Claims

1. An antibody or antigen-binding fragment thereof comprising the VH CDR1-3 and VL CDR1-3 polypeptide sequences selected from the group consisting of:

(a) SEQ ID NOs:3-8, respectively;

(b) SEQ ID NOs:9-14, respectively;

(c) SEQ ID NOs:15-20, respectively;

(d) SEQ ID NOs:21-26, respectively;

(e) SEQ ID NOs: 3-5 and SEQ ID NOs: 59, 7, and 8, respectively;

(f) SEQ ID NOs: 3, 60, and 5 and SEQ ID NOs: 6-8, respectively;

(g) SEQ ID NOs: 3, 61, and 5 and SEQ ID NOs: 6-8, respectively;

(h) SEQ ID NOs: 3, 60, and 5 and SEQ ID NOs: 59, 7, and 8, respectively; and

(i) SEQ ID NOs: 3, 61, and 5 and SEQ ID NOs: 59, 7, and 8, respectively;

wherein the antibody or antigen-binding fragment thereof binds to an epitope of FOLR1 comprising an N-glycosylated amino acid.

2. The antibody or antigen-binding fragment thereof of claim 1, comprising:

(a) a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:27 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:28;

(b) a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:29 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:30;

(c) a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:31 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:32;

(d) a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:62 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:63 or SEQ ID NO:64;

(e) a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:65 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:66 or SEQ ID NO:67; or

(f) a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO:68 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO:69.

3. The antibody or antigen-binding fragment thereof of claim 1 or 2, comprising:

(a) a full-length heavy chain comprising the amino acid sequence of SEQ ID NO:33 and a full-length light chain comprising the amino acid sequence of SEQ ID NO:34;

(b) a full-length heavy chain comprising the amino acid sequence of SEQ ID NO:35 and a full-length light chain comprising the amino acid sequence of SEQ ID NO:36; or

(c) a full-length heavy chain comprising the amino acid sequence of SEQ ID NO:37 and a full-length light chain comprising the amino acid sequence of SEQ ID NO:38.

4. The antibody or antigen-binding fragment thereof of any one of claims 1-3, wherein the antibody or antigen-binding fragment thereof is recombinantly produced.

5. The antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein said antibody or antigen-binding fragment thereof is murine, non-human, humanized, chimeric, resurfaced, or human.

6. The antibody or antigen-binding fragment thereof of any one of claims 1-5, wherein said antibody binds to human FOLR1 but not FOLR2 or FOLR3.

7. The antibody or antigen-binding fragment thereof of any one of claims 1-6, which is a full length antibody.

8. The antibody or antigen-binding fragment thereof of any one of claims 1-6, which is an antigen-binding fragment.

9. A polypeptide that specifically binds FOLR1, wherein said polypeptide comprises sequences selected from the group consisting of:

(a) SEQ ID NOs:3-8, respectively;

(b) SEQ ID NOs:9-14, respectively;

(c) SEQ ID NOs:15-20, respectively;

(d) SEQ ID NOs:21-26, respectively;

(e) SEQ ID NOs: 3-5 and SEQ ID NOs: 59, 7, and 8, respectively;

(f) SEQ ID NOs: 3, 60, and 5 and SEQ ID NOs: 6-8, respectively;

(g) SEQ ID NOs: 3, 61, and 5 and SEQ ID NOs: 6-8, respectively

(h) SEQ ID NOs: 3, 60, and 5 and SEQ ID NOs: 59, 7, and 8, respectively; and

SEQ ID NOs: 3, 61, and 5 and SEQ ID NOs: 59, 7, and 8, respectively;

wherein the polypeptide binds to an epitope of FOLR1 comprising an N-glycosylated amino acid.

10. The polypeptide of claim 9, wherein the sequences comprise the amino acids of sequences selected from the group consisting of:

(a) SEQ ID NO:27 and SEQ ID NO:28;

(b) SEQ ID NO:29 and SEQ ID NO:30;

(c) SEQ ID NO:31 and SEQ ID NO:32;

(d) SEQ ID NO:62 and SEQ ID NO:63 or SEQ ID NO:64;

(e) SEQ ID NO:65 and SEQ ID NO:66 or SEQ ID NO:67; and

(f) SEQ ID NO:68 and SEQ ID NO:69.

11. The antibody, antigen-binding fragment thereof, or polypeptide of any one of claim 1-10, which binds to a human folate receptor 1 with a Kd of ~~about~~ 0.5 to ~~about~~ 10 nM.

12. The antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-11, which binds to a human folate receptor 1 with a Kd of ~~about~~ 1.0 nM or better.

13. The antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-12, wherein the antibody, antigen-binding fragment thereof, or polypeptide is detectably labeled.

14. A cell producing the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13.

15. A method of making the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13, comprising (a) culturing the cell of claim 14; and (b) isolating said antibody, antigen-binding fragment thereof, or polypeptide from said cultured cell.

16. A composition comprising the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13 and buffer selected from the group consisting of: a FACS buffer, an IHC buffer, and an ELISA buffer.

17. An *in vitro* method of detecting FOLR1 expression in a sample comprising contacting said sample with an antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13 or the composition of claim 16.

18. The method of claim 17, wherein said antibody or antigen-binding fragment thereof, or polypeptide is detectably labeled.

19. The method of claim 18, wherein said label is selected from the group consisting of immunofluorescent label, chemiluminescent label, phosphorescent label, enzyme label, radiolabel, avidin/biotin, colloidal gold particles, colored particles and magnetic particles.

20. The method of any one of claims 17-19, wherein FOLR1 expression is determined by radioimmunoassay, Western blot assay, cytometry, immunofluorescent assay, enzyme immunoassay, immunoprecipitation assay, chemiluminescent assay, or immunohistochemical assay.

21. The method of claim 20, wherein the cytometry is flow cytometry.

22. The method of claim 20, wherein FOLR1 expression is determined by IHC.

23. An active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof for use in increasing the efficacy of cancer treatment in a patient, wherein the active agent is to be administered to a subject having cancer, wherein increased expression of FOLR1 has been detected in a cancerous sample from said subject using the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13 or the composition of claim 16.

24. A method for identifying a cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof, said method comprising:

(a) contacting an *in vitro* biological sample comprising cells from said cancer with the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13 or the composition of claim 16;

(b) detecting binding of said antibody, antibody-fragment, or polypeptide to FOLR1 in said biological sample of (a);

(c) assigning a score to said binding of step (b), wherein said score is assigned based on comparison to one or more reference samples; and

(d) comparing said score in step (c) to the score of a reference tissue or cell, wherein a score for said cancer FOLR1 level that is greater than the score for a normal or low FOLR1 expressing reference sample or a score for said cancer FOLR1 level that is equal to or greater than the score for a high FOLR1 expressing reference sample identifies said cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody.

25. An active agent comprising an antibody or antigen-binding fragment thereof for use in treating a patient with cancer, wherein the treatment comprises:

(a) determining a FOLR1 expression score from a detection of FOLR1 expression in a cancerous sample obtained from the patient, wherein the detection is performed using the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13 or the composition of claim 16; and

(b) wherein the active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof is to be administered to the patient if the score indicates the patient will benefit from administration of the active agent.

26. An active agent comprising an antibody or antigen-binding fragment thereof for use in treating a patient with cancer, wherein the treatment comprises:

(a) submitting a cancerous sample taken from a patient having cancer for determining a FOLR1 expression score from a detection of FOLR1 expression using the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13 or the composition of claim 16; and

(b) wherein the active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof is to be administered to the patient if the score indicates the patient will benefit from administration of the active agent.

27. An active agent comprising an antibody or antigen-binding fragment thereof for use in treating a patient with cancer, wherein the treatment comprises:

(a) detecting FOLR1 expression in a cancerous sample obtained from said patient, wherein the detection is performed using the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13 or the composition of claim 16;

(b) determining a FOLR1 expression score for said cancerous sample; and

(c) wherein the active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof is to be administered to the patient if the score indicates the patient will benefit from administration of the active agent.

28. An anti-FOLR1 active agent comprising an antibody or antigen-binding fragment thereof for identifying a cancer as sensitive to treatment, said identifying comprising:

(a) detecting the level of FOLR1 expression in a cancerous sample from said cancer using the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13 or the composition of claim 16, wherein said detecting comprises the use of a method that distinguishes between staining intensity or staining uniformity in a FOLR1 expressing cancerous sample as compared to staining intensity or staining uniformity in one or more reference samples;

(b) determining a FOLR1 staining intensity or staining uniformity score for said cancerous sample; and

(c) comparing the FOLR1 staining intensity or staining uniformity score determined in step (b) to a relative value determined by measuring FOLR1 protein expression in at least one reference sample, wherein said at least one reference sample is a tissue, cell, or cell pellet sample which is not sensitive to treatment with an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof and wherein a FOLR1 staining intensity score for said cancerous sample determined in step (b) that is higher than said relative value identifies said cancer as being sensitive to treatment with the active agent.

29. An anti-FOLR1 active agent comprising an antibody or antigen-binding fragment thereof for identifying a cancer as sensitive to treatment, said identifying comprising:

(a) detecting the level of membrane FOLR1 expression in a cancerous sample from said cancer using the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13 or the composition of claim 16, as compared to membrane FOLR1 in one or more reference samples;

(b) determining a FOLR1 score for said cancerous sample; and

(c) comparing the FOLR1 score determined in step (b) to a relative value determined by measuring membrane FOLR1 in at least one reference sample, wherein said at least one reference sample is a tissue, cell, or cell pellet sample which is not sensitive to treatment with an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof and wherein a FOLR1 score for said cancerous sample determined in step (b) that is higher than said relative value identifies said cancer as being sensitive to treatment with the active agent.

30. An anti-FOLR1 active agent comprising an antibody or antigen-binding fragment thereof for identifying a cancer as sensitive to treatment, said identifying comprising:

(a) detecting the level of FOLR1 expression in a cancerous sample from said cancer using the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13 or the composition of claim 16, wherein said detecting comprises the use of a method that distinguishes between staining intensity or staining uniformity in a FOLR1 expressing cancerous sample as compared to staining intensity or staining uniformity in one or more reference samples;

(b) determining a FOLR1 staining intensity or staining uniformity score for said cancerous sample; and

(c) comparing the FOLR1 staining intensity or staining uniformity score determined in step (b) to a relative value determined by measuring FOLR1 protein expression in at least one reference sample, wherein said at least one reference sample is a tissue, cell, or cell pellet sample which is sensitive to treatment with an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof and wherein a FOLR1 staining intensity score for said cancerous sample determined in step (b) that is greater than or equal to said relative value identifies said cancer as being sensitive to treatment with the active agent.

31. An anti-FOLR1 active agent comprising an antibody or antigen-binding fragment thereof for identifying a cancer as sensitive to treatment, said identifying comprising:

(a) detecting the level of membrane FOLR1 expression in a cancerous sample from said cancer using the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13 or the composition of claim 16, compared to membrane FOLR1 one or more reference samples;

(b) determining a FOLR1 score for said cancerous sample; and

(c) comparing the FOLR1 score determined in step (b) to a relative value determined by measuring membrane FOLR1 in at least one reference sample, wherein said at least one reference sample is a tissue, cell, or cell pellet sample which is sensitive to treatment with an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof and wherein a FOLR1 score for said cancerous sample determined in step (b) that is greater than or equal to said relative value identifies said cancer as being sensitive to treatment with the active agent.

32. The active agent of any one of claims 24 or 28-31, wherein an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof is to be administered to the subject from whom the cancerous sample or biological sample was obtained.

33. The active agent of any one of claims 23 or 25-32, wherein said cancerous sample or biological sample is a bodily fluid, cell, or tissue sample.

34. The active agent of claim 33, wherein said bodily fluid is blood, ascites, urine, plasma, serum, or peripheral blood.

35. The active agent of any one of claims 17-28, 30, and 32-34, wherein the FOLR1 is membrane FOLR1.

36. The active agent of any one of claims 17-27, 32, 33, or 34, wherein the FOLR1 is shed FOLR1.

37. The active agent of any one of claims 17-20, 23-27, or 32-36, wherein the detecting is by enzyme linked immunosorbent assay (ELISA).

38. The active agent of any one of claims 17-20, 22-33, or 35, wherein the detecting is by immunohistochemistry (IHC).

39. The active agent of claim 38, wherein said IHC is calibrated IHC that can distinguish different levels of FOLR1 expression.

40. The active agent of claim 38 or 39, wherein said IHC produces a range of staining intensity for samples having low cell surface FOLR1 expression, intermediate FOLR1 cell surface expression, or high FOLR1 cell surface expression.

41. The active agent of any one of claims 38-40, wherein said IHC distinguishes between staining intensity and staining uniformity in a FOLR1 expressing cancerous sample or biological sample as compared to a reference sample.

42. The use of any one of claims 38-41, wherein the IHC is performed manually.

43. The active agent of any one of claims 38-41, wherein the IHC is performed using an automated system.

44. The active agent of any one of claims 38-43, wherein a FOLR1 score is determined from the IHC.

45. The active agent of claim 44, wherein a score of at least 1 identifies the cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof or indicates that the patient will benefit from administration of an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof.

46. The active agent of claim 44, wherein a score of at least 1 homo identifies the cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof or indicates that the patient will benefit from administration of an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof.

47. The active agent of claim 44, wherein a score of at least 1 hetero identifies the cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof or indicates that the patient will benefit from administration of an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof.

48. The active agent of claim 44, wherein a score of at least 2 identifies the cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof or indicates that the patient will benefit from administration of an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof.

49. The active agent of claim 44, wherein a score of at least 2 homo identifies the cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof or indicates that the patient will benefit from administration of an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof.

50. The active agent of claim 44, wherein a score of at least 2 hetero identifies the cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof or indicates that the patient will benefit from administration of an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof.

51. The active agent of one of claims 45-50, wherein the cancer is lung cancer endometrial cancer, ovarian cancer, or cancer of the peritoneum.

52. The active agent of claim 44, wherein a score of at least 3 identifies the cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof or indicates that the patient will benefit from administration of an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof.

53. [[The active agent of claim 44, wherein a score of at least 3 homo identifies the cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody or antigen-binding

fragment thereof or indicates that the patient will benefit from administration of an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof.

54. The active agent of claim 44, wherein a score of at least 3 hetero identifies the cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof or indicates that the patient will benefit from administration of an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof.

55. The active agent of any one of claims 52-54, wherein the cancer is lung cancer, endometrial cancer, ovarian cancer, or cancer of the peritoneum.

56. The active agent of claim 44, wherein the cancer is ovarian cancer, and wherein at least 25% of FOLR1 membrane expression with an intensity of at least 2 identifies the ovarian cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof or indicates that the patient will benefit from administration of an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof.

57. The active agent of claim 44, wherein a score of 2 or greater in 25-75% of cells of identifies the cancer as likely to respond to an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof or indicates that the patient will benefit from administration of an active agent comprising an anti-FOLR1 antibody or antigen-binding fragment thereof.

58. The active agent of any one of claims 24 and 28-57, wherein said reference sample is a positive reference sample or a negative reference sample.

59. The active agent of any one of claims 24 and 28-58, wherein the reference sample comprises cells, cell pellets, or tissue.

60. The active agent of any one of claims 24 and 28-59, wherein the antibody, antigen-binding fragment thereof, or polypeptide of any one of claims 1-13, further comprises a detection reagent selected from the group consisting of: an enzyme, a fluorophore, a radioactive label, and a luminophore.

61. The active agent of claim 60, wherein said detection reagent is selected from the group consisting of: biotin, digoxigenin, fluorescein, tritium, and rhodamine.

62. The active agent of any one of claims 23-61, wherein said cancer is a FOLR1 positive cancer.

63. The active agent of any one of claims 23-61, wherein said cancer is selected from the group consisting of ovarian, brain, breast, uterine, endometrial, pancreatic, renal, lung cancer, and cancer of the peritoneum.

64. The active agent of claim 63, wherein the lung cancer is non small cell lung cancer or bronchioloalveolar carcinoma.

65. The active agent of claim 63, wherein the ovarian cancer is epithelial ovarian cancer.

66. The active agent of claim 65, wherein the cancer is platinum resistant, relapsed, or refractory.

67. The active agent of any one of claims 23-66, wherein the active agent comprises a FOLR1 antibody comprising a heavy chain variable region of SEQ ID NO:45 and a light chain variable region of SEQ ID NO:47.

68. The active agent of claim 67, wherein the active agent is an antibody maytansinoid conjugate comprising a FOLR1 antibody comprising a heavy chain variable region of SEQ ID NO:45 and a light chain variable region of SEQ ID NO:47, the maytansinoid DM4, and the cleavable sulfo-SPDB linker.

69. An antibody maytansinoid conjugate comprising a FOLR1 antibody comprising a heavy chain variable region of SEQ ID NO:45 and a light chain variable region of SEQ ID NO:47, the maytansinoid DM4 and a sulfo-SPDB linker for use in treating a patient with cancer wherein FOLR1 in a sample from the cancer is measured using an antibody comprising a heavy chain variable region comprising the amino acids of SEQ ID NO:27 and a light chain variable region comprising the amino acids of SEQ ID NO:28 in an IHC assay, wherein a score of at least 2 hetero indicates the cancer is likely to responds to the treatment.

70. An antibody maytansinoid conjugate comprising a FOLR1 antibody comprising a heavy chain variable region of SEQ ID NO:45 and a light chain variable region of SEQ ID NO:47, the maytansinoid DM4 and a sulfo-SPDB linker for use in treating a patient with cancer wherein FOLR1 in a sample from the cancer is measured using an antibody comprising a heavy chain variable region comprising the amino acids of SEQ ID NO:27 and a light chain variable region comprising the amino acids of SEQ ID NO:28 in an IHC assay, wherein a

score of at least 2 in 25-75% of cells indicates the cancer is likely to responds to the treatment.

71. An antibody maytansinoid conjugate comprising a FOLR1 antibody comprising a heavy chain variable region of SEQ ID NO:45 and a light chain variable region of SEQ ID NO:47, the maytansinoid DM4 and a sulfo-SPDB linker for use in treating a patient with cancer wherein FOLR1 in a sample from the cancer is measured using an antibody comprising a heavy chain variable region comprising the amino acids of SEQ ID NO:27 and a light chain variable region comprising the amino acids of SEQ ID NO:28 in an IHC assay, wherein at least 25% of FOLR1 membrane expression with an intensity of at least 2 indicates the cancer is likely to responds to the treatment.

72. An antibody maytansinoid conjugate comprising a FOLR1 antibody comprising a heavy chain variable region of SEQ ID NO:45 and a light chain variable region of SEQ ID NO:47, the maytansinoid DM4 and a sulfo-SPDB linker for use in treating a patient with cancer wherein FOLR1 in a sample from the cancer is measured using an antibody comprising a heavy chain variable region comprising the amino acids of SEQ ID NO:27 and a light chain variable region comprising the amino acids of SEQ ID NO:28 in an IHC assay, wherein at least 25% of FOLR1 membrane expression with an intensity of at least 2 in 25-75% of cells indicates the cancer is likely to responds to the treatment.