METHODS OF TREATING CANCER

BACKGROUND

[0001] Soluble forms of Fibroblast Growth Factor Receptor 1 (FGFR1) have been shown to inhibit tumor cell growth *in vitro* and *in vivo*. *See, e.g.*, U.S. Patent No. 7,678,890. The efficacy of anti-cancer therapies is, in some instances, dependent on the genetic makeup of the cancer being targeted.

SUMMARY ~~OF THE INVENTION~~

[0002] In some embodiments, methods of treating breast cancer having *FGFR1* gene amplification, FGFR1 overexpression, *FGFR3* gene amplification, FGFR3 overexpression, *FGF2* gene amplification and/or FGF2 overexpression are provided, comprising administering to the subject a therapeutically effective amount of a fibroblast growth factor receptor 1 (FGFR1) extracellular domain (ECD) or an FGFR1 ECD fusion molecule. In some embodiments, the breast cancer has been determined to be estrogen receptor (ER) positive, progesterone (PR) positive, or ER positive and PR positive. In some embodiments, the breast cancer has been determined to be ER positive. In some embodiments, the breast cancer has been determined to be PR positive. In some embodiments, the breast cancer has been determined to be ER positive and PR positive. In some embodiments, the breast cancer has been determined to be HER2 positive. In some embodiments, the breast cancer has been determind to be p95HER2 positive. In some embodiments, the breast cancer has been determined to be HER2 negative. In any of the embodiments described herein, the breast cancer may be metastatic breast cancer. In any of the embodiments described herein, the subject with breast cancer is post-menopausal.

[0003] In some embodiments, the subject with breast cancer has previously been administered, or is currently being administered, trastuzumab (*e.g.*, Herceptin®) and/or lapatinib (*e.g.*, Tykerb®). In some embodiments, the subject has previously been administered, or is currently being administered, an aromatase inhibitor. In some embodiments, the aromatase inhibitor is selected from aminoglutethimide, testolactone (*e.g.*, Teslac®), anastrozole (*e.g.*, Arimidex®), letrozole (*e.g.*, Femara®), exemestane (*e.g.*, Aromasin®), vorozole (*e.g.*, Rivisor®), formestane (*e.g.*, Lentaron®), megestrol acetate (*e.g.*, Megase®), and fadrozole (*e.g.*, Afema®). In some embodiments, a subject with breast cancer has previously been administered, or is currently being administered, an ER antagonist. In some embodiments, the subject has previously been determined to have ER

administering to the subject a therapeutically effective amount of a fibroblast growth factor receptor 1 (FGFR1) extracellular domain (ECD) or an FGFR1 ECD fusion molecule. In some embodiments, the subject has previously been administered, or is currently being administered, an ER antagonist or an aromatase inhibitor. In some embodiments, the aromatase inhibitor is selected from aminoglutethimide, testolactone (*e.g.*, Teslac®), anastrozole (*e.g.*, Arimidex®), letrozole (*e.g.*, Femara®), exemestane (*e.g.*, Aromasin®), vorozole (*e.g.*, Rivisor®), formestane (*e.g.*, Lentaron®), megestrol acetate (*e.g.*, Megase®), and fadrozole (*e.g.*, Afema®). Nonlimiting exemplary ER antagonists include tamoxifen (*e.g.*, Nolvadex®, Istabul®, Valodex®) and fulvestrant (*e.g.*, Faslodex®). In some embodiments, the ovarian cancer is estrogen receptor (ER) positive, progesterone (PR) positive, or ER positive and PR positive.

[0006a] In one aspect, there is provided the use of an FGFR1 ECD or an FGFR1 ECD fusion molecule for preparation of a medicament for treatment of lung cancer in a subject, wherein said FGFR1 ECD or an FGFR1 ECD fusion molecule at a dose of at least 5 mg/kg is to be administered in combination either with at least 135 mg/m^2 paclitaxel and at least AUC 4 carboplatin, or with at least 40 mg/m^2 docetaxel to the subject.

[0007] In some embodiments, methods of treating lung cancer in a subject are provided. In some embodiments, a method comprises administering at least 5 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule and at least 135 mg/m^2 paclitaxel and at least AUC 4 carboplatin to the subject. In some embodiments, the method comprises administering from 135 mg/m^2 paclitaxel to 200 mg/m^2 paclitaxel, at least 175 mg/m^2 paclitaxel, from 175 mg/m^2 paclitaxel to 200 mg/m^2 paclitaxel, or 200 mg/m^2 paclitaxel. In some embodiments, the method comprises administering from AUC 4 carboplatin to AUC 6 carboplatin, at least AUC 5 carboplatin, from AUC 5 carboplatin to AUC 6 carboplatin, or AUC 6 carboplatin. In some embodiments, the lung cancer is non-small cell lung cancer. In some embodiments, the non-small cell lung cancer is squamous non-small cell lung cancer.

[0008] In some embodiments, a method of treating lung cancer in a subject comprises administering at least 5 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule and at least 40 mg/m^2 docetaxel. In some embodiments, the method comprises administering from 40 mg/m^2 docetaxel to 75 mg/m^2 docetaxel, at least 55 mg/m^2 docetaxel, from 55 mg/m^2 docetaxel to 75 mg/m^2 docetaxel, or 75 mg/m^2 docetaxel. In some embodiments, the lung cancer is non-small cell lung cancer. In some embodiments, the non-small cell lung cancer is squamous non-small cell lung cancer.

[0009] In any of the embodiments described herein, a method may comprise administering from 5 mg/kg to 20 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, at least 10 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, from 10 mg/kg to 20 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, at least 15 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, from 15 mg/kg to 20 mg/kg of an FGFR1 ECD or an

in a sample obtained from the subject overexpress at least one, at least two, at least three, or at least four markers selected from FGFR1, FGFR3IIIc, FGF2, DKK3, and FGF18. In some embodiments, the method comprises determining whether at least a portion of the cancer cells in a sample obtained from the subject overexpress ETV4. In some embodiments, including any of the foregoing embodiments, the method comprises determining whether at least a portion of the cancer cells in a sample obtained from the subject overexpress Gene 1 and Gene 2 from any line in Table 6 below, or any comination thereof. In some embodiments, FGFR1 is FGFR1IIIc. In some embodiments, including any of the foregoing embodiments, the method comprises determining whether at least a portion of the cancer cells in a sample obtained from the subject have an *FGFR1* gene amplification.

[0022] Any embodiment described herein or any combination thereof applies to any and all methods of the ~~invention~~ disclosure described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] **FIG. 1** shows % tumor growth inhibition by FGFR1-ECD.339-Fc in mouse xenografts of tumor cells having *FGFR1* gene amplification and tumor cells having a non-amplified *FGFR1* gene, as described in Example 1.

[0024] **FIG. 2** shows a scatter plot of FGFR1 mRNA expression in lung cancer cell lines with and without *FGFR1* gene amplification, as described in Example 2.

[0025] **FIG. 3** shows graphs of (A) average luminescence in the CellTiterGlo® assay and (B) counts per minute in the tritiated thymidine incorporation assay carried out on NCI-H226 cells grown with varying amounts of serum and in the presence or absence of FGFR1-ECD.339-Fc, as described in Example 2.

[0026] **FIG. 4** shows a scatter plot of FGFR1 mRNA expression in lung cancer xenografts with and without *FGFR1* gene amplification, as described in Example 2.

[0027] **FIG. 5** shows mean tumor volume at various time points in mice implanted with PDX D35087 cells and treated with FGFR1-ECD.339-Fc or albumin, as described in Example 2.

[0028] **FIG. 6** shows (A) FGF2 mRNA (normalized to GUSB) and (B) FGF2 protein expression (normalized to total protein) in FGFR1-ECD.339-Fc responder and non-responder xenografts, as described in Example 3.

[0029] **FIG. 7** shows DKK3 mRNA expression (normalized to GUSB) in FGFR1-ECD.339-Fc responder and non-responder xenografts, as described in Example 4.

CLAIMS

1. A method of treating breast cancer in a subject comprising administering a therapeutically effective amount of an FGFR1 ECD or an FGFR1 ECD fusion molecule to the subject, wherein prior to administration at least a portion of the cells of the breast cancer were determined to have *FGFR1* gene amplification, FGFR1 overexpression, FGFR3 overexpression, or FGF2 overexpression; and to be estrogen receptor (ER) positive, progesterone (PR) positive, or ER positive and PR positive.

2. The method of claim 1, wherein prior to administration the cancer was determined to be HER2 positive.

3. The method of claim 2, wherein prior to administration the cancer was determined to be p95HER2 positive.

4. The method of any one of claims 1 to 3, wherein the subject has previously been administered, or is currently being administered, trastuzumab or lapatinib.

5. The method of claim 1, wherein prior to administration the cancer was determined to be HER2 negative.

6. The method of any one of the preceding claims, wherein the breast cancer is ER positive.

7. The method of any one of the preceding claims, wherein the breast cancer is PR positive.

8. The method of any one of the preceding claims, wherein the subject has previously been administered, or is currently being administered, an aromatase inhibitor.

9. A method of treating prostate cancer in a subject comprising administering a therapeutically effective amount of an FGFR1 ECD or an FGFR1 ECD fusion molecule to the subject, wherein prior to administration at least a portion of the cells of the prostate cancer were determined to have *FGFR1* gene amplification, FGFR1 overexpression, FGFR3 overexpression, or FGF2 overexpression, and wherein the subject has previously been administered, or is currently being administered, a therapeutic agent selected from a gonadotropin releasing hormone (GnRH) agonist, a GnRH antagonist, an androgen receptor (AR) inhibitor, and a 17-hydroxylase inhibitor.

10. The method of claim 9, wherein the subject has previously been administered, or is currently being administered, a gonadotropin releasing hormone (GnRH) agonist or a GnRH antagonist.

11. The method of claim 10, wherein the subject has previously been administered, or is currently being administered, a GnRH antagonist.

12. A method of treating carcinoid cancer in a subject comprising administering a

therapeutically effective amount of an FGFR1 ECD or an FGFR1 ECD fusion molecule to the subject, wherein prior to administration at least a portion of the cells of the carcinoid cancer were determined to have *FGFR1* gene amplification, FGFR1 overexpression, FGFR3 overexpression, or FGF2 overexpression, and wherein the subject has previously been administered, or is currently being administered, octreotide.

13. A method of treating ovarian cancer in a subject comprising administering a therapeutically effective amount of an FGFR1 ECD or an FGFR1 ECD fusion molecule to the subject, wherein prior to administration at least a portion of the cells of the ovarian cancer were determined to have *FGFR1* gene amplification, FGFR1 overexpression, FGFR3 overexpression, or FGF2 overexpression, and wherein the subject has previously been administered, or is currently being administered, tamoxifen or an aromatase inhibitor.

14. The method of claim 13, wherein the ovarian cancer is estrogen receptor (ER) positive, progesterone (PR) positive, or ER positive and PR positive.

15. A method of treating lung cancer in a subject comprising administering at least 5 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule and at least 135 mg/m^2 paclitaxel and at least AUC 4 carboplatin to the subject.

16. The method of claim 15, wherein the method comprises administering from 135 mg/m^2 paclitaxel to 200 mg/m^2 paclitaxel, at least 175 mg/m^2 paclitaxel, from 175 mg/m^2 paclitaxel to 200 mg/m^2 paclitaxel, or 200 mg/m^2 paclitaxel.

17. The method of claim 15 or claim 16, wherein the method comprises administering from AUC 4 carboplatin to AUC 6 carboplatin, at least AUC 5 carboplatin, from AUC 5 carboplatin to AUC 6 carboplatin, or AUC 6 carboplatin.

18. A method of treating lung cancer in a subject comprising administering at least 5 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule and at least 40 mg/m^2 docetaxel.

19. The method of claim 18, wherein the method comprises administering from 40 mg/m^2 docetaxel to 75 mg/m^2 docetaxel, at least 55 mg/m^2 docetaxel, from 55 mg/m^2 docetaxel to 75 mg/m^2 docetaxel, or 75 mg/m^2 docetaxel.

20. The method of any one of claims 15 to 19, wherein the method comprises administering from 5 mg/kg to 20 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, at least 10 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, from 10 mg/kg to 20 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, at least 15 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, from 15 mg/kg to 20 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, or 20 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule.

21. The method of any one of claims 15 to 20, wherein the lung cancer is non-small cell lung cancer.

22. The method of claim 21, wherein the non-small cell lung cancer is squamous non-small cell lung cancer.

23. The method of any one of the preceding claims, wherein at least a portion of the cells of the cancer have an *FGFR1* gene amplification.

24. The method of claim 23, wherein at least a portion of the cells of the cancer having *FGFR1* gene amplification comprise at least three copies of the *FGFR1* gene.

25. The method of claim 24, wherein at least a portion of the cells of the cancer having *FGFR1* gene amplification comprise at least four, at least five, at least six, or at least eight copies of the *FGFR1* gene.

26. The method of claim 23, wherein at least a portion of the cells of the cancer having an *FGFR1* gene amplification have a ratio of *FGFR1* gene to chromosome 8 centromere of at least 1.5.

27. The method of claim 26, wherein the ratio of *FGFR1* gene to chromosome 8 centromere is at least 2, at least 2.5, at least 3, at least 3.5, or at least 4.

28. The method of claim 26, wherein the ratio of *FGFR1* gene to chromosome 8 centromere is greater than 2.

29. The method of any one of claims 23 to 28, wherein *FGFR1* gene amplification was determined by a method selected from fluorescence *in situ* hybridization, array comparative genomic hybridization, DNA microarray, spectral karyotyping, quantitative PCR, southern blotting, or sequencing.

30. The method of any one of the preceding claims, wherein at least a portion of the cells of the cancer have FGFR1 overexpression.

31. The method of claim 30, wherein FGFR1 is FGFR1IIIc.

32. The method of any one of the preceding claims, wherein at least a portion of the cells of the cancer have FGF2 overexpression.

33. The method of any one of the preceding claims, wherein at least a portion of the cells of the cancer have FGFR3 overexpression.

34. The method of claim 33, wherein FGFR3 is FGFR3IIIc.

35. The method of any one of the preceding claims, wherein at least a portion of the cells of the cancer overexpress at least one, at least two, or three markers selected from DKK3, FGF18, and ETV4.

36. The method of any one of the preceding claims, wherein at least a portion of the cells of the cancer overexpress at least one or two markers selected from DKK3 and

FGF18.

37. The method of any one of the preceding claims, wherein at least a portion of the cells of the cancer overexpress ETV4.

38. The method of any one of claims 30 to 37, wherein the cancer does not have an FGFR1 gene amplification.

39. The method of any one of claims 30 to 38, wherein the overexpression is protein overexpression.

40. The method of claim 39, wherein protein overexpression is determined using immunohistochemistry.

41. The method of any one of claims 30 to 38, wherein the overexpression is mRNA overexpression.

42. The method of claim 41, wherein mRNA overexpression is determined using quantitative RT-PCR.

43. The method of any one of the preceding claims, wherein the method comprises administering an FGFR1 ECD.

44. The method of claim 43, wherein the FGFR1 ECD comprises an amino acid sequence selected from SEQ ID NOs: 1 to 4.

45. The method of any one of claims 1 to 42, wherein the method comprises administering an FGFR1 ECD fusion molecule.

46. The method of claim 45, wherein the FGFR1 ECD fusion molecule comprises an FGFR1 ECD and a fusion partner, and wherein the fusion partner is Fc.

47. The method of claim 46, wherein the FGFR1 ECD fusion molecule comprises a sequence selected from SEQ ID NO: 5 and SEQ ID NO: 6.

CLAIMS

1. Use of an FGFR1 ECD or an FGFR1 ECD fusion molecule for preparation of a medicament for treatment of lung cancer in a subject, wherein said FGFR1 ECD or an FGFR1 ECD fusion molecule at a dose of at least 5 mg/kg is to be administered in combination either with at least 135 mg/m^2 paclitaxel and at least AUC 4 carboplatin, or with at least 40 mg/m^2 docetaxel to the subject.

2. The use of claim 1, wherein from 135 mg/m^2 paclitaxel to 200 mg/m^2 paclitaxel, at least 175 mg/m^2 paclitaxel, from 175 mg/m^2 paclitaxel to 200 mg/m^2 paclitaxel, or 200 mg/m^2 paclitaxel is to be administered to the subject.

3. The use of claim 1, wherein from AUC 4 carboplatin to AUC 6 carboplatin, at least AUC 5 carboplatin, from AUC 5 carboplatin to AUC 6 carboplatin, or AUC 6 carboplatin is to be administered to the subject.

4. The use of claim 1, wherein from 40 mg/m^2 docetaxel to 75 mg/m^2 docetaxel, at least 55 mg/m^2 docetaxel, from 55 mg/m^2 docetaxel to 75 mg/m^2 docetaxel, or 75 mg/m^2 docetaxel is to be administered to the subject.

5. The use of any one of claims 1 to 4, wherein from 5 mg/kg to 20 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, at least 10 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, from 10 mg/kg to 20 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, at least 15 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, from 15 mg/kg to 20 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule, or 20 mg/kg of an FGFR1 ECD or an FGFR1 ECD fusion molecule is to be administered to the subject.

6. The use of any one of claims 1 to 5, wherein the lung cancer is non-small cell lung cancer.

7. The use of claim 6, wherein the non-small cell lung cancer is squamous non-small cell lung cancer.

8. The use of any one of claims 1 to 7, wherein at least a portion of the cells of the lung cancer have an *FGFR1* gene amplification.

9. The use of claim 8, wherein at least a portion of the cells of the cancer having *FGFR1* gene amplification comprise at least three copies of the *FGFR1* gene.

10. The use of claim 9, wherein at least a portion of the cells of the cancer having *FGFR1* gene amplification comprise at least four, at least five, at least six, or at least eight copies of the *FGFR1* gene.

11. The use of claim 8, wherein at least a portion of the cells of the cancer having an *FGFR1* gene amplification have a ratio of *FGFR1* gene to chromosome 8 centromere of at

least 1.5.

12. The use of claim 11, wherein the ratio of *FGFR1* gene to chromosome 8 centromere is at least 2, at least 2.5, at least 3, at least 3.5, or at least 4.

13. The use of claim 12, wherein the ratio of *FGFR1* gene to chromosome 8 centromere is greater than 2.

14. The use of any one of claims 8 to 13, wherein *FGFR1* gene amplification was determined by a method selected from fluorescence *in situ* hybridization, array comparative genomic hybridization, DNA microarray, spectral karyotyping, quantitative PCR, southern blotting, or sequencing.

15. The use of any one of claims 1 to 14, wherein at least a portion of the cells of the cancer have FGFR1 overexpression.

16. The use of claim 15, wherein FGFR1 is FGFR1IIIc.

17. The use of any one of claims 1 to 16, wherein at least a portion of the cells of the cancer have FGF2 overexpression.

18. The use of any one of claims 1 to 17, wherein at least a portion of the cells of the cancer have FGFR3 overexpression.

19. The use of claim 18, wherein FGFR3 is FGFR3IIIc.

20. The use of any one of claims 1 to 19, wherein at least a portion of the cells of the cancer overexpress at least one, at least two, or three markers selected from DKK3, FGF18, and ETV4.

21. The use of any one of claims 1 to 20, wherein at least a portion of the cells of the cancer overexpress at least one or two markers selected from DKK3 and FGF18.

22. The use of any one of claims 1 to 21, wherein at least a portion of the cells of the cancer overexpress ETV4.

23. The use of any one of claims 15 to 22, wherein the cancer does not have an FGFR1 gene amplification.

24. The use of any one of claims 15 to 22, wherein the overexpression is protein overexpression.

25. The use of claim 24, wherein protein overexpression is determined using immunohistochemistry.

26. The use of any one of claims 15 to 22, wherein the overexpression is mRNA overexpression.

27. The use of claim 26, wherein mRNA overexpression is determined using quantitative RT-PCR.

28. The use of any one of claims 1 to 27, wherein the FGFR1 ECD comprises an

amino acid sequence selected from SEQ ID NOs: 1 to 4.

29. The use of any one of claims 1 to 28, wherein the FGFR1 ECD fusion molecule comprises an FGFR1 ECD and a fusion partner, and wherein the fusion partner is Fc.

30. The use of claim 29, wherein the FGFR1 ECD fusion molecule comprises a sequence selected from SEQ ID NO: 5 and SEQ ID NO: 6.