oral antibiotics for urinary tract infections, however, IV antibiotics for UTIs would need to end at least 7 days prior to the first dose of trial treatment.* • Has a known history of human immunodeficiency virus (HIV) and/or history of Hepatitis B or C infection infections, or known to be positive for Hepatitis B antigen (HBsAg)/Hepatitis B virus (HBV) DNA or Hepatitis C Antibody or RNA. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay. *Note: No testing for HIV, Hepatitis B or Hepatitis C is required unless mandated by local health authority.* • Has known allergies, hypersensitivity, or intolerance to any part of the specific trial treatment regimen selected for the subject. • Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator. • Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the trial. • Has had an allogenic tissue/solid organ transplant. • Is a WOCBP who has a positive serum pregnancy test prior to treatment. Subjects that are postmenopausal or permanently sterilized can be considered as not having reproductive potential. • Has a history of a clinically significant fistula, or gastrointestinal perforation. • Has muscular and/or mucosal tumor infiltration of bowel or bladder. • Requires anti-coagulation therapy.

[0222] Tisotumab vedotin will be supplied in vials containing 40 mg of tisotumab vedotin as lyophilized powder. Tisotumab vedotin (lyophilized vials) must be stored in a refrigerator at 2°C to 8°C. The powder must be reconstituted with 4 mL water for injection leading to a 10 mg/mL solution. The reconstituted tisotumab vedotin must be diluted into 0.9% NaCl 100 mL infusion bag according to the dose calculated for the subject. The infusion must be completed within 24 hours after the tisotumab vedotin vials have been reconstituted. A 0.2 µm in-line filter must

be used for the infusion. The entire 100 mL infusion volume from the prepared infusion bag needs to be administered, no dead volume is provided. Bevacizumab will be provided by the Sponsor.

[0223] Objectives and endpoints are described in Table 4. Subjects are treated until disease progression, toxicity, or withdrawal of consent. Treatment cycles will occur every 21 days (±3 days). All treatment components will be administered intravenously. Subjects will be treated until unacceptable toxicity, withdrawal of consent, or initial evidence of radiographic progression.

[0224] Imaging will be obtained every 6 weeks for the first 31 weeks for subjects in the dose escalation part and every 6 weeks for the first 31 or 37 weeks and then every 12 weeks thereafter, calculated from the date of first dose. On-trial imaging should continue until the subject experiences radiographic disease progression, begins a new anti-cancer therapy, withdrawal of consent or the subject dies. objective response rate (ORR) will be analyzed up to 2 time points: futility assessment and primary efficacy assessment.

Table 4. Objectives and endpoints

OBJECTIVES	ENDPOINTS
Primary	
• To establish the minimum tolerated dose (MTD) and Recommended phase 2 dose (RP2D) of tisotumab vedotin in combination with bevacizumab in subjects with advanced cervical cancer	• Incidences of dose limiting toxicities (DLTs), adverse events (AEs), serious adverse events (SAEs), infusion-related AEs, common terminology for adverse events (CTCAE) grade ≥ 3 AEs, and AEs related to trial treatment during the trial
Secondary	
• Assess safety and tolerability of tisotumab vedotin in combination with bevacizumab	• Adverse events (AEs) and safety laboratory parameters
• Evaluate antitumor activity	• Objective Response Rate (ORR) per RECIST v1.1
	• Duration of Response (DOR) per RECIST v1.1

• Evaluate durability of response of tisotumab vedotin in combination with bevacizumab • Evaluate clinical efficacy with tisotumab vedotin in combination with bevacizumab	• Time to Response (TTR) per RECIST v1.1 • Progression free survival (PFS) per RECIST v1.1 • Overall survival (OS)
• To evaluate the pharmacokinetics (PK) and immunogenicity of tisotumab vedotin in combination with bevacizumab	• PK-concentrations and anti-drug antibodies (ADA) associated with tisotumab vedotin
Exploratory	
• Explore relationship between biomarkers and clinical response • Assess potential pharmacodynamic biomarkers	• TF expression in tumor biopsies, circulating TF, proteomic analyses and genomic signatures • Circulating TF and proteomic analyses

[0225] For subjects that do not tolerate the protocol-specified dosing schedule, dose reductions are permitted for tisotumab vedotin in order to allow the subject to continue treatment with tisotumab vedotin (Table 5).

Table 5. Dose modification scheme for tisotumab vedotin

Current Dose of Tisotumab Vedotin	Reduced Dose of Tisotumab Vedotin
2.0 mg/kg	1.3 mg/kg
1.3 mg/kg	0.9 mg/kg

[0226] The dose of bevacizumab cannot be reduced, but may be held. Adverse reactions such as increased bleeding and hemorrhage, increased lacrimation, exfoliative dermatitis, and rhinitis is associated with bevacizumab administration and may exacerbated by tisotumab vedotin administration.

[0227] Tisotumab vedotin may cause infusion-related reactions (IRRs) including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion. All subjects should be observed for 2 hours after ending their first infusion of

tisotumab vedotin and 15 minutes for all subsequent cycles. In case any clinical significant IRR is observed during or after the first infusion of tisotumab vedotin or at subsequent treatment cycles, the subject should be observed for 2 hours after the end of tisotumab vedotin administration for all subsequent infusions. At all times during infusion, immediate emergency treatment of an anaphylactic reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents must always be available along with equipment for assisted ventilation.

[0228] Discontinuation of trial treatment (all trial components) does not represent withdrawal from the trial. Subjects should continue to be monitored. subjects must be discontinued from trial treatment if one of the following criteria is met:

- Radiographic disease progression
- Death
- Unacceptable AEs requiring treatment discontinuation
- The investigator believes that it is in the best interest of the subject to stop treatment
- Pregnancy
- Subject choice
- New anti-cancer therapy is initiated

[0229] When treatment is discontinued, investigators must perform treatment discontinuation visit and the required safety follow-up visits. The treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of all trial components of trial treatment (preferably within 7 days after treatment discontinuation has been decided) and prior to initiation of new anti-cancer treatment. Upon treatment discontinuation, subjects will continue to be followed for post–treatment assessments until death or withdrawal from the trial.

CLAIMS

1. 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.

2. The method of claim 1, wherein the antibody-drug conjugate is administered at a dose ranging from about 0.65 mg/kg to about 2.1 mg/kg.

3. The method of claim 2, wherein the antibody-drug conjugate is administered at a dose of about 0.65 mg/kg.

4. The method of claim 2, wherein the antibody-drug conjugate is administered at a dose of 0.65 mg/kg.

5. The method of claim 2, wherein the antibody-drug conjugate is administered at a dose of about 0.9 mg/kg.

6. The method of claim 2, wherein the antibody-drug conjugate is administered at a dose of 0.9 mg/kg.

7. The method of claim 2, wherein the antibody-drug conjugate is administered at a dose of about 1.2 mg/kg.

8. The method of claim 2, wherein the antibody-drug conjugate is administered at a dose of 1.2 mg/kg.

9. The method of claim 2, wherein the antibody-drug conjugate is administered at a dose of about 1.3 mg/kg.

10. The method of claim 2, wherein the antibody-drug conjugate is administered at a dose of 1.3 mg/kg.

11. The method of claim 2, wherein the antibody-drug conjugate is administered at a dose of about 2.0 mg/kg.

12. The method of claim 2, wherein the antibody-drug conjugate is administered at a dose of 2.0 mg/kg.

13. The method of any one of claims 1-12, wherein the antibody-drug conjugate is administered once about every 3 weeks.

14. The method of any one of claims 1-12, wherein the antibody-drug conjugate is administered once every 3 weeks.

15. The method of any one of claims 1-12, wherein the antibody-drug conjugate is 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.

16. The method of any one of claims 1-12, wherein the antibody-drug conjugate is administered once every 1 week for 3 consecutive weeks followed by a 1 week rest period without any administration of the antibody-drug conjugate so that each cycle time is 28 days including the resting period.

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

18. The method of any one of claims 1-12, wherein the antibody-drug conjugate is administered on days 1, 8, and 15 of a 4-week cycle.

19. The method of any one of claims 1-18, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose ranging from about 5 mg/kg to about 20 mg/kg.

20. The method of any one of claims 1-19, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 7.5 mg/kg.

21. The method of any one of claims 1-19, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 7.5 mg/kg.

22. The method of any one of claims 1-19, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of about 15 mg/kg.

23. The method of any one of claims 1-19, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered at a dose of 15 mg/kg.

24. The method of any one of claims 1-23, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered once about every 3 weeks.

25. The method of any one of claims 1-23, wherein the anti-VEGF antibody or antigen-binding fragment thereof is administered once every 3 weeks.

26. The method of any one of claims 1-25, wherein the antibody-drug conjugate is administered at least 30 minutes after the administration of the anti-VEGF antibody or antigen-binding fragment thereof.

27. The method of any one of claims 1-26, 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.

28. The method of any one of claims 1-26, 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.

29. The method of any one of claims 1-26, 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.

30. The method of any one of claims 27-29, 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.

31. The method of any one of claims 1-30, wherein the subject is not a candidate for curative therapy.

32. The method of claim 31, wherein curative therapy comprises radiotherapy and/or exenterative surgery.

33. The method of any one of claims 1-32, wherein the cervical cancer is an adenocarcinoma, an adenosquamous carcinoma or a squamous cell carcinoma.

34. The method of any one of claims 1-33, wherein the cervical cancer is an advanced stage cervical cancer.

35. The method of claim 34, wherein the advanced stage cervical cancer is a stage 3 or stage 4 cervical cancer.

36. The method of claim 34 or claim 35, wherein the advanced stage cervical cancer is metastatic cervical cancer.

37. The method of any one of claims 1-36, wherein the cervical cancer is recurrent cervical cancer.

38. The method of any one of claims 1-37, 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.

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

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

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

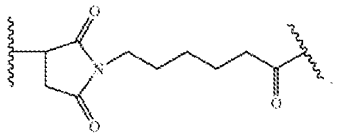
42. The method of any one of claims 1-41, wherein the anti-TF antibody of the antibody-drug conjugate is tisotumab.

43. The method of any one of claims 1-42, wherein the antibody-drug conjugate further comprises a linker between the anti-TF antibody or antigen-binding fragment thereof and the monomethyl auristatin.

44. The method of claim 43, wherein the linker is a cleavable peptide linker.

45. The method of claim 44, wherein the cleavable peptide linker has a formula: -MC-vc-PAB-, wherein:

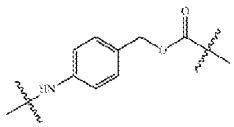
a) MC is:



,

b) vc is the dipeptide valine-citrulline, and

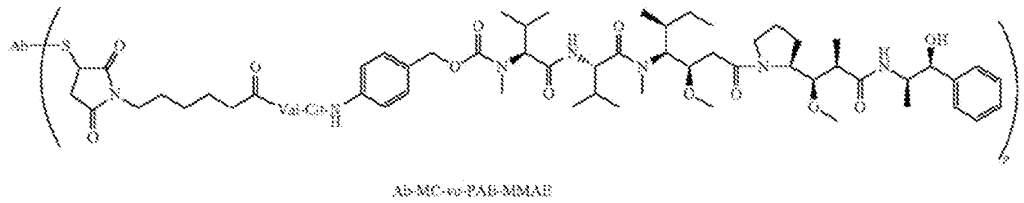
c) PAB is:



.

46. The method of any one of claims 43-45, 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.

47. The method of claim 46, 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.

48. The method of claim 47, wherein the average value of p in a population of the antibody-drug conjugates is about 4.

49. The method of any one of claims 1-48, wherein the antibody-drug conjugate is tisotumab vedotin.

50. The method of any one of claims 1-49, wherein the route of administration for the antibody-drug conjugate is intravenous.

51. The method of any one of claims 1-50, 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.

52. The method of any one of claims 1-51, 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.

53. The method of any one of claims 1-52, 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.

54. The method of any one of claims 1-53, 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.

55. The method of any one of claims 1-54, wherein the anti-VEGF antibody is bevacizumab.

56. The method of any one of claims 1-54, wherein the anti-VEGF antibody is a biosimilar of bevacizumab.

57. The method of claim 56, 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.

58. The method of claim 56, wherein the biosimilar of bevacizumab is selected from the group consisting of bevacizumab-awwb, bevacizumab-bvzr, Krabeva, Cizumab, Bevax, and Bevacirel.

59. The method of any one of claims 1-58, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous or subcutaneous.

60. The method of claim 59, wherein the route of administration for the anti-VEGF antibody or antigen-binding fragment thereof is intravenous.

61. The method of any one of claims 1-60, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered sequentially.

62. The method of any one of claims 1-60, wherein the anti-VEGF antibody or antigen-binding fragment thereof and the antibody-drug conjugate are administered simultaneously.

63. The method of any one of claims 1-62, 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.

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

65. The method of claim 64, 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.

66. The method of any one of claims 1-65, 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.

67. The method of any one of claims 1-66, 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%.

68. The method of any one of claims 1-67, 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.

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

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

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

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

73. The method of claim 71 or claim 72, 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.

74. The method of any one of claims 71-73, wherein the one or more adverse events is a grade 3 or greater adverse event.

75. The method of any one of claims 71-73, wherein the one or more adverse events is a serious adverse event.

76. The method of claim 71 or claim 72, 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.

77. The method of any one of claims 1-76, wherein the subject is a human.

78. The method of any one of claims 1-77, wherein the antibody-drug conjugate is in a pharmaceutical composition comprising the antibody-drug conjugate and a pharmaceutical acceptable carrier.

79. The method of any one of claims 1-78, 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.

80. 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 a monomethyl 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 method of any one of claims 1-79.

81. The kit of claim 80, wherein the anti-VEGF antibody or antigen-binding fragment thereof is bevacizumab.

82. The kit of claim 80 or claim 81, wherein the antibody-drug conjugate is tisotumab vedotin.