CLAIMS

1. A method of treating PRLR positive breast cancer, the method 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 maytansinoid, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and
(b) fulvestrant.

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

20. The method of claim 1, wherein the maytansinoid is DM4

21. The method of claim 1, wherein the maytansinoid is DM1.

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

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

24. The method 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 method 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 method of claim 1, wherein the ADC inhibits prolactin mediated STAT5 activity.

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

28. The method of claim 1, wherein the ADC inhibits the growth of cells expressing PRLR.

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

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

31. The method of claim 1, wherein the ADC is administered intravenously.

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

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

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

35. The method 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 method 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 method 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 method 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 method 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 method 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 method 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 method 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 method 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 method 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 method 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 method 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 method 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. A method of treating PRLR positive breast cancer in a patient, the method 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 DM1 through an MCC linker, wherein the antibody or antigen-binding fragment thereof binds to human prolactin receptor (PRLR), and

(b) fulvestrant.

49. The method 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 method 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. 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.

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

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

54. The method 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 method 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 method of claim 51, wherein the maytansinoid is DM1.

57. The method 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).