FGFR1 EXTRACELLULAR DOMAIN COMBINATION THERAPIES

RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional application numbers 61/413,940 filed November 15, 2010, and 61/421,462 filed December 9, 2010, the content of which are incorporated herein by reference.

BACKGROUND AND SUMMARY ~~OF THE INVENTION~~

[0002] 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. Combining an anti-cancer therapeutic molecule, such as a soluble form of FGFR1, with another anti-cancer therapeutic molecule, can result in antagonistic, additive, or synergistic effects on the efficacy of each of the anti-cancer therapeutics.

[0003] The inventors have discovered that administration of an FGFR1 ECD and docetaxel in a mouse xenograft model of non-small cell lung cancer shows synergistic anti-tumor activity of the therapeutic agents. In addition, the inventors have discovered that administration of an FGFR1 ECD and at least one additional therapeutic molecule selected from paclitaxel, vincristine, carboplatin, cisplatin, oxaliplatin, doxorubicin, 5-fluorouracil (5-FU), leucovorin, pemetrexed, and bevacizumab, has at least additive activity relative to each molecule administered alone in certain mouse xenograft models.

[003a] In one aspect, there is provided the use of a fibroblast growth factor receptor 1 (FGFR1) extracellular domain (ECD) in the manufacture of a medicament for the treatment of cancer, wherein the FGFR1 ECD is to be administered in combination with docetaxel, wherein the FGFR1 ECD comprises an amino acid sequence selected from SEQ ID NOs: 1 to 4, and wherein the combination results in synergistic inhibition of tumor growth in a mouse xenograft cancer model.

[0004] In some embodiments, methods of treating cancer comprising administering to a subject a fibroblast growth factor receptor 1 (FGFR1) extracellular domain (ECD) and at least one additional therapeutic agent selected from docetaxel, paclitaxel, vincristine, carboplatin, cisplatin, oxaliplatin, doxorubicin, 5-fluorouracil (5-FU), leucovorin, pemetrexed, sorafenib, etoposide, topotecan, a vascular endothelial growth factor (VEGF) antagonist, a VEGF trap, an anti-VEGF antibody, and bevacizumab are provided. In some embodiments, the at least one additional therapeutic agent is docetaxel. In some embodiments, the at least one additional

therapeutic agent is pemetrexed. In some embodiments, the at least one additional therapeutic agent is cisplatin. In some embodiments, the at least one additional therapeutic agent is paclitaxel. In some embodiments, the at least one additional therapeutic agent is 5-FU. In some embodiments, the at least one additional therapeutic agent is topotecan. In some embodiments, the at least one additional therapeutic agent is viscristine. In some embodiments, the at least one additional therapeutic agents is a VEGF antagonist, such as an anti-VEGF antibody or a VEGF trap. In some embodiments, the at least one additional therapeutic agent is bevacizumab. In

antagonist, such as an anti-VEGF antibody or a VEGF trap. In some embodiments, at least one of the two additional therapeutic agents is bevacizumab. In some embodiments, the two additional therapeutic agents are paclitaxel and carboplatin. In some embodiments, the two additional therapeutic agents are doxorubicin and paclitaxel. In some embodiments, the two additional therapeutic agents are cisplatin and etoposide. In some embodiments, the two additional therapeutic agents are oxaliplatin and 5-FU. In some embodiments, the two additional therapeutic agents are 5-FU and leucovorin. In some embodiments, the two additional therapeutic agents are 5-FU and bevacizumab. In some embodiments, the two additional therapeutic agents are paclitaxel and bevacizumab. In some embodiments, the two additional therapeutic agents are cisplatin and etoposide.

[0007] In some embodiments, methods of treating cancer comprising administering to a subject an FGFR1 ECD or FGFR1 ECD fusion molecule and at least three additional therapeutic agents selected from docetaxel, paclitaxel, vincristine, carboplatin, cisplatin, oxaliplatin, doxorubicin, 5-fluorouracil (5-FU), leucovorin, pemetrexed, etoposide, sorafenib, a VEGF antagonist, an anti-VEGF antibody, a VEGF trap, and bevacizumab are provided, wherein the FGFR1 ECD fusion molecule comprises an FGFR1 ECD and a fusion partner. In some embodiments, at least one of the three additional therapeutic agents is oxaliplatin. In some embodiments, at least one of the three additional therapeutic agents is 5-FU. In some embodiments, at least one of the three additional therapeutic agents is leucovorin. In some embodiments, at least one of the three additional therapeutic agents is carboplatin. In some embodiments, at least one of the three additional therapeutic agents is paclitaxel. In some embodiments, at least one of the three additional therapeutic agents is bevacizumab. In some embodiments, the three additional therapeutic agents are oxaliplatin, 5-FU and leucovorin. In some embodiments, the three additional therapeutic agents are bevacizumab, 5-FU and leucovorin. In some embodiments, at least two of the three additional therapeutic agents are cisplatin and etoposide.

[0008] The ~~invention~~disclosure also relates, in some embodiments, to a combination of an FGFR1 ECD or FGFR1 ECD fusion molecule and at least one additional therapeutic agent selected from docetaxel, paclitaxel, vincristine, carboplatin, cisplatin, oxaliplatin, doxorubicin, 5-fluorouracil (5-FU), leucovorin, pemetrexed, sorafenib, etoposide, topotecan, a vascular endothelial growth factor (VEGF) antagonist, a VEGF trap, an anti-VEGF antibody, and bevacizumab, for treatment of cancer. The ~~invention~~disclosure further relates, in some embodiments to a combination of an FGFR1 ECD or FGFR1 ECD fusion molecule and at least two additional therapeutic agents selected from docetaxel, paclitaxel, vincristine, carboplatin, cisplatin, oxaliplatin, doxorubicin, 5-

fluorouracil (5-FU), leucovorin, pemetrexed, etoposide, sorafenib, etoposide, topotecan, a vascular epithelial growth factor (VEGF) antagonist, a VEGF trap, an anti-VEGF antibody, and bevacizumab, for treatment of cancer. The ~~invention~~disclosure also relates, in some embodiments, to a combination of an FGFR1 ECD or FGFR1 ECD fusion molecule and at least three additional therapeutic agents selected from docetaxel, paclitaxel, vincristine, carboplatin, cisplatin, oxaliplatin, doxorubicin, 5-fluorouracil (5-FU), leucovorin, pemetrexed, etoposide, sorafenib, a VEGF antagonist, an anti-VEGF antibody, a VEGF trap, and bevacizumab, for treatment of cancer.

[0009] In some embodiments, the FGFR1 ECD and/or FGFR1 ECD fusion molecule is packaged separately from the at least one, at least two, or at least three additional therapeutic agents. In some embodiments, the FGFR1 ECD and/or FGFR1 ECD fusion molecule is not mixed with the at least one, at least two, or at least three additional therapeutic agents prior to administration.

[0010] In some embodiments, a method of treating cancer comprising administering to a subject an FGFR1-ECD.339-Fc and docetaxel is provided, wherein the FGFR1-ECD.339-Fc comprises the amino acid sequence of SEQ ID NO: 6. In some embodiments, a method of treating cancer comprising administering to a subject an FGFR1-ECD.339-Fc and docetaxel is provided, wherein the FGFR1-ECD.339-Fc consists of the amino acid sequence of SEQ ID NO: 6.

[0011] In some embodiments, an FGFR1 ECD or FGFR1 ECD fusion molecule is glycosylated and/or sialylated. In some embodiments, an FGFR1 ECD or the polypeptide portion of the FGFR1 ECD fusion molecule is expressed in Chinese hamster ovary (CHO) cells. In some embodiments, an FGFR1 ECD comprises an amino acid sequence selected from SEQ ID NO: 1 and SEQ ID NO: 3.

[0012] In some embodiments, at least one dose of an FGFR1 ECD and/or an FGFR1 ECD fusion molecule and at least one dose of at least one additional therapeutic agent are administered concurrently. In some embodiments, at least one dose of an FGFR1 ECD and/or an FGFR1 ECD fusion molecule and at least one dose of at least one additional therapeutic agent are administered at the same time.

[0013] In some embodiments, the FGFR1 ECD comprises an amino acid sequence selected from SEQ ID NOs: 1 to 4. In some embodiments, at least one fusion partner is selected from an Fc, albumin, and polyethylene glycol. In some embodiments, at least one fusion partner is an Fc. In some embodiments, the Fc comprises an amino acid sequence selected from SEQ ID NOs: 8 to 10. In some embodiments, the FGFR1 ECD fusion molecule comprises a sequence selected

from SEQ ID NO: 5 and SEQ ID NO: 6. In some embodiments, the at least one fusion partner is an Fc and polyethylene glycol. In some embodiments, the at least one fusion partners is polyethylene glycol. In some embodiments, the fusion molecule comprises a linker between the FGFR1 ECD and one or more fusion partners. In some embodiments, the FGFR1 ECD comprises a signal peptide. In some embodiments, the signal peptide comprises the amino acid sequence of SEQ ID NO: 7.

[0014] In some embodiments, the FGFR1 ECD fusion molecule is an amount in the range of about 0.5 mg/kg body weight to about 20 mg/kg body weight, such as an amount in the range of about 8 to about 16 mg/kg body weight. In some embodiments, the therapeutically effective amount of the FGFR1 ECD fusion molecule is a dose of about 8 mg/kg body weight, while in some embodiments, the therapeutically effective amount of the FGFR1 ECD fusion molecule is a dose of about 16 mg/kg body weight (or at about 10 mg/kg body weight or about 20 mg/kg body weight, respectively, when calculated using an extinction coefficient of 1.11 mL/mg*cm). In some embodiments, the therapeutically effective amount of FGFR1 ECD fusion molecule is a dose of about 20 mg/kg body weight. In some embodiments, dosages may be administered twice a week, weekly, every other week, at a frequency between weekly and every other week, every three weeks, every four weeks, or every month.

[0015] The ~~invention~~disclosure also relates, in some embodiments, to a dosage pack. In some embodiments, a dosage pack comprising at least one component selected from: (i) a fibroblast growth factor receptor 1 (FGFR1) extracellular domain (ECD), (ii) a fibroblast growth factor receptor 1 (FGFR1) extracellular domain (ECD) fusion molecule, and (iii) at least one additional therapeutic agent selected from docetaxel, paclitaxel, vincristine, carboplatin, cisplatin, oxaliplatin, doxorubicin, 5-fluorouracil (5-FU), leucovorin, pemetrexed, etoposide, topotecan, a VEGF antagonist, an anti-VEGF antibody, a VEGF trap, bevacizumab, and sorafenib; and instructions for administering an FGFR1 ECD or FGFR1 ECD fusion molecule and the at least one additional therapeutic to a patient is provided. In some embodiments, the instructions included with the dosage pack comprise instructions for administering a therapeutically effective amount of FGFR1 ECD fusion molecule. In some embodiments, the therapeutically effective amount of the FGFR1 ECD fusion molecule is an amount in the range of about 0.5 mg/kg body weight to about 20 mg/kg body weight, such as an amount in the range of about 8 to about 16 mg/kg body weight. In some embodiments, the therapeutically effective amount of the FGFR1 ECD fusion molecule is a dose of about 8 mg/kg body weight. In some embodiments, the therapeutically effective amount of the FGFR1 ECD fusion molecule is a dose of about 16 mg/kg body weight. In some embodiments, the therapeutically effective amount of FGFR1 ECD fusion

glycol. In some embodiments, at least one fusion partner is an Fc. In some embodiments, the Fc comprises an amino acid sequence selected from SEQ ID NOs: 8 to 10. In some embodiments, the FGFR1 ECD fusion molecule comprises a sequence selected from SEQ ID NO: 5 and SEQ ID NO: 6. In some embodiments, the FGFR1 ECD fusion molecule consists of a sequence selected from SEQ ID NO: 5 and SEQ ID NO: 6. In some embodiments, the at least one fusion partner is an Fc and polyethylene glycol. In some embodiments, the at least one fusion partners is polyethylene glycol.

[0018] In certain embodiments, the cancer is prostate cancer, breast cancer, colorectal cancer, lung cancer, endometrial cancer, head and neck cancer, laryngeal cancer, liver cancer, renal cancer glioblastoma or pancreatic cancer. In certain embodiments, the cancer is lung cancer. In certain embodiments, the cancer is renal cancer. In certain embodiments, the cancer is colon cancer. In certain embodiments, the cancer is breast cancer. In certain embodiments, the cancer is endometrial cancer. In certain embodiments, the cancer is prostate cancer.

[0019] Any embodiment described herein or any combination of additional therapeutic agents thereof applies to any and all methods of the ~~invention~~disclosure described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] FIG. 1 shows the mean tumor volume in mice administered FGFR1-ECD.339-Fc alone, docetaxel alone, FGFR1-ECD.339-Fc and docetaxel sequentially, and FGFR1-ECD.339-Fc and docetaxel concurrently, as described in Example 1.

[0021] FIG. 2 shows the mean tumor volume (A) and body weight (B) of mice administered FGFR1-ECD.339-Fc alone, pemetrexed alone (62.5 mg/kg dose), or FGFR1-ECD.339-Fc and pemetrexed (62.5 mg/kg dose), as described in Example 2.

[0022] FIG. 3 shows the mean tumor volume (A) and body weight (B) of mice administered FGFR1-ECD.339-Fc alone, pemetrexed alone (125 mg/kg dose), or FGFR1-ECD.339-Fc and pemetrexed (125 mg/kg dose), as described in Example 2.

[0023] FIG. 4 shows the mean tumor volume (A) and body weight (B) of mice administered FGFR1-ECD.339-Fc alone, pemetrexed alone (250 mg/kg dose), or FGFR1-ECD.339-Fc and pemetrexed (250 mg/kg dose), as described in Example 2.

[0024] FIG. 5 shows the mean tumor volume in mice administered FGFR1-ECD.339-Fc alone, cisplatin alone, or the combination of FGFR1-ECD.339-Fc and cisplatin, as described in Example 3A.