

of the Auristatin-Based Antibody-Drug Conjugate BAY 1187982 for the Treatment of FGFR2-Positive Solid Tumors” Cancer Res 76(21):6331-6339; Sommer et al. (2014) “FGFR2-ADC Potently and Selectively Inhibits Growth of Gastric and Breast Cancer Xenograft Models” AACR Abstract ID 4491)

[0009] There remains a significant unmet medical need for improved anti-cancer drugs that are effective in FGFR2 expressing cancers.

BRIEF SUMMARY

[0010] Provided herein are antibodies and antigen-binding fragments thereof that bind human FGF receptor 2 protein (FGFR2). The antibodies are useful, *inter alia*, for targeting tumor cells that express FGFR2. The anti-FGFR2 antibodies, and antigen-binding portions thereof, may be used alone in unmodified form, or may be included as part of an antibody-drug conjugate.

[0011] Other examples ~~embodiments~~ will become apparent from a review of the ensuing detailed description.

[0011a] In one aspect, the present disclosure provides an isolated monoclonal antibody or antigen-binding fragment thereof that binds to FGFR2, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3), wherein: (a) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 4, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 6, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 8, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 12, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 14, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 16; or (b) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 24, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 6, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 26, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 30, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 32, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 34.

[0011b] In one aspect, the present disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of the antibody or antigen-binding fragment as disclosed herein together with one or more pharmaceutically acceptable excipients.

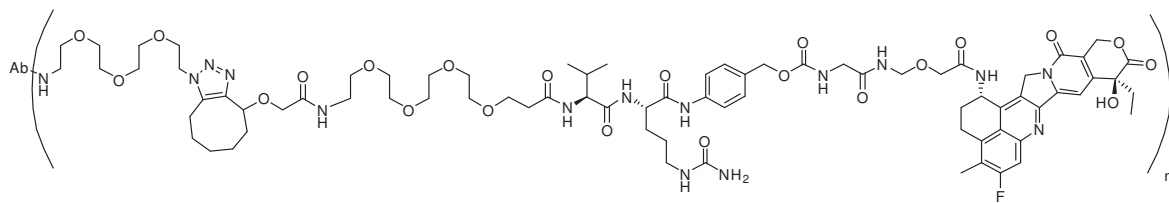
[0011c] In one aspect, the present disclosure provides a nucleic acid molecule encoding the antibody or antigen-binding fragment as disclosed herein.

[0011d] In one aspect, the present disclosure provides an expression vector comprising the nucleic acid molecule as disclosed herein.

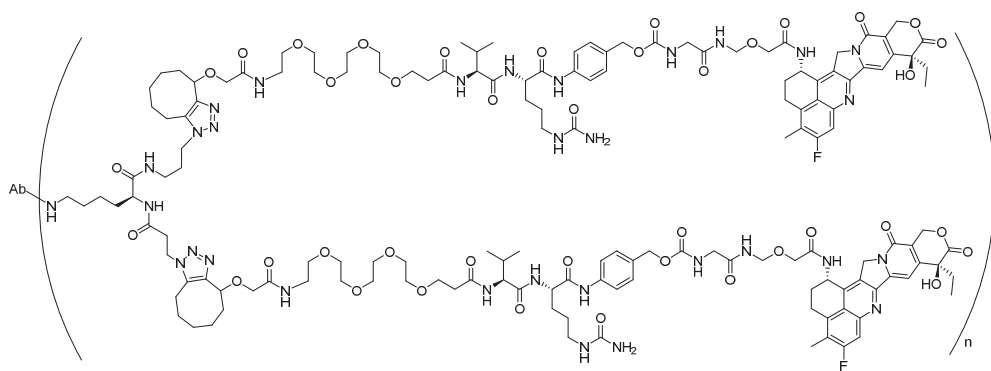
[0011e] In one aspect, the present disclosure provides a host cell containing the expression

vector as disclosed herein.

[0011f] In one aspect, the present disclosure provides an antibody-drug conjugate comprising an anti-FGFR2 antibody, or an antigen-binding fragment thereof, conjugated to a camptothecin analog, wherein the antibody-drug conjugate has the following structure:



or

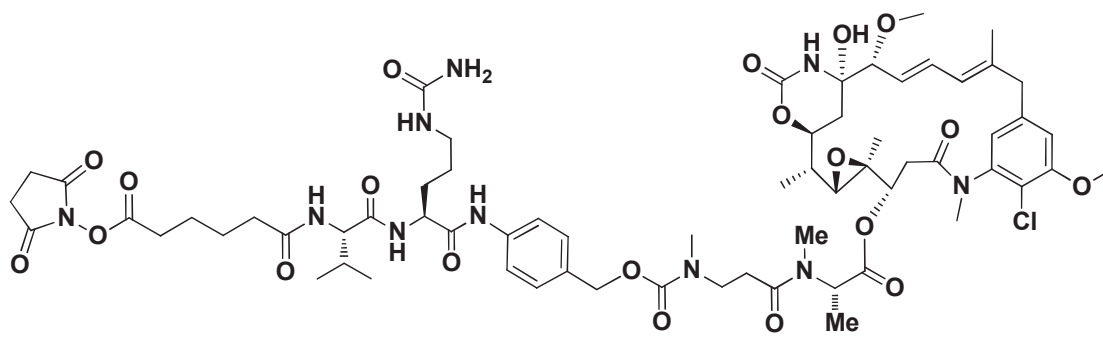


wherein n is a value between 2 and 12; and

wherein Ab is the anti-FGFR2 antibody or antigen-binding fragment thereof, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises: (i) an HCDR1 comprising the amino acid sequence of SEQ ID NO:4, an HCDR2 comprising the amino acid sequence of SEQ ID NO:6, an HCDR3 comprising the amino acid sequence of SEQ ID NO:8, an LCDR1 comprising the amino acid sequence of SEQ ID NO:12, an LCDR2 comprising the amino acid sequence of SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:16; or (ii) an HCDR1 comprising the amino acid sequence of SEQ ID NO:24, an HCDR2 comprising the amino acid sequence of SEQ ID NO:6, an HCDR3 comprising the amino acid sequence of SEQ ID NO:26, an LCDR1 comprising the amino acid sequence of SEQ ID NO:30, an LCDR2 comprising the amino acid sequence of SEQ ID NO:32, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:34.

[0011g] In one aspect, the present disclosure provides a use of the anti-FGFR2 antibody or antigen-binding fragment as disclosed herein, or the antibody-drug conjugate as disclosed herein, in the preparation of a medicament for treating a disease or disorder associated with FGFR2 expression.

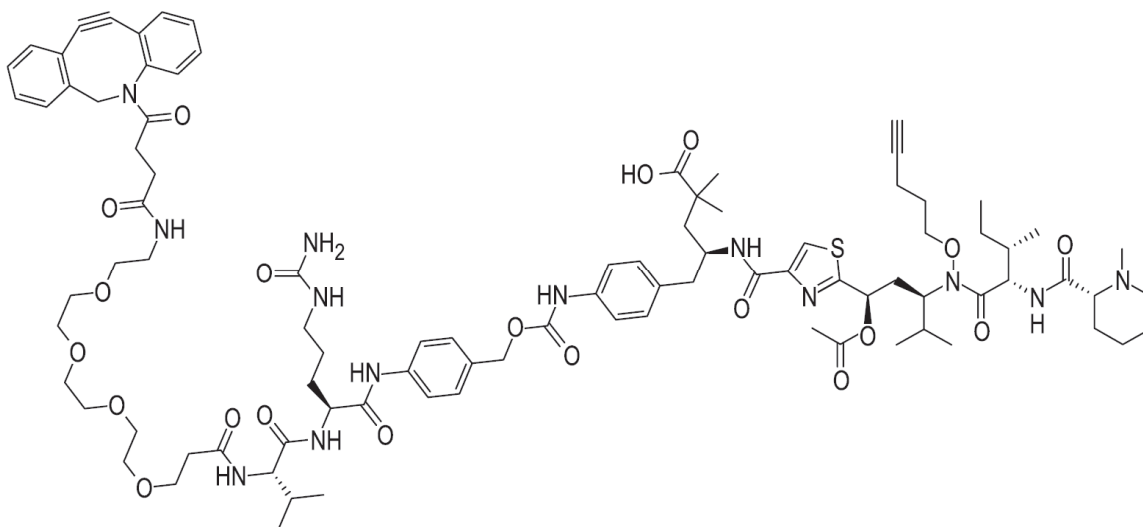
[0011h] In one aspect, the present disclosure provides a process for preparing an antibody-drug conjugate comprising contacting an anti-FGFR2 antibody or antigen-binding fragment thereof with a compound having the following formula B¹:



B¹

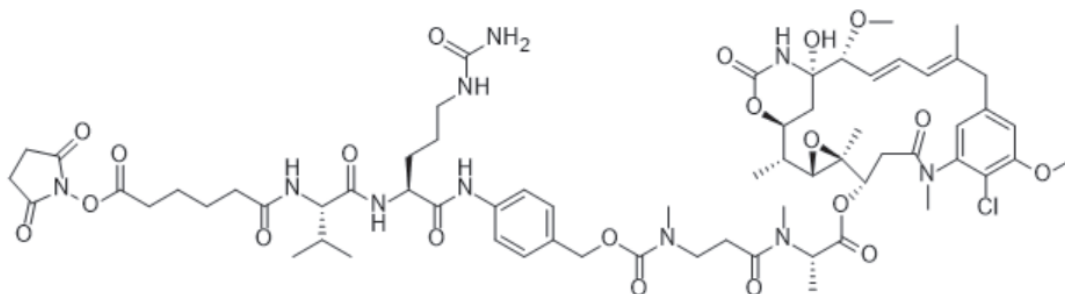
and aqueous diluent.

[0011i] In one aspect, the present disclosure provides a process for preparing an antibody-drug conjugate comprising contacting an anti-FGFR2 antibody or antigen-binding fragment thereof with a compound having the following structure:



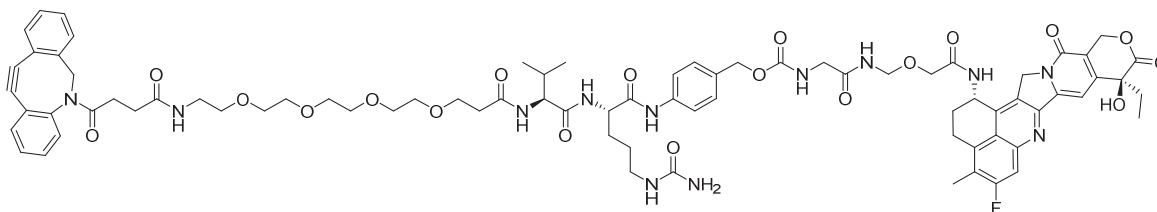
wherein the antibody or antigen-binding fragment thereof is functionalized with an azido group.

[0011j] In one aspect, the present disclosure provides a process for preparing an antibody-drug conjugate comprising contacting an anti-FGFR2 antibody or antigen-binding fragment thereof with a compound having the following formula:



and aqueous diluent.

[0011k] In one aspect, the present disclosure provides a process for preparing an antibody-drug conjugate comprising contacting an anti-FGFR2 antibody or antigen-binding fragment thereof with a compound having the following formula:



wherein the antibody or antigen-binding fragment thereof is functionalized with an azido group.

BRIEF DESCRIPTION OF THE FIGURES

[0012] Figure 1A and Figure 1B. **Figure 1A** depicts a monoclonal antibody with a click moiety spacer, a cathepsin B cleavable linker, and a tubulysin payload. **Figure 1B** depicts a process for site specific conjugation on the antibody.

[0013] Figure 2 provides SEC-HPLC analyses of the anti-FGFR2 antibody – tubulysin conjugate.

[0014] Figure 3 shows change in tumor volume and body weight in human gastric cancer xenografts over time with treatment using different dosages of Anti-FGFR2 antibody-tubulysin conjugate.

[0015] Figure 4 shows change in tumor volume and body weight in mice having human gastric cancer xenografts over time with treatment using different dosages of Anti-FGFR2 antibody-maytansinoid conjugate.

[0016] Figure 5 shows change in tumor volume and body weight in mice with human gastric cancer PDX GA0033 tumors over time with treatment using different dosages of Anti-FGFR2 antibody-tubulysin conjugate and Anti-FGFR2 antibody-maytansinoid conjugate. Mice were dosed on day 0 and day 7 with the respective ADCs or control antibodies.

[0017] Figure 6 shows change in tumor volume and body weight in mice with SNU-16 human

Claims

What is claimed is:

1. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to FGFR2, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3), wherein:

(a) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 4, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 6, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 8, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 12, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 14, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 16; or

(b) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 24, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 6, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 26, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 30, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 32, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 34~~exhibits one or more of the following characteristics:~~

~~(a) is a fully human monoclonal antibody;~~

~~(b) binds to FGFR2b with a K_D equal to or less than 2.5×10^{-8} M as measured by surface plasmon resonance;~~

~~(c) selectively binds hFGFR2b over hFGFR2c; and~~

~~(d) comprises three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 22, or an amino acid sequence that is at least 90% identical thereto; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10 or SEQ ID NO: 28, or an amino acid sequence that is at least 90% identical thereto.~~

2. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a comprising: three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 22, or an amino acid

sequence that is at least 90% identical thereto; and ~~three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the a~~ light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 10 or SEQ ID NO: 28, or an amino acid sequence that is at least 90% identical thereto.

3. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~2~~1, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof ~~has one or more of the following~~ characteristics:

~~(a) is a fully human monoclonal antibody;~~

~~(b) binds to FGFR2b with a K_D equal to or less than 2.5×10^{-8} M as measured by surface plasmon resonance;~~

~~(c) has a half-life ($t_{1/2}$) of greater than about 10 minutes as measured by surface plasmon resonance; and~~

~~(d) selectively binds hFGFR2b over hFGFR2c.~~

4. ~~The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 2, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence of SEQ ID NO: 4 comprising two or fewer amino acid substitutions; HCDR2 comprises the amino acid sequence of SEQ ID NO: 6 or an amino acid sequence of SEQ ID NO: 6 comprising two or fewer amino acid substitutions; HCDR3 comprises the amino acid sequence of SEQ ID NO: 8 or an amino acid sequence of SEQ ID NO: 8 comprising two or fewer amino acid substitutions; LCDR1 comprises the amino acid sequence of SEQ ID NO: 12 or an amino acid sequence of SEQ ID NO: 12 comprising two or fewer amino acid substitutions; LCDR2 comprises the amino acid sequence of SEQ ID NO: 14 or an amino acid sequence of SEQ ID NO: 14 comprising two or fewer amino acid substitutions; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 16 or an amino acid sequence of SEQ ID NO: 16 comprising two or fewer amino acid substitutions.~~

~~54.~~ The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~2~~1, wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 4; the HCDR2 comprises the amino acid sequence of SEQ ID NO: 6; the HCDR3 comprises the amino acid sequence of SEQ ID NO: 8; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 12; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 14; and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 16.

~~65.~~ The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~24~~1, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises an HCVR comprising

the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence that is at least 95% identical thereto; and an LCVR comprising the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence that is at least 95% identical thereto.

~~76.~~ The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~25~~, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2; and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

~~8.~~ The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 1, comprising: three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 22, or an amino acid sequence that is at least 90% identical thereto; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 28, or an amino acid sequence that is at least 90% identical thereto.

~~9.~~ The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 8, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof has one or more of the following characteristics:

(a) is a fully human monoclonal antibody;

(b) binds to FGFR2b with a K_D equal to or less than 8.9×10^{-9} M as measured by surface plasmon resonance;

(c) has a half-life ($t_{1/2}$) of greater than about 25 minutes as measured by surface plasmon resonance; and

(d) selectively binds hFGFR2b over hFGFR2c.

~~10.~~ The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 8, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 24 or an amino acid sequence of SEQ ID NO: 24 comprising two or fewer amino acid substitutions; HCDR2 comprises the amino acid sequence of SEQ ID NO: 6 or an amino acid sequence of SEQ ID NO: 6 comprising two or fewer amino acid substitutions; HCDR3 comprises the amino acid sequence of SEQ ID NO: 26 or an amino acid sequence of SEQ ID NO: 26 comprising two or fewer amino acid substitutions; LCDR1 comprises the amino acid sequence of SEQ ID NO: 30 or an amino acid sequence of SEQ ID NO: 30 comprising two or fewer amino acid substitutions; LCDR2 comprises the amino acid sequence of SEQ ID NO: 32 or an amino acid sequence of SEQ ID NO: 32 comprising two or fewer amino acid substitutions; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 34 or an amino acid sequence of SEQ ID NO: 34 comprising two or fewer amino acid substitutions.

~~1417.~~ The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~81~~, wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 24; the HCDR2 comprises the amino acid sequence of SEQ ID NO: 6; the HCDR3 comprises the amino acid sequence of SEQ ID NO: 26; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 30; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 32; and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 34.

~~1428.~~ The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~87~~, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22 or an amino acid sequence that is at least 95% identical thereto; and an LCVR comprising the amino acid sequence of SEQ ID NO: 28 or an amino acid sequence that is at least 95% identical thereto.

~~1439.~~ The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 8, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22; and an LCVR comprising the amino acid sequence of SEQ ID NO: 28.

~~1410.~~ A pharmaceutical composition comprising a therapeutically effective amount of the antibody or antigen-binding fragment thereof ~~one or more isolated human monoclonal antibodies, or antigen-binding fragments thereof,~~ of any of claims 1 to ~~138~~ together with one or more pharmaceutically acceptable excipients.

~~1511.~~ A nucleic acid molecule encoding the antibody or antigen-binding fragment thereof ~~of a human monoclonal antibody or fragment thereof that binds to FGFR2 according to any one~~ of claims 1 to ~~138~~.

~~1612.~~ An expression vector comprising the nucleic acid molecule of claim 11 ~~encoding a human monoclonal antibody or fragment thereof that binds to FGFR2 according to claim 15.~~

~~1713.~~ A host cell containing the expression vector of claim ~~142~~.

~~1814.~~ The anti-FGFR2 antibody or antigen-binding fragment thereof of any one of claims 1 to ~~138~~, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof is conjugated to a cytotoxin.

~~19.~~ ~~The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 18, wherein the anti-FGFR2 antibody, or antigen-binding fragment thereof, exhibits one or more of the following characteristics:~~

~~(a) is selectively cytotoxic to hFGFR2b-expressing cells over hFGFR2c-expressing cells;~~

~~(b) binds to FGFR2b with a K_D equal to or less than 4.8×10^{-8} M as measured by surface plasmon resonance;~~

~~(c) has a half-life ($t_{1/2}$) of greater than about 7 minutes as measured by surface plasmon resonance; and~~

~~(d) induces regression of FGFR2b positive tumors in a dose dependent manner.~~

~~2015.~~ The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~18~~14, wherein the cytotoxin is selected from the group consisting of biotoxins, chemotherapeutic agents, and radioisotopes.

~~21~~16. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~20~~14, wherein the cytotoxin is a tubulysin, a maytansinoid, or a camptothecin, or an analog thereof.

~~22~~17. The anti-FGFR2 antibody or antigen-binding fragment thereof of any one of claims ~~1 to 13~~14 to 16, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof is conjugated to ~~a~~the cytotoxin through a linker.

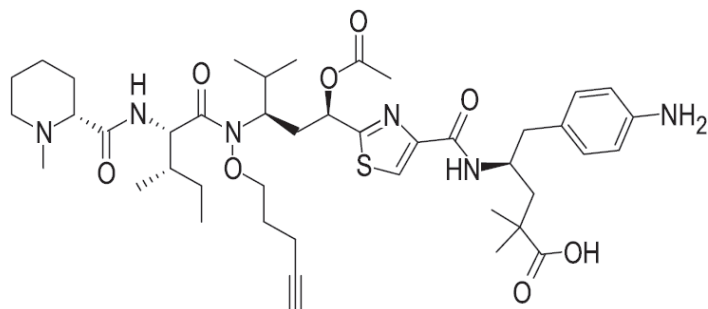
18. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 17, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof is conjugated to the cytotoxin through an azido-PEG₃-amine linker.

19. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 16, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof is conjugated to the cytotoxin at heavy chain residue Q295 and/or Q297.

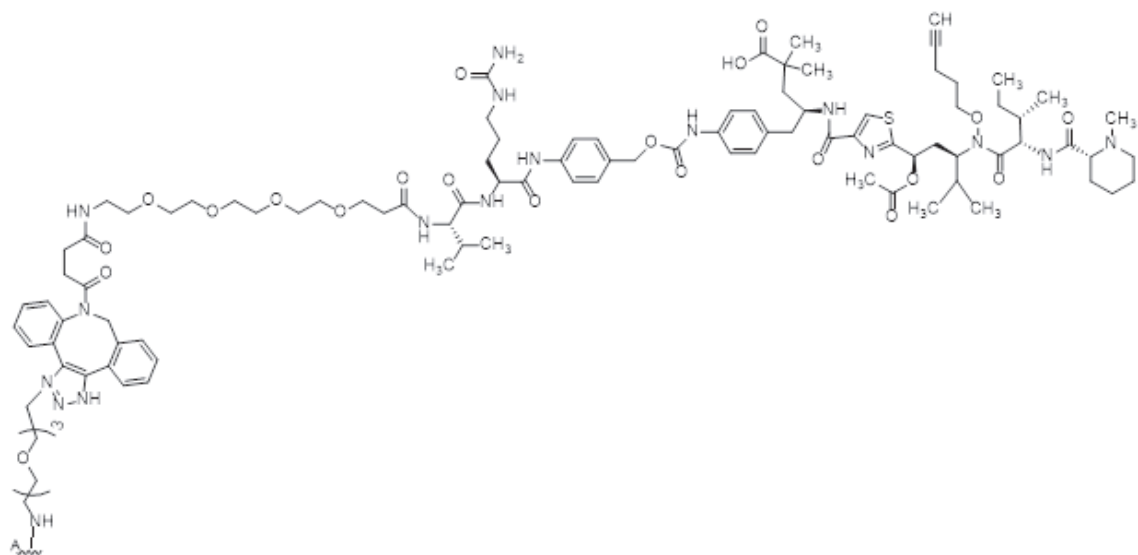
~~23~~20. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~22~~16, wherein the cytotoxin is a tubulysin.

~~24. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 23, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof is conjugated to tubulysin through an azido-PEG₃-amine linker.~~

~~25~~21. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~23~~20, wherein the tubulysin is:



2622. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 2521, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof is conjugated to



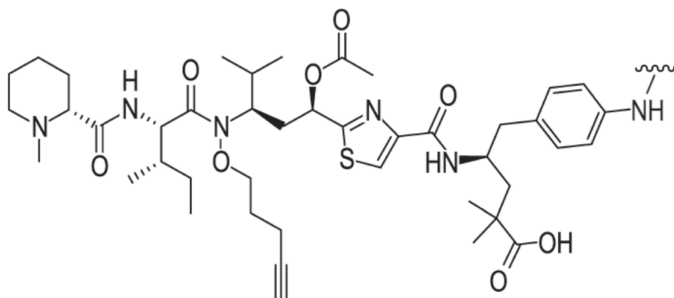
or a regioisomer thereof, wherein ξ^A is a bond to a heavy chain glutamine.

~~27. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 23, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof is conjugated to tubulysin through Q295.~~

~~28. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 27, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof further comprises a tubulysin conjugated through Q297.~~

2923. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 2320,

wherein the tubulysin is



wherein the  is the bond to the linker.

~~30~~24. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~29~~23, wherein the linker comprises a valine-citrulline moiety and a PAB moiety.

~~31. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 29 or 30, comprising three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the HCVR amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the LCVR amino acid sequence of SEQ ID NO: 10.~~

~~32. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 29 or 30, comprising: an HCDR1 having the amino acid sequence of SEQ ID NO: 4; an HCDR2 having the amino acid sequence of SEQ ID NO: 6; an HCDR3 having the amino acid sequence of SEQ ID NO: 8; an LCDR1 having the amino acid sequence of SEQ ID NO: 12; an LCDR2 having the amino acid sequence of SEQ ID NO: 14; and an LCDR3 having the amino acid sequence of SEQ ID NO: 16.~~

~~33. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 29 or 30, comprising an HCVR comprising the amino acid sequence of SEQ ID NO: 2; and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.~~

~~34. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 29 or 30, comprising three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the HCVR amino acid sequence of SEQ ID NO: 22; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the LCVR amino acid sequence of SEQ ID NO: 28.~~

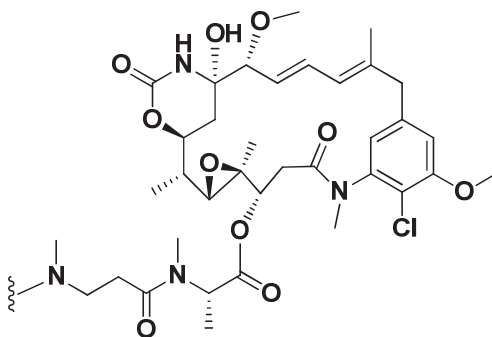
~~35. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 29 or 30, comprising: an HCDR1 having the amino acid sequence of SEQ ID NO: 24; an HCDR2 having the amino acid sequence of SEQ ID NO: 6; an HCDR3 having the amino acid sequence of SEQ ID NO: 26; an LCDR1 having the amino acid sequence of SEQ ID NO: 30; an LCDR2 having the~~

amino acid sequence of SEQ ID NO: 32; and an LCDR3 having the amino acid sequence of SEQ ID NO: 34.

36. ~~The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 29 or 30, comprising an HCVR comprising the amino acid sequence of SEQ ID NO: 22; and an LCVR comprising the amino acid sequence of SEQ ID NO: 28.~~

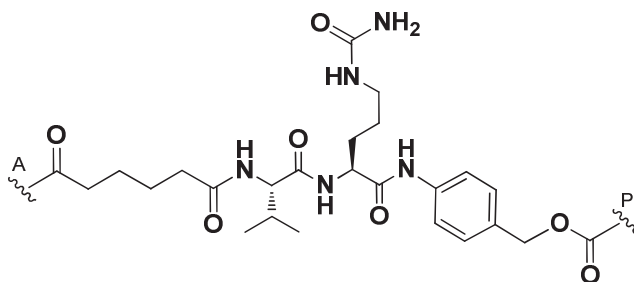
~~3725.~~ The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~2216~~, wherein the ~~cytotoxin~~ ~~cytotoxic agent~~ is a maytansinoid.

~~3826~~. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~3725~~, wherein the maytansinoid is



wherein the  is the bond to the linker.

~~3927~~. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~3826~~, wherein the linker is:



wherein the bond noted with $\overset{\text{A}}{\sim}$ represents the bond to the antibody or antigen-binding fragment thereof and the bond noted with $\overset{\text{P}}{\sim}$ represents the bond to the maytansinoid.

~~40. The anti-FGFR2 antibody or antigen-binding fragment thereof of either claim 38 or 39, comprising three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the~~

~~HCVR amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the LCVR amino acid sequence of SEQ ID NO: 10.~~

~~41. The anti-FGFR2 antibody or antigen-binding fragment thereof of either claim 38 or 39, comprising: an HCDR1 having the amino acid sequence of SEQ ID NO: 4; an HCDR2 having the amino acid sequence of SEQ ID NO: 6; an HCDR3 having the amino acid sequence of SEQ ID NO: 8; an LCDR1 having the amino acid sequence of SEQ ID NO: 12; an LCDR2 having the amino acid sequence of SEQ ID NO: 14; and an LCDR3 having the amino acid sequence of SEQ ID NO: 16.~~

~~42. The anti-FGFR2 antibody or antigen-binding fragment thereof of either claim 38 or 39, comprising an HCVR comprising the amino acid sequence of SEQ ID NO: 2; and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.~~

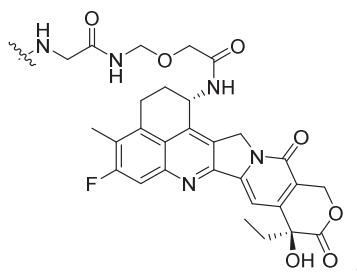
~~43. The anti-FGFR2 antibody or antigen-binding fragment thereof of either claim 38 or 39, comprising three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the HCVR amino acid sequence of SEQ ID NO: 22; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the LCVR amino acid sequence of SEQ ID NO: 28.~~

~~44. The anti-FGFR2 antibody or antigen-binding fragment thereof of either claim 38 or 39, comprising: an HCDR1 having the amino acid sequence of SEQ ID NO: 24; an HCDR2 having the amino acid sequence of SEQ ID NO: 6; an HCDR3 having the amino acid sequence of SEQ ID NO: 26; an LCDR1 having the amino acid sequence of SEQ ID NO: 30; an LCDR2 having the amino acid sequence of SEQ ID NO: 32; and an LCDR3 having the amino acid sequence of SEQ ID NO: 34.~~

~~45. The anti-FGFR2 antibody or antigen-binding fragment thereof of either claim 38 or 39, comprising an HCVR comprising the amino acid sequence of SEQ ID NO: 22; and an LCVR comprising the amino acid sequence of SEQ ID NO: 28.~~

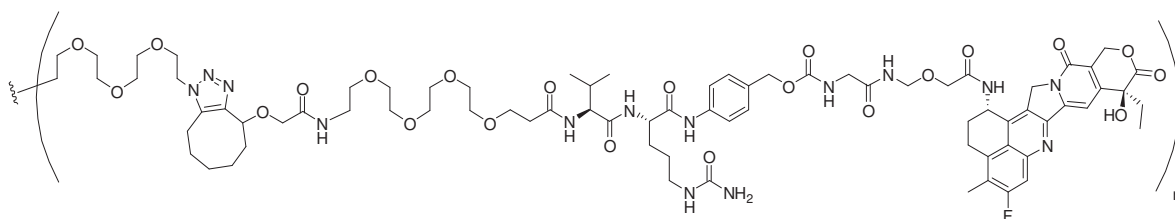
~~46~~28. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~22~~16, wherein the cytotoxin ~~eytotoxic agent~~ is a camptothecin analog.

~~47~~29. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim ~~22~~16, wherein the cytotoxin ~~eytotoxic agent~~ is



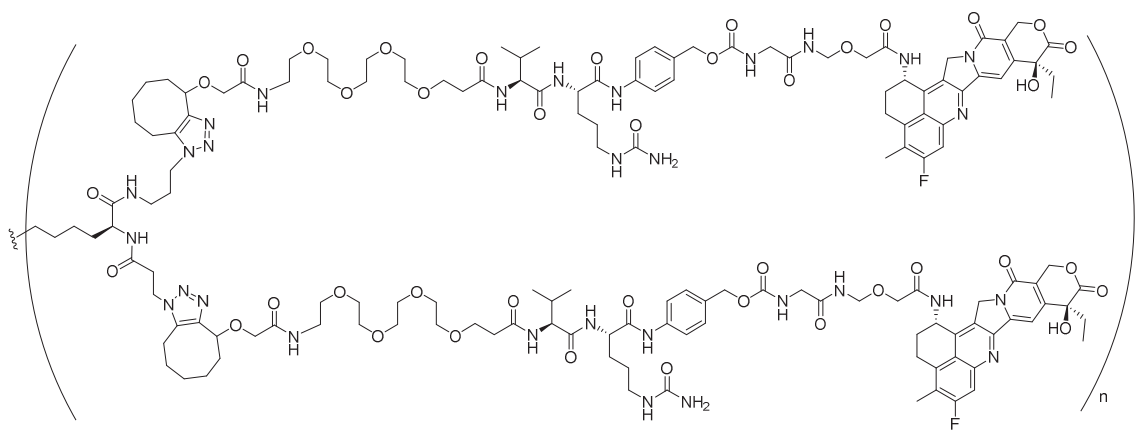
wherein $\sim$ represents the point of attachment to a linker.

4830. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 4628, wherein the antibody or antigen-binding fragment thereof is conjugated to:



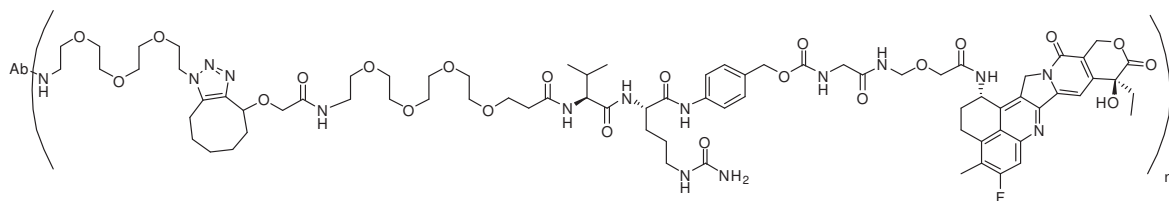
, wherein $\sim$ is a bond to a glutamine residue of said antibody or antigen binding fragment thereof and n is 42 to 8.

4931. The anti-FGFR2 antibody or antigen-binding fragment thereof of claim 4628, wherein the antibody or antigen-binding fragment thereof is conjugated to:

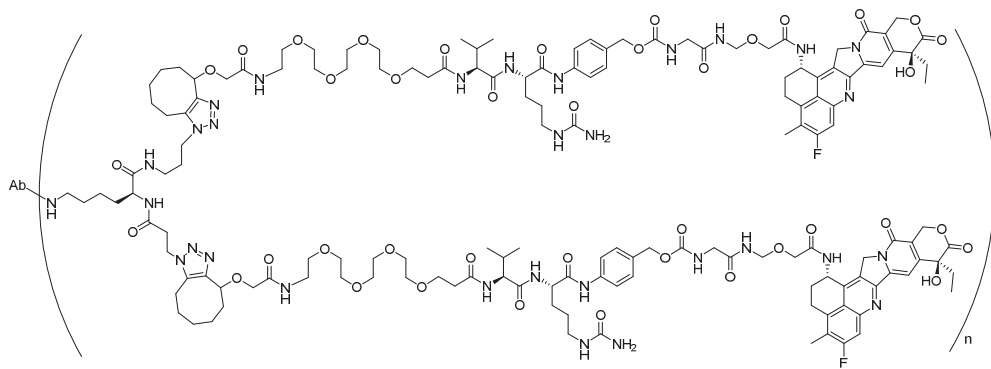


wherein $\sim$ is a bond to a glutamine residue of said antibody or antigen binding fragment thereof and n is 42 to 8.

32. An antibody-drug conjugate comprising an anti-FGFR2 antibody, or an antigen-binding fragment thereof, conjugated to a camptothecin analog, wherein the antibody-drug conjugate has the following structure:



or



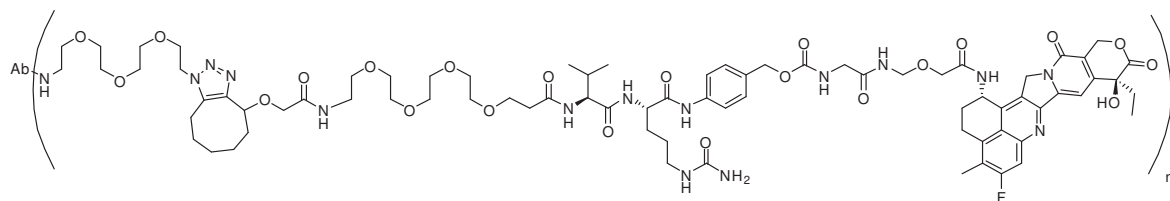
wherein n is a value between 2 and 12; and

wherein Ab is the anti-FGFR2 antibody or antigen-binding fragment thereof, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises:

(i) an HCDR1 comprising the amino acid sequence of SEQ ID NO:4, an HCDR2 comprising the amino acid sequence of SEQ ID NO:6, an HCDR3 comprising the amino acid sequence of SEQ ID NO:8, an LCDR1 comprising the amino acid sequence of SEQ ID NO:12, an LCDR2 comprising the amino acid sequence of SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:16; or

(ii) an HCDR1 comprising the amino acid sequence of SEQ ID NO:24, an HCDR2 comprising the amino acid sequence of SEQ ID NO:6, an HCDR3 comprising the amino acid sequence of SEQ ID NO:26, an LCDR1 comprising the amino acid sequence of SEQ ID NO:30, an LCDR2 comprising the amino acid sequence of SEQ ID NO:32, and an LCDR3 comprising the amino acid sequence of SEQ ID NO:34.

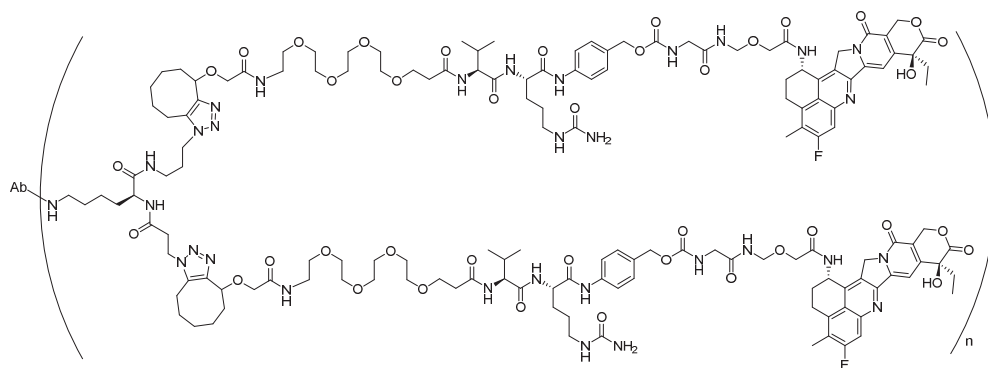
33. The antibody-drug conjugate of claim 32, wherein the antibody-drug conjugate has the structure



1

wherein n is a value between 2 and 12.

34. The antibody-drug conjugate of claim 32, wherein the antibody-drug conjugate has the structure



1

wherein n is a value between 2 and 12.

35. The antibody-drug conjugate of claim 32, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain comprising a Q295 residue and a Q297 residue, and wherein the camptothecin analog is conjugated to the antibody or antigen-binding fragment thereof at Q295 and Q297.

50.—The anti-FGFR2 antibody or antigen-binding fragment thereof of any one of claims 47 through 49, comprising three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the HCVR amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the LCVR amino acid sequence of SEQ ID NO: 10.

51-36. The antibody-drug conjugate of claim 32, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises of any one of claims 47 through 49, comprising: an HCDR1 having the amino acid sequence of SEQ ID NO: 4; an HCDR2 having the amino acid sequence of SEQ ID NO: 6; an HCDR3 having the amino acid sequence of SEQ ID NO: 8; an LCDR1 having the amino acid sequence of SEQ ID NO: 12; an LCDR2 having the amino acid

sequence of SEQ ID NO: 14; and an LCDR3 having the amino acid sequence of SEQ ID NO: 16.

~~5237.~~ The antibody-drug conjugate of claim 36, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises ~~of any one of claims 47 through 49, comprising an HCVR comprising the amino acid sequence of SEQ ID NO: 2; and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.~~

~~53.~~ The ~~anti-FGFR2 antibody or antigen-binding fragment thereof of any one of claims 47 through 49, comprising three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the HCVR amino acid sequence of SEQ ID NO: 22; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the LCVR amino acid sequence of SEQ ID NO: 28.~~

~~5438.~~ The antibody-drug conjugate of claim 32, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises ~~of any one of claims 47 through 49, comprising:~~ an HCDR1 having the amino acid sequence of SEQ ID NO: 24; an HCDR2 having the amino acid sequence of SEQ ID NO: 6; an HCDR3 having the amino acid sequence of SEQ ID NO: 26; an LCDR1 having the amino acid sequence of SEQ ID NO: 30; an LCDR2 having the amino acid sequence of SEQ ID NO: 32; and an LCDR3 having the amino acid sequence of SEQ ID NO: 34.

~~5539.~~ The antibody-drug conjugate of claim 38, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises ~~of any one of claims 47 through 49, comprising an HCVR comprising the amino acid sequence of SEQ ID NO: 22; and an LCVR comprising the amino acid sequence of SEQ ID NO: 28.~~

~~56.~~ A pharmaceutical composition comprising the anti-FGFR2 antibody or antigen-binding fragment thereof of any one of claims 18 to 55, and a pharmaceutically acceptable carrier.

40. Use of the anti-FGFR2 antibody or antigen-binding fragment thereof of any one of claims 14-31, or the antibody-drug conjugate of any one of claims 32-39, in the preparation of a medicament for treating a disease or disorder associated with FGFR2 expression.

~~5741.~~ The A use method of treating a cancer in a subject suffering from a tumor overexpressing FGFR2, the method comprising administering to the subject the anti-FGFR2 antibody or antigen-binding fragment thereof of claim 40, wherein the disease or disorder is a cancer of any one of claims 18 to 55.

~~5842.~~ The use method of claim ~~5741~~, wherein the cancer is selected from the group

consisting of breast invasive ductal carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, colon adenocarcinoma, and adenocarcinoma of the gastroesophageal junction.

~~59.—The method of claim 57, further comprising administering to the subject a second anti-cancer therapeutic agent.~~

~~60.—A method of treating a cancer, reducing tumor growth, and/or causing tumor regression in a subject, the method comprising administering to a subject in need thereof an antibody-drug conjugate (ADC) comprising an anti-FGFR2 antibody or antigen-binding fragment thereof and a cytotoxin, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises:~~

~~(i) an HCDR1 having the amino acid sequence of SEQ ID NO: 4; an HCDR2 having the amino acid sequence of SEQ ID NO: 6; an HCDR3 having the amino acid sequence of SEQ ID NO: 8; an LCDR1 having the amino acid sequence of SEQ ID NO: 12; an LCDR2 having the amino acid sequence of SEQ ID NO: 14; and an LCDR3 having the amino acid sequence of SEQ ID NO: 16; or~~

~~——(ii) an HCDR1 having the amino acid sequence of SEQ ID NO: 24; an HCDR2 having the amino acid sequence of SEQ ID NO: 6; an HCDR3 having the amino acid sequence of SEQ ID NO: 26; an LCDR1 having the amino acid sequence of SEQ ID NO: 30; an LCDR2 having the amino acid sequence of SEQ ID NO: 32; and an LCDR3 having the amino acid sequence of SEQ ID NO: 34.~~

~~61.—The method of claim 60, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2; and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.~~

~~62.—The method of claim 60, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22; and an LCVR comprising the amino acid sequence of SEQ ID NO: 28.~~

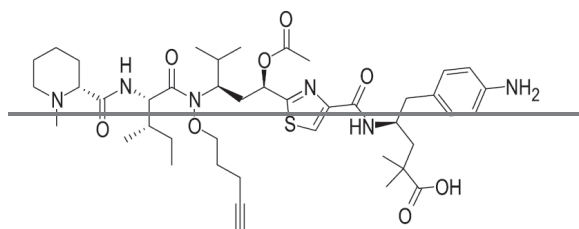
~~63.—The method of any one of claims 60 through 62, wherein the cytotoxin is selected from the group consisting of biotoxins, chemotherapeutic agents, and radioisotopes.~~

~~64.—The method of any one of claims 60 through 63, wherein the cytotoxin is a tubulysin, a maytansinoid, or a camptothecin.~~

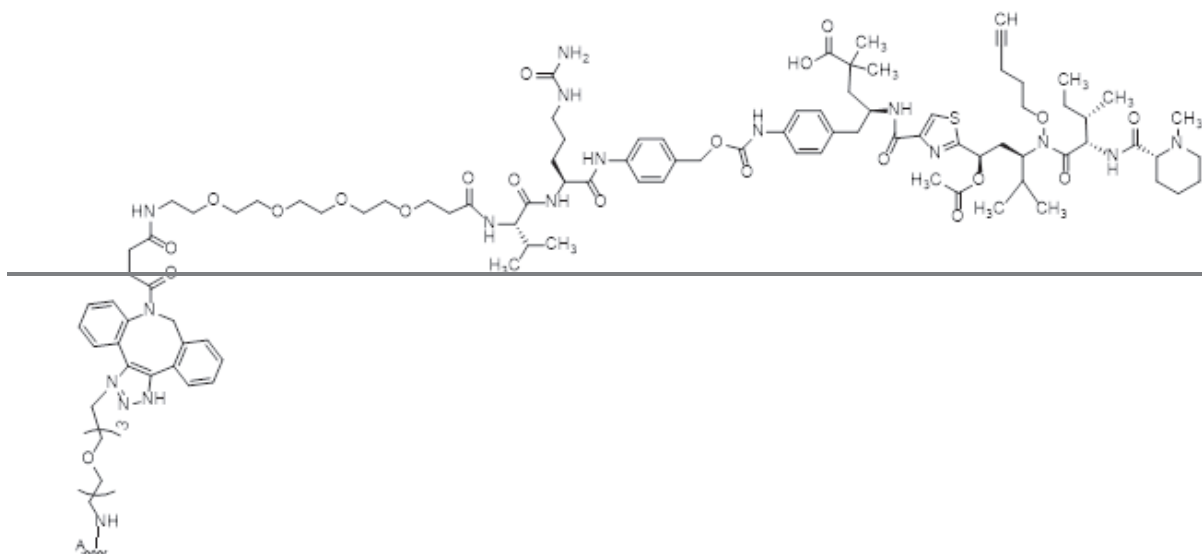
~~65.—The method of any one of claims 60 through 64, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof is conjugated to a cytotoxin through a linker.~~

~~66.—The method of claim 65, wherein the cytotoxin is a tubulysin.~~

67.—The method of claim 66, wherein the tubulysin is



68.—The method of claim 65, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof is conjugated to



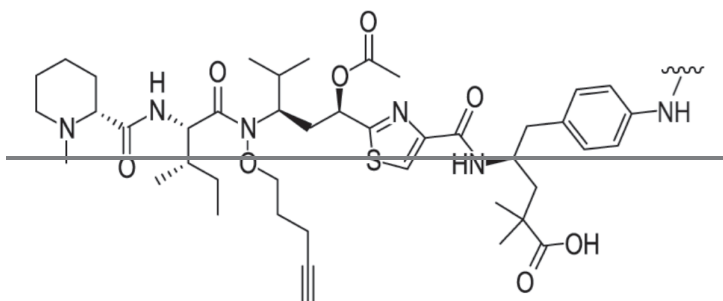
or a regioisomer thereof, wherein $\overset{\text{A}}{\text{---}}$ is a bond to a heavy chain glutamine.

69.—The method of claim 66, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof is conjugated to tubulysin through Q295.

70.—The method of claim 69, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof further comprises a tubulysin conjugated through Q297.

71.—The method of claim 66,

wherein the tubulysin is



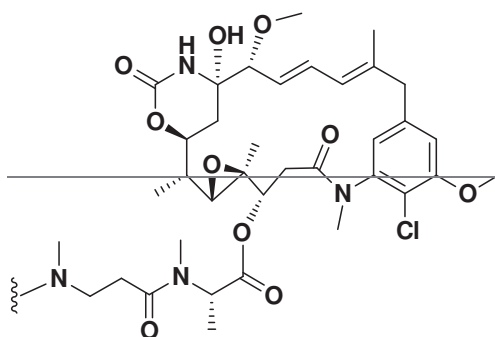
wherein the  is the bond to the linker.

72. The method of claim 71, wherein the linker comprises a valine-citrulline moiety and a PAB moiety.

73. The method of any one of claims 66 through 71, wherein the tubulysin is conjugated to the anti-EGFR2 antibody or antigen-binding fragment thereof through a linker, wherein the linker is azido-PEG₃-amine.

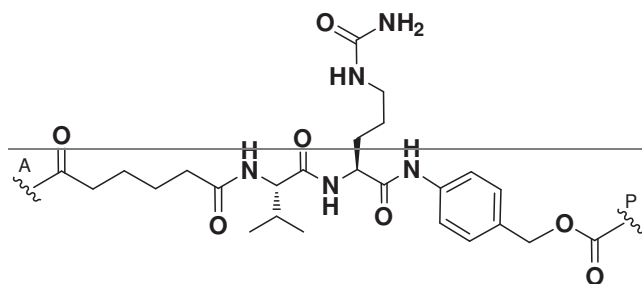
74. The method of claim 65, wherein the cytotoxic agent is a maytansinoid.

75. The method of claim 74, wherein the maytansinoid is:



wherein the  is the bond to the linker.

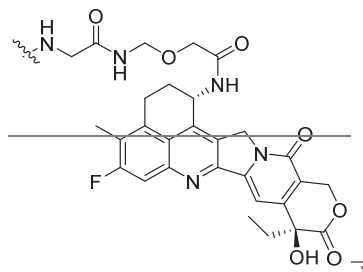
76. The method of claim 75, wherein the linker is



wherein the bond noted with $\overset{\delta A}{\sim}$ represents the bond to the anti-FGFR2 antibody or antigen-binding fragment thereof and the bond noted with $\overset{\delta P}{\sim}$ represents the bond to the cytotoxin.

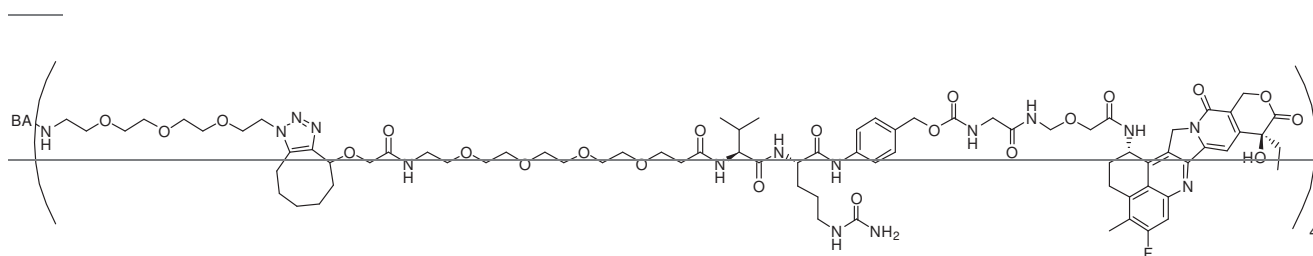
77. The method of claim 55, wherein the cytotoxin is a camptothecin analog.

78. The method of claim 77, wherein the camptothecin analog is



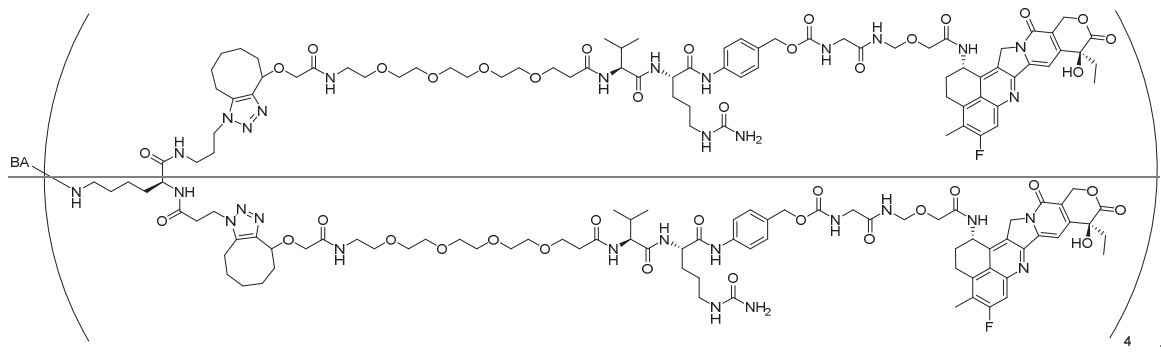
wherein $\sim$ represents the point of attachment to a linker.

79. The method of claim 76, wherein the ADC is:



, wherein BA represents the anti-FGFR2 antibody or antigen-binding fragment thereof.

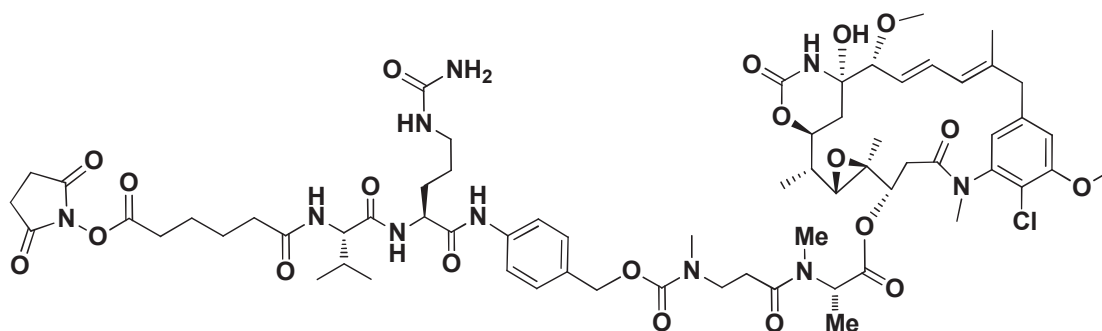
80. The method of claim 76, wherein the ADC is:



wherein BA represents the anti-FGFR2 antibody or antigen-binding fragment thereof.

8143. A process for preparing an antibody-drug conjugate comprising contacting an anti-FGFR2 antibody or antigen-binding fragment thereof with a compound having the following

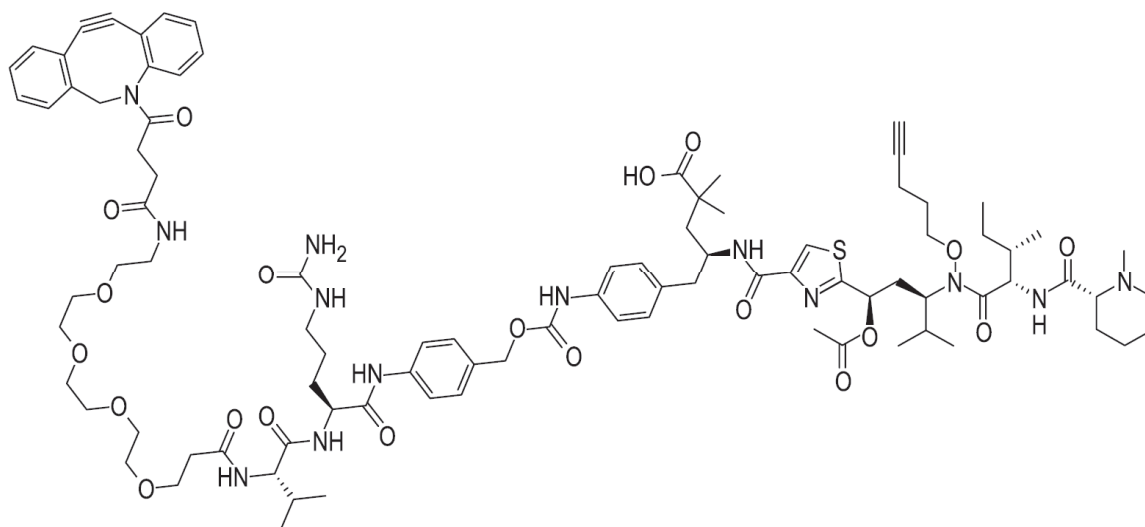
formula B¹:



B¹

and aqueous diluent.

8244. A process for preparing an antibody-drug conjugate comprising contacting an anti-FGFR2 antibody or antigen-binding fragment thereof with a compound having the following structure:

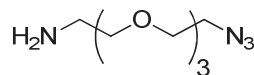


wherein the antibody or antigen-binding fragment thereof is functionalized with an azido group.

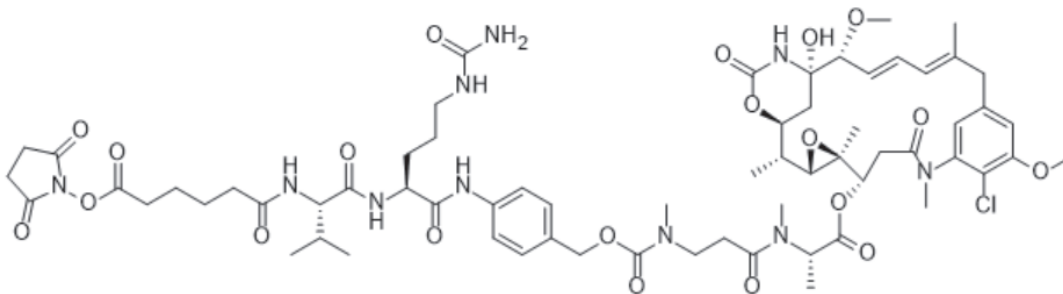
8345. The process of claim 8044, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof that is functionalized with an azido group is prepared by contacting an anti-FGFR2 antibody or antigen-binding fragment thereof with transglutaminase and a compound comprising a primary amine, PEG group, and azido group.

8446. The process of claim 8145, wherein the compound comprising a primary amine,

PEG group, and azido group is:

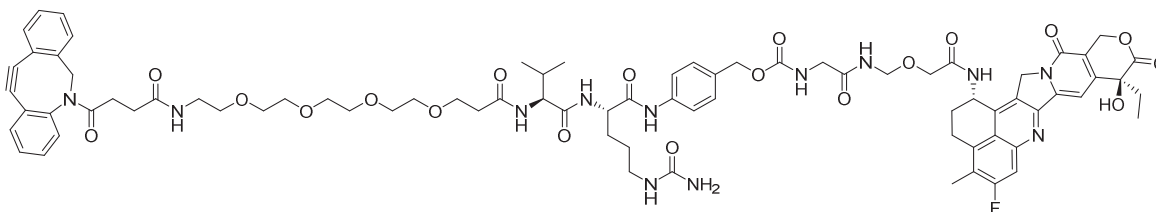


~~8547~~. A process for preparing an antibody-drug conjugate comprising contacting an anti-FGFR2 antibody or antigen-binding fragment thereof with a compound having the following formula:



and aqueous diluent.

~~8648~~. A process for preparing an antibody-drug conjugate comprising contacting an anti-FGFR2 antibody or antigen-binding fragment thereof with a compound having the following formula:



wherein the antibody or antigen-binding fragment thereof is functionalized with an azido group.

~~8749~~. The process of claim ~~8648~~, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof that is functionalized with an azido group is prepared by contacting an anti-FGFR2 antibody or antigen-binding fragment thereof with transglutaminase and a compound comprising a primary amine and azido group.

~~88. The process of any one of claims 81 through 87, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises:~~

~~(i) three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the HCVR~~

~~amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the LCVR amino acid sequence of SEQ ID NO: 10; or~~

~~(ii) three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the HCVR amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the LCVR amino acid sequence of SEQ ID NO: 10.~~

~~89~~50. The process of any one of claims ~~43-49~~ 81 through 88, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises:

(i) an HCDR1 having the amino acid sequence of SEQ ID NO: 4; an HCDR2 having the amino acid sequence of SEQ ID NO: 6; an HCDR3 having the amino acid sequence of SEQ ID NO: 8; an LCDR1 having the amino acid sequence of SEQ ID NO: 12; an LCDR2 having the amino acid sequence of SEQ ID NO: 14; and an LCDR3 having the amino acid sequence of SEQ ID NO: 16; or

(ii) an HCDR1 having the amino acid sequence of SEQ ID NO: 24; an HCDR2 having the amino acid sequence of SEQ ID NO: 6; an HCDR3 having the amino acid sequence of SEQ ID NO: 26; an LCDR1 having the amino acid sequence of SEQ ID NO: 30; an LCDR2 having the amino acid sequence of SEQ ID NO: 32; and an LCDR3 having the amino acid sequence of SEQ ID NO: 34.

~~90~~51. The process of ~~any one of claims 81 through 89~~ claim 50, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2; and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

~~91~~52. The process of ~~any one of claims 81 through 89~~ claim 50, wherein the anti-FGFR2 antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22; and an LCVR comprising the amino acid sequence of SEQ ID NO: 28.

~~92~~53. The product of the process of any one of claims ~~81 through 91~~ 43-52.

54. The anti-FGFR2 antibody or antigen-binding fragment thereof of any one of claims 14-31, or the antibody-drug conjugate of any one of claims 32-39 for use in therapy.