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 ~~embodiments~~examples, the methods comprise administering to a patient a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and

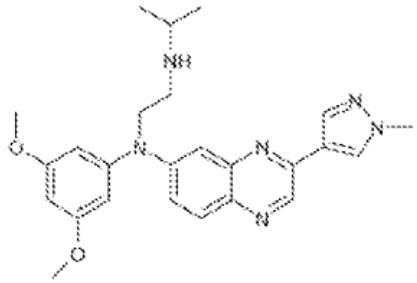
PD-L1 and a pharmaceutically effective amount of an FGFR inhibitor, wherein the antibody that blocks the interaction between PD-1 and PD-L1 and the FGFR inhibitor are administered if one or more FGFR variants are present in a biological sample from the patient.

[0006] In other examples~~embodiments~~, 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~~embodiments~~, 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~~embodiments~~, 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~~embodiments~~, 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.

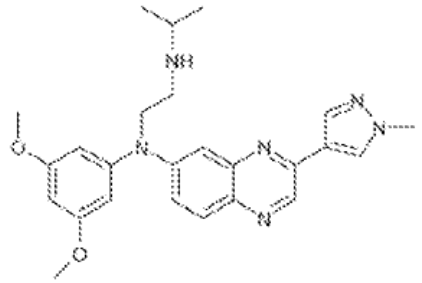
[0008a] In one aspect, there is provided use of an FGFR inhibitor in the manufacture of a medicament for treating cancer in a patient in combination with an antibody that blocks the interaction between PD-1 and PD-Ll if one or more FGFR variants are present in a biological sample that has been obtained 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):



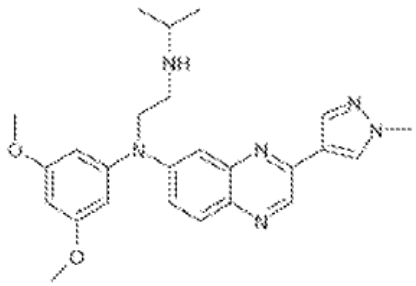
(I)

or a pharmaceutically acceptable salt thereof.

What is Claimed:

1. Use of an FGFR inhibitor in the manufacture of a medicament for ~~A method of~~ treating cancer in a patient in combination with ~~, comprising:~~

~~administering to the patient a pharmaceutically effective amount of~~ an antibody that blocks the interaction between PD-1 and PD-Ll ~~and a pharmaceutically effective amount of an FGFR inhibitor, wherein the antibody that blocks the interaction between PD-1 and PD-Ll and the FGFR inhibitor are administered~~ 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 ~~method~~ 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~~administering step~~.

3. The use ~~method~~ 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 ~~method~~ 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 ~~method~~ 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 ~~method~~ 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 ~~method~~ of any one of the previous claims, wherein the medicament is to be administered ~~administering step is performed~~ if PD-L l expression ~~is low~~ 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.

~~8. The method 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.~~

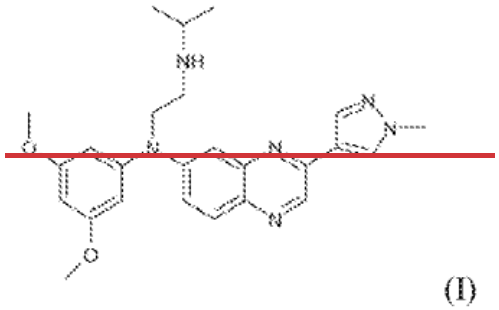
~~9. The method of claim 8, wherein the lung cancer is non-small cell lung cancer (NSCLC) adenocarcinoma, NSCLC squamous cell carcinoma, small cell lung cancer, or any combination thereof.~~

~~10. The method of any one of the previous claims, wherein the one or more FGFR variants comprise an FGFR mutation, an FGFR amplification, an FGFR fusion gene, or a combination thereof.~~

~~11. The method of claim 10, wherein the FGFR fusion gene is FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFDl; FGFR3:BAIAP2L; FGFR3:TACC3 Intron; FGFR3:TACC3V1; FGFR3:TACC3V3; or a combination thereof.~~

~~12. The method of any one of the previous claims, wherein the antibody that blocks the interaction between PD-1 and PD-Ll is an anti-PD-l antibody, an anti -PD-Ll antibody, or a combination thereof.~~

~~13. The method of any one of the previous claim s, wherein the FGFR inhibitor is the compound of formula (I):~~



(I)

~~or a pharmaceutically acceptable salt thereof.~~

~~14.~~9. Use of an FGFR inhibitor in the manufacture of a medicament for ~~A method of~~ treating cancer in a patient in combination with an antibody that blocks the interaction between PD-1 and PD-Ll, wherein ~~comprising:~~

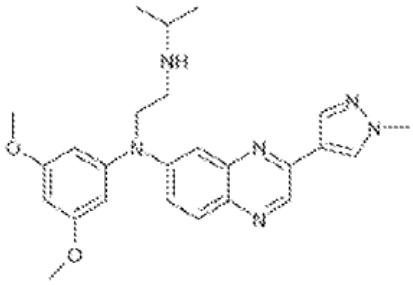
~~administering to the patient a pharmaceutically effective amount of an antibody that blocks the interaction between PD-1 and PD-Ll;~~

~~monitoring~~ the efficacy of the antibody is to be monitored; and

if the antibody is not efficacious,

~~evaluating~~ 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 ~~administering to the patient a pharmaceutically effective amount of an FGFR inhibitor~~ 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.

~~15.~~10. The ~~method~~ use of claim ~~14~~9, further comprising ~~wherein the~~ evaluating ~~step further comprises measuring an expression level of~~ PD-Ll expression in a biological sample that has been obtained from the patient~~and wherein the second administering step comprises administering the FGFR inhibitor if the expression level of PD-Ll is low~~.

~~16.~~11. The ~~method~~ use of claim ~~15~~10, wherein the biological sample for the one or more FGFR variants and the PD-Ll is the same biological sample.

~~17.~~12. The use ~~method~~ of claim ~~15~~10, wherein the biological sample for the one or more FGFR variants is different from the biological sample for PD-Ll expression.

~~18.~~13. The use ~~method~~ of any one of claims ~~16 or 17~~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.

~~19.~~15. The ~~method~~ use of any one of the previous claims ~~16-18~~, wherein the cancer is ~~Sung~~ lung cancer, bladder cancer, gastric cancer, breast cancer, ovarian cancer, head and neck cancer, esophageal cancer, glioblastoma, or any combination thereof.

~~20.~~16. The ~~method~~ use of claim ~~19~~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.

~~21. The method of any one of claims 16-20, wherein the one or more FG FR variants comprise an FGFR mutation, an FGFR amplification, an FGFR fusion gene, or a combination thereof.~~

~~22. The method of claim 21, wherein the FGFR fusion gene is FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFDl; FGFR3:BAlAP2L1; FGFR3:TACC3-Intron; FGFR3:TACC3V1; FGFR3:TACC3V3; or a combination thereof.~~

~~23.~~18. The ~~method~~ use of any one of the preceding claims ~~16-22~~, wherein the antibody that blocks ~~an~~ 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.

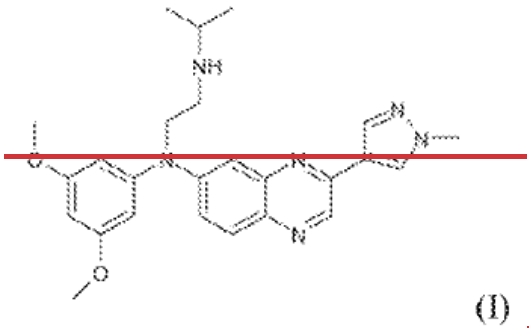
26. The use of any one of claims 1 to 20, wherein the one or more FGFR variants comprise FGFR3 R248C.

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.

~~24. The method of any one of claims 16-23, wherein the FGFR inhibitor is the compound of formula (I):~~



(I)

~~or a pharmaceutically acceptable salt thereof.~~