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(71) Applicant: **MORPHOTEK, INC.** [US/US]; 210 Welsh Pool Road, Exton, PA 19341 (US).

(72) Inventors: **SCHWEIZER, Charles**; 4520 Blue Ridge Drive, Doylestown, PA 18902 (US). **O'SHANNESSY, Daniel, John**; 515 Gerloff Road, Schwenksville, PA 19473 (US).

(74) Agent: **GROTH, Felicity, E.**; Baker & Hostetler LLP, 2929 Arch Street, Cira Centre, 12th Floor, Philadelphia, PA 19104-2891 (US).

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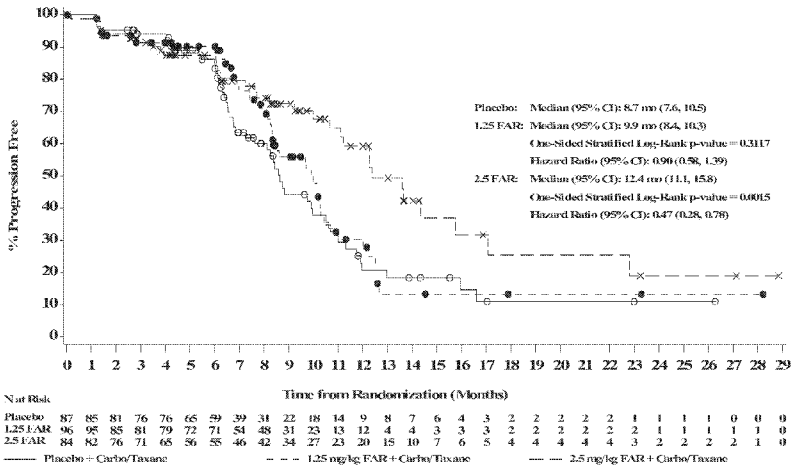

Figure 1

(57) Abstract: Provided herein are methods of identifying a subpopulation of ovarian cancer patients who would be responsive to treatment regimens that target folate receptor alpha (FRA)- expressing ovarian tumors and methods of treatment of such patients using an anti-FRA therapeutic agent, such as an antigen-binding protein (e.g., antibody or antigen-binding fragment thereof) that specifically binds to FRA. Also provided are related kits for identification and treatment of the subpopulation of ovarian cancer patients.

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AMENDED CLAIMS
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What is Claimed:

1. A method for identifying a subject having a folate receptor alpha (FRA)-expressing ovarian cancer that will be responsive to treatment with an anti-FRA therapeutic agent, said method comprising determining a baseline level of cancer antigen 125 (CA125) of said subject; wherein a baseline CA125 level that is less than about eight times the upper limit of normal (ULN) for CA125 is indicative of a subject who would benefit from treatment with an anti-FRA therapeutic agent.

2. The method of claim 1 wherein a baseline CA125 level that is less than about three times the ULN for CA125 is indicative of a subject who would benefit from treatment with an anti-FRA therapeutic agent.

3. A method of treating a subject with folate receptor alpha (FRA)-expressing ovarian cancer, said method comprising:

determining a baseline level of cancer antigen 125 (CA125) of said subject, and

administering an anti-FRA therapeutic agent to said subject when said CA125 level is less than about eight times the upper limit of normal (ULN) for CA125.

4. The method of claim 3 wherein said anti-FRA therapeutic agent is administered to said subject when said baseline CA125 level in said biological sample is less than about three times the ULN for CA125.

5. The method of claim claim 1 or claim 3 wherein said step of determining a baseline level of CA125 of said subject is performed *in vivo*.

6. The method of claim 1 or claim 3 wherein said step of determining a baseline level of CA125 of said subject is performed on a biological sample obtained from said subject.

7. The method of claim 6 wherein said step of determining a baseline level of CA125 of said subject comprises contacting said biological sample with an anti-CA125 antibody.

8. The method of claim 6 wherein said biological sample used in determining said baseline level of CA125 comprises whole blood, serum, plasma, pleural effusion, ascites, or a tissue.

9. The method of claim 1 or claim 3, wherein said step of determining a baseline level of CA125 comprises using an antibody to detect protein expression, nucleic acid hybridization, quantitative RT-PCR, western blot analysis, radioimmunoassay, immunofluorimetry, immunoprecipitation, equilibrium dialysis, immunodiffusion, electrochemiluminescence (ECL) immunoassay, immunohistochemistry, fluorescence-activated cell sorting (FACS), or ELISA assay.

10. The method of claim 1 or claim 3 wherein said anti-FRA therapeutic agent comprises farletuzumab.

11. The method of claim 1 or claim 3 wherein said ovarian cancer is epithelial ovarian cancer.

12. The method of claim 1 or claim 3 wherein said ovarian cancer is platinum-sensitive.

13. The method of claim 1 or claim 3 wherein said ovarian cancer is platinum-resistant.

14. The method of claim 1 or claim 3 further comprising determining a baseline level of albumin of said subject, wherein a baseline serum albumin concentration of at least 3.2 g/dL is further indicative of a subject who would benefit from treatment with an anti-FRA therapeutic agent.

15. The method of claim 14 wherein said baseline SA concentration is determined *ex vivo* or *in vivo*.

16. The method of claim 1 or claim 3 further comprising determining the level of folate receptor alpha (FRA) of in a sample derived from said subject by contacting said sample with an antibody that binds FRA and comparing the level of FRA in said sample derived from said subject with the level of FRA in a control sample, wherein an increase in the level of FRA in the sample derived from said subject as compared to the level of FRA in the control sample is indicative that the subject would benefit from treatment with an anti-FRA therapeutic agent.

17. The method according to claim 16 wherein the sample derived from said subject for determining the level of FRA is a tumor biopsy, urine, serum, plasma, or ascites.

18. The method according to claim 16 wherein the antibody that binds FRA is:

(a) an antibody that binds the same epitope as the MORAb-003 antibody;

(b) an antibody comprising SEQ ID NO: 1 (GFTFSGYGLS) as CDRH1, SEQ ID NO: 2 (MISSGGSYTYYADSVKG) as CDRH2, SEQ ID NO: 3 (HGDDPAWFAY) as CDRH3, SEQ ID NO:4 (SVSSSISSNNLH) as CDRL1, SEQ ID NO: 5 (GTSNLAS) as CDRL2 and SEQ ID NO: 6 (QQWSSYPYMYT) as CDRL3;

(c) the 548908 antibody;

(d) an antibody that binds the same epitope as the 548908 antibody;

(e) the 6D398 antibody;

(f) an antibody that binds the same epitope as the 6D398 antibody;

(g) an antibody that binds the same epitope as the 26B3 antibody;

(h) an antibody comprising SEQ ID NO: 14 (GYFMN) as CDRHl, SEQ ID NO: 15 (RIFPYNGDTFYNQKFKG) as CDRH2, SEQ ID NO: 16 (GTHYFDY) as CDRH3, SEQ

ID NO: 17 (RTSENIFSYLA) as CDRL1 , SEQ ID NO:18 (NAKTLAE) as CDRL2 and SEQ ID NO: 19 (QHHYAFPWT) as CDRL3;

(i) the 26B3 antibody;

(j) an antibody that binds the same epitope as the 19D4 antibody;

(k) an antibody comprising SEQ ID NO: 20 (HPYMH) as CDRH1, SEQ ID NO: 21 (RIDPANGNTKYDPKFQG) as CDRH2, SEQ ID NO: 22 (EEVADYTMDY) as CDRH3, SEQ ID NO: 23 (RASESVDTYGNNFIH) as CDRL1, SEQ ID NO: 24 (LASNLES) as CDRL2 and SEQ ID NO:25 (QQNNGDPWT) as CDRL3;

(l) the 19D4 antibody;

(m) an antibody that binds the same epitope as the 9F3 antibody;

(n) an antibody comprising SEQ ID NO:26 (SGYYWN) as CDRH1, SEQ ID NO:27 (YIKSDGSNNYNPSLKN) as CDRH2, SEQ ID NO:28 (EWKAMDY) as CDRH3, SEQ ID NO:29 (RASSTVSYSYLH) as CDRL1, SEQ ID NO:30 (GTSNLAS) as CDRL2 and SEQ ID NO:31 (QQYSGYPLT) as CDRL3;

(o) the 9F3 antibody;

(p) an antibody that binds the same epitope as the 24F12 antibody;

(q) an antibody comprising SEQ ID NO:32 (SYAMS) as CDRH1, SEQ ID NO:33 (EIGSGGSYTYYPDTVTG) as CDRH2, SEQ ID NO:34 (ETTAGYFDY) as CDRH3, SEQ ID NO:35 (SASQGINNFLN) as CDRL1, SEQ ID NO:36 (YTSSLHS) as CDRL2 and SEQ ID NO:37 (QHFSKLPWT) as CDRL3;

(r) the 24F12 antibody;

(s) an antibody that comprises a variable region light chain selected from the group consisting ofLK26HuVK (SEQ ID NO: 38); LK26HuVKY (SEQ ID NO: 39); LK26HuVKPW (SEQ ID NO: 40); and LK26HuVKPW,Y (SEQ ID NO: 41);

(t) an antibody that comprises a variable region heavy chain selected from the group consisting ofLK26HuVH (SEQ ID NO: 42); LK26HuVH FAIS,N (SEQ ID NO: 43); LK26HuVHSLF (SEQ ID NO: 44); LK26HuVH 1,1 (SEQ ID NO: 45); and LK26KOLHuVH (SEQ ID NO: 46);

(u) an antibody that comprises the heavy chain variable region LK26KOLHuVH (SEQ ID NO: 46) and the light chain variable region LK26HuVKPW,Y (SEQ ID NO: 41);

(v) an antibody that comprises the heavy chain variable region LK26HuVH SLF (SEQ ID NO: 44) and the light chain variable region LK26HuVKPW,Y (SEQ ID NO: 41);

(w) an antibody that comprises the heavy chain variable region LK26KOLHuVH (SEQ ID NO: 46) and the light chain variable region LK26HuVKPW,Y (SEQ ID NO: 41); and

(x) an antibody that comprises the heavy chain variable region LK26HuVH FAIS,N (SEQ ID NO: 43) and the light chain variable region LK26HuVKPW,Y (SEQ ID NO: 41).

19. The method of any one of claim 16, wherein the antibody that binds FRA is labeled.

20. The method of claim 19, wherein the antibody that binds FRA is labeled with a radiolabel, a biotin-label, a chromophore-label, a fluorophore-label, an ECL label, or an enzyme-label.

21. The method of claim 16, wherein the level of FRA is determined by using a sandwich assay, western blot analysis, radioimmunoassay, immunofluorimetry, immunoprecipitation, equilibrium dialysis, immunodiffusion, solution phase assay, electrochemiluminescence immunoassay (ECLIA), or an ELISA assay.

22. The method of claim 16, wherein the control sample comprises a standardized control level of FRa in a healthy subject.

23. The method of claim 3 wherein said anti-FRA therapeutic agent is farletuzumab and wherein farletuzumab is administered to achieve a minimum serum farletuzumab concentration of at least about 57.6 μg/ml.

24. The method of claim 3 wherein said anti-FRA therapeutic agent is farletuzumab and wherein farletuzumab is administered to achieve a minimum serum farletuzumab concentration of at least about 88.8 μg/ml.

25. The method of claim 3 wherein said anti-FRA therapeutic agent is farletuzumab, wherein serum farletuzumab concentration in said subject is determined, and wherein a minimum serum farletuzumab concentration of at least about 57.6 μg/ml is indicative of a positive therapeutic response for said subject.

26. The method of claim 3 wherein said anti-FRA therapeutic agent is farletuzumab, wherein serum farletuzumab concentration in said subject is determined, and wherein a minimum serum farletuzumab concentration of at least about 88.8 μg/ml is indicative of a positive therapeutic response for said subject.

27. The method of claim 3 wherein said anti-FRA therapeutic agent is farletuzumab, wherein the average farletuzumab area under the curve pharmacokinetic exposure level is determined, and wherein average farletuzumab area under the curve pharmacokinetic exposure level of at least about 15.22 mg.h/L is indicative of a positive therapeutic response for said subject.

28. The method of claim 3 wherein said anti-FRA therapeutic agent is farletuzumab, wherein the average farletuzumab area under the curve pharmacokinetic exposure level is determined, and wherein average farletuzumab area under the curve pharmacokinetic exposure level of at least about 22.2 mg.h/L is indicative of a positive therapeutic response for said subject.

29. The method of claim 3 wherein said step of administering comprises intravenous injection of said anti-FRA therapeutic agent.

30. The method of claim 3 wherein said step of administering comprises intraperitoneal administration of said anti-FRA therapeutic agent.

31. The method of claim 3 wherein said step of administering comprises weekly administration of said anti-FRA therapeutic agent to said subject.

32. The method of claim 3 or claim 31 wherein said anti-FRA therapeutic agent is administered at a dose of about 2.5 mg/kg to about 10 mg/kg.

33. The method of claim 3 or claim 31 wherein said anti-FRA therapeutic agent is administered at a dose of about 5.0 mg/kg to about 7.5 mg/kg.

34. The method of claim 3 or claim 31 wherein said step of administering comprises administering a loading dose of said anti-FRA therapeutic agent of about 7.5 mg/kg to about 12.5 mg/kg to said subject.

35. The method of claim 34 wherein said step of administering further comprises administering a second loading dose of said anti-FRA therapeutic agent of about 7.5 mg/kg to about 12.5 mg/kg to said subject.

36. The method of claim 34 wherein said loading dose is about 10 mg/kg.

37. The method of claim 3 further comprising administering a platinum-containing compound to said subject.

38. The method of claim 3 further comprising administering a taxane to said subject.

39. The method of claim 37 further comprising administering a taxane to said subject.

40. The method of claim 37 or claim 39 wherein said platinum-containing compound comprises cisplatin or carboplatin.

41. The method of claim 38 or claim 39 wherein said taxane comprises paclitaxel, docetaxel, nab-paclitaxel, cabazitaxel, DJ-927, paclitaxel poliglumex, XRP9881, EndoTAG + paclitaxel, Polymeric-micellar paclitaxel, DHA-paclitaxel, and BMS-184476.

42. The method of claim 37 or claim 39 wherein said platinum-containing compound is administered once every three weeks.

43. The method claim 38 or claim 39 wherein said taxane is administered once every three weeks.

44. The method of claim 39 wherein said taxane is administered before, after, or simultaneously with said platinum-containing compound.

45. The method of claim 1 or claim 3 wherein said subject received surgical resection of the ovarian cancer, first-line platinum-based therapy, first-line taxane-based therapy, and/or first-line platinum and taxane-based therapy for treatment of the ovarian cancer for treatment of said ovarian cancer prior to said step of determining said baseline level of CA125.

46. The method of claim 45 wherein said subject exhibits symptomatic progression, serologic progression, and/or radiologic progression of said ovarian cancer prior to said step of determining said baseline level of CA125.

47. The method of claim 1 or claim 3 wherein said step of determining said baseline level of CA125 comprises determining a CA125 level in said subject at a single timepoint.

48. The method of claim 1 or claim 3 wherein said step of determining said baseline level of CA125 comprises determining a CA125 level in said subject at at least two timepoints.

49. The method of claim 1 or claim 3 wherein said subject received first-line platinum-based therapy.

50. A kit for identifying a subject having ovarian cancer that will be responsive to treatment with an anti-folate receptor alpha (FRA) therapeutic agent comprising an anti-CA125 antibody, a vessel for containing the antibody when not in use, and instructions for using said anti-CA125 antibody for determining a baseline level of CA125 in a biological sample obtained from said subject.

51. The kit of claim 50 wherein said instructions specify that a baseline CA125 level that is less than about eight times the upper limit of normal for CA125 is indicative of a subject who would benefit from treatment with an anti-FRA therapeutic agent.

52. The kit of claim 50 wherein said instructions specify that a baseline CA125 level that is less than three times the upper limit of normal for CA125 is indicative of a subject who would benefit from treatment with an anti-FRA therapeutic agent.

53. The kit of any one of claims 50 to 52 wherein said anti-FRA therapeutic agent comprises farletuzumab.

54. The kit of claim 50 further comprising an anti-folate receptor alpha (FRA) antibody, a vessel for containing the anti-FRA antibody when not in use, and instructions for using said anti-FRA antibody for determining a level of FRA in a biological sample obtained from said subject.

55. The kit of claim 50 or claim 54 further comprising an anti-serum albumin (SA) antibody, a vessel for containing the anti-SA antibody when not in use, and instructions for using said anti-SA antibody for determining a level of SA in a biological sample obtained from said subject.

56. A kit for treating a subject having ovarian cancer that will be responsive to treatment with an anti-folate receptor alpha (FRA) therapeutic agent comprising said anti-FRA

therapeutic agent, a vessel for containing said anti-FRA therapeutic agent when not in use, and instructions for use of said anti-FRA therapeutic agent, wherein said instructions specify that a baseline CA125 level that is less than about eight times the upper limit of normal for CA125 is indicative of a subject who would benefit from treatment with said anti-FRA therapeutic agent.

57. A kit for treating a subject having ovarian cancer that will be responsive to treatment with an anti-folate receptor alpha (FRA) therapeutic agent comprising said anti-FRA therapeutic agent, a vessel for containing said anti-FRA therapeutic agent when not in use, and instructions for use of said anti-FRA therapeutic agent, wherein said instructions specify that a baseline CA125 level that is less than about three times the upper limit of normal for CA125 is indicative of a subject who would benefit from treatment with said anti-FRA therapeutic agent.

58. The kit of claim 56 or claim 57 further comprising an anti-CA125 antibody, a vessel for containing said antibody when not in use, and instructions for using said anti-CA125 antibody for determining a baseline level of CA125 of said subject.

59. The kit of claim 56 or claim 57 wherein said anti-FRA therapeutic agent comprises farletuzumab.

60. The kit of claim 56 or claim 57 further comprising an anti-folate receptor alpha (FRA) antibody, a vessel for containing the anti-FRA antibody when not in use, and instructions for using said anti-FRA antibody for determining a level of FRA in a biological sample obtained from said subject.

61. The kit of claim 56 or claim 57 further comprising an anti-serum albumin (SA) antibody, a vessel for containing the anti-SA antibody when not in use, and instructions for using said anti-SA antibody for determining a level of SA in a biological sample obtained from said subject.

62. The method of claim 14 further comprising determining the level of folate receptor alpha (FRA) of in a sample derived from said subject by contacting said sample with an antibody that binds FRA and comparing the level of FRA in said sample derived from said subject with the level of FRA in a control sample, wherein an increase in the level of FRA in the sample derived from said subject as compared to the level of FRA in the control sample is indicative that the subject would benefit from treatment with an anti-FRA therapeutic agent.

63. The kit of claim 58 wherein said anti-FRA therapeutic agent comprises farletuzumab.

64. The kit of claim 58 or claim 63 further comprising an anti-folate receptor alpha (FRA) antibody, a vessel for containing the anti-FRA antibody when not in use, and instructions for using said anti-FRA antibody for determining a level of FRA in a biological sample obtained from said subject.

65. The kit of claim 63 further comprising an anti-serum albumin (SA) antibody, a vessel for containing the anti-SA antibody when not in use, and instructions for using said anti-SA antibody for determining a level of SA in a biological sample obtained from said subject.

66. The kit of claim 64 further comprising an anti-serum albumin (SA) antibody, a vessel for containing the anti-SA antibody when not in use, and instructions for using said anti-SA antibody for determining a level of SA in a biological sample obtained from said subject.