

cytotoxic agent. The ADCs can be useful to treat PRLR positive breast cancer, and are particularly useful when used as a combination therapy with fulvestrant.

[0007] Provided is a method of treating PRLR positive breast cancer, comprising co-administering to a patient a therapeutically effective amount of: (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to a cytotoxic agent, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and (b) fulvestrant.

[0007a] In one aspect, provided is use of (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to a maytansinoid, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and (b) fulvestrant in the manufacture of a medicament for treating PRLR positive breast cancer.

[0008] In some examples, the cytotoxic agent is a maytansinoid.

[0009] Provided is a method of treating PRLR positive breast cancer in a patient, comprising co-administering to the patient a therapeutically effective amount of: (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to maytansinoid, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and (b) fulvestrant.

[0010] In some examples, the maytansinoid is DM1 or DM4.

[0011] In some examples, the ADC kills cells that express PRLR at an expression level of less than 30-fold above background, for example, at an expression level of less than 20-fold above background. In some examples, the ADC kills cells that express PRLR at an expression level greater than 12-fold above background but less than 30-fold above background.

[0012] Provided is a method of treating PRLR positive breast cancer in a patient, comprising co-administering to the patient a therapeutically effective amount of: (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to DM1 through an MCC linker, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and (b) fulvestrant.

[0012a] In another aspect, provided is use of (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to DM1 through an MCC linker, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and (b) fulvestrant in the manufacture of a medicament for treating PRLR positive breast cancer in a patient.

[0013] In some examples, the patient was previously treated with an estrogen receptor inhibitor.

[0014] Treatment of a PRLR positive breast cancer with an ADC described herein can have one or more of the following effects, among others: the ADC can inhibit prolactin mediated STAT5 activity; the ADC can induce mitotic arrest in cells expressing PRLR; and/or the ADC can inhibit the growth of cells expressing PRLR.

[0015] Provided herein is a method for killing tumor cells that express low levels of PRLR, the method comprising contacting the cells with: (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof

conjugated to a cytotoxic agent, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and (b) fulvestrant. In some examples, the tumor cells express less than 1 million copies of PRLR per cell. In some examples, the tumor cells express between 300 and 500,000 copies of PRLR per cell.

[0016] Provided herein is a method for killing tumor cells that express low levels of PRLR, the method comprising contacting the cells with: (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to a maytansinoid, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and (b) fulvestrant.

[0016a] In another aspect, provided herein is use of (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to a maytansinoid, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and (b) fulvestrant in the manufacture of a medicament for killing tumor cells that express low levels of PRLR.

[0017] The antibodies useful according to the methods provided herein can be full-length, for example, an IgG1 or and IgG4 antibody, or may comprise only an antigen-binding portion, for example, a Fab, F(ab')₂, or scFv fragment, and can be modified to affect functionality, e.g., to eliminate residual effector functions (Reddy et al., (2000), J. Immunol. 164: 1925-1933).

[0018] Provided herein are methods of using ADC comprising antibodies and antigen-binding fragments thereof that bind human prolactin receptor (PRLR). The ADCs are useful, *inter alia*, for targeting tumor cells that express PRLR.

[0019] Exemplary anti-PRLR antibodies useful herein are listed in Tables 1 and 2. Table 1 sets forth the amino acid sequence identifiers of the heavy chain variable regions (HCVRs), light chain variable regions (LCVRs), heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3), and light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of the exemplary anti-PRLR antibodies. Table 2 sets forth the nucleic acid sequence identifiers of the HCVRs, LCVRs, HCDR1, HCDR2 HCDR3, LCDR1, LCDR2 and LCDR3 of the exemplary anti-PRLR antibodies.

[0020] The ADCs useful herein comprise antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising an HCVR comprising an amino acid sequence selected from any of the HCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0021] The ADCs useful herein comprise antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising an LCVR comprising an amino acid sequence selected from any of the LCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0022] The ADCs useful herein comprise antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising an HCVR and an LCVR amino acid sequence pair (HCVR/LCVR) comprising any of the HCVR amino acid sequences listed in Table 1 paired with any of the LCVR amino acid sequences listed in Table 1. According to certain examples, the ADCs useful herein comprise antibodies, or antigen-binding fragments thereof, comprising an HCVR/LCVR amino acid sequence pair contained within any of the exemplary anti-PRLR antibodies listed in Table 1. In certain examples, the HCVR/LCVR amino acid sequence pair is selected from the group consisting of: 18/26; 66/74; 274/282; 290/298; and 370/378.

[0023] The ADCs useful herein comprise antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a heavy chain CDR1 (HCDR1) comprising an amino acid sequence selected from any of the HCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0024] The ADCs useful herein comprise antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a heavy chain CDR2 (HCDR2) comprising an amino acid sequence selected from any of the HCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0025] The ADCs useful herein comprise antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a heavy chain CDR3 (HCDR3) comprising an amino acid sequence selected from any of the HCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0026] The ADCs useful herein comprise antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a light chain CDR1 (LCDR1) comprising an amino acid sequence selected from any of the LCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0027] The ADCs useful herein comprise antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a light chain CDR2 (LCDR2) comprising an amino acid sequence selected from any of the LCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0028] The ADCs useful herein comprise antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a light chain CDR3 (LCDR3) comprising an amino acid sequence selected from any of the LCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0029] The ADCs useful herein comprise antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising an HCDR3 and an LCDR3 amino acid sequence pair (HCDR3/LCDR3) comprising any of the HCDR3 amino acid sequences listed in Table 1 paired with any of the LCDR3 amino acid sequences listed in Table 1. According to certain examples, the ADCs useful herein comprise antibodies, or antigen-binding fragments thereof, comprising an HCDR3/LCDR3 amino acid sequence pair contained within any of the exemplary anti-PRLR antibodies listed in Table 1. In certain examples, the HCDR3/LCDR3 amino acid sequence pair is selected from the group consisting of: 24/32; 72/80; 280/288; 296/304; and 376/384.

[0030] The ADCs useful herein comprise antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within any of the exemplary anti-PRLR antibodies listed in Table 1. In certain examples, the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set is selected from the group consisting of: 20-22-24-28-30-32; 68-70-72-76-78-80; 276-278-280-284-286-288; 292-294-296-300-302-304; and 372-374-376-380-382-384.

[0031] In a related example, the ADCs useful herein comprise antibodies, or antigen-binding fragments thereof that specifically bind PRLR, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within an HCVR/LCVR amino acid sequence pair as defined by any of the exemplary anti-PRLR antibodies listed in Table 1. For example, the antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprise the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of: 18/26; 66/74; 274/282; 290/298; and 370/378. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the

Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See, e.g.,* Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, *J. Mol. Biol.* 273:927-948 (1997); and Martin *et al.*, *Proc. Natl. Acad. Sci. USA* 86:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[0032] Also provided are nucleic acid molecules encoding anti-PRLR antibodies or portions thereof, which are useful in the methods described herein. For example, nucleic acid molecules are provided encoding any of the HCVR amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto. In another example, nucleic acid molecules are provided encoding any of the LCVR amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0033] Also provided herein are nucleic acid molecules encoding any of the HCDR1 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0034] Also provided herein are nucleic acid molecules encoding any of the HCDR2 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0035] Also provided herein are nucleic acid molecules encoding any of the HCDR3 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0036] Also provided herein are nucleic acid molecules encoding any of the LCDR1 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule

comprises a polynucleotide sequence selected from any of the LCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0037] Also provided herein are nucleic acid molecules encoding any of the LCDR2 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0038] Also provided herein are nucleic acid molecules encoding any of the LCDR3 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0039] Also provided herein are nucleic acid molecules encoding an HCVR, wherein the HCVR comprises a set of three CDRs (*i.e.*, HCDR1-HCDR2-HCDR3), wherein the HCDR1-HCDR2-HCDR3 amino acid sequence set is as defined by any of the exemplary anti-PRLR antibodies listed in Table 1.

[0040] Also provided herein are nucleic acid molecules encoding an LCVR, wherein the LCVR comprises a set of three CDRs (*i.e.*, LCDR1-LCDR2-LCDR3), wherein the LCDR1-LCDR2-LCDR3 amino acid sequence set is as defined by any of the exemplary anti-PRLR antibodies listed in Table 1.

[0041] Also provided herein are nucleic acid molecules encoding both an HCVR and an LCVR, wherein the HCVR comprises an amino acid sequence of any of the HCVR amino acid sequences listed in Table 1, and wherein the LCVR comprises an amino acid sequence of any of the LCVR amino acid sequences listed in Table 1. In certain examples, the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto, and a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto. In certain examples, the nucleic acid molecule encodes an HCVR and LCVR, wherein the HCVR and LCVR are both derived from the same anti-PRLR antibody listed in Table 1.

[0042] Also provided herein are recombinant expression vectors capable of expressing a polypeptide comprising a heavy or light chain variable region of an anti-PRLR antibody. For example, the recombinant expression vectors can comprise any of the nucleic acid molecules mentioned above, *i.e.*, nucleic acid molecules encoding any of the HCVR, LCVR, and/or CDR sequences as set forth in Table 1. Also provided herein are host cells into which such vectors have been introduced, as well as methods of producing the antibodies or portions thereof by culturing the host cells under conditions permitting production of the antibodies or antibody fragments, and recovering the antibodies and antibody fragments so produced.

[0043] In some examples, the ADCs useful herein comprise anti-PRLR antibodies having a modified glycosylation pattern. Modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety present on the oligosaccharide chain, for example, to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield et al. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0044] The disclosure provides a pharmaceutical composition comprising an ADC, wherein the ADC comprises a recombinant human antibody or fragment thereof which specifically binds PRLR conjugated to cytotoxic agent, and a pharmaceutically acceptable carrier. In a related part, the composition is an ADC comprising combination of an anti-PRLR antibody conjugated to a cytotoxic agent, and a second therapeutic agent. In one example, the second therapeutic agent is any agent that is advantageously combined with an anti-PRLR antibody, for example, fulvestrant. The ADCs can comprise an anti-PRLR antibody conjugated to a cytotoxic agent, for example, a maytansinoid. In some examples, the maytansinoid is DM1 or DM4. Exemplary combination therapies, co-formulations, and ADCs involving the anti-PRLR antibodies useful in the methods provided herein are disclosed elsewhere in the present disclosure.

[0045] Provided are therapeutic methods for killing tumor cells or for inhibiting or attenuating tumor cell growth using an anti-PRLR antibody or antigen-binding portion of an antibody as provided herein. The therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an ADC described herein to a subject having PRLR-positive breast cancer, in addition to treatment with fulvestrant.

[0046] The ADCs useful herein comprise anti-PRLR antibodies that interact with one or more amino acids contained within the sequence

MHECPDYITGGPNSCHFGKQYTSMWRTYIMM (SEQ ID NO:405, corresponding to amino acids 72 to 102 of SEQ ID NO:404).

[0047] Provided herein is a peptide that comprises an amino acid sequence that is the same as that of a fragment having no more than 102 amino acids of the amino acid sequence of SEQ. ID NO.:404. In a related part, the fragment is within the first fibronectin-like type III domain of the extracellular domain of PRLR (amino acids 27-128 of SEQ ID NO:404). Also provided is a peptide consisting essentially of an amino acid sequence that is the same as that of a fragment having no more than 102 amino acids of the amino acid sequence of SEQ. ID NO.:404. In a related part, the fragment is within the first fibronectin-like type III domain of the extracellular domain of PRLR (amino acids 27-128 of SEQ ID NO:404). Further provided is a peptide that consists of an amino acid sequence that is the same as that of a fragment having no more than 102 amino acids of the amino acid sequence of SEQ. ID NO.:404. In a related part, the fragment is within the first fibronectin-like type III domain of the extracellular domain of PRLR (amino acids 27-128 of SEQ ID NO:404). In another related part, the fragment is selected from the group consisting of (a) amino acids 72 to 94 of SEQ ID NO:404; (b) amino acids 72 to 95 of SEQ ID NO:404; (c) amino acids 96 to 101 of SEQ ID NO:404; and (d) amino acids 96 to 102 of SEQ ID NO:404. The peptide can be manufactured synthetically or isolated.

[0048] Also provided herein is a composition comprising a peptide that comprises an amino acid sequence that is the same as that of a fragment having no more than 102 amino acids of the amino acid sequence of SEQ. ID NO.:404. In a related part, the fragment is within the first fibronectin-like type III domain of the extracellular domain of PRLR (amino acids 27-128 of SEQ ID NO:404). Also provided herein are methods of detecting the presence and/or quantity of specific antibodies to the peptide in a sample, the method comprising contacting the sample with the composition, and detecting the presence and/or measuring the quantity of the specific antibodies bound to the composition. In a related part, the peptide is bound to a solid support. In another related part, the peptide is labeled such as with an enzyme, florescent, biotin, or radioactive label.

[0049] Also provided herein is a nucleic acid sequence encoding an amino acid sequence that is the same as that of a fragment having no more than 102 amino acids of the amino acid sequence of SEQ. ID NO.:404. In a related part, the fragment is within the first

fibronectin-like type III domain of the extracellular domain of PRLR (amino acids 27-128 of SEQ ID NO:404).

[0050] Also provided herein is a peptide that comprises an amino acid sequence of SEQ. ID NO.:405. Also provided is a peptide that consists essentially of an amino acid sequence of SEQ. ID NO.:405. Further provided is a peptide that consists of an amino acid sequence SEQ. ID NO.:405. The peptide can be manufactured synthetically or isolated.

[0051] Other examples will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0052] Figure 1A and 1B demonstrates H1H6958N2 and H1H6958N2-DM1 blocking PRLR binding to prolactin (PRL). Human (A) or monkey (B) PRLR bound to captured PRL with EC_{50} values of 4.9nM and 5.7nM, respectively (solid squares in insets in A and B). H1H6958N2-DM1 (solid circles) and H1H6958N2 (open circles) blocked human and monkey PRLR binding to PRL. Specifically, H1H6958N2-DM1 and H1H6958N2 blocked binding of 10nM human PRLR to PRL with IC_{50} values of 4.4nM and 5.0nM, respectively (A). Similarly, H1H6958N2-DM1 and H1H6958N2 blocked binding of 10nM monkey PRLR to PRL with IC_{50} values of 4.2nM and 5.8nM, respectively (B). Both control ADC (solid triangles) and control mAb (open triangles) displayed no blockade under identical assay conditions (A, B). Molarity indicates antibody concentration for ADCs and mAbs. Error bars represent SD.

[0053] Figure 1C shows HEK293/PRLR/STAT5-Luc cells treated with increasing concentrations of PRL (stars) resulting in an increase of luminescence (plotted as RLU), indicative of PRLR signaling-mediated induction of luciferase expression (C). In the presence of a constant concentration of 2nM PRL, increasing concentrations (3.3pM to 200nM) of H1H6958N2-DM1 (closed circles) or H1H6958N2 (open circles) blocked PRLR-driven luciferase expression with IC_{50} values of 0.4nM for both antibodies. The non-binding control ADC (closed triangles) and the unconjugated control mAb (gray, open triangles) did not block PRL-mediated PRLR signaling under identical assay conditions. Mean and SD data is shown. RLU: relative light units. The x-axis indicates the molar concentration of ADC or mAb except for the PRL dose response curve, where molar concentration of PRL is indicated.

[0054] Figures 2A, 2B, 2C, and 2D demonstrate H1H6958N2-DM1 is active against MCF7 tumors and MCF7/PRLR tumors in vivo. NCr Nude mice bearing established MCF7

CLAIMS

1. Use of (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to a maytansinoid, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and (b) fulvestrant in the manufacture of a medicament for treating PRLR positive breast cancer.
2. The use of claim 1, wherein the antibody blocks prolactin mediated signaling in cells expressing PRLR with an IC50 of less than about 1.3 nM.
3. The use of claim 1, wherein the antibody blocks prolactin mediated signaling in cells expressing PRLR with an IC50 of less than about 1.2 nM.
4. The use of claim 1, wherein the antibody blocks prolactin mediated signaling in cells expressing PRLR with an IC50 of less than about 1.0 nM.
5. The use of claim 1, wherein the antibody blocks prolactin mediated signaling in cells expressing PRLR with an IC50 of less than about 900 pM.
6. The use of claim 1, wherein the antibody blocks prolactin mediated signaling in cells expressing PRLR with an IC50 of less than about 800 pM.
7. The use of claim 1, wherein the antibody blocks prolactin mediated signaling in cells expressing PRLR with an IC50 of less than about 600 pM.
8. The use of claim 1, wherein the antibody blocks prolactin mediated signaling in cells expressing PRLR with an IC50 of less than about 400 pM.
9. The use of claim 1, wherein the antibody blocks prolactin mediated signaling in cells expressing PRLR with an IC50 of less than about 200 pM.

10. The use of claim 1, wherein the antibody blocks prolactin mediated signaling in cells expressing PRLR with an IC50 of less than about 100 pM.
11. The use of claim 1, wherein the antibody blocks prolactin mediated signaling in cells expressing PRLR with an IC50 of less than about 80 pM.
12. The use of claim 1, wherein the antibody blocks prolactin mediated signaling in cells expressing PRLR with an IC50 of less than about 60 pM.
13. The use of claim 1, wherein the antibody blocks prolactin mediated signaling in cells expressing PRLR with an IC50 of less than about 40 pM.
14. The use of claim 1, wherein the antibody or antigen-binding fragment thereof that binds prolactin receptor (PRLR) interacts with one or more amino acids contained within the first fibronectin-like type III domain of the extracellular domain of PRLR (amino acids 27-128 of SEQ ID NO:404), as determined by hydrogen/deuterium exchange.
15. The use of claim 14, wherein the antibody or antigen-binding fragment thereof interacts with one or more amino acids contained within SEQ ID NO:405, as determined by hydrogen/deuterium exchange.
16. The use of claim 14, wherein the antibody or antigen-binding fragment thereof interacts with an amino acid sequence selected from the group consisting of (a) amino acids 72 to 94 of SEQ ID NO:404; (b) amino acids 72 to 95 of SEQ ID NO:404; (c) amino acids 96 to 101 of SEQ ID NO:404; and (d) amino acids 96 to 102 of SEQ ID NO:404.
17. The use of claim 15, wherein the antibody or antigen-binding fragment thereof interacts with at least ten amino acids contained within SEQ ID NO: 405.
18. The use of claim 15, wherein the antibody or antigen-binding fragment thereof interacts with at least twenty amino acids contained within SEQ ID NO: 405.
19. The use of claim 14, wherein the antibody or antigen-binding fragment thereof interacts with the amino acid sequence of SEQ ID NO: 405.

20. The use of claim 1, wherein the maytansinoid is DM4
21. The use of claim 1, wherein the maytansinoid is DM1.
22. The use of claim 1, wherein the maytansinoid is conjugated to the antibody via a cleavable linker.
23. The use of claim 1, wherein the maytansinoid is conjugated to the antibody via a non-cleavable linker.
24. The use of claim 1, wherein the maytansinoid is conjugated to the antibody via a linker selected from the group consisting of 4-[-maleimidomethyl] cyclohexane-1-carboxylate), SPDB, mc-val-cit, and mc-val-cit-PAB.
25. The use of claim 1, wherein the maytansinoid is conjugated to the antibody via a linker, and wherein the linker is 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (MCC).
26. The use of claim 1, wherein the ADC inhibits prolactin mediated STAT5 activity.
27. The use of claim 1, wherein the ADC induces mitotic arrest in cells expressing PRLR.
28. The use of claim 1, wherein the ADC inhibits the growth of cells expressing PRLR.
29. The use of claim 1, wherein the patient was previously treated with an estrogen receptor inhibitor.
30. The use of claim 1, wherein the effective amount is sufficient to delay or inhibit progression of the cancer.
31. The use of claim 1, wherein the ADC is administered intravenously.

32. The use of claim 1, wherein the expression of PRLR in the breast cancer is not substantially reduced after treatment.
33. The use of claim 1, wherein the ADC kills cells that express PRLR at an expression level of less than 30-fold above background.
34. The use of claim 1, wherein the ADC kills cells that express PRLR at an expression level of less than 20-fold above background.
35. The use of claim 1, wherein the ADC kills cells that express PRLR at an expression level greater than 12-fold above background but less than 30-fold above background.
36. The use of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR)/light chain variable region (LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26; 66/74; 274/282; 290/298; and 370/378.
37. The use of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region (HCDR)-1 comprising SEQ ID NO: 20; an HCDR2 comprising SEQ ID NO: 22; an HCDR3 comprising SEQ ID NO: 24; a light chain complementarity determining region (LCDR)-1 comprising SEQ ID NO: 28; an LCDR2 comprising SEQ ID NO: 30; and an LCDR3 comprising SEQ ID NO: 32.
38. The use of claim 37, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising SEQ ID NO: 18 and a LCVR comprising SEQ ID NO: 26.
39. The use of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCDR1 comprising SEQ ID NO: 68; an HCDR2 comprising SEQ ID NO: 70; an HCDR3 comprising SEQ ID NO: 72; an LCDR1 comprising SEQ ID NO: 76; an LCDR2 comprising SEQ ID NO: 78; and an LCDR3 comprising SEQ ID NO: 80.
40. The use of claim 39, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising SEQ ID NO: 66 and a LCVR comprising SEQ ID NO: 74.

41. The use of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCDR1 comprising SEQ ID NO: 276; an HCDR2 comprising SEQ ID NO: 278; an HCDR3 comprising SEQ ID NO: 280; an LCDR1 comprising SEQ ID NO: 284; an LCDR2 comprising SEQ ID NO: 286; and an LCDR3 comprising SEQ ID NO: 288.
42. The use of claim 41, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising SEQ ID NO: 274 and a LCVR comprising SEQ ID NO: 282.
43. The use of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCDR1 comprising SEQ ID NO: 292; an HCDR2 comprising SEQ ID NO: 294; an HCDR3 comprising SEQ ID NO: 296; an LCDR1 comprising SEQ ID NO: 300; an LCDR2 comprising SEQ ID NO: 302; and an LCDR3 comprising SEQ ID NO: 304.
44. The use of claim 43, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising SEQ ID NO: 290 and a LCVR comprising SEQ ID NO: 298.
45. The use of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCDR1 comprising SEQ ID NO: 372; an HCDR2 comprising SEQ ID NO: 374; an HCDR3 comprising SEQ ID NO: 376; an LCDR1 comprising SEQ ID NO: 380; an LCDR2 comprising SEQ ID NO: 382; and an LCDR3 comprising SEQ ID NO: 384.
46. The use of claim 45, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising SEQ ID NO: 370 and a LCVR comprising SEQ ID NO: 378.
47. The use of claim 1, wherein the antibody or antigen-binding fragment thereof competes for binding to PRLR with a reference antibody comprising an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26; 66/74; 274/282; 290/298; and 370/378.
48. Use of (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to DM1 through an MCC linker, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and (b) fulvestrant in the manufacture of a medicament for treating PRLR positive breast cancer in a patient.

49. The use of claim 48, wherein the antibody or antigen-binding fragment thereof comprises an HCDR1 comprising SEQ ID NO: 292; an HCDR2 comprising SEQ ID NO: 294; an HCDR3 comprising SEQ ID NO: 296; an LCDR1 comprising SEQ ID NO: 300; an LCDR2 comprising SEQ ID NO: 302; and an LCDR3 comprising SEQ ID NO: 304.

50. The use of claim 49, wherein the antibody or antigen-binding fragment thereof comprises an HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 290/298.

51. Use of (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to a maytansinoid, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and (b) fulvestrant in the manufacture of a medicament for killing tumor cells that express low levels of PRLR.

52. The use of claim 51, wherein the tumor cells express less than 1 million copies of PRLR per cell.

53. The use of claim 52, wherein the tumor cells express between 3000 and 500,000 copies of PRLR per cell.

54. The use of claim 51, wherein the antibody or antigen-binding fragment thereof comprises an HCDR1 comprising SEQ ID NO: 292; an HCDR2 comprising SEQ ID NO: 294; an HCDR3 comprising SEQ ID NO: 296; an LCDR1 comprising SEQ ID NO: 300; an LCDR2 comprising SEQ ID NO: 302; and an LCDR3 comprising SEQ ID NO: 304.

55. The use of claim 54, wherein the antibody or antigen-binding fragment thereof comprises an HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 290/298.

56. The use of claim 51, wherein the maytansinoid is DM1.

57. The use of claim 56, wherein the antibody or antigen-binding fragment thereof is conjugated to DM1 via a linker, and wherein the linker is 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (MCC).