# FGFR/PD-1 COMBINATION THERAPY FOR THE TREATMENT OF CANCER

## CROSS REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims priority to U.S. Provisional Application No. 62/142,569, filed April 3, 2015, the disclosure of which is hereby incorporated by reference in its entirety.

## SEQUENCE LISTING

**[0002]** The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on March 22, 2016, is named PRD3366USNP_SL.txt and is 53,086 bytes in size.

## TECHNICAL FIELD

**[0003]** Provided herein are combination therapies for the treatment of cancer. In particular, the disclosed methods are directed to treatment of cancer in a patient comprising administering an antibody that blocks the interaction between PD-1 and PD-L1 and a fibroblast growth factor receptor (FGFR) inhibitor.

## BACKGROUND

**[0004]** For cancer patients failing the main therapeutic option (front-line therapy) for that cancer type, there is often no accepted standard of care for second and subsequent-line therapy, unless a particular genetic abnormality is identified and a specific therapy is available. Fibroblast growth factor receptors (FGFRs) are a family of receptor tyrosine kinases involved in regulating cell survival, proliferation, migration and differentiation. FGFR alterations have been observed in some cancers. To date, there are no approved therapies that are efficacious in patients with FGFR alterations.

## SUMMARY

**[0005]** Disclosed herein are methods of using a combination therapy that comprises an antibody that blocks the interaction between PD-1 and PD-L1 and an FGFR inhibitor to treat cancer in a patient. In some examples, the methods comprise administering to a patient a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and

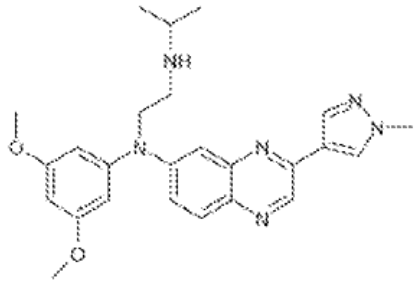
PD-L1 and a pharmaceutically effective amount of an FGFR inhibitor, wherein the antibody that blocks the interaction between PD-1 and PD-L1 and the FGFR inhibitor are administered if one or more FGFR variants are present in a biological sample from the patient.

**[0006]** In other examples, the methods of treating cancer in a patient comprise: administering to the patient a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-L1; monitoring the efficacy of the antibody; and, if the antibody is not efficacious, evaluating a biological sample from the patient for a presence of one or more FGFR variants and administering to the patient a pharmaceutically effective amount of an FGFR inhibitor if the one or more FGFR variants are present in the sample.

**[0007]** Also, disclosed herein are uses of an antibody that blocks the interaction between PD-1 and PD-L1 and an FGFR inhibitor for the manufacture of a medicament for the treatment of cancer, in particular for the treatment of cancer in a patient wherein one or more FGFR variants are present in a biological sample from the patient. In some examples, the medicament contains a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-L1 and a pharmaceutically effective amount of an FGFR inhibitor, wherein the medicament is used in a patient wherein one or more FGFR variants are present in a biological sample from the patient.

**[0008]** Also disclosed herein are combinations of an antibody that blocks the interaction between PD-1 and PD-L1 and an FGFR inhibitor for use in the treatment of cancer, in particular for use in the treatment of cancer in a patient wherein one or more FGFR variants are present in a biological sample from the patient. In some examples, the combination comprises a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-L1 and a pharmaceutically effective amount of an FGFR inhibitor for use in the treatment of cancer in a patient wherein one or more FGFR variants are present in a biological sample from the patient. In other examples, the combination for treating cancer comprises administration of a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-L1; monitoring the efficacy of the antibody; and, if the antibody is not efficacious, evaluating a biological sample from the patient for a presence of one or more FGFR variants, followed by administration to the patient a pharmaceutically effective amount of an FGFR inhibitor if the one or more FGFR variants are present in the sample.

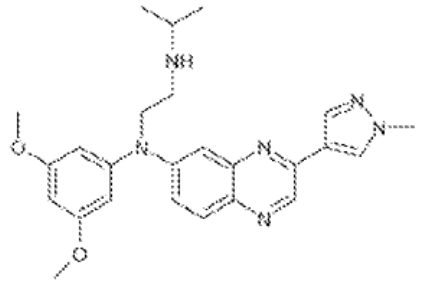
**[0008a]** In one aspect, there is provided use of an FGFR inhibitor in the manufacture of a medicament for treating cancer in a patient in combination with an antibody that blocks the interaction between PD-1 and PD-Ll if one or more FGFR variants are present in a biological sample that has been obtained from the patient, wherein the one or more FGFR variants comprise an FGFR fusion gene, a FGFR mutation, or a combination thereof, wherein the FGFR fusion gene is FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFDl; FGFR3:BAIAP2L1; FGFR3:TACC3-Intron; FGFR3:TACC3V1; FGFR3:TACC3V3; or a combination thereof; and wherein the FGFR mutation is FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, FGFR3 Y373C, or a combination thereof; and wherein the FGFR inhibitor is the compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

**[0008b]** In another aspect, there is provided use of an FGFR inhibitor in the manufacture of a medicament for treating cancer in a patient in combination with an antibody that blocks the interaction between PD-1 and PD-Ll, wherein the efficacy of the antibody is to be monitored; and if the antibody is not efficacious, a biological sample that has been obtained from the patient is evaluated for a presence of one or more FGFR variants; and wherein the FGFR inhibitor is to be administered if the one or more FGFR variants are present in the sample, wherein the one or more FGFR variants comprise an FGFR fusion gene, a FGFR mutation, or a combination thereof; and wherein the FGFR fusion gene is FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFDl; FGFR3:BAIAP2L1; FGFR3:TACC3-Intron; FGFR3:TACC3V1; FGFR3:TACC3V3; or a combination thereof; and wherein the FGFR mutation is FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, FGFR3 Y373C, or a combination thereof; and wherein the FGFR inhibitor is the compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

**[0009]** The summary, as well as the following detailed description, is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the disclosed methods, there are shown in the drawings exemplary embodiments of the methods; however, the methods are not limited to the specific embodiments disclosed. In the drawings:

**[0010]** **FIG. 1** illustrates PD-L1 expression in a 120 lung cancer samples set by histology and FGFR mutant and amplification status. PD-L1 H-scores (Y-axis) were plotted for NSCLC adenocarcinoma (left), small cell lung cancer (middle), and NSCLC squamous (right). The FGFR mutation and/or amplification status versus the PD-L1 staining for each of the 120 samples is shown. Mutation – an FGFR mutation was identified, but no amplification or fusion was detected; No FGFR Alteration – no mutation, amplification, or fusion was detected; Amplification – an FGFR gene amplification was identified, but no FGFR mutation or fusion was detected; Mutation + Amp – samples were positive for both FGFR mutation and gene amplification, but no fusion was detected; Not Tested – IHC for PD-L1 was performed, but sample was not tested on Foundation Medicine panel.

**[0011]** **FIG. 2** illustrates PD-L1 expression in an 80 non-small-cell lung carcinoma (NSCLC) sample set by FGFR fusion status by NSCLC histology. PD-L1 H-scores (Y-axis) were plotted for NSCLC adenocarcinoma (left), and NSCLC squamous (right). The FGFR fusion status versus the PD-L1 staining for each of the 80 samples is shown. Fusion Positive – an FGFR fusion was detected; Fusion Wild-Type – no FGFR fusion was detected; Not Tested – insufficient sample for testing or quality control (QC) failure.

**[0012]** **FIG. 3** illustrates the effect of JNJ42756493 on immune cell viability. Normal donor peripheral blood mononuclear cells (PBMCs), either unstimulated or stimulated with anti-CD3 antibodies, were treated with increasing concentrations of JNJ42756493 ( 0.0000077, 0.000023, 0.000070, 0.00021, 0.00063, 0.00188, 0.00565, 0.01694, 0.051, 0.152, 0.457, 1.372, 4.115, 12.346, 37.037, 111.111, 333.333, and 1000 nM). On days 1, 2, 5 and 6 after plating, cell viability was assessed by CellTiter-Glo (Promega).

**[0013]** **FIG. 4** illustrates the effect of JNJ42756493 on IFN-γ levels induced by anti-PD-1 antibodies in a Mixed Lymphocyte Reaction (MLR) Assay. Cultures of $CD4^+$ T and allogeneic dendritic cells were treated with anti-PD-1 antibodies (concentrations left to right - 30, 10, 3.33, 1.11, 0.37, 0.12 nM). JNJ42756493 was added at 100, 1, or 0.01 nM alone (concentrations left to right), together with anti-PD-1 antibodies (100, 1, or 0.01 nM

JNJ42756493 together with 30, 10, 3.33, 1.11, 0.37, or 0.12 nM of anti-PD-1 antibody), or in the presence of isotype control (IC). 5 days after treatment, IFN-γ levels in the supernatant were measured by Meso Scale Discovery (MSD).

**[0014]** **FIG. 5** illustrates the effect of JNJ42756493 on IFN-γ levels induced by anti-PD-1 antibodies in a Cytomegalovirus antigen assay (CMV) Assay. Peripheral blood mononuclear cells (PMBCs) were stimulated with CMV antigen and treated with anti-PD-1 antibodies (concentration left to right - 30, 10, 3.33, 1.11, 0.37, 0.12 nM) as indicated. JNJ42756493 was added at 100, 1, or 0.01 nM alone (concentrations left to right), together with anti-PD-1 antibodies (100, 1, or 0.01 nM JNJ42756493 together with 30, 10, 3.33, 1.11, 0.37, or 0.12 nM of anti-PD-1 antibody), or in the presence of isotype control (IC). 6 days after treatment, IFN-γ levels in the supernatant were measured by MSD.

## DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

**[0015]** The disclosed methods may be understood more readily by reference to the following detailed description taken in connection with the accompanying figures, which form a part of this disclosure. It is to be understood that the disclosed methods are not limited to the specific methods described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed methods.

**[0016]** Unless specifically stated otherwise, any description as to a possible mechanism or mode of action or reason for improvement is meant to be illustrative only, and the disclosed methods are not to be constrained by the correctness or incorrectness of any such suggested mechanism or mode of action or reason for improvement.

**[0017]** Reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise. When a range of values is expressed, another embodiment includes from the one particular value and/or to the other particular value. Further, reference to values stated in ranges include each and every value within that range. All ranges are inclusive and combinable.

**[0018]** When values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment.

**[0019]** The term "about" when used in reference to numerical ranges, cutoffs, or specific values is used to indicate that the recited values may vary by up to as much as 10% from the listed value. Thus, the term "about" is used to encompass variations of ± 10% or less,

variations of ± 5% or less, variations of ± 1% or less, variations of ± 0.5% or less, or variations of ± 0.1% or less from the specified value.

**[0020]** It is to be appreciated that certain features of the disclosed methods which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosed methods that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any subcombination.

**[0021]** As used herein, the singular forms "a," "an," and "the" include the plural.

**[0022]** The following abbreviations are used throughout the disclosure: FFPE (formalin-fixed, paraffin-embedded); NSCLC (non-small-cell lung carcinoma); SCLC (small-cell lung cancer); FGFR (fibroblast growth factor receptor); PD-1 (programmed cell death 1); PD-L1 (programmed death-ligand 1); FGFR3:TACC3 (fusion between genes encoding FGFR3 and transforming acidic coiled-coil containing protein 3); FGFR3:BAIAP2L1 (fusion between genes encoding FGFR3 and brain-specific angiogenesis inhibitor 1-associated protein 2-like protein 1); FGFR2:AFF3 (fusion between genes encoding FGFR2 and AF4/FMR2 family, member 3); FGFR2:BICC1 (fusion between genes encoding FGFR2 and bicaudal C homolog 1); FGFR2: CASP7 (fusion between genes encoding FGFR2 and caspase 7); FGFR2:CCDC6 (fusion between genes encoding FGFR2 and coiled-coil domain containing 6); FGFR2:OFD1 (fusion between genes encoding FGFR2 and oral-facial-digital syndrome 1).

**[0023]** The term "antibody" refers to (a) immunoglobulin polypeptides, *i.e.*, polypeptides of the immunoglobulin family that contain an antigen binding site that specifically binds to a specific antigen (e.g., PD-1 or PD-L1), including all immunoglobulin isotypes (IgG, IgA, IgE, IgM, IgD, and IgY), classes (e.g. IgG1, IgG2, IgG3, IgG4, IgA1, IgA2), subclasses, and various monomeric and polymeric forms of each isotype, unless otherwise specified, and (b) conservatively substituted variants of such immunoglobulin polypeptides that immunospecifically bind to the antigen (e.g., PD-1 or PD-L1). Antibodies are generally described in, for example, Harlow & Lane, Antibodies: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1988). Unless otherwise apparent from the context, reference to an antibody also includes antibody derivatives as described in more detail below.

**[0024]** "Antibody fragments" comprise a portion of a full length antibody, generally the antigen-binding or variable region thereof, such as Fab, Fab', $F(ab')_2$ , and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments. Various techniques have been developed for the production

of antibody fragments, including proteolytic digestion of antibodies and recombinant production in host cells; however, other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In some embodiments, the antibody fragment of choice is a single chain Fv fragment (scFv). "Single-chain Fv" or "scFv" antibody fragments comprise the $V_H$ and $V_L$ domains of antibody, wherein these domains are present in a single polypeptide chain. Generally, the Fv polypeptide further comprises a polypeptide linker between the $V_H$ and $V_L$ domains which enables the scFv to form the desired structure for antigen binding. For a review of scFv and other antibody fragments, see James D. Marks, Antibody Engineering, Chapter 2, Oxford University Press (1995) (Carl K. Borrebaeck, Ed.).

**[0025]** An "antibody derivative" means an antibody, as defined above, that is modified by covalent attachment of a heterologous molecule such as, e.g., by attachment of a heterologous polypeptide (e.g., a cytotoxin) or therapeutic agent (e.g., a chemotherapeutic agent), or by glycosylation, deglycosylation, acetylation or phosphorylation not normally associated with the antibody, and the like.

**[0026]** The term "monoclonal antibody" refers to an antibody that is derived from a single cell clone, including any eukaryotic or prokaryotic cell clone, or a phage clone, and not the method by which it is produced. Thus, the term "monoclonal antibody" is not limited to antibodies produced through hybridoma technology.

**[0027]** "Biological sample" refers to any sample from a patient in which cancerous cells can be obtained and protein expression can be evaluated and/or RNA can be isolated. Suitable biological samples include, but are not limited to, blood, lymph fluid, bone marrow, sputum, a solid tumor sample, or any combination thereof. In some embodiments, the biological sample can be formalin-fixed paraffin-embedded tissue (FFPET).

**[0028]** As used here, "block(s) the interaction" refers to the ability of an anti-PD-1 antibody or an anti-PD-L1 antibody to inhibit or reduce binding of PD-L1 to PD-1, such that signaling/functioning through PD-1 is abolished or diminished.

**[0029]** As used herein, "FGFR variant" refers to an alteration in the wild type FGFR gene, including, but not limited to, FGFR fusion genes, FGFR mutations, FGFR amplifications, or any combination thereof. The terms "variant" and "alteration" are used interchangeably herein. "FGFR fusion" or "FGFR fusion gene" refers to a gene encoding a portion of FGFR (e.g., FGRF2 or FGFR3) and one of the herein disclosed fusion partners created by a translocation between the two genes.

**[0030]** As used herein, "patient" is intended to mean any animal, in particular, mammals. Thus, the methods are applicable to human and nonhuman animals, although most preferably with humans. "Patient" and "subject" may be used interchangeably herein.

**[0031]** "Pharmaceutically effective amount" refers to an amount of an antibody that blocks the interaction between PD-1 and PD-L1 and an amount of an FGFR inhibitor that treats the patient.

**[0032]** As used herein, "pharmaceutically acceptable salt" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, and the like. Examples of pharmaceutically acceptable salts are discussed in Berge, et al. (1977) "Pharmaceuticall Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

**[0033]** As used herein, "treating" and like terms refer to reducing the severity and/or frequency of cancer symptoms, eliminating cancer symptoms and/or the underlying cause of said symptoms, reducing the frequency or likelihood of cancer symptoms and/or their underlying cause, and improving or remediating damage caused, directly or indirectly, by cancer.

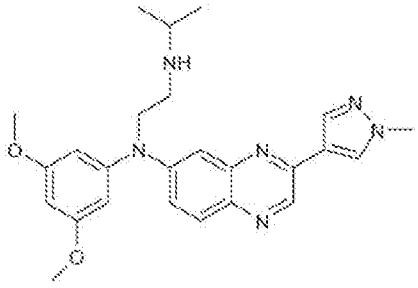
**[0034]** Disclosed herein are methods of treating cancer in a patient comprising: administering to the patient a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-L1 and a pharmaceutically effective amount of an FGFR inhibitor, wherein the antibody that blocks the interaction between PD-1 and PD-L1 and the FGFR inhibitor are administered if one or more FGFR variants are present in a biological sample from the patient.

**[0035]** PD-1 is a cell surface receptor expressed on the surface of CD4+ and CD8+ T cells, B cells, and myeloid cells. The ligands of PD-1, PD-L1 and PD-L2, are expressed on immune cells; in addition, PD-L1 is also expressed on cancer cells. When engaged by its ligands, PD-1 downregulates the immune response by reducing T cell proliferation, cytokine production and effector function. Antibodies against PD-1 (anti-PD-1 antibodies) and/or its ligands (anti-PD-L1 antibodies, for example) can block the interaction between PD-1 and PD-L1, thereby inhibiting the downregulation of the immune response. The disclosed methods comprise administering to the patient a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-L1. In some embodiments, the methods can comprise administering to the patient a pharmaceutically effective amount of an anti-PD-1 antibody. In some embodiments, the methods can comprise administering to the patient a pharmaceutically effective amount of an anti-PD-L1 antibody. In some embodiments, the

methods can comprise administering to the patient a pharmaceutically effective amount of an anti-PD-1 antibody and an anti-PD-L1 antibody.

**[0036]** Exemplary anti-PD-1 antibodies include, but are not limited to, OPDIVO® (nivolumab) (Bristol-Myers Squibb) and KEYTRUDA® (pembrolizumab) (Merck). Exemplary anti-PD-L1 antibodies include, but are not limited to, MPDL3208A (Roche) and MEDI4736 (AstraZeneca).

**[0037]** Exemplary FGFR inhibitors are described in U.S. Publ. No. 2013/0072457 A1 (incorporated herein by reference) and include N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine (referred to herein "JNJ-42756493"), including any tautomeric or stereochemically isomeric forms thereof, N-oxides thereof, pharmaceutically acceptable salts thereof, or solvates thereof (suitable R groups are also disclosed in U.S. Publ. No. 2013/0072457 A1). Thus, in some embodiments, the FGFR inhibitor can be the compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof. In some aspects, the pharmaceutically acceptable salt is a HCl salt.

**[0038]** The antibody that blocks the interaction between PD-1 and PD-L1 and the FGFR inhibitor can be administered as a single therapeutic agent or can be co-administered as individual agents. When administered as individual agents, the antibody and FGFR inhibitor can be administered contemporaneously or sequentially in either order. In some embodiments, the antibody that blocks the interaction between PD-1 and PD-L1 and the FGFR inhibitor can be administered contemporaneously. In some embodiments, the antibody that blocks the interaction between PD-1 and PD-L1 and the FGFR inhibitor can be administered sequentially. In some aspects, for example, the antibody that blocks the interaction between PD-1 and PD-L1 can be administered first, followed by administration of the FGFR inhibitor. In other aspects, the FGFR inhibitor can be administered first, followed by administration of the antibody that blocks the interaction between PD-1 and PD-L1. When administered sequentially, the antibody

and FGFR inhibitor can be administered within seconds, minutes, hours, days, or weeks of each other.

**[0039]** The pharmaceutically effective amount of the antibody that blocks the interaction between PD-1 and PD-L1 and of the FGFR inhibitor will be dependent on several factors including, but not limited to, stage and severity of the cancer, as well as other factors relating to the health of the patient. Those skilled in the art would know how to determine the pharmaceutically effective amount.

**[0040]** The disclosed methods are suitable for treating cancer in a patient if one or more FGFR variants are present in a biological sample from the patient. In some embodiments, the FGFR variant can be one or more FGFR fusion genes. In some embodiments, the FGFR variant can be one or more FGFR mutations. In some embodiments, the FGFR variant can be one or more FGFR amplifications. In some embodiments, a combination of the one or more FGFR variants can be present in the biological sample from the patient. For example, in some embodiments, the FGFR variants can be one or more FGFR fusion genes and one or more FGFR mutations. In some embodiments, the FGFR variants can be one or more FGFR fusion genes and one or more FGFR amplifications. In some embodiments, the FGFR variants can be one or more FGFR mutations and one or more FGFR amplifications. In yet other embodiments, the FGFR variants can be one or more FGFR fusion genes, mutations, and amplifications.

**[0041]** Exemplary FGFR fusion genes are provided in Table 1 and include, but are not limited to: FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFD1; FGFR3:BAIAP2L1; FGFR3:TACC3-Intron; FGFR3:TACC3V1; FGFR3:TACC3V3; or a combination thereof. The sequences of the FGFR fusion genes are disclosed in Table 7.

**Table 1**. Exemplary FGFR fusion genes

| Fusion Gene | FGFR Exon | Partner Exon |
|---|---|---|
| **FGFR2** | | |
| FGFR2:AFF3 | 19 | 8 |
| FGFR2:BICC1 | 19 | 3 |
| FGFR2:CASP7 | 19 | 4 |
| FGFR2:CCDC6 | 19 | 2 |
| FGFR2:OFD1 | 19 | 3 |
| **FGFR3** | | |
| FGFR3:BAIAP2L1 | 18 | 2 |
| FGFR3:TACC3 Intron | 18 | 4 |
| FGFR3:TACC3 v1 | 18 | 11 |

| | | |
|---|---|---|
| FCFR3:TACC3 v3 | 18 | 10 |

**[0042]** FGFR mutations include FGFR single nucleotide polymorphism (SNP). "FGFR single nucleotide polymorphism" (SNP) refers to a FGFR2 or FGFR3 gene in which a single nucleotide differs among individuals. In particular, FGFR single nucleotide polymorphism" (SNP) refers to a FGFR3 gene in which a single nucleotide differs among individuals. The presence of one or more of the following FGFR SNPs in a biological sample from a patient can be determined by methods known to those of ordinary skill in the art or methods disclosed in U.S. Provisional Patent App. No. 62/056,159, U.S. Patent Publication No. US2016-0090633, and WO 2016/048833, FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, FGFR3 Y373C, or any combination thereof. The sequences of the FGFR SNPs are provided in Table 2.

**Table 2**

| FGFR3 mutant | Sequence |
|---|---|
| FGFR3 R248C | TCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG TACACGCTGGACGTGCTGGAG**{T}**GCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCC GGCCAACCAGACGGCGGTGCTGGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTG ACGCACAGCCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGAATGGCAGCAAGGTGGGC CCGGACGGCACACCCTACGTTACCGTGCTCA (SEQ ID NO:1) |
| FGFR3 S249C | GACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACGTAC ACGCTGGACGTGCTGGGTGAGGGCCCTGGGGCGGCGCGGGGGTGGGGGCGGCAGTGGC GGTGGTGGTGAGGGAGGGGGTGGCCCCTGAGCGTCATCTGCCCCCACAGAGCGCT**{G}**CC CGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCTGGGCAGC GACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAG CACGTGGAGGTGAATGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTACCGTGCTC AAGGTGGGCCACCGTGTGCACGT (SEQ ID NO:2) |
| FGFR3 G370C | GCGGGCAATTCTATTGGGTTTTCTCATCACTCTGCGTGGCTGGTGGTGCTGCCAGCCGAGG AGGAGCTGGTGGAGGCTGACGAGGCG**{T}**GCAGTGTGTATGCAGGCATCCTCAGCTACGG GGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTGCGCAGC CCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCG (SEQ ID NO:3) |
| FGFR3 Y373C* | CTAGAGGTTCTCTCCTTGCACAACGTCACCTTTGAGGACGCCGGGGAGTACACCTGCCTGG CGGGCAATTCTATTGGGTTTTCTCATCACTCTGCGTGGCTGGTGGTGCTGCCAGCCGAGGA GGAGCTGGTGGAGGCTGACGAGGCGGGCAGTGTGT**{G}**TGCAGGCATCCTCAGCTACGGG GTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTGCGCAGCC CCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGC (SEQ ID NO:4) |

Sequences correspond to nucleotides 920-1510 of FGFR3 (Genebank ID # NM_000142.4).
Nucleotides in bold underline represent the SNP.
*Sometimes mistakenly referred to as Y375C in the literature.

**[0043]** The methods can further comprise evaluating the presence of one or more FGFR variants in the biological sample before the administering step. Suitable methods for evaluating a biological sample for the presence of one or more FGFR variants are disclosed elsewhere herein.

**[0044]** The disclosed methods can be dependent upon PD-L1 expression in the cancer or can be carried out irrespectively of PD-L1 expression in the cancer. In some embodiments, for example, the methods can comprise administering to the patient a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-L1 and a pharmaceutically effective amount of an FGFR inhibitor, wherein the antibody that blocks the interaction between PD-1 and PD-L1 and the FGFR inhibitor are administered if one or more FGFR variants are present in a biological sample from the patient and PD-L1 expression in the biological sample from the patient is at a specified level or within a specified range. In some aspects, for example, the methods can be carried out if the PD-L1 expression is high in the biological sample. Accordingly, in some embodiments the methods can comprise administering to the patient a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-L1 and a pharmaceutically effective amount of an FGFR inhibitor, wherein the antibody that blocks the interaction between PD-1 and PD-L1 and the FGFR inhibitor are administered if PD-L1 expression is high and one or more FGFR variants are present in a biological sample from the patient. Alternatively, the methods can be carried out if the PD-L1 expression is low in the biological sample. Accordingly, the methods can comprise administering to the patient a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-L1 and a pharmaceutically effective amount of an FGFR inhibitor, wherein the antibody that blocks the interaction between PD-1 and PD-L1 and the FGFR inhibitor are administered if PD-L1 expression is low and one or more FGFR variants are present in a biological sample from the patient. The methods can be carried out if the PD-L1 expression is moderate. Accordingly, the methods can comprise administering to the patient a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-L1 and a pharmaceutically effective amount of an FGFR inhibitor, wherein the antibody that blocks the interaction between PD-1 and PD-L1 and the FGFR inhibitor are administered if PD-L1 expression is moderate and one or more FGFR variants are present in a biological sample from the patient. As discussed elsewhere herein, PD-L1 expression levels can be based upon a numerical H-score (low includes an H-score of about 0 to

about 99; moderate includes an H-score of about 100 to about 199; and high includes an H-score of about 200 to about 300) or can be based upon a comparison to a reference value.

**[0045]** In other embodiments, the methods can be carried out irrespectively of PD-L1 expression in the biological sample from the patient and can be based on the presence of one or more FGFR variants without factoring in PD-L1 expression.

**[0046]** The methods can further comprise evaluating PD-L1 expression in the biological sample from the patient. Exemplary methods of evaluating PD-L1 expression are disclosed elsewhere herein. PD-L1 expression can be evaluated before, during, or after the administering step.

**[0047]** In some embodiments, the methods can comprise evaluating the presence of one or more FGFR variants and PD-L1 expression in the biological sample from the patient before the administering step.

**[0048]** Suitable biological samples for evaluating PD-L1 expression, evaluating the presence of one or more FGFR variants, or for evaluating both PD-L1 expression and the presence of one or more FGFR variants include, but are not limited to, blood, lymph fluid, bone marrow, a solid tumor sample, or any combination thereof.

**[0049]** The disclosed methods can be used to treat a variety of cancer types including, but not limited to, lung cancer, bladder cancer, gastric cancer, breast cancer, ovarian cancer, head and neck cancer, esophageal cancer, glioblastoma, or any combination thereof. In some embodiments, the methods can be used to treat lung cancer. The lung cancer can be non-small cell lung cancer (NSCLC) adenocarcinoma, NSCLC squamous cell carcinoma, small cell lung cancer, or any combination thereof. Thus, in some aspects, the methods can be used to treat NSCLC adenocarcinoma. In other aspects, the methods can be used to treat NSCLC squamous cell carcinoma. In yet other aspects, the methods can be used to treat small cell lung cancer. In some embodiments, the methods can be used to treat bladder cancer. In some embodiments, the methods can be used to treat gastric cancer. In some embodiments, the methods can be used to treat breast cancer. In some embodiments, the methods can be used to treat ovarian cancer. In some embodiments, the methods can be used to treat head and neck cancer. In some embodiments, the methods can be used to treat esophageal cancer. In some embodiments, the methods can be used to treat glioblastoma. In some embodiments, the methods can be used to treat any combination of the above cancers.

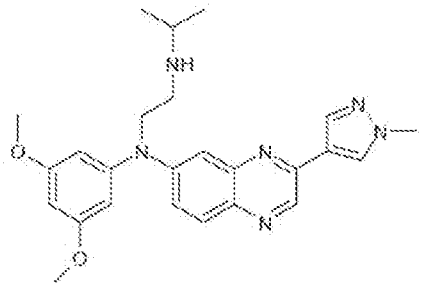
**[0050]** Also disclosed are methods of treating cancer in a patient comprising: administering to the patient a pharmaceutically effective amount of an antibody that blocks the

interaction between PD-1 and PD-L1; monitoring the efficacy of the antibody; and if the antibody is not efficacious, evaluating a biological sample from the patient for a presence of one or more FGFR variants and administering to the patient a pharmaceutically effective amount of an FGFR inhibitor if the one or more FGFR variants are present in the sample.

**[0051]** The efficacy of the antibody can be monitored by, for example, evaluating the patient's symptoms for progression of the cancer, evaluating the severity of the cancer symptoms, evaluating the frequency of the cancer symptoms, measuring tumor size, or any combination thereof. Without intent to be limiting, progression or failure to reduce the progression of the cancer, increased severity or no change in severity of the cancer symptoms, increased frequency or no change in the frequency of the cancer symptoms, increased size or no change in size of the tumor, or any combination thereof, can be indications that the antibody is not efficacious.

**[0052]** In some embodiments, the methods can comprise administering to the patient a pharmaceutically effective amount of an anti-PD-1 antibody. In some embodiments, the methods can comprise administering to the patient a pharmaceutically effective amount of an anti-PD-L1 antibody. In some embodiments, the methods can comprise administering to the patient a pharmaceutically effective amount of an anti-PD-1 antibody and an anti-PD-L1 antibody. Exemplary anti-PD-1 antibodies include, but are not limited to, OPDIVO® (nivolumab) (Bristol-Myers Squibb) and KEYTRUDA® (pembrolizumab) (Merck). Exemplary anti-PD-L1 antibodies include, but are not limited to, MPDL3208A (Roche) and MEDI4736 (AstraZeneca).

**[0053]** Exemplary FGFR inhibitors include those disclosed above, including N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine (referred to herein "JNJ-42756493"), including any tautomeric or stereochemically isomeric forms thereof, N-oxides thereof, pharmaceutically acceptable salts thereof, or solvates thereof (suitable R groups are also disclosed in U.S. Publ. No. 2013/0072457 A1). In some embodiments, the FGFR inhibitor can be the compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof. In some aspects, the pharmaceutically acceptable salt is a HCl salt.

**[0054]** The pharmaceutically effective amount of the antibody and FGFR inhibitor will be dependent on several factors including, but not limited to, stage and severity of the cancer, as well as other factors relating to the health of the patient. Those skilled in the art would know how to determine the pharmaceutically effective amount.

**[0055]** The disclosed methods are suitable for treating cancer in a patient if one or more FGFR variants are present in a biological sample from the patient. In some embodiments, the FGFR variant can be one or more FGFR fusion genes. In some embodiments, the FGFR variant can be one or more FGFR mutations. In some embodiments, the FGFR variant can be one or more FGFR amplifications. In some embodiments, a combination of the one or more FGFR variants can be present in the biological sample from the patient. For example, in some embodiments, the FGFR variants can be one or more FGFR fusion genes and one or more FGFR mutations. In some embodiments, the FGFR variants can be one or more FGFR fusion genes and one or more FGFR amplifications. In some embodiments, the FGFR variants can be one or more FGFR mutations and one or more FGFR amplifications. In yet other embodiments, the FGFR variants can be one or more FGFR fusion genes, mutations, and amplifications. Exemplary FGFR fusion genes are provided in Table 1 and include, but are not limited to: FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFD1; FGFR3:BAIAP2L1; FGFR3:TACC3-Intron; FGFR3:TACC3V1; FGFR3:TACC3V3; or a combination thereof.

**[0056]** Suitable methods for evaluating a biological sample for the presence of one or more FGFR variants are disclosed elsewhere herein.

**[0057]** The disclosed methods can be dependent upon PD-L1 expression in the biological sample or can be carried out irrespectively of PD-L1 expression in the cancer. In some aspects, for example, if the antibody is not efficacious, the methods can comprise

measuring an expression level of PD-L1 in the biological sample and administering to the patient a pharmaceutically effective amount of an FGFR inhibitor if the PD-L1 expression is at a specified level or within a specified range. Methods of evaluating PD-L1 expression are disclosed elsewhere herein. The methods can be carried out if the PD-1 expression in the biological sample is low. In some embodiments, for example, the evaluating step can further comprise measuring an expression level of PD-L1 in the biological sample and the second administering step can comprise administering the FGFR inhibitor if the expression level of PD-L1 is low. In some aspects, methods of treating cancer in a patient comprise: administering to the patient a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-L1; monitoring the efficacy of the antibody; and if the antibody is not efficacious, evaluating a biological sample from the patient for a presence of one or more FGFR variants and measuring an expression level of PD-L1 in the biological sample, and administering to the patient a pharmaceutically effective amount of an FGFR inhibitor if the one or more FGFR variants are present and if the expression level of PD-L1 is low in the sample.

**[0058]** The methods can be carried out if the PD-1 expression in the biological sample is moderate. Thus, the evaluating step can further comprise measuring an expression level of PD-L1 in the biological sample and the second administering step can comprise administering the FGFR inhibitor if the expression level of PD-L1 is moderate. The methods can be carried out if the PD-1 expression in the biological sample is high. For example, the evaluating step can further comprise measuring an expression level of PD-L1 in the biological sample and the second administering step can comprise administering the FGFR inhibitor if the expression level of PD-L1 is high.

**[0059]** As discussed elsewhere herein, PD-L1 expression levels can be based upon a numerical H-score (low includes an H-score of about 0 to about 99; moderate includes an H-score of about 100 to about 199; and high includes an H-score of about 200 to about 300) or can be based upon a comparison to a reference value.

**[0060]** In other embodiments, the methods can be carried out irrespectively of PD-L1 expression in the cancer and can be based on the presence of one or more FGFR variants in the biological sample without factoring in PD-L1 expression.

**[0061]** Suitable biological samples include, but are not limited to, blood, lymph fluid, bone marrow, a solid tumor sample, or any combination thereof.

**[0062]** The disclosed methods can be used to treat a variety of cancer types including, but not limited to, lung cancer, bladder cancer, gastric cancer, breast cancer, ovarian cancer, head and neck cancer, esophageal cancer, glioblastoma, or any combination thereof. In some embodiments, the methods can be used to treat lung cancer. The lung cancer can be non-small cell lung cancer (NSCLC) adenocarcinoma, NSCLC squamous cell carcinoma, small cell lung cancer, or any combination thereof. Thus, in some aspects, the methods can be used to treat NSCLC adenocarcinoma. In other aspects, the methods can be used to treat NSCLC squamous cell carcinoma. In yet other aspects, the methods can be used to treat small cell lung cancer. In some embodiments, the methods can be used to treat bladder cancer. In some embodiments, the methods can be used to treat gastric cancer. In some embodiments, the methods can be used to treat breast cancer. In some embodiments, the methods can be used to treat ovarian cancer. In some embodiments, the methods can be used to treat head and neck cancer. In some embodiments, the methods can be used to treat esophageal cancer. In some embodiments, the methods can be used to treat glioblastoma. In some embodiments, the methods can be used to treat any combination of the above cancers.

**[0063]** Also, disclosed herein are uses of an antibody that blocks the interaction between PD-1 and PD-L1 and an FGFR inhibitor for the manufacture of a medicament for the treatment of cancer, in particular for the treatment of cancer in a patient wherein one or more FGFR variants are present in a biological sample from the patient. Each of the above embodiments described in terms of a method of treating cancer can be employed in the use of an antibody that blocks the interaction between PD-1 and PD-L1 and an FGFR inhibitor for the manufacture of a medicament for the treatment of cancer, in particular for the treatment of cancer in a patient wherein one or more FGFR variants are present in a biological sample from the patient.

**[0064]** Also disclosed herein are combinations of an antibody that blocks the interaction between PD-1 and PD-L1 and an FGFR inhibitor for use in the treatment of cancer, in particular for the treatment of cancer in a patient wherein one or more FGFR variants are present in a biological sample from the patient. Each of the above embodiments described in terms of a method of treating cancer can be employed with a combination of an antibody that blocks the interaction between PD-1 and PD-L1 and an FGFR inhibitor for use in the treatment of cancer, in particular for the treatment of cancer in a patient wherein one or more FGFR variants are present in a biological sample from the patient.

*Evaluating a sample for the presence of one or more FGFR variants*

**[0065]** The following methods for evaluating a biological sample for the presence of one or more FGFR variants apply equally to any of the above disclosed methods of treatment.

**[0066]** Suitable methods for evaluating a biological sample for the presence of one or more FGFR variants are described in the methods section herein and in U.S. Provisional Patent App. No. 62/056,159, U.S. Patent Publication No. US2016-0090633, and WO 2016/048833, which are incorporated herein in their entirety. For example, and without intent to be limiting, evaluating a biological sample for the presence of one or more FGFR variants can comprise any combination of the following steps: isolating RNA from the biological sample; synthesizing cDNA from the RNA; and amplifying the cDNA (preamplified or non-preamplified). In some embodiments, evaluating a biological sample for the presence of one or more FGFR variants can comprise: amplifying cDNA from the patient with a pair of primers that bind to and amplify one or more FGFR variants; and determining whether the one or more FGFR variants are present in the sample. In some aspects, the cDNA can be pre-amplified. In some aspects, the evaluating step can comprise isolating RNA from the sample, synthesizing cDNA from the isolated RNA, and pre-amplifying the cDNA.

**[0067]** Suitable primer pairs for performing an amplification step include, but are not limited to, those disclosed in U.S. Provisional Patent App. No. 62/056,159, U.S. Patent Publication No. US2016-0090633, and WO 2016/048833, as exemplified below:

| | |
|---|---|
| FGFR3TACC3 V1 | Forward: GACCTGGACCGTGTCCTTACC (SEQ ID NO:1) |
| | Reverse: CTTCCCCAGTTCCAGGTTCTT (SEQ ID NO:2) |
| FGFR3TACC3 V3 | Forward: AGGACCTGGACCGTGTCCTT (SEQ ID NO:3) |
| | Reverse: TATAGGTCCGGTGGACAGGG (SEQ ID NO:4) |
| FGFR3TACC3 Intron | Forward: GGCCATCCTGCCCCC (SEQ ID NO:5) |
| | Reverse: GAGCAGTCCAGGTCAGCCAG (SEQ ID NO:6) |
| FGFR3BAIAP2L1 | Forward: CTGGACCGTGTCCTTACCGT (SEQ ID NO:7) |
| | Reverse: GCAGCCCAGGATTGAACTGT (SEQ ID NO:8) |
| FGFR2BICC1 | Forward: TGGATCGAATTCTCACTCTCACA (SEQ ID NO:9) |

Reverse: GCCAAGCAATCTGCGTATTTG (SEQ ID NO:10)

FGFR2AFF3 Forward: TGGTAGAAGACTTGGATCGAATTCT (SEQ ID NO:11)
Reverse: TCTCCCGGATTATTTCTTCAACA (SEQ ID NO:12)

FGFR2CASP7 Forward: GCTCTTCAATACAGCCCTGATCA (SEQ ID NO:13)
Reverse: ACTTGGATCGAATTCTCACTCTCA (SEQ ID NO:14)

FGFR2CCDC6 Forward: TGGATCGAATTCTCACTCTCACA (SEQ ID NO:15)
Reverse: GCAAAGCCTGAATTTTCTTGAATAA (SEQ ID NO:16)

FGFR2OFD1 Forward: AGGGTGCATCAACTCATGAATTAG (SEQ ID NO:17)
Reverse: ACTTGGATCGAATTCTCACTCTCA (SEQ ID NO:18)

**[0068]** The presence of one or more FGFR variants can be evaluated at any suitable time point including upon diagnosis, following tumor resection, following first-line therapy, during clinical treatment, or any combination thereof.

*Evaluating PD-L1 expression in the cancer*

**[0069]** The following methods for evaluating PD-L1 expression in a biological sample apply equally to any of the above disclosed methods of treatment.

**[0070]** In some embodiments, the disclosed methods can be dependent upon PD-L1 expression in the biological sample from the patient. Thus, administering to the patient a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-L1 and a pharmaceutically effective amount of an FGFR inhibitor may be based upon PD-L1 expression and the presence of one or more FGFR variants in the biological sample from the patient. The methods can comprise evaluating PD-L1 expression in a biological sample from the patient. The biological sample from which PD-L1 expression is evaluated can be the same biological sample from which the presence of one or more FGFR variants are evaluated, or the biological samples from which PD-L1 expression is evaluated can be a different biological sample from which the presence of one or more FGFR variants are evaluated. "Same biological sample" refers to a single sample from which both PD-L1 expression and FGFR variants are evaluated. "Different biological sample" includes the same source of sample (blood, lymph fluid, bone marrow, a solid tumor sample, etc.) taken at different time points or

different sources of sample. For example, a blood sample can be obtained from the patient, evaluated for PD-L1 expression or the presence of one or more FGFR variants, and at a later time point, another blood sample can be obtained from the patient and evaluated for the presence of one or more FGFR variants or PD-L1 expression. Conversely, a blood sample can be obtained from the patient and evaluated for PD-L1 expression and/or the presence of one or more FGFR variants and a solid tumor sample can be obtained from the patient and evaluated for the presence of one or more FGFR variants and/or PD-L1 expression.

**[0071]** In some embodiments, the level of PD-L1 expression can be converted into a numerical H-score (as described in the methods section herein). The level of PD-L1 expression can be converted into a numerical H-score of: low PD-L1 expression, which includes an H-score of about 0 to about 99; moderate PD-L1 expression, which includes an H-score of about 100 to about 199; or high PD-L1 expression, which includes an H-score of about 200 to about 300. Treating the patient can be based upon these H-scores. For example, if the treatment methods are carried out on a patient with a low H-score, that patient would have PD-L1 expression corresponding to an H-score of about 0 to about 99. If the treatment methods are carried out on a patient with a moderate H-score, that patient would have PD-L1 expression corresponding to an H-score of about 100 to about 199. If the treatment methods are carried out on a patient with a high H-score, that patient would have PD-L1 expression corresponding to an H-score of about 200 to about 300.

**[0072]** In other embodiments, the level of PD-L1 expression can be compared to a reference PD-L1 expression level. In a preferred embodiment, the reference PD-L1 expression level can be predetermined. For example, a reference data set may be established using samples from unrelated patients with low, moderate and high PD-L1 expression levels. This data set can represent a standard by which relative PD-L1 expression levels are compared among patients and/or quantified using the H-Score method. In some embodiments, the reference PD-L1 expression level can be determined by comparing a patient population that is administered the antibody that blocks the interaction between PD-1 and PD-L1 to a patient population that is administered placebo. The PD-L1 expression level for each patient in the respective populations can be determined in accordance with the methods described herein. Clinical outcomes (e.g., progression-free survival or overall survival) for the patient populations can be monitored. Clinical outcomes for the patient populations relative to PD-L1 expression levels can then be compared. The reference PD-L1 expression level can correspond to the PD-L1 expression level above which the patient population that is administered the

antibody that blocks the interaction between PD-1 and PD-L1 demonstrates a statistically significant improvement in at least one clinical outcome relative to the patient population that is administered placebo. A patient PD-L1 expression level that is less than the reference PD-L1 expression level, particularly when combined with the presence of one or more FGFR variants in a patient sample, can be indicative that the patient will benefit from treatment with the antibody that blocks the interaction between PD-1 and PD-L1 in combination with an FGFR inhibitor. For example, in some embodiments, the methods can comprise administering an antibody that blocks the interaction between PD-1 and PD-L1 and an FGFR inhibitor, wherein the antibody that blocks the interaction between PD-1 and PD-L1 and the FGFR inhibitor are administered if one or more FGFR variants are present in a biological sample from the patient and the PD-L1 expression in the biological sample is less than a reference PD-L1 expression level, wherein the reference PD-L1 expression level corresponds to a PD-L1 expression level above which treatment with the antibody that blocks the interaction between PD-1 and PD-L1 alone is likely to be efficacious.

**[0073]** Methods for determining PD-L1 expression include, but are not limited to, immunohistochemistry (IHC), Western Blotting, microscopy, immunoprecipitation, BCA assays, spectrophotometry, or any combination thereof. Exemplary methods for evaluating PD-L1 expression are described in the methods section herein.

**[0074]** PD-L1 expression can be evaluated at any suitable time point including upon diagnosis, following tumor resection, following first-line therapy, during clinical treatment, or any combination thereof.

**[0075]** The following examples are provided to further describe some of the embodiments disclosed herein. The examples are intended to illustrate, not to limit, the disclosed embodiments.

## EXAMPLES

## METHODS

*PD-L1 Immunohistochemistry*

**[0076]** PD-L1 immunohistochemistry (IHC) was performed at a CRO (QualTek, Newtown, PA). Samples were stained using a CD274 PD-L1 (RUO) assay. Slides stained with a CD274 PD-L1 (RUO) assay were examined in random order and/or in blinded fashion by a board-certified clinical pathologist, the Medical Director of QualTek Clinical Laboratories (CAP/CLIA facility). The entire tissue section was evaluated for CD274 PD-L1. Only viable

tissue was evaluated; areas of necrosis or obviously poorly fixed areas of tissue were not evaluated.

**[0077]** The tumor H-Score was calculated from the intensity of CD274 PD-L1 membrane reactivity on a four-point semi-quantitative scale (0: null, negative or non-specific staining of cell membranes; 1+: low or weak intensity staining of cell membranes; 2+: medium or moderate intensity staining of cell membranes; and 3+: high or strong intensity staining of cell membranes) and the estimated percentage of CD274 PD-L1 positive tumor cells (0 - 100%) for each discrete intensity value.

**[0078]** Tumor CD274 PD-L1 membrane reactivity was captured by a standard H-Score - the tumor H-Score minimum of 0 and the tumor H-Score maximum of 300: Tumor H-Score = ([% positive cells at 1+]*1) + ([% positive cells at 2+]*2) + ([% positive cells at 3+]*3)

*Next-generation sequencing (NGS)*

**[0079]** NGS for FGFR mutations and gene amplification was performed by Foundation Medicine, Cambridge, MA using the FoundationOne panel (http://www.foundationmedicine.com).

*FGFR Fusions*

**[0080]** FGFR fusions were determined using a proprietary qRT-PCR assay developed by Janssen Oncology Translational Research as described in U.S. Provisional Application No.: 62/056,159, U.S. Patent Publication No. US2016-0090633, and WO 2016/048833.

RESULTS

*PD-L1 Expression in tumors with FGFR Fusions and Mutations*

**[0081]** To determine the overlap of PD-L1 expression with FGFR alterations, immunohistochemistry (IHC) for PD-L1 was performed on human tumor tissue samples which were subsequently assessed for FGFR alterations. FGFR amplifications and mutations were identified using next-generation sequencing (Foundation Medicine panel, FMI). FGFR fusions were screened for using a Janssen-developed qRT-PCR assay.

*Correlation of FGFR mutations and amplification with PD-L1*

**[0082]** PD-L1 expression was first assessed in a set of 120 commercially sourced lung FFPE tumor tissues comprised of forty of each of the following lung tumor histologies; non-

small-cell lung carcinoma (NSCLC) adenocarcinoma; NSCLC squamous cell carcinoma; and small-cell lung cancer (SCLC). FGFR mutations and gene amplification were detected using the Foundation Medicine panel. PD-L1 staining versus FGFR status was plotted for each tumor type (FIG 1). PD-L1 expression was largely reserved to tumors without FGFR mutations or amplifications. Out of nine samples with FGFR mutations, no PD-L1 staining was observed in seven samples (78%). Two of the nine samples showed very low PD-L1 staining with H-scores of 20 and 70, respectively. Of four samples with FGFR gene amplification, one sample showed moderate-high PD-L1 staining (H-score = 140), with three having almost no staining (H-score = 4, n=1). No staining was observed in the one tumor sample harboring both an FGFR mutation and FGFR gene amplification. FGFR mutation and amplification status was unknown for 24 tumor samples, of which nine exhibited PD-L1 staining with H-scores ranging from 55 to 220.

*FGFR fusions and PD-L1 expression in bladder and NSCLC*

**[0083]** The set of 120 lung FFPE tumor tissues was subsequently screened for FGFR fusions using a Janssen-developed qRT-PCR assay (as described in U.S. Provisional Application No.: 62/056,159, U.S. Patent Publication No. US2016-0090633, and WO 2016/048833) detecting nine fusions (Table 1). Results for PD-L1 expression by FGFR fusion status for the NSCLC tumor samples (n=80) are shown in FIG. 2. Twenty-three percent (7/31) of NSCLC adenocarcinoma samples, and 52% (13/25) of NSCLC squamous cell carcinoma tumor samples were positive for FGFR fusions. All fusion-positive adenocarcinoma samples exhibited no or low PD-L1 expression, 6/7 (86%) or 1/7 (14%), respectively (Table 3). Fusion-negative adenocarcinoma samples showed a range of PD-L1 from no expression (12/31, 39%), low (12/31, 39%), moderate (4/31, 13%), to high PD-L1 (3/31, 10%) (Table 3). Fusion-positive squamous cell carcinoma sample PD-L1 H-scores were equally distributed across the no expression, low, moderate, or high expression categories (4/31, 31% each respectively) (Table 4). Fusion-negative squamous samples also showed a range of H-scores from no expression (6/25, 24%), low (11/25, 44%), moderate (5/25, 20%), and high expression (3/25, 12%) (Table 4).

Table 3. NSCLC Adenocarcinoma – PD-L1 H-Scores by FGFR fusion status

| *NSCLC Adenocarcinoma* | H-Score Range | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 1-25 | 26-50 | 51-99 | 100-199 | 200-300 |
| Category: | No | Low | | | Mod. | High |
| **Fusion Positive** | 6 (86%) | -- | -- | 1 (14%) | -- | -- |
| **Fusion Negative** | 12 (39%) | 9 (29%) | 2 (6%) | 1 (3%) | 4 (13%) | 3 (10%) |

Table 4. NSCLC Squamous Cell Carcinoma – PD-L1 H-Scores by FGFR fusion status

| *NSCLC Squamous* | H-Score Range | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 1-25 | 26-50 | 51-99 | 100-199 | 200-300 |
| Category: | No | Low | | | Mod. | High |
| **Fusion Positive** | 4 (31%) | 2 (15%) | 1 (8%) | 1 (8%) | 4 (31%) | 1 (8%) |
| **Fusion Negative** | 6 (24%) | 8 (32%) | 2 (8%) | 1 (4%) | 5 (20%) | 3 (12%) |

**[0084]** Forty-five commercially sourced bladder tumors were sequenced for mutations by the Foundation Medicine panel (FMI), stained for PD-L1 expression, and screened for FGFR gene fusions using the Janssen qRT-PCR assay. Forty-two of 45 samples (93%) were positive for FGFR fusions. Five samples (11%) were positive for an FGFR mutation (FGFR3-R248C or FGFR3-S249C), all of which were also positive for FGFR fusions. PD-L1 staining H-scores for samples with FGFR alterations are summarized in Table 5, and listed in Table 6. For FGFR fusion positive samples, 22/37 (59%) were negative for PD-L1 staining. Ten FGFR fusion-positive samples (27%) expressed low levels of PD-L1, and five samples (14%) showed high PD-L1 expression. All samples with both FGFR mutations and FGFR fusions in the same tumor sample (n=5) were negative for PD-L1 staining. Overall, PD-L1 staining was absent in 64% (27/42) of bladder samples with FGFR alterations, keeping in mind that almost all of the tumors in this sample set were positive for FGFR fusions.

**[0085]** FGFR mutation and PD-L1 expression data were available for seven commercially sourced metastatic NSCLC samples with FGFR fusions (Janssen). No PD-L1 staining was observed in 4/7 (57%) of samples. Two samples exhibited very low PD-L1 staining, H-scores of 4 and 15. One sample showed moderate PD-L1 with an H-score of 160. Interestingly, the FGFR fusion-positive sample with moderate PD-L1 staining harbored an

FGFR4 V550I mutation - an FGFR gatekeeper residue mutation with potential to confer resistance to tyrosine kinase inhibitors.

**[0086]** Overall these data show that the majority of commercially available tumor samples harboring FGFR alterations have very little expression or do not express PD-L1.

**Table 5**. PD-L1 staining in FGFR fusion positive bladder samples

| *n=42* | H-Score Range | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 1-25 | 26-50 | 51-99 | 100-199 | 200-300 |
| Category: | No | Low | | | Mod. | High |
| **Fusion Positive** | 22 | 8 | -- | 2 | -- | 5 |
| **Fusion + Mutation** | 5 | -- | -- | -- | -- | -- |
| *% of Total FGFR+ Samples Expressing per Category* | *64%* | *19%* | *0%* | *5%* | *0%* | *12%* |

**Table 6**. PD-L1 expression, FGFR fusion and mutation status in commercial bladder and NSCLC tumor samples

| **Janssen Sample ID** | **Tumor Type** | **FGFR Fusion Gene(s)** | **FGFR Mutation** | **H-Score (0-300)** |
|---|---|---|---|---|
| 2329 | **Bladder** | None | None | 300 |
| 2425 | **Bladder** | FGFR3:BAIA / FGFR2:CASP7 / FGFR2:OFD1 | None | 300 |
| F26993.C3a | **Bladder** | FGFR3:BAIA/FGFR2:AFF/ FGFR2:CASP7/FGFR2:CCDC6 | None | 300 |
| F5244.E22b | **Bladder** | FGFR2:CASP7 | None | 300 |
| F28052.E14a | **Bladder** | FGFR2:BICC1 / FGFR2:AFF3 / FGFR2:CCDC6 | None | 280 |
| F27999.D25 | **Bladder** | FGFR3:BAIA/FGFR2:CCDC6 | None | 250 |
| F7799.H25b | **Bladder** | FGFR3:BAIAP2L/FGFR2:CASP7/ FGFR2:OFD | None | 70 |
| F28057.D1a | **Bladder** | FGFR3:BAIA | None | 60 |
| F15377.A2 | **Bladder** | FGFR2:AFF3 | None | 21 |
| F28137.G3b | **Bladder** | FGFR3:TACC3v3/FGFR2:AFF3 | None | 20 |
| F7538.A1b | **Bladder** | FGFR3:BAIAP2L/FGFR2:BICC1/ FGFR:AFF3/FGFR2:CASP7 | None | 20 |
| F26375.A2 | **Bladder** | FGFR3:BAIA/FGFR2:AFF/ FGFR2:CASP7 | None | 18 |
| F7830.G3ba | **Bladder** | FGFR2:CASP7 | None | 10 |
| F7860.B2b | **Bladder** | FGFR2:AFF3FGFR2:CASP7 | None | 10 |

| | | | | |
|---|---|---|---|---|
| F27338.C4a | **Bladder** | FGFR3:BAIA/FGFR2:CASP7 | None | 6 |
| F5242.G10ba | **Bladder** | FGFR2:CASP7 | None | 3 |
| 2319 | **Bladder** | FGFR2:CASP7 | None | 0 |
| 2321 | **Bladder** | None | None | 0 |
| 2346 | **Bladder** | FGFR3:BAIA / FGFR2:CASP7 / FGFR2:OFD1 | None | 0 |
| 2347 | **Bladder** | FGFR3: BAIAP2L1 / FGFR2:CCDC6 | FGFR3-S249C | 0 |
| 2362 | **Bladder** | FGFR3:TACC3v1/FGFR3:TACC3 v3/FGFR3:BAIA/FGFR2:BICC1/F GFR2:AFF3/FGFR2:CASP7/FGFR 2:CCDC6 | FGFR3-S249C | 0 |
| 2376 | **Bladder** | FGFR3:TACC3,v1 / FGFR2: BICC1 / FGFR2:CASP7 | None | 0 |
| 2381 | **Bladder** | FGFR3:BAIA/FGFR2:AFF3/ FGFR2:CASP7 | FGFR3-R248C FGFR3-S249C | 0 |
| 2430 | **Bladder** | FGFR3:BAIA/FGFR2:CASP7 | None | 0 |
| 2434 | **Bladder** | FGFR3:BAIA | None | 0 |
| 2458 | **Bladder** | FGFR3:BAIA/FGFR2:AFF3/ FGFR2:CASP7 | FGFR3-R248C | 0 |
| 2455 | **Bladder** | None | None | 0 |
| 2473 | **Bladder** | FGFR2:AFF3 / FGFR2:OFD1 | None | 0 |
| 2480 | **Bladder** | FGFR2:OFD1 | None | 0 |
| 2518 | **Bladder** | FGFR3:BAIA/FGFR2:AFF3 /FGFR2:CASP7/FGFGFR2:OFD1 | None | 0 |
| 2533 | **Bladder** | FGFR2:OFD1 | None | 0 |
| 2541 | **Bladder** | FGFR2:CASP7 / FGFR2:OFD1 | None | 0 |
| 2561 | **Bladder** | FGFR3:BAIA/FGFR2:BICC1 / FGFR2:AFF3/FGFR2:CASP7 | None | 0 |
| 2563 | **Bladder** | FGFR2:OFD1 | None | 0 |
| 4916 | **Bladder** | FGFR2:OFD1 | None | 0 |
| F27064.CFS | **Bladder** | FGFR3:BAIA/FGFR2:AFF/ FGFR2:CASP7 | None | 0 |
| F28132.Ba | **Bladder** | FGFR3:TACC3v1/FGFR3:BAIAP2 L/FGFR2:BICC1/FGFR2:CCDC6 | None | 0 |
| F7269.C2 | **Bladder** | FGFR3:BAIAP2L/FGFR2:CASP7 | None | 0 |
| F7271.AFSb | **Bladder** | FGFR2:AFF3/FGFR2:CASP7 | None | 0 |
| F7467.D1bb | **Bladder** | FGFR2:AFF3/FGFR2:CASP7/ FGFR2:CCDC6 | None | 0 |
| F7484.BFSc | **Bladder** | FGFR2:AFF3 | None | 0 |
| F7502.D1b | **Bladder** | FGFR2:AFF3/FGFR2:CASP7 | FGFR3-S249C | 0 |
| F7789.DFSb | **Bladder** | FGFR3:BAIAP2L/FGFR2:CASP7 | FGFR2-M537I | 0 |
| F7876.D1bb | **Bladder** | FGFR3:BAIAP2L/FGFR2:OFD1 | None | 0 |
| I-7290.E13a | **Bladder** | FGFR2:CASP7 | None | 0 |
| CNT06GK | **NSCLC** | FGFR3:TACC3intron | FGFR4-V550I | 160 |

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|---|---|---|---|---|
| CNT0RHX | NSCLC | FGFR3:BAIAP2L | None | 15 |
| CNT0RFD | NSCLC | FGFR2:BICC1 | None | 4 |
| CNT06FI | NSCLC | FGFR2:AFF3 | None | 0 |
| CNT06FJ | NSCLC | FGFR2:CCDC6 | None | 0 |
| CNT06G5 | NSCLC | FGFR3:TACC3v1/FGFR3:TACC3intron/FGFR2:AFF3 | None | 0 |
| CNT0RFX | NSCLC | FGFR3:BAIAP2L/FGFR2:CASP7 | None | 0 |

*FGFR in vitro experiments*

**[0087]** To determine the effects of JNJ427564493 on immune cell viability *in vitro*, peripheral blood mononuclear cells (PBMCs) from normal donors were stimulated with anti-CD3 antibodies to activate T cells, in the presence of increasing concentrations of JNJ42756493. Unstimulated PBMCs were also included to determine if JNJ42756493 affected unactivated immune populations. Cell viability was assessed at four different time points, over 6 days. FIG. 3 shows the luminescence signal, as a measurement of cell viability, in the presence of increasing concentrations of JNJ42756493 (up to 1 μM) at days 1, 2, 5 and 6 post-treatment. For both the stimulated and unstimulated groups, at all time points tested, cell viability remained constant with increasing concentrations of compound. These data suggest that the addition of JNJ42756493 does not impair immune cell viability.

**[0088]** JNJ42756493 was next tested to analyze the impact on the activity of anti-PD-1 antibodies in two *in vitro* functional assays: Mixed Lymphocyte Reaction (MLR); and Cytomegalovirus antigen assay (CMV). For the MLR assay, $CD4^+$ T cells are stimulated with allogeneic dendritic cells, leading to T cell activation and IFN-γ secretion. In this assay, anti-PD-1 antibodies caused dose-dependent increases in IFN-γ levels (FIG. 4, PD-1 alone). When T cells and DCs were treated with 0.01, 1 or 100 nM of JNJ42756493, IFN-γ levels were similar to those observed in the untreated samples (FIG. 4, JNJ-493 alone vs controls), suggesting that FGFR inhibition does not affect T cell activation. Furthermore, combinations of JNJ42756493 with anti-PD-1 antibodies caused similar IFN-γ secretion as observed with anti-PD-1 treatment alone (FIG. 4, JNJ-493+ anti-PD-1 compared to PD-1 alone). These results suggest that JNJ42756493 does not impair the functional activity of anti-PD-1 antibodies in the MLR assay.

**[0089]** In the CMV assay, PBMCs from CMV-reactive donors were stimulated by the addition of CMV antigen. CMV-reactive T cells are active, expand and secrete pro-inflammatory cytokines such as IFN-γ. In the presence of anti-PD-1 antibodies, significantly higher levels of IFN-γ were secreted upon CMV stimulation (FIG. 5, PD-1 alone). In contrast,

JNJ42756493 alone had no impact on cytokine levels (FIG. 5, JNJ-493 alone). Similarly, JNJ42756493 combinations with anti-PD-1 antibodies led to similar increases of IFN-γ as seen with anti-PD-1 alone (FIG. 5, JNJ42756493 + anti-PD-1 compared to PD-1 alone). These data show that JNJ42756493 does not affect the activity of anti-PD-1 antibodies in the CMV assay.

**[0090]** Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

**[0091]** The disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference, in its entirety.

**Nucleotide Sequence of FGFR fusion genes**

**[0092]** The nucleotide sequences for the FGFR fusion cDNA are provided in Table 7. The underlined sequences correspond to either FGFR3 or FGFR2, the sequences in black represent the fusion partners and the sequence in *italic* fonts represent the intron sequence of the FGFR3 gene.

**Table 7**

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|---|---|
| FGFR3:TACC3 v1 (2850 base pairs) (SEQ ID NO:19) | >ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCC<br>GGCGCCTCCTCGGAGTCCTTGGGGACGGAGCAGCGCGTCGTGGGGCGAGCGGCA<br>GAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCGGG<br>GATGCTGTGGAGCTGAGCTGTCCCCCGCCCCGGGGGTGGTCCCATGGGGCCCACTG<br>TCTGGGTCAAGGATGGCACAGGGCTGGTGCCCTCGGAGCGTGTCCTGGTGGGGC<br>CCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTACAGCT<br>GCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAG<br>ACGCTCCATCCTCGGGAGATGACGAAGACGGGGAGGACGAGGCTGAGGACACA<br>GGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGACAAGAAG<br>CTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCA<br>ACCCCACTCCCTCCATCTCCTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGC<br>ACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGGTCATGGAAA<br>GCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTG<br>GCAGCATCCGGCAGACGTACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGC<br>CCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCTGGGCAGCGACG<br>TGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCA<br>AGCACGTGGAGGTGAATGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTA<br>CCGTGCTCAAGACGGCGGGCGCTAACACCACCGACAAGGAGCTAGAGGTTCTCT<br>CCTTGCACAACGTCACCTTTGAGGACGCCGGGGAGTACACCTGCCTGGCGGGCA<br>ATTCTATTGGGTTTTCTCATCACTCTGCGTGGCTGGTGGTGCTGCCAGCCGAGGA<br>GGAGCTGGTGGAGGCTGACGAGGCGGGCAGTGTGTATGCAGGCATCCTCAGCTA<br>CGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGC<br>CTGCGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCC<br>GCTTCCCGCTCAAGCGACAGGTGTCCCTGGAGTCCAACGCGTCCATGAGCTCCAA<br>CACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGGC<br>CAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCC<br>CGGCTGACCCTGGGCAAGCCCCTTGGGGAGGGCTGCTTCGGCCAGGTGGTCATG<br>GCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGTAGCC<br>GTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCT<br>GAGATGGAGATGATGAAGATGATCGGGAAACACAAAAACATCATCAACCTGCTG<br>GGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCGGCCAAG<br>GGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCT<br>TCGACACCTGCAAGCCGCCCGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTG<br>TGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGAAGTGCATCCAC<br>AGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATC<br>GCAGACTTCGGGCTGGCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACG<br>ACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGCCTTGTTTGACCGA<br>GTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCT<br>TCACGCTGGGGGGCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCT<br>GCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAACTGCACACACGACCTGTA<br>CATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAG<br>CAGCTGGTGGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGTAAAG<br>GCGACACAGGAGGAGAACCGGGAGCTGAGGAGCAGGTGTGAGGAGCTCCACGG<br>GAAGAACCTGGAACTGGGGAAGATCATGGACAGGTTCGAAGAGGTTGTGTACCA<br>GGCCATGGAGGAAGTTCAGAAGCAGAAGGAACTTTCCAAAGCTGAAATCCAGAA<br>AGTTCTAAAAGAAAAAGACCAACTTACCACAGATCTGAACTCCATGGAGAAGTC |

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| | CTTCTCCGACCTCTTCAAGCGTTTTGAGAAACAGAAAGAGGTGATCGAGGGCTAC<br>CGCAAGAACGAAGAGTCACTGAAGAAGTGCGTGGAGGATTACCTGGCAAGGATC<br>ACCCAGGAGGGCCAGAGGTACCAAGCCCTGAAGGCCCACGCGGAGGAGAAGCT<br>GCAGCTGGCAAACGAGGAGATCGCCCAGGTCCGGAGCAAGGCCCAGGCGGAAG<br>CGTTGGCCCTCCAGGCCAGCCTGAGGAAGGAGCAGATGCGCATCCAGTCGCTGG<br>AGAAGACAGTGGAGCAGAAGACTAAAGAGAACGAGGAGCTGACCAGGATCTGC<br>GACGACCTCATCTCCAAGATGGAGAAGATCTGA |
| FGFR3:TACC3 v3<br>(2955 base pairs)<br>(SEQ ID NO:20) | >ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCC<br>GGCGCCTCCTCGGAGTCCTTGGGGACGGAGCAGCGCGTCGTGGGGCGAGCGGCA<br>GAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCGGG<br>GATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTG<br>TCTGGGTCAAGGATGGCACAGGGCTGGTGCCCTCGGAGCGTGTCCTGGTGGGGC<br>CCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTACAGCT<br>GCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAG<br>ACGCTCCATCCTCGGGAGATGACGAAGACGGGGAGGACGAGGCTGAGGACACA<br>GGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGACAAGAAG<br>CTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCA<br>ACCCCACTCCCTCCATCTCCTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGC<br>ACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGGTCATGGAAA<br>GCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTG<br>GCAGCATCCGGCAGACGTACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGC<br>CCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCTGGGCAGCGACG<br>TGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCA<br>AGCACGTGGAGGTGAATGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTA<br>CCGTGCTCAAGACGGCGGGCGCTAACACCACCGACAAGGAGCTAGAGGTTCTCT<br>CCTTGCACAACGTCACCTTTGAGGACGCCGGGGAGTACACCTGCCTGGCGGGCA<br>ATTCTATTGGGTTTTCTCATCACTCTGCGTGGCTGGTGGTGCTGCCAGCCGAGGA<br>GGAGCTGGTGGAGGCTGACGAGGCGGGCAGTGTGTATGCAGGCATCCTCAGCTA<br>CGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGC<br>CTGCGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCC<br>GCTTCCCGCTCAAGCGACAGGTGTCCCTGGAGTCCAACGCGTCCATGAGCTCCAA<br>CACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGGC<br>CAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCC<br>CGGCTGACCCTGGGCAAGCCCCTTGGGGAGGGCTGCTTCGGCCAGGTGGTCATG<br>GCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGTAGCC<br>GTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCT<br>GAGATGGAGATGATGAAGATGATCGGGAAACACAAAAACATCATCAACCTGCTG<br>GGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCGGCCAAG<br>GGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCT<br>TCGACACCTGCAAGCCGCCCGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTG<br>TGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGAAGTGCATCCAC<br>AGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATC<br>GCAGACTTCGGGCTGGCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACG<br>ACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGCCTTGTTTGACCGA<br>GTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCT<br>TCACGCTGGGGGGCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCT<br>GCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAACTGCACACACGACCTGTA<br>CATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAG<br>CAGCTGGTGGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGTGCCAG<br>GCCCACCCCCAGGTGTTCCCGCGCCTGGGGGCCCACCCCTGTCCACCGGACCTAT<br>AGTGGACCTGCTCCAGTACAGCCAGAAGGACCTGGATGCAGTGGTAAAGGCGAC<br>ACAGGAGGAGAACCGGGAGCTGAGGAGCAGGTGTGAGGAGCTCCACGGGAAGA<br>ACCTGGAACTGGGGAAGATCATGGACAGGTTCGAAGAGGTTGTGTACCAGGCCA<br>TGGAGGAAGTTCAGAAGCAGAAGGAACTTTCCAAAGCTGAAATCCAGAAAGTTC<br>TAAAAGAAAAAGACCAACTTACCACAGATCTGAACTCCATGGAGAAGTCCTTCT<br>CCGACCTCTTCAAGCGTTTTGAGAAACAGAAAGAGGTGATCGAGGGCTACCGCA<br>AGAACGAAGAGTCACTGAAGAAGTGCGTGGAGGATTACCTGGCAAGGATCACCC<br>AGGAGGGCCAGAGGTACCAAGCCCTGAAGGCCCACGCGGAGGAGAAGCTGCAG<br>CTGGCAAACGAGGAGATCGCCCAGGTCCGGAGCAAGGCCCAGGCGGAAGCGTTG |

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| | GCCCTCCAGGCCAGCCTGAGGAAGGAGCAGATGCGCATCCAGTCGCTGGAGAAG<br>ACAGTGGAGCAGAAGACTAAAGAGAACGAGGAGCTGACCAGGATCTGCGACGA<br>CCTCATCTCCAAGATGGAGAAGATCTGA |
| FGFR3<br>Intron:TACC3<br>(4462 base pairs)<br>(SEQ ID NO:21) | >ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCC<br>GGCGCCTCCTCGGAGTCCTTGGGGACGGAGCAGCGCGTCGTGGGGCGAGCGGCA<br>GAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCGGG<br>GATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTG<br>TCTGGGTCAAGGATGGCACAGGGCTGGTGCCCTCGGAGCGTGTCCTGGTGGGGC<br>CCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTACAGCT<br>GCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAG<br>ACGCTCCATCCTCGGGAGATGACGAAGACGGGGAGGACGAGGCTGAGGACACA<br>GGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGACAAGAAG<br>CTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCA<br>ACCCCACTCCCTCCATCTCCTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGC<br>ACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGGTCATGGAAA<br>GCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTG<br>GCAGCATCCGGCAGACGTACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGC<br>CCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCTGGGCAGCGACG<br>TGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCA<br>AGCACGTGGAGGTGAATGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTA<br>CCGTGCTCAAGACGGCGGGCGCTAACACCACCGACAAGGAGCTAGAGGTTCTCT<br>CCTTGCACAACGTCACCTTTGAGGACGCCGGGGAGTACACCTGCCTGGCGGGCA<br>ATTCTATTGGGTTTTCTCATCACTCTGCGTGGCTGGTGGTGCTGCCAGCCGAGGA<br>GGAGCTGGTGGAGGCTGACGAGGCGGGCAGTGTGTATGCAGGCATCCTCAGCTA<br>CGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGC<br>CTGCGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCC<br>GCTTCCCGCTCAAGCGACAGGTGTCCCTGGAGTCCAACGCGTCCATGAGCTCCAA<br>CACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGGC<br>CAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCC<br>CGGCTGACCCTGGGCAAGCCCCTTGGGGAGGGCTGCTTCGGCCAGGTGGTCATG<br>GCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGTAGCC<br>GTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCT<br>GAGATGGAGATGATGAAGATGATCGGGAAACACAAAAACATCATCAACCTGCTG<br>GGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCGGCCAAG<br>GGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCT<br>TCGACACCTGCAAGCCGCCCGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTG<br>TGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGAAGTGCATCCAC<br>AGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATC<br>GCAGACTTCGGGCTGGCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACG<br>ACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGCCTTGTTTGACCGA<br>GTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCT<br>TCACGCTGGGGGGCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCT<br>GCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAACTGCACACACGACCTGTA<br>CATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAG<br>CAGCTGGTGGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGAC*gtgagtgctgg*<br>*ctctggcctggtgccacccgcctatgccccttccccctgccgtccccggccatcctgccccccagagtgctgagggtgtggggcgggc*<br>*ctt*TCTGGCCCAGGTGCCCTGGCTGACCTGGACTGCTCAAGCTCTTCCCAGAGCCCA<br>GGAAGTTCTGAGAACCAAATGGTGTCTCCAGGAAAAGTGTCTGGCAGCCCTGAG<br>CAAGCCGTGGAGGAAAACCTTAGTTCCTATTCCTTAGACAGAAGAGTGACACCC<br>GCCTCTGAGACCCTAGAAGACCCTTGCAGGACAGAGTCCCAGCACAAAGCGGAG<br>ACTCCGCACGGAGCCGAGGAAGAATGCAAAGCGGAGACTCCGCACGGAGCCGA<br>GGAGGAATGCCGGCACGGTGGGGTCTGTGCTCCCGCAGCAGTGGCCACTTCGCC<br>TCCTGGTGCAATCCCTAAGGAAGCCTGCGGAGGAGCACCCCTGCAGGGTCTGCCT<br>GGCGAAGCCCTGGGCTGCCCTGCGGGTGTGGGCACCCCCGTGCCAGCAGATGGC<br>ACTCAGACCCTTACCTGTGCACACACCTCTGCTCCTGAGAGCACAGCCCCAACCA<br>ACCACCTGGTGGCTGGCAGGGCCATGACCCTGAGTCCTCAGGAAGAAGTGGCTG<br>CAGGCCAAATGGCCAGCTCCTCGAGGAGCGGACCTGTAAAACTAGAATTTGATG<br>TATCTGATGGCGCCACCAGCAAAAGGGCACCCCCACCAAGGAGACTGGGAGAGA<br>GGTCCGGCCTCAAGCCTCCCTTGAGGAAAGCAGCAGTGAGGCAGCAAAAGGCCC |

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| | CGCAGGAGGTGGAGGAGGACGACGGTAGGAGCGGAGCAGGAGAGGACCCCCCC<br>ATGCCAGCTTCTCGGGGCTCTTACCACCTCGACTGGGACAAAATGGATGACCCAA<br>ACTTCATCCCGTTCGGAGGTGACACCAAGTCTGGTTGCAGTGAGGCCCAGCCCCC<br>AGAAAGCCCTGAGACCAGGCTGGGCCAGCCAGCGGCTGAACAGTTGCATGCTGG<br>GCCTGCCACGGAGGAGCCAGGTCCCTGTCTGAGCCAGCAGCTGCATTCAGCCTCA<br>GCGGAGGACACGCCTGTGGTGCAGTTGGCAGCCGAGACCCCAACAGCAGAGAGC<br>AAGGAGAGAGCCTTGAACTCTGCCAGCACCTCGCTTCCCACAAGCTGTCCAGGC<br>AGTGAGCCAGTGCCCACCCATCAGCAGGGGCAGCCTGCCTTGGAGCTGAAAGAG<br>GAGAGCTTCAGAGACCCCGCTGAGGTTCTAGGCACGGGCGCGGAGGTGGATTAC<br>CTGGAGCAGTTTGGAACTTCCTCGTTTAAGGAGTCGGCCTTGAGGAAGCAGTCCT<br>TATACCTCAAGTTCGACCCCCTCCTGAGGGACAGTCCTGGTAGACCAGTGCCCGT<br>GGCCACCGAGACCAGCAGCATGCACGGTGCAAATGAGACTCCCTCAGGACGTCC<br>GCGGGAAGCCAAGCTTGTGGAGTTCGATTTCTTGGGAGCACTGGACATTCCTGTG<br>CCAGGCCCACCCCCAGGTGTTCCCGCGCCTGGGGGCCCACCCCTGTCCACCGGAC<br>CTATAGTGGACCTGCTCCAGTACAGCCAGAAGGACCTGGATGCAGTGGTAAAGG<br>CGACACAGGAGGAGAACCGGGAGCTGAGGAGCAGGTGTGAGGAGCTCCACGGG<br>AAGAACCTGGAACTGGGGAAGATCATGGACAGGTTCGAAGAGGTTGTGTACCAG<br>GCCATGGAGGAAGTTCAGAAGCAGAAGGAACTTTCCAAAGCTGAAATCCAGAAA<br>GTTCTAAAAGAAAAAGACCAACTTACCACAGATCTGAACTCCATGGAGAAGTCC<br>TTCTCCGACCTCTTCAAGCGTTTTGAGAAACAGAAAGAGGTGATCGAGGGCTACC<br>GCAAGAACGAAGAGTCACTGAAGAAGTGCGTGGAGGATTACCTGGCAAGGATCA<br>CCCAGGAGGGCCAGAGGTACCAAGCCCTGAAGGCCCACGCGGAGGAGAAGCTG<br>CAGCTGGCAAACGAGGAGATCGCCCAGGTCCGGAGCAAGGCCCAGGCGGAAGC<br>GTTGGCCCTCCAGGCCAGCCTGAGGAAGGAGCAGATGCGCATCCAGTCGCTGGA<br>GAAGACAGTGGAGCAGAAGACTAAAGAGAACGAGGAGCTGACCAGGATCTGCG<br>ACGACCTCATCTCCAAGATGGAGAAGATCTGA |
| FGFR3:BAIAP2L1<br>(3765 base pairs)<br>(SEQ ID NO:22) | >ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCC<br>GGCGCCTCCTCGGAGTCCTTGGGGACGGAGCAGCGCGTCGTGGGGCGAGCGGCA<br>GAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCGGG<br>GATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTG<br>TCTGGGTCAAGGATGGCACAGGGCTGGTGCCCTCGGAGCGTGTCCTGGTGGGGC<br>CCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTACAGCT<br>GCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAG<br>ACGCTCCATCCTCGGGAGATGACGAAGACGGGGAGGACGAGGCTGAGGACACA<br>GGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGACAAGAAG<br>CTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCA<br>ACCCCACTCCCTCCATCTCCTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGC<br>ACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGGTCATGGAAA<br>GCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTG<br>GCAGCATCCGGCAGACGTACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGC<br>CCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCTGGGCAGCGACG<br>TGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCA<br>AGCACGTGGAGGTGAATGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTA<br>CCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGACGTGCGCCTCCGCCT<br>GGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTT<br>CATAGGCGTGGCCGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGC<br>CGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTGTGTATGCAGGCATCCT<br>CAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTC<br>TGCCGCCTGCGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAG<br>ATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCTGGAGTCCAACGCGTCCATGA<br>GCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCA<br>CGCTGGCCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTC<br>TCGGGCCCGGCTGACCCTGGGCAAGCCCCTTGGGGAGGGCTGCTTCGGCCAGGT<br>GGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCAC<br>CGTAGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCT<br>GGTGTCTGAGATGGAGATGATGAAGATGATCGGGAAACACAAAAACATCATCAA<br>CCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGC<br>GGCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGA<br>CTACTCCTTCGACACCTGCAAGCCGCCCGAGGAGCAGCTCACCTTCAAGGACCTG |

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| | GTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGAAGT<br>GCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGA<br>TGAAGATCGCAGACTTCGGGCTGGCCCGGGACGTGCACAACCTCGACTACTACA<br>AGAAGACGACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGCCTTGT<br>TTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTG<br>GGAGATCTTCACGCTGGGGGGCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTC<br>TTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAACTGCACACAC<br>GACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCC<br>ACCTTCAAGCAGCTGGTGGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCG<br>ACAATGTTATGGAACAGTTCAATCCTGGGCTGCGAAATTTAATAAACCTGGGGA<br>AAAATTATGAGAAAGCTGTAAACGCTATGATCCTGGCAGGAAAAGCCTACTACG<br>ATGGAGTGGCCAAGATCGGTGAGATTGCCACTGGGTCCCCCGTGTCAACTGAACT<br>GGGACATGTCCTCATAGAGATTTCAAGTACCCACAAGAAACTCAACGAGAGTCT<br>TGATGAAAATTTTAAAAAATTCCACAAAGAGATTATCCATGAGCTGGAGAAGAA<br>GATAGAACTTGACGTGAAATATATGAACGCAACTCTAAAAAGATACCAAACAGA<br>ACACAAGAATAAATTAGAGTCTTTGGAGAAATCCCAAGCTGAGTTGAAGAAGAT<br>CAGAAGGAAAAGCCAAGGAAGCCGAAACGCACTCAAATATGAACACAAAGAAA<br>TTGAGTATGTGGAGACCGTTACTTCTCGTCAGAGTGAAATCCAGAAATTCATTGC<br>AGATGGTTGCAAAGAGGCTCTGCTTGAAGAGAAGAGGCGCTTCTGCTTTCTGGTT<br>GATAAGCACTGTGGCTTTGCAAACCACATACATTATTATCACTTACAGTCTGCAG<br>AACTACTGAATTCCAAGCTGCCTCGGTGGCAGGAGACCTGTGTTGATGCCATCAA<br>AGTGCCAGAGAAAATCATGAATATGATCGAAGAAATAAAGACCCCAGCCTCTAC<br>CCCCGTGTCTGGAACTCCTCAGGCTTCACCCATGATCGAGAGAAGCAATGTGGTT<br>AGGAAAGATTACGACACCCTTTCTAAATGCTCACCAAAGATGCCCCCCGCTCCTT<br>CAGGCAGAGCATATACCAGTCCCTTGATCGATATGTTTAATAACCCAGCCACGGC<br>TGCCCCGAATTCACAAAGGGTAAATAATTCAACAGGTACTTCCGAAGATCCCAGT<br>TTACAGCGATCAGTTTCGGTTGCAACGGGACTGAACATGATGAAGAAGCAGAAA<br>GTGAAGACCATCTTCCCGCACACTGCGGGCTCCAACAAGACCTTACTCAGCTTTG<br>CACAGGGAGATGTCATCACGCTGCTCATCCCCGAGGAGAAGGATGGCTGGCTCT<br>ATGGAGAACACGACGTGTCCAAGGCGAGGGGTTGGTTCCCGTCGTCGTACACGA<br>AGTTGCTGGAAGAAAATGAGACAGAAGCAGTGACCGTGCCCACGCCAAGCCCCA<br>CACCAGTGAGAAGCATCAGCACCGTGAACTTGTCTGAGAATAGCAGTGTTGTCAT<br>CCCCCCACCCGACTACTTGGAATGCTTGTCCATGGGGGCAGCTGCCGACAGGAG<br>AGCAGATTCGGCCAGGACGACATCCACCTTTAAGGCCCCAGCGTCCAAGCCCGA<br>GACCGCGGCTCCTAACGATGCCAACGGGACTGCAAAGCCGCCTTTTCTCAGCGG<br>AGAAAACCCCTTTGCCACTGTGAAACTCCGCCCGACTGTGACGAATGATCGCTCG<br>GCACCCATCATTCGATGA |
| FGFR2:BICC1<br>(4989 base pairs)<br>(SEQ ID NO:23) | >ATGGTCAGCTGGGGTCGTTTCATCTGCCTGGTCGTGGTCACCATGGCAACCTTGT<br>CCCTGGCCCGGCCCTCCTTCAGTTTAGTTGAGGATACCACATTAGAGCCAGAAGA<br>GCCACCAACCAAATACCAAATCTCTCAACCAGAAGTGTACGTGGCTGCGCCAGG<br>GGAGTCGCTAGAGGTGCGCTGCCTGTTGAAAGATGCCGCCGTGATCAGTTGGACT<br>AAGGATGGGGTGCACTTGGGGCCCAACAATAGGACAGTGCTTATTGGGGAGTAC<br>TTGCAGATAAAGGGCGCCACGCCTAGAGACTCCGGCCTCTATGCTTGTACTGCCA<br>GTAGGACTGTAGACAGTGAAACTTGGTACTTCATGGTGAATGTCACAGATGCCAT<br>CTCATCCGGAGATGATGAGGATGACACCGATGGTGCGGAAGATTTTGTCAGTGA<br>GAACAGTAACAACAAGAGAGCACCATACTGGACCAACACAGAAAAGATGGAAA<br>AGCGGCTCCATGCTGTGCCTGCGGCCAACACTGTCAAGTTTCGCTGCCCAGCCGG<br>GGGGAACCCAATGCCAACCATGCGGTGGCTGAAAAACGGGAAGGAGTTTAAGCA<br>GGAGCATCGCATTGGAGGCTACAAGGTACGAAACCAGCACTGGAGCCTCATTAT<br>GGAAAGTGTGGTCCCATCTGACAAGGGAAATTATACCTGTGTAGTGGAGAATGA<br>ATACGGGTCCATCAATCACACGTACCACCTGGATGTTGTGGAGCGATCGCCTCAC<br>CGGCCCATCCTCCAAGCCGGACTGCCGGCAAATGCCTCCACAGTGGTCGGAGGA<br>GACGTAGAGTTTGTCTGCAAGGTTTACAGTGATGCCCAGCCCCACATCCAGTGGA<br>TCAAGCACGTGGAAAAGAACGGCAGTAAATACGGGCCCGACGGGCTGCCCTACC<br>TCAAGGTTCTCAAGGCCGCCGGTGTTAACACCACGGACAAAGAGATTGAGGTTC<br>TCTATATTCGGAATGTAACTTTTGAGGACGCTGGGGAATATACGTGCTTGGCGGG<br>TAATTCTATTGGGATATCCTTTCACTCTGCATGGTTGACAGTTCTGCCAGCGCCTG<br>GAAGAGAAAAGGAGATTACAGCTTCCCCAGACTACCTGGAGATAGCCATTTACT<br>GCATAGGGGTCTTCTTAATCGCCTGTATGGTGGTAACAGTCATCCTGTGCCGAAT |

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| | GAAGAACACGACCAAGAAGCCAGACTTCAGCAGCCAGCCGGCTGTGCACAAGCT<br>GACCAAACGTATCCCCCTGCGGAGACAGGTAACAGTTTCGGCTGAGTCCAGCTCC<br>TCCATGAACTCCAACACCCCGCTGGTGAGGATAACAACACGCCTCTCTTCAACGG<br>CAGACACCCCCATGCTGGCAGGGGTCTCCGAGTATGAACTTCCAGAGGACCCAA<br>AATGGGAGTTTCCAAGAGATAAGCTGACACTGGGCAAGCCCCTGGGAGAAGGTT<br>GCTTTGGGCAAGTGGTCATGGCGGAAGCAGTGGGAATTGACAAAGACAAGCCCA<br>AGGAGGCGGTCACCGTGGCCGTGAAGATGTTGAAAGATGATGCCACAGAGAAAG<br>ACCTTTCTGATCTGGTGTCAGAGATGGAGATGATGAAGATGATTGGGAAACACA<br>AGAATATCATAAATCTTCTTGGAGCCTGCACACAGGATGGGCCTCTCTATGTCAT<br>AGTTGAGTATGCCTCTAAAGGCAACCTCCGAGAATACCTCCGAGCCCGGAGGCC<br>ACCCGGGATGGAGTACTCCTATGACATTAACCGTGTTCCTGAGGAGCAGATGACC<br>TTCAAGGACTTGGTGTCATGCACCTACCAGCTGGCCAGAGGCATGGAGTACTTGG<br>CTTCCCAAAAATGTATTCATCGAGATTTAGCAGCCAGAAATGTTTTGGTAACAGA<br>AAACAATGTGATGAAAATAGCAGACTTTGGACTCGCCAGAGATATCAACAATAT<br>AGACTATTACAAAAAGACCACCAATGGGCGGCTTCCAGTCAAGTGGATGGCTCC<br>AGAAGCCCTGTTTGATAGAGTATACACTCATCAGAGTGATGTCTGGTCCTTCGGG<br>GTGTTAATGTGGGAGATCTTCACTTTAGGGGGCTCGCCCTACCCAGGGATTCCCG<br>TGGAGGAACTTTTTAAGCTGCTGAAGGAAGGACACAGAATGGATAAGCCAGCCA<br>ACTGCACCAACGAACTGTACATGATGATGAGGGACTGTTGGCATGCAGTGCCCTC<br>CCAGAGACCAACGTTCAAGCAGTTGGTAGAAGACTTGGATCGAATTCTCACTCTC<br>ACAACCAATGAGATCATGGAGGAAACAAATACGCAGATTGCTTGGCCATCAAAA<br>CTGAAGATCGGAGCCAAATCCAAGAAAGATCCCCATATTAAGGTTTCTGGAAAG<br>AAAGAAGATGTTAAAGAAGCCAAGGAAATGATCATGTCTGTCTTAGACACAAAA<br>AGCAATCGAGTCACACTGAAGATGGATGTTTCACATACAGAACATTCACATGTA<br>ATCGGCAAAGGTGGCAACAATATTAAAAAAGTGATGGAAGAAACCGGATGCCAT<br>ATCCACTTTCCAGATTCCAACAGGAATAACCAAGCAGAAAAAAGCAACCAGGTA<br>TCTATAGCGGGACAACCAGCAGGAGTAGAATCTGCCCGAGTTAGAATTCGGGAG<br>CTGCTTCCTTTGGTGCTGATGTTTGAGCTACCAATTGCTGGAATTCTTCAACCGGT<br>TCCTGATCCTAATTCCCCCTCTATTCAGCATATATCACAAACGTACAATATTTCAG<br>TATCATTTAAACAGCGTTCCCGAATGTATGGTGCTACTGTCATAGTACGAGGGTC<br>TCAGAATAACACTAGTGCTGTGAAGGAAGGAACTGCCATGCTGTTAGAACATCTT<br>GCTGGGAGCTTAGCATCAGCTATTCCTGTGAGCACACAACTAGATATTGCAGCTC<br>AACATCATCTCTTTATGATGGGTCGAAATGGGAGCAACATCAAACATATCATGCA<br>GAGAACAGGTGCTCAGATCCACTTTCCTGATCCCAGTAATCCACAAAAGAAATCT<br>ACCGTCTACCTCCAGGGCACCATTGAGTCTGTCTGTCTTGCAAGGCAATATCTCA<br>TGGGTTGTCTTCCTCTTGTGTTGATGTTTGATATGAAGGAAGAAATTGAAGTAGA<br>TCCACAATTCATTGCGCAGTTGATGGAACAGCTTGATGTCTTCATCAGTATTAAA<br>CCAAAGCCCAAACAGCCAAGCAAGTCTGTGATTGTGAAAAGTGTTGAGCGAAAT<br>GCCTTAAATATGTATGAAGCAAGGAAATGTCTCCTCGGACTTGAAAGCAGTGGG<br>GTTACCATAGCAACCAGTCCATCCCCAGCATCCTGCCCTGCCGGCCTGGCATGTC<br>CCAGCCTGGATATCTTAGCTTCAGCAGGCCTTGGACTCACTGGACTAGGTCTTTT<br>GGGACCCACCACCTTATCTCTGAACACTTCAACAACCCCAAACTCACTCTTGAAT<br>GCTCTTAATAGCTCAGTCAGTCCTTTGCAAAGTCCAAGTTCTGGTACACCCAGCC<br>CCACATTATGGGCACCCCCACTTGCTAATACTTCAAGTGCCACAGGTTTTTCTGCT<br>ATACCACACCTTATGATTCCATCTACTGCCCAAGCCACATTAACTAATATTTTGTT<br>GTCTGGAGTGCCCACCTATGGGCACACAGCTCCATCTCCCCCTCCTGGCTTGACT<br>CCTGTTGATGTCCATATCAACAGTATGCAGACCGAAGGCAAAAAAATCTCTGCTG<br>CTTTAAATGGACATGCACAGTCTCCAGATATAAAATATGGTGCAATATCCACTTC<br>ATCACTTGGAGAAAAAGTGCTGAGTGCAAATCACGGGGATCCGTCCATCCAGAC<br>AAGTGGGTCTGAGCAGACATCTCCCAAATCAAGCCCCACTGAAGGTTGTAATGA<br>TGCTTTTGTTGAAGTAGGCATGCCTCGAAGTCCTTCCCATTCTGGGAATGCTGGT<br>GACTTGAAACAGATGATGTGTCCCTCCAAGGTTTCCTGTGCCAAAAGGCAGACA<br>GTGGAACTATTGCAAGGCACGAAAAACTCACACTTACACAGCACTGACAGGTTG<br>CTCTCAGACCCTGAACTGAGTGCTACCGAAAGCCCTTTGGCTGACAAGAAGGCTC<br>CAGGGAGTGAGCGCGCTGCAGAGAGGGCAGCAGCTGCCCAGCAAAACTCCGAA<br>AGGGCCCACCTTGCTCCACGGTCATCATATGTCAACATGCAGGCATTTGACTATG<br>AACAGAAGAAGCTATTAGCCACCAAAGCTATGTTAAAGAAACCAGTGGTGACGG<br>AGGTCAGAACGCCCACAAATACCTGGAGTGGCCTGGGTTTTTCTAAATCCATGCC<br>AGCTGAAACTATCAAGGAGTTGAGAAGGGCCAATCATGTGTCCTATAAGCCCAC |

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| | AATGACAACCACTTATGAGGGCTCATCCATGTCCCTTTCACGGTCCAACAGTCGT<br>GAGCACTTGGGAGGTGGAAGCGAATCTGATAACTGGAGAGACCGAAATGGAATT<br>GGACCTGGAAGTCATAGTGAATTTGCAGCTTCTATTGGCAGCCCTAAGCGTAAAC<br>AAAACAAATCAACGGAACACTATCTCAGCAGTAGCAATTACATGGACTGCATTT<br>CCTCGCTGACAGGAAGCAATGGCTGTAACTTAAATAGCTCTTTCAAAGGTTCTGA<br>CCTCCCTGAGCTCTTCAGCAAACTGGGCCTGGGCAAATACACAGATGTTTTCCAG<br>CAACAAGAGATCGATCTTCAGACATTCCTCACTCTCACAGATCAGGATCTGAAGG<br>AGCTGGGAATAACTACTTTTGGTGCCAGGAGGAAAATGCTGCTTGCAATTTCAGA<br>ACTAAATAAAAACCGAAGAAAGCTTTTTGAATCGCCAAATGCACGCACCTCTTTC<br>CTGGAAGGTGGAGCGAGTGGAAGGCTACCCCGTCAGTATCACTCAGACATTGCT<br>AGTGTCAGTGGCCGCTGGTAG |
| FGFR2:AFF3<br>(5109 base pairs)<br>(SEQ ID NO:24) | >ATGGTCAGCTGGGGTCGTTTCATCTGCCTGGTCGTGGTCACCATGGCAACCTTGT<br>CCCTGGCCCGGCCCTCCTTCAGTTTAGTTGAGGATACCACATTAGAGCCAGAAGA<br>GCCACCAACCAAATACCAAATCTCTCAACCAGAAGTGTACGTGGCTGCGCCAGG<br>GGAGTCGCTAGAGGTGCGCTGCCTGTTGAAAGATGCCGCCGTGATCAGTTGGACT<br>AAGGATGGGGTGCACTTGGGGCCCAACAATAGGACAGTGCTTATTGGGGAGTAC<br>TTGCAGATAAAGGGCGCCACGCCTAGAGACTCCGGCCTCTATGCTTGTACTGCCA<br>GTAGGACTGTAGACAGTGAAACTTGGTACTTCATGGTGAATGTCACAGATGCCAT<br>CTCATCCGGAGATGATGAGGATGACACCGATGGTGCGGAAGATTTTGTCAGTGA<br>GAACAGTAACAACAAGAGAGCACCATACTGGACCAACACAGAAAAGATGGAAA<br>AGCGGCTCCATGCTGTGCCTGCGGCCAACACTGTCAAGTTTCGCTGCCCAGCCGG<br>GGGGAACCCAATGCCAACCATGCGGTGGCTGAAAAACGGGAAGGAGTTTAAGCA<br>GGAGCATCGCATTGGAGGCTACAAGGTACGAAACCAGCACTGGAGCCTCATTAT<br>GGAAAGTGTGGTCCCATCTGACAAGGGAAATTATACCTGTGTAGTGGAGAATGA<br>ATACGGGTCCATCAATCACACGTACCACCTGGATGTTGTGGAGCGATCGCCTCAC<br>CGGCCCATCCTCCAAGCCGGACTGCCGGCAAATGCCTCCACAGTGGTCGGAGGA<br>GACGTAGAGTTTGTCTGCAAGGTTTACAGTGATGCCCAGCCCCACATCCAGTGGA<br>TCAAGCACGTGGAAAAGAACGGCAGTAAATACGGGCCCGACGGGCTGCCCTACC<br>TCAAGGTTCTCAAGGCCGCCGGTGTTAACACCACGGACAAAGAGATTGAGGTTC<br>TCTATATTCGGAATGTAACTTTTGAGGACGCTGGGGAATATACGTGCTTGGCGGG<br>TAATTCTATTGGGATATCCTTTCACTCTGCATGGTTGACAGTTCTGCCAGCGCCTG<br>GAAGAGAAAAGGAGATTACAGCTTCCCCAGACTACCTGGAGATAGCCATTTACT<br>GCATAGGGGTCTTCTTAATCGCCTGTATGGTGGTAACAGTCATCCTGTGCCGAAT<br>GAAGAACACGACCAAGAAGCCAGACTTCAGCAGCCAGCCGGCTGTGCACAAGCT<br>GACCAAACGTATCCCCCTGCGGAGACAGGTAACAGTTTCGGCTGAGTCCAGCTCC<br>TCCATGAACTCCAACACCCCGCTGGTGAGGATAACAACACGCCTCTCTTCAACGG<br>CAGACACCCCCATGCTGGCAGGGGTCTCCGAGTATGAACTTCCAGAGGACCCAA<br>AATGGGAGTTTCCAAGAGATAAGCTGACACTGGGCAAGCCCCTGGGAGAAGGTT<br>GCTTTGGGCAAGTGGTCATGGCGGAAGCAGTGGGAATTGACAAAGACAAGCCCA<br>AGGAGGCGGTCACCGTGGCCGTGAAGATGTTGAAAGATGATGCCACAGAGAAAG<br>ACCTTTCTGATCTGGTGTCAGAGATGGAGATGATGAAGATGATTGGGAAACACA<br>AGAATATCATAAATCTTCTTGGAGCCTGCACACAGGATGGGCCTCTCTATGTCAT<br>AGTTGAGTATGCCTCTAAAGGCAACCTCCGAGAATACCTCCGAGCCCGGAGGCC<br>ACCCGGGATGGAGTACTCCTATGACATTAACCGTGTTCCTGAGGAGCAGATGACC<br>TTCAAGGACTTGGTGTCATGCACCTACCAGCTGGCCAGAGGCATGGAGTACTTGG<br>CTTCCCAAAAATGTATTCATCGAGATTTAGCAGCCAGAAATGTTTTGGTAACAGA<br>AAACAATGTGATGAAAATAGCAGACTTTGGACTCGCCAGAGATATCAACAATAT<br>AGACTATTACAAAAAGACCACCAATGGGCGGCTTCCAGTCAAGTGGATGGCTCC<br>AGAAGCCCTGTTTGATAGAGTATACACTCATCAGAGTGATGTCTGGTCCTTCGGG<br>GTGTTAATGTGGGAGATCTTCACTTTAGGGGGCTCGCCCTACCCAGGGATTCCCG<br>TGGAGGAACTTTTTAAGCTGCTGAAGGAAGGACACAGAATGGATAAGCCAGCCA<br>ACTGCACCAACGAACTGTACATGATGATGAGGGACTGTTGGCATGCAGTGCCCTC<br>CCAGAGACCAACGTTCAAGCAGTTGGTAGAAGACTTGGATCGAATTCTCACTCTC |

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| | ACAACCAATGAGGAGAGTAGATCTGGAGAAACCAACAGCTGTGTTGAAGAAATA<br>ATCCGGGAGATGACCTGGCTTCCACCACTTTCTGCTATTCAAGCACCTGGCAAAG<br>TGGAACCAACCAAATTTCCATTTCCAAATAAGGACTCTCAGCTTGTATCCTCTGG<br>ACACAATAATCCAAAGAAAGGTGATGCAGAGCCAGAGAGTCCAGACAGTGGCA<br>CATCGAATACATCAATGCTGGAAGATGACCTTAAGCTAAGCAGTGATGAAGAGG<br>AGAATGAACAGCAGGCAGCTCAGAGAACGGCTCTCCGCGCTCTCTCTGACAGCG<br>CCGTGGTCCAGCAGCCCAACTGCAGAACCTCGGTGCCTTCCAGCAAGGGCAGCA<br>GCAGCAGCAGCAGCAGCGGCAGCAGCAGCTCCTCCAGCGACTCAGAGAGCAGCT<br>CCGGATCTGACTCGGAGACCGAGAGCAGCTCCAGCGAGAGTGAGGGCAGCAAGC<br>CCCCCCACTTCTCCAGCCCCGAGGCTGAACCGGCATCCTCTAACAAGTGGCAGCT<br>GGATAAATGGCTAAACAAAGTTAATCCCCACAAGCCTCCTATTCTGATCCAAAAT<br>GAAAGCCACGGGTCAGAGAGCAATCAGTACTACAACCCGGTGAAAGAGGACGTC<br>CAGGACTGTGGGAAAGTCCCCGACGTTTGCCAGCCCAGCCTGAGAGAGAAGGAG<br>ATCAAGAGCACTTGCAAGGAGGAGCAAAGGCCAAGGACAGCCAACAAGGCCCC<br>TGGGAGTAAAGGCGTGAAGCAGAAGTCCCCGCCCGCGGCCGTGGCCGTGGCGGT<br>GAGCGCAGCCGCCCCGCCACCCGCAGTGCCCTGTGCGCCCGCGGAGAACGCGCC<br>CGCGCCTGCCCGGAGGTCCGCGGGCAAGAAGCCCACCAGGCGCACCGAGAGGAC<br>CTCAGCCGGGGACGGCGCCAACTGCCACCGGCCCGAGGAGCCCGCGGCCGCGGA<br>CGCGCTGGGGACGAGCGTGGTGGTCCCCCCGGAGCCCACCAAAACCAGGCCCTG<br>TGGCAACAACAGAGCGAGCCACCGCAAGGAGCTGCGCTCCTCCGTGACCTGCGA<br>GAAGCGCCGCACGCGGGGGCTAAGCAGGATCGTCCCCAAATCCAAGGAGTTCAT<br>TGAGACAGAGTCGTCATCTTCATCCTCCTCCTCGGACTCCGACCTGGAGTCCGAG<br>CAGGAGGAGTACCCTCTGTCCAAAGCACAGACCGTGGCTGCCTCTGCCTCCTCCG<br>GGAATGATCAGAGGCTGAAGGAGGCCGCTGCCAACGGGGGCAGTGGTCCTAGGG<br>CCCCTGTAGGCTCCATCAACGCCAGGACCACCAGTGACATCGCCAAGGAGCTGG<br>AGGAGCAGTTCTACACACTGGTCCCCTTTGGCCGGAACGAACTTCTCTCCCCTCT<br>AAAGGACAGTGATGAGATCAGGTCTCTCTGGGTCAAAATCGACCTGACCCTCCTG<br>TCCAGGATCCCAGAACACCTGCCCCAGGAGCCAGGGGTATTGAGCGCCCCTGCC<br>ACCAAGGACTCTGAGAGCGCACCGCCCAGCCACACCTCGGACACACCTGCAGAA<br>AAGGCTTTGCCAAAATCCAAGAGGAAACGCAAGTGTGACAACGAAGACGACTAC<br>AGGGAGATCAAGAAGTCCCAGGGAGAGAAAGACAGCTCTTCAAGACTGGCCACC<br>TCCACCAGTAATACTTTGTCTGCAAACCACTGCAACATGAACATCAACAGTGTGG<br>CAATACCAATAAATAAAAATGAAAAAATGCTTCGGTCGCCCATCTCACCCCTCTC<br>TGATGCATCTAAACACAAATACACCAGCGAGGACTTAACTTCTTCCAGCCGACCT<br>AATGGCAACAGTTTGTTTACTTCAGCCTCTTCCAGCAAAAAGCCTAAGGCCGACA<br>GCCAGCTGCAGCCTCACGGCGGAGACCTCACGAAAGCAGCTCACAACAATTCTG<br>AAAACATTCCCCTCCACAAGTCACGGCCGCAGACGAAGCCGTGGTCTCCAGGCT<br>CCAACGGCCACAGGGACTGCAAGAGGCAGAAACTTGTCTTCGATGATATGCCTC<br>GCAGTGCCGATTATTTTATGCAAGAAGCTAAACGAATGAAGCATAAAGCAGATG<br>CAATGGTGGAAAAGTTTGGAAAGGCTTTGAACTATGCTGAAGCAGCATTGTCGTT<br>TATCGAGTGTGGAAATGCAATGGAACAAGGCCCCATGGAATCCAAATCTCCTTAT<br>ACGATGTATTCAGAAACAGTAGAGCTCATCAGGTATGCTATGAGACTAAAAACC<br>CACTCAGGCCCCAATGCCACACCAGAAGACAAACAACTGGCTGCATTATGTTAC<br>CGATGCCTGGCCCTCCTGTACTGGCGGATGTTTCGACTCAAAAGGGACCACGCTG<br>TAAAGTATTCAAAAGCACTAATCGACTATTTCAAGAACTCATCTAAAGCCGCCCA<br>AGCCCCATCTCCGTGGGGGGCCAGTGGAAAGAGCACTGGAACCCCATCCCCCAT<br>GTCTCCCAACCCCTCTCCCGCCAGCTCCGTGGGGTCTCAGGGCAGCCTCTCCAAC<br>GCCAGCGCCCTGTCCCCGTCGACCATCGTCAGCATCCCACAGCGCATCCACCAGA<br>TGGCGGCCAACCACGTCAGCATCACCAACAGCATCCTGCACAGCTACGACTACT<br>GGGAGATGGCCGACAACCTGGCCAAGGAAAACCGAGAATTCTTCAACGACCTGG<br>ATCTGCTCATGGGGCCGGTCACCCTGCACAGCAGCATGGAGCACCTGGTCCAGTA |

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| | CTCCCAACAGGGCCTGCACTGGCTGCGGAACAGCGCCCACCTGTCATAG |
| FGFR2:CASP7<br>(3213 base pairs)<br>(SEQ ID NO:25) | >ATGGTCAGCTGGGGTCGTTTCATCTGCCTGGTCGTGGTCACCATGGCAACCTTGT<br>CCCTGGCCCGGCCCTCCTTCAGTTTAGTTGAGGATACCACATTAGAGCCAGAAGA<br>GCCACCAACCAAATACCAAATCTCTCAACCAGAAGTGTACGTGGCTGCGCCAGG<br>GGAGTCGCTAGAGGTGCGCTGCCTGTTGAAAGATGCCGCCGTGATCAGTTGGACT<br>AAGGATGGGGTGCACTTGGGGCCCAACAATAGGACAGTGCTTATTGGGGAGTAC<br>TTGCAGATAAAGGGCGCCACGCCTAGAGACTCCGGCCTCTATGCTTGTACTGCCA<br>GTAGGACTGTAGACAGTGAAACTTGGTACTTCATGGTGAATGTCACAGATGCCAT<br>CTCATCCGGAGATGATGAGGATGACACCGATGGTGCGGAAGATTTTGTCAGTGA<br>GAACAGTAACAACAAGAGAGCACCATACTGGACCAACACAGAAAAGATGGAAA<br>AGCGGCTCCATGCTGTGCCTGCGGCCAACACTGTCAAGTTTCGCTGCCCAGCCGG<br>GGGGAACCCAATGCCAACCATGCGGTGGCTGAAAAACGGGAAGGAGTTTAAGCA<br>GGAGCATCGCATTGGAGGCTACAAGGTACGAAACCAGCACTGGAGCCTCATTAT<br>GGAAAGTGTGGTCCCATCTGACAAGGGAAATTATACCTGTGTAGTGGAGAATGA<br>ATACGGGTCCATCAATCACACGTACCACCTGGATGTTGTGGAGCGATCGCCTCAC<br>CGGCCCATCCTCCAAGCCGGACTGCCGGCAAATGCCTCCACAGTGGTCGGAGGA<br>GACGTAGAGTTTGTCTGCAAGGTTTACAGTGATGCCCAGCCCCACATCCAGTGGA<br>TCAAGCACGTGGAAAAGAACGGCAGTAAATACGGGCCCGACGGGCTGCCCTACC<br>TCAAGGTTCTCAAGGCCGCCGGTGTTAACACCACGGACAAAGAGATTGAGGTTC<br>TCTATATTCGGAATGTAACTTTTGAGGACGCTGGGGAATATACGTGCTTGGCGGG<br>TAATTCTATTGGGATATCCTTTCACTCTGCATGGTTGACAGTTCTGCCAGCGCCTG<br>GAAGAGAAAAGGAGATTACAGCTTCCCCAGACTACCTGGAGATAGCCATTTACT<br>GCATAGGGGTCTTCTTAATCGCCTGTATGGTGGTAACAGTCATCCTGTGCCGAAT<br>GAAGAACACGACCAAGAAGCCAGACTTCAGCAGCCAGCCGGCTGTGCACAAGCT<br>GACCAAACGTATCCCCCTGCGGAGACAGGTAACAGTTTCGGCTGAGTCCAGCTCC<br>TCCATGAACTCCAACACCCCGCTGGTGAGGATAACAACACGCCTCTCTTCAACGG<br>CAGACACCCCCATGCTGGCAGGGGTCTCCGAGTATGAACTTCCAGAGGACCCAA<br>AATGGGAGTTTCCAAGAGATAAGCTGACACTGGGCAAGCCCCTGGGAGAAGGTT<br>GCTTTGGGCAAGTGGTCATGGCGGAAGCAGTGGGAATTGACAAAGACAAGCCCA<br>AGGAGGCGGTCACCGTGGCCGTGAAGATGTTGAAAGATGATGCCACAGAGAAAG<br>ACCTTTCTGATCTGGTGTCAGAGATGGAGATGATGAAGATGATTGGGAAACACA<br>AGAATATCATAAATCTTCTTGGAGCCTGCACACAGGATGGGCCTCTCTATGTCAT<br>AGTTGAGTATGCCTCTAAAGGCAACCTCCGAGAATACCTCCGAGCCCGGAGGCC<br>ACCCGGGATGGAGTACTCCTATGACATTAACCGTGTTCCTGAGGAGCAGATGACC<br>TTCAAGGACTTGGTGTCATGCACCTACCAGCTGGCCAGAGGCATGGAGTACTTGG<br>CTTCCCAAAAATGTATTCATCGAGATTTAGCAGCCAGAAATGTTTTGGTAACAGA<br>AAACAATGTGATGAAAATAGCAGACTTTGGACTCGCCAGAGATATCAACAATAT<br>AGACTATTACAAAAAGACCACCAATGGGCGGCTTCCAGTCAAGTGGATGGCTCC<br>AGAAGCCCTGTTTGATAGAGTATACACTCATCAGAGTGATGTCTGGTCCTTCGGG<br>GTGTTAATGTGGGAGATCTTCACTTTAGGGGGCTCGCCCTACCCAGGGATTCCCG<br>TGGAGGAACTTTTTAAGCTGCTGAAGGAAGGACACAGAATGGATAAGCCAGCCA<br>ACTGCACCAACGAACTGTACATGATGATGAGGGACTGTTGGCATGCAGTGCCCTC<br>CCAGAGACCAACGTTCAAGCAGTTGGTAGAAGACTTGGATCGAATTCTCACTCTC<br>ACAACCAATGAGATGGCAGATGATCAGGGCTGTATTGAAGAGCAGGGGGTTGAG<br>GATTCAGCAAATGAAGATTCAGTGGATGCTAAGCCAGACCGGTCCTCGTTTGTAC<br>CGTCCCTCTTCAGTAAGAAGAAGAAAAATGTCACCATGCGATCCATCAAGACCA<br>CCCGGGACCGAGTGCCTACATATCAGTACAACATGAATTTTGAAAAGCTGGGCA<br>AATGCATCATAATAAACAACAAGAACTTTGATAAAGTGACAGGTATGGGCGTTC<br>GAAACGGAACAGACAAAGATGCCGAGGCGCTCTTCAAGTGCTTCCGAAGCCTGG<br>GTTTTGACGTGATTGTCTATAATGACTGCTCTTGTGCCAAGATGCAAGATCTGCTT<br>AAAAAAGCTTCTGAAGAGGACCATACAAATGCCGCCTGCTTCGCCTGCATCCTCT<br>TAAGCCATGGAGAAGAAAATGTAATTTATGGGAAAGATGGTGTCACACCAATAA<br>AGGATTTGACAGCCCACTTTAGGGGGGATAGATGCAAAACCCTTTTAGAGAAAC<br>CCAAACTCTTCTTCATTCAGGCTTGCCGAGGGACCGAGCTTGATGATGGCATCCA<br>GGCCGACTCGGGGCCCATCAATGACACAGATGCTAATCCTCGATACAAGATCCC<br>AGTGGAAGCTGACTTCCTCTTCGCCTATTCCACGGTTCCAGGCTATTACTCGTGG<br>AGGAGCCCAGGAAGAGGCTCCTGGTTTGTGCAAGCCCTCTGCTCCATCCTGGAGG<br>AGCACGGAAAAGACCTGGAAATCATGCAGATCCTCACCAGGGTGAATGACAGAG<br>TTGCCAGGCACTTTGAGTCTCAGTCTGATGACCCACACTTCCATGAGAAGAAGCA |

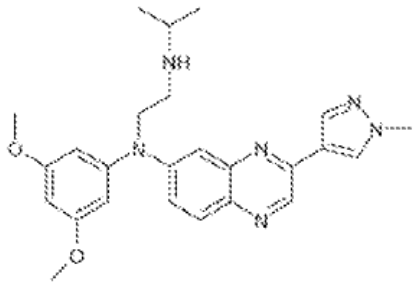
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|---|---|
| | GATCCCCTGTGTGGTCTCCATGCTCACCAAGGAACTCTACTTCAGTCAATAG |
| FGFR2:CCDC6<br>(3423 base pairs)<br>(SEQ ID NO:26) | >ATGGTCAGCTGGGGTCGTTTCATCTGCCTGGTCGTGGTCACCATGGCAACCTTGT<br>CCCTGGCCCGGCCCTCCTTCAGTTTAGTTGAGGATACCACATTAGAGCCAGAAGA<br>GCCACCAACCAAATACCAAATCTCTCAACCAGAAGTGTACGTGGCTGCGCCAGG<br>GGAGTCGCTAGAGGTGCGCTGCCTGTTGAAAGATGCCGCCGTGATCAGTTGGACT<br>AAGGATGGGGTGCACTTGGGGCCCAACAATAGGACAGTGCTTATTGGGGAGTAC<br>TTGCAGATAAAGGGCGCCACGCCTAGAGACTCCGGCCTCTATGCTTGTACTGCCA<br>GTAGGACTGTAGACAGTGAAACTTGGTACTTCATGGTGAATGTCACAGATGCCAT<br>CTCATCCGGAGATGATGAGGATGACACCGATGGTGCGGAAGATTTTGTCAGTGA<br>GAACAGTAACAACAAGAGAGCACCATACTGGACCAACACAGAAAAGATGGAAA<br>AGCGGCTCCATGCTGTGCCTGCGGCCAACACTGTCAAGTTTCGCTGCCCAGCCGG<br>GGGGAACCCAATGCCAACCATGCGGTGGCTGAAAAACGGGAAGGAGTTTAAGCA<br>GGAGCATCGCATTGGAGGCTACAAGGTACGAAACCAGCACTGGAGCCTCATTAT<br>GGAAAGTGTGGTCCCATCTGACAAGGGAAATTATACCTGTGTAGTGGAGAATGA<br>ATACGGGTCCATCAATCACACGTACCACCTGGATGTTGTGGAGCGATCGCCTCAC<br>CGGCCCATCCTCCAAGCCGGACTGCCGGCAAATGCCTCCACAGTGGTCGGAGGA<br>GACGTAGAGTTTGTCTGCAAGGTTTACAGTGATGCCCAGCCCCACATCCAGTGGA<br>TCAAGCACGTGGAAAAGAACGGCAGTAAATACGGGCCCGACGGGCTGCCCTACC<br>TCAAGGTTCTCAAGGCCGCCGGTGTTAACACCACGGACAAAGAGATTGAGGTTC<br>TCTATATTCGGAATGTAACTTTTGAGGACGCTGGGGAATATACGTGCTTGGCGGG<br>TAATTCTATTGGGATATCCTTTCACTCTGCATGGTTGACAGTTCTGCCAGCGCCTG<br>GAAGAGAAAAGGAGATTACAGCTTCCCCAGACTACCTGGAGATAGCCATTTACT<br>GCATAGGGGTCTTCTTAATCGCCTGTATGGTGGTAACAGTCATCCTGTGCCGAAT<br>GAAGAACACGACCAAGAAGCCAGACTTCAGCAGCCAGCCGGCTGTGCACAAGCT<br>GACCAAACGTATCCCCCTGCGGAGACAGGTAACAGTTTCGGCTGAGTCCAGCTCC<br>TCCATGAACTCCAACACCCCGCTGGTGAGGATAACAACACGCCTCTCTTCAACGG<br>CAGACACCCCCATGCTGGCAGGGGTCTCCGAGTATGAACTTCCAGAGGACCCAA<br>AATGGGAGTTTCCAAGAGATAAGCTGACACTGGGCAAGCCCCTGGGAGAAGGTT<br>GCTTTGGGCAAGTGGTCATGGCGGAAGCAGTGGGAATTGACAAAGACAAGCCCA<br>AGGAGGCGGTCACCGTGGCCGTGAAGATGTTGAAAGATGATGCCACAGAGAAAG<br>ACCTTTCTGATCTGGTGTCAGAGATGGAGATGATGAAGATGATTGGGAAACACA<br>AGAATATCATAAATCTTCTTGGAGCCTGCACACAGGATGGGCCTCTCTATGTCAT<br>AGTTGAGTATGCCTCTAAAGGCAACCTCCGAGAATACCTCCGAGCCCGGAGGCC<br>ACCCGGGATGGAGTACTCCTATGACATTAACCGTGTTCCTGAGGAGCAGATGACC<br>TTCAAGGACTTGGTGTCATGCACCTACCAGCTGGCCAGAGGCATGGAGTACTTGG<br>CTTCCCAAAAATGTATTCATCGAGATTTAGCAGCCAGAAATGTTTTGGTAACAGA<br>AAACAATGTGATGAAAATAGCAGACTTTGGACTCGCCAGAGATATCAACAATAT<br>AGACTATTACAAAAAGACCACCAATGGGCGGCTTCCAGTCAAGTGGATGGCTCC<br>AGAAGCCCTGTTTGATAGAGTATACACTCATCAGAGTGATGTCTGGTCCTTCGGG<br>GTGTTAATGTGGGAGATCTTCACTTTAGGGGGCTCGCCCTACCCAGGGATTCCCG<br>TGGAGGAACTTTTTAAGCTGCTGAAGGAAGGACACAGAATGGATAAGCCAGCCA<br>ACTGCACCAACGAACTGTACATGATGATGAGGGACTGTTGGCATGCAGTGCCCTC<br>CCAGAGACCAACGTTCAAGCAGTTGGTAGAAGACTTGGATCGAATTCTCACTCTC<br>ACAACCAATGAGCAAGCCAGGGCTGAGCAGGAAGAAGAATTCATTAGTAACACT<br>TTATTCAAGAAAATTCAGGCTTTGCAGAAGGAGAAAGAAACCCTTGCTGTAAATT<br>ATGAGAAAGAAGAAGAATTCCTCACTAATGAGCTCTCCAGAAAATTGATGCAGT<br>TGCAGCATGAGAAAGCCGAACTAGAACAGCATCTTGAACAAGAGCAGGAATTTC<br>AGGTCAACAAACTGATGAAGAAAATTAAAAAACTGGAGAATGACACCATTTCTA<br>AGCAACTTACATTAGAACAGTTGAGACGGGAGAAGATTGACCTTGAAAATACAT<br>TGGAACAAGAACAAGAAGCACTAGTTAATCGCCTCTGGAAAAGGATGGATAAGC<br>TTGAAGCTGAAAAGCGAATCCTGCAGGAAAAATTAGACCAGCCCGTCTCTGCTC<br>CACCATCGCCTAGAGATATCTCCATGGAGATTGATTCTCCAGAAAATATGATGCG<br>TCACATCAGGTTTTTAAAGAATGAAGTGGAACGGCTGAAGAAGCAACTGAGAGC<br>TGCTCAGTTACAGCATTCAGAGAAAATGGCACAGTATCTGGAGGAGGAACGTCA<br>CATGAGAGAAGAGAACTTGAGGCTCCAGAGGAAGCTGCAGAGGGAGATGGAGA<br>GAAGAGAAGCCCTCTGTCGACAGCTCTCCGAGAGTGAGTCCAGCTTAGAAATGG<br>ACGACGAAAGGTATTTTAATGAGATGTCTGCACAAGGATTAAGACCTCGCACTGT<br>GTCCAGCCCGATCCCTTACACACCTTCTCCGAGTTCAAGCAGGCCTATATCACCT<br>GGTCTATCATATGCAAGTCACACGGTTGGTTTCACGCCACCAACTTCACTGACTA |

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| | GAGCTGGAATGTCTTATTACAATTCCCCGGGTCTTCACGTGCAGCACATGGGAAC<br>ATCCCATGGTATCACAAGGCCTTCACCACGGAGAAGCAACAGTCCTGACAAATT<br>CAAACGGCCCACGCCGCCTCCATCTCCCAACACACAGACCCCAGTCCAGCCACCT<br>CCGCCTCCACCTCCGCCACCCATGCAGCCCACGGTCCCCTCAGCAGCCACCTCGC<br>AGCCTACTCCTTCGCAACATTCGGCGCACCCCTCCTCCCAGCCTTAA |
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What is Claimed:

1. Use of an FGFR inhibitor in the manufacture of a medicament for treating cancer in a patient in combination with an antibody that blocks the interaction between PD-1 and PD-Ll if one or more FGFR variants are present in a biological sample that has been obtained from the patient, wherein the one or more FGFR variants comprise an FGFR fusion gene, a FGFR mutation, or a combination thereof, wherein the FGFR fusion gene is FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFDl; FGFR3:BAIAP2L1; FGFR3:TACC3-Intron; FGFR3:TACC3V1; FGFR3:TACC3V3; or a combination thereof; and wherein the FGFR mutation is FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, FGFR3 Y373C, or a combination thereof; and wherein the FGFR inhibitor is the compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

2. The use of claim 1, further comprising evaluating the presence of one or more FGFR variants in the biological sample before the medicament is to be administered.

3. The use of claim 1 or 2, further comprising evaluating PD-Ll expression in a biological sample that has been obtained from the patient.

4. The use of claim 3, wherein the biological sample for the one or more FGFR variants and the PD-Ll is the same biological sample.

5. The use of claim 3, wherein the biological sample for the one or more FGFR variants is different from the biological sample for PD-Ll expression.

6. The use of any one of the previous claims, wherein the biological sample is blood, lymph fluid, bone marrow, a solid tumor sample, or any combination thereof.

7. The use of any one of the previous claims, wherein the medicament is to be administered if PD-L l expression in the biological sample corresponds to an H-score of 0 to 99.

8. The use of any one of claims 1 to 7 wherein the FGFR inhibitor is to be administered if the antibody is not efficacious.

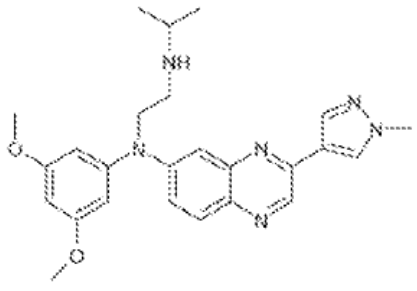
9. Use of an FGFR inhibitor in the manufacture of a medicament for treating cancer in a patient in combination with an antibody that blocks the interaction between PD-1 and PD-Ll, wherein

the efficacy of the antibody is to be monitored; and

if the antibody is not efficacious,

a biological sample that has been obtained from the patient is evaluated for a presence of one or more FGFR variants; and

wherein the FGFR inhibitor is to be administered if the one or more FGFR variants are present in the sample, wherein the one or more FGFR variants comprise an FGFR fusion gene, a FGFR mutation, or a combination thereof; and wherein the FGFR fusion gene is FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFDl; FGFR3:BAIAP2L1; FGFR3:TACC3-Intron; FGFR3:TACC3V1; FGFR3:TACC3V3; or a combination thereof; and wherein the FGFR mutation is FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, FGFR3 Y373C, or a combination thereof; and wherein the FGFR inhibitor is the compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

10. The use of claim 9, further comprising evaluating PD-Ll expression in a biological sample that has been obtained from the patient.

11. The use of claim 10, wherein the biological sample for the one or more FGFR variants and the PD-Ll is the same biological sample.

12. The use of claim 10, wherein the biological sample for the one or more FGFR variants is different from the biological sample for PD-Ll expression.

13. The use of any one of claims 9 to 12, wherein the biological sample is blood, lymph fluid, bone marrow, a solid tumor sample, or any combination thereof.

14. The use of any one of claims 9 to 13, wherein the medicament is be administered if PD-L l expression in the biological sample corresponds to an H-score of 0 to 99.

15. The use of any one of the previous claims, wherein the cancer is lung cancer, bladder cancer, gastric cancer, breast cancer, ovarian cancer, head and neck cancer, esophageal cancer, glioblastoma, or any combination thereof.

16. The use of claim 15, wherein the lung cancer is non-small cell lung cancer (NSCLC) adenocarcinoma, NSCLC squamous cell carcinoma, small cell lung cancer, or any combination thereof.

17. The use of any one of the preceding claims, wherein the cancer is bladder cancer.

18. The use of any one of the preceding claims, wherein the antibody that blocks the interaction between PD-1 and PD-Ll is an anti-PD-1 antibody, an anti-PD-Ll antibody, or a combination thereof.

19. The use of claim 18 wherein the antibody that blocks the interaction between PD-1 and PD-L1 is an anti-PD-1 antibody.

20. The use of claim 18 wherein the antibody that blocks the interaction between PD-1 and PD-L1 is an anti-PD-L1 antibody.

21. The use of any one of the preceding claims, wherein the one or more FGFR variants comprise FGFR2:BICC1.

22. The use of any one of claims 1 to 20, wherein the one or more FGFR variants comprise FGFR2:CASP7.

23. The use of any one of claims 1 to 20, wherein the one or more FGFR variants comprise FGFR3:BAIAP2L1.

24. The use of any one of claims 1 to 20, wherein the one or more FGFR variants comprise FGFR3:TACC3V1.

25. The use of any one of claims 1 to 20, wherein the one or more FGFR variants comprise FGFR3:TACC3V3.

26. The use of any one of claims 1 to 20, wherein the one or more FGFR variants comprise FGFR3 R248C.

27. The use of any one of claims 1 to 20, wherein the one or more FGFR variants comprise FGFR3 S249C.

28. The use of any one of claims 1 to 20, wherein the one or more FGFR variants comprise FGFR3 G370C.

29. The use of any one of claims 1 to 20, wherein the one or more FGFR variants comprise FGFR3 Y373C.

**FGFR/PD-1 COMBINATION THERAPY FOR THE TREATMENT OF CANCER**

## ABSTRACT

Provided herein are combination therapies for the treatment of cancer. In particular, the disclosed methods are directed to treatment of cancer in a patient comprising administering an antibody that blocks the interaction between PD-1 and PD-L1 and an FGFR inhibitor, wherein the antibody that blocks the interaction between PD-1 and PD-L1 and the FGFR inhibitor are administered if one or more FGFR variants are present in a biological sample from the patient.

[Fig. 1]