CLAIMS

1. Use of (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to a maytansinoid in the manufacture of a medicament for treating PRLR positive breast cancer, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (CDRs) within the heavy chain variable region (HCVR) amino acid sequence and three light chain complementarity determining regions within light chain variable region (LCVR) amino acid sequence of the HCVR/LCVR pair 290/298, wherein the ADC is to be administered in combination with (b) fulvestrant.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

10. The use of claim 9, 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.

11. The use of claim 9, 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.

12. The use of claim 10, wherein the antibody or antigen-binding fragment thereof interacts with at least ten amino acids contained within SEQ ID NO: 405.

13. The use of claim 10, wherein the antibody or antigen-binding fragment thereof interacts with at least twenty amino acids contained within SEQ ID NO: 405.

14. The use of claim 9, wherein the antibody or antigen-binding fragment thereof interacts with the amino acid sequence of SEQ ID NO: 405.

15. The use of claim 1, wherein the maytansinoid is DM4

16. The use of claim 1, wherein the maytansinoid is DM1.

17. The use of claim 1, wherein the maytansinoid is conjugated to the antibody via a cleavable linker.

18. The use of claim 1, wherein the maytansinoid is conjugated to the antibody via a non-cleavable linker.

19. 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.

20. 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).

21. The use of claim 1, wherein the ADC inhibits prolactin mediated STAT5 activity.

22. The use of claim 1, wherein the ADC induces mitotic arrest in cells expressing PRLR.

23. The use of claim 1, wherein the ADC inhibits the growth of cells expressing PRLR.

24. The use of claim 1, wherein the patient was previously treated with an estrogen receptor inhibitor.

25. The use of claim 1, wherein the effective amount is sufficient to delay or inhibit progression of the cancer.

26. The use of claim 1, wherein the ADC is to be administered intravenously.

27. The use of claim 1, wherein the expression of PRLR in the breast cancer is not substantially reduced after treatment.

28. The use of claim 1, wherein the ADC kills cells that express PRLR at an expression level of less than 30-fold above background.

29. The use of claim 1, wherein the ADC kills cells that express PRLR at an expression level of less than 20-fold above background.

30. 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.

~~31. 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: 290/298.~~

~~32~~31. 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.

~~33~~32. The use of claim 1, wherein the antibody or antigen-binding fragment thereof competes for binding to PRLR with a reference antibody, wherein the reference antibody is capable of binding to PRLR, in competition experiments ~~comprising an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 290/298~~.

~~34~~33. Use of (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to DM1 through an MCC linker in the manufacture of a medicament for treating PRLR positive breast cancer, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (CDRs) within the heavy chain variable region (HCVR) amino acid sequence and three light chain complementarity determining regions within light chain variable region (LCVR) amino acid sequence of the HCVR/LCVR pair 290/298, wherein the ADC is to be administered in combination with (b) fulvestrant.

~~35~~34. The use of claim ~~34~~33, 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.

~~36~~35. Use of (a) an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to a maytansinoid in the manufacture of a medicament for *in vivo* killing tumor cells that express low levels of PRLR, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and wherein the antibody or antigen binding fragment comprises three heavy chain complementarity determining regions (CDRs) within the heavy chain variable region (HCVR) amino acid sequence and three light chain complementarity determining regions within light chain variable region (LCVR) amino acid sequence of the HCVR/LCVR pair 290/298, wherein the ADC is to be administered in combination with (b) fulvestrant.

~~37~~36. The use of claim ~~36~~35, wherein the tumor cells express less than 1 million copies of PRLR per cell.

~~38~~37. The use of claim ~~37~~36, wherein the tumor cells express between 3000 and 500,000 copies of PRLR per cell.

~~39~~38. The use of claim ~~36~~35, 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.

~~40~~39. The use of claim ~~36~~35, wherein the maytansinoid is DM1.

~~41~~40. The use of claim ~~40~~39, 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).

~~42~~41. The use of claim 1, wherein the fulvestrant is to be administered before the ADC at a predetermined time point.

~~43~~42. The use of claim 1, wherein the ADC is to be administered before the fulvestrant at a predetermined time point.

~~44~~43. The use of claim 1, wherein the ADC and the fulvestrant are to be administered at the same time point.

~~45~~44. The use of claim 1, wherein the ADC and the fulvestrant are to be administered at a different time point.

~~46~~45. The use of claim 1, wherein the ADC and the fulvestrant are to be administered on different days separated by a predetermined interval.