USE OF FGFR INHIBITORS IN FGFR-GENETICALLY ALTERED CANCERS TO ENHANCE PATIENT RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN SEQUENTIAL TREATMENT SETTINGS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Application No. 62/906,517, filed on September 26, 2019, which is incorporated by reference herein, in its entirety and for all purposes.

FIELD OF THE INVENTION

[0002] The present invention relates to methods of treating cancers using fibroblast growth factor receptor (FGFR) inhibitors. In particular, the present invention relates to methods of using FGFR inhibitors in FGFR-genetically altered cancers to enhance patient response to immune checkpoint inhibitors in sequential treatment settings.

BACKGROUND

[0003] Urothelial carcinoma (UC) is the most common form of bladder cancers and nearly 20% of patients with metastatic UC (mUC) have fibroblast growth factor receptor (FGFR) gene alterations. Clinical outcomes with platinum-based or taxane chemotherapy and immunotherapy (checkpoint inhibitors) have been suboptimal and there exists a significant unmet treatment need for mUC. It is accordingly an object of the present disclosure to provide such methods.

SUMMARY

[0001] According to particular ~~embodiments~~examples, the present ~~invention~~ disclosure relates to methods of treating any FGFR-genetically altered cancer with sequential systemic or local therapies, wherein the patient is first administered an FGFR inhibitor for a period of time, which functions to “prime” the immune system, and the patient is subsequently administered an immune checkpoint inhibitor for a period of time, e.g., until progression of disease. According to certain examples~~embodiments~~, the patient’s response to the immune checkpoint inhibitor following administration of the FGFR inhibitor is greater

than the patient's response to an immune checkpoint inhibitor in the absence of pre-treatment with an FGFR inhibitor.

[0002] According to particular examples~~embodiments~~, the present ~~invention~~ disclosure provides a method of treating cancer in a patient comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to the patient, wherein the patient has an FGFR genetic variant (in particular a FGFR mutation or FGFR fusion), and has been treated with an FGFR inhibitor. Stated another way, the method may comprise administering an FGFR inhibitor to the patient for a period of time (e.g., as a monotherapy and/or without simultaneous administration of an immune checkpoint inhibitor), and after said period of time, administering an immune checkpoint inhibitor to the patient for a subsequent period of time (e.g., as a monotherapy and/or without simultaneous administration of an FGFR inhibitor). According to particular examples~~embodiments~~, the present ~~invention~~ disclosure provides an immune checkpoint inhibitor for use in the treatment of cancer in a patient, wherein the patient has an FGFR genetic variant (in particular a FGFR mutation or FGFR fusion), and has been treated with an FGFR inhibitor. Stated another way, the present ~~invention~~ disclosure provides an FGFR inhibitor for use in the treatment of cancer in a patient for a period of time (e.g., as a monotherapy and/or without simultaneous administration of an immune checkpoint inhibitor), and after said period of time, administering an immune checkpoint inhibitor to the patient for a subsequent period of time (e.g., as a monotherapy and/or without simultaneous administration of an FGFR inhibitor). According to particular examples~~embodiments~~, the present ~~invention~~ disclosure provides the use of an immune checkpoint inhibitor for the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has an FGFR genetic variant (in particular a FGFR mutation or FGFR fusion), and has been treated with an FGFR inhibitor. In one aspect, there is provided use of an immune checkpoint inhibitor in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has an FGFR variant, and has been treated with an FGFR inhibitor. Stated another way, the present ~~invention~~ disclosure provides the use of an FGFR inhibitor for the manufacture of a medicament for the treatment of cancer in a patient for a period of time (e.g., as a monotherapy and/or without simultaneous administration of an immune checkpoint inhibitor), and after said period of time, administering an

immune checkpoint inhibitor to the patient for a subsequent period of time (e.g., as a monotherapy and/or without simultaneous administration of an FGFR inhibitor).

[0003] As used herein, administration of a drug for a period of time refers to a particular number of days, weeks, or months during which time the patient is

administered the drug according to a prescribed dosing regimen for said drug (e.g., daily, twice daily, etc.). According to particular examples~~embodiments~~, when an FGFR inhibitor is administered for a period of time, an immune checkpoint inhibitor is not administered during that period of time. Likewise, according to particular examples~~embodiments~~, when an immune checkpoint inhibitor is administered for a period of time, an FGFR inhibitor is not administered during that period of time.

[0004] According to particular examples~~embodiments~~, the FGFR inhibitor is erdafitinib or a pharmaceutically acceptable salt thereof.

[0005] According to particular examples~~embodiments~~, prior to the step of administering the immune checkpoint inhibitor, the patient did not respond and/or exhibited disease progression, in response to the FGFR inhibitor. According to particular examples~~embodiments~~, prior to the step of administering the immune checkpoint inhibitor, the patient did no longer respond to the FGFR inhibitor or the response to the FGFR inhibitor decreased.

[0006] According to particular examples~~embodiments~~, prior to the step of administering the FGFR inhibitor, the patient was treated with a first immune checkpoint inhibitor (prior to treatment with the FGFR inhibitor) and exhibited disease progression in response to said first immune checkpoint inhibitor (thus, in accordance with this embodiment, the patient did not previously respond to an immune checkpoint inhibitor, but is re-treated or "re-challenged" with the checkpoint inhibitor following exposure to the FGFR inhibitor).

[0007] According to particular examples~~embodiments~~, the immune checkpoint inhibitor is an antibody that blocks the interaction between PD-1 and PD-L1, such as pembrolizumab, atezolizumab, nivolumab, cetrelimab, or the like. It is alternatively an antibody that blocks the interaction between CTLA-4 and CD80 or CD86 on the surface of antigen-presenting cells. Non-limiting examples of immune checkpoint inhibitors that may be suitable in accordance with the present ~~invention~~ disclosure include atezolizumab, pembrolizumab, nivolumab, durvalumab, avelumab, anti-CSF1R antibody, tremelimumab, ipilimumab and the like.

[0008] According to particular examples~~embodiments~~, the patient has been diagnosed with bladder cancer, such as locally advanced or metastatic urothelial cancer; or locally advanced or metastatic urothelial cancer harboring FGFR2 or FGFR3 genetic alterations; or locally advanced or metastatic urothelial cancer harboring FGFR2 or

FGFR3 genetic alterations and who progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

[0009] According to particular examples~~embodiments~~, the FGFR variant is selected from the group consisting of FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFD1; FGFR3:BAIAP2L1; FGFR3:TACC3-Intron; FGFR3:TACC3v1; FGFR3:TACC3v3; and a combination thereof; in particular FGFR2:BICC1; FGFR2:CASP7; FGFR3:BAIAP2L1; FGFR3:TACC3v1; FGFR3:TACC3v3 and a combination thereof.

[0010] According to particular examples~~embodiments~~, the FGFR variant is a FGFR3 mutation, in particular a FGFR 3 mutation selected from the group consisting of FGFR3 R248C; FGFR3 S249C; FGFR3 G370C; FGFR3 Y373C; and a combination thereof.

[0011] According to particular examples~~embodiments~~, the FGFR inhibitor is erdafitinib and is administered in an amount of between about 8 mg and about 9 mg daily.

[0012] According to particular examples~~embodiments~~, the method is effective in achieving a complete or partial response in the patient, e.g., in reducing a tumor volume in the patient and/or stopping or reducing disease progression.

[0012a] In another aspect, there is provided use of an FGFR inhibitor in the manufacture of a medicament for the treatment of cancer in a patient diagnosed with cancer, wherein the FGFR inhibitor is effective to sensitize the patient to an immune checkpoint inhibitor, the use comprising: an FGFR inhibitor to be administered to the patient during a second period of time, wherein an immune checkpoint inhibitor is not administered during said second period of time; and after said second period of time, an immune checkpoint inhibitor to be administered to the patient during a third period of time, wherein an FGFR inhibitor is not administered to the patient during said third period of time, wherein the patient: (a) has been diagnosed with an FGFR-genetically altered cancer, (b) was administered a first immune checkpoint inhibitor during a first period of time prior to the second period of time, wherein an FGFR inhibitor was not administered to the patient during said first period of time, and (c) did not respond to the first immune checkpoint inhibitor during said first period of time.

[0012b] In another aspect, there is provided use of a FGFR inhibitor in the manufacture of a medicament for sensitizing a cancer patient to an immune checkpoint inhibitor.

[0013] In the following passages, different aspects of the disclosure are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Embodiments of the invention may be further understood when read in conjunction with the appended figures.

[0015] Fig. 1 is a graph illustrating response rate with prior systemic therapies.

[0016] Fig. 2 is a Kaplan-Meier plot of PFS following subsequent therapy to erdafitinib

[0017] Fig. 3 is a Kaplan-Meier plot of OS following subsequent therapy to erdafitinib.

What is claimed is:

1. Use ~~A method of treating cancer in a patient, the method comprising: administering a therapeutically effective amount~~ of an immune checkpoint inhibitor in the manufacture of a medicament for the treatment of cancer in a ~~to the~~ patient, wherein the patient has an FGFR variant, and has been treated with an FGFR inhibitor.

2. The use ~~method~~ according to claim 1, wherein the FGFR inhibitor is erdafitinib or a pharmaceutically acceptable salt thereof.

3. The use ~~method~~ according to any of claims 1-2, wherein before ~~prior to the step of administering~~ the immune checkpoint inhibitor is to be administered, the patient exhibited disease progression in response to the FGFR inhibitor.

4. The use ~~method~~ according to any of claims 1-3, wherein before ~~prior to the step of administering~~ the FGFR inhibitor is to be administered, the patient was treated with a first immune checkpoint inhibitor and exhibited disease progression in response to said first immune checkpoint inhibitor.

5. The use ~~method~~ according to any of claims 1-4, wherein the immune checkpoint inhibitor is an antibody that blocks the interaction between PD-1 and PD-L1.

6. The use ~~method~~ according to any of claims 1-4, wherein the immune checkpoint inhibitor is pembrolizumab, atezolizumab or nivolumab.

7. The use ~~method~~ according to any of claims 1-4, wherein the immune checkpoint inhibitor is an antibody that blocks the interaction between CTLA-4 and CD80 or CD86.

8. The use ~~method~~ according to any of claims 1-4, wherein the immune checkpoint inhibitor is selected from the group consisting of atezolizumab, pembrolizumab, nivolumab, durvalumab, avelumab, anti-CSF1R antibody, tremelimumab and ipilimumab.

9. The use ~~method~~ according to any of claims 1-8, wherein the patient has been diagnosed with an FGFR-genetically altered tumor.

10. The use ~~method~~ according to any of claims 1-8, wherein the patient has been diagnosed with bladder cancer

11. The use ~~method~~ according to any of claims 1-8, wherein the patient has been diagnosed with locally advanced or metastatic urothelial cancer.

12. The use ~~method~~ according to any of claims 1-8, wherein the patient has been diagnosed with locally advanced or metastatic urothelial cancer harboring FGFR2 or FGFR3 genetic alterations.

13. The use ~~method~~ according to any of claims 1-8, wherein the patient has been diagnosed with locally advanced or metastatic urothelial cancer harboring FGFR2 or FGFR3 genetic alterations and who progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

14. The use ~~method~~ according to any of claims 1-13, wherein the FGFR variant is selected from the group consisting of FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFD1; FGFR3:BAIAP2L1; FGFR3:TACC3-Intron; FGFR3:TACC3V1; FGFR3:TACC3V3; and a combination thereof.

15. The use ~~method~~ according to any of claims 1-14, wherein the FGFR inhibitor is erdafitinib and is to be administered in an amount of between about 8 mg and about 9 mg daily.

16. The use ~~method~~ according to any of claims 1-15, wherein the use ~~method~~ is effective in achieving a complete or partial response in the patient, e.g., in reducing a tumor volume in the patient and/or stopping or reducing disease progression.

17. The use ~~method~~ according to any of claims 1-16, wherein the ~~the~~ immune checkpoint inhibitor is cetrelimab.

18. Use of ~~A method of treating a patient diagnosed with cancer by administering~~ an FGFR inhibitor in the manufacture of a medicament for the treatment of cancer in a patient diagnosed with cancer, wherein the FGFR inhibitor is~~in an amount~~ effective to sensitize the patient to an immune checkpoint inhibitor, the use ~~method~~ comprising:

~~administering~~ an FGFR inhibitor to be administered to the patient during a second period of time, wherein an immune checkpoint inhibitor is not administered during said second period of time; and

after said second period of time, ~~administering~~ an immune checkpoint inhibitor to be administered to the patient during a third period of time, wherein an FGFR inhibitor is not administered to the patient during said third period of time, wherein the patient:

(a) has been diagnosed with an FGFR-genetically altered cancer,

(b) was administered a first immune checkpoint inhibitor during a first period of time prior to the second period of time, wherein an FGFR inhibitor was not administered to the patient during said first period of time, and

(c) did not respond to the first immune checkpoint inhibitor during said first period of time.

19. The use ~~method~~ according to claim 18, wherein the FGFR inhibitor is erdafitinib or a pharmaceutically acceptable salt thereof.

20. The use ~~method~~ according to claim 18, wherein the FGFR inhibitor is erdafitinib free base.

21. The use ~~method~~ according to any of claims 18-20, wherein the patient responded to the FGFR inhibitor during said second period of time.

22. The use ~~method~~ according to any of claims 18-21, wherein the immune checkpoint inhibitor is an antibody that blocks the interaction between PD-1 and PD-L1.

23. The use ~~method~~ according to any of claims 18-21, wherein the immune checkpoint inhibitor is pembrolizumab, atezolizumab or nivolumab.

24. The use ~~method~~ according to any of claims 18-21, wherein the immune checkpoint inhibitor is an antibody that blocks the interaction between CTLA-4 and CD80 or CD86.

25. The use ~~method~~ according to any of claims 18-21, wherein the immune checkpoint inhibitor is selected from the group consisting of atezolizumab, pembrolizumab, nivolumab, durvalumab, avelumab, anti-CSF1R antibody, tremelimumab and ipilimumab.

26. The use ~~method~~ according to any of claims 18-21, wherein the immune checkpoint inhibitor is cetrelimab.

27. The use ~~method~~ according to any of claims 18-26, wherein the patient has been diagnosed with bladder cancer

28. The use ~~method~~ according to any of claims 18-26, wherein the patient has been diagnosed with locally advanced or metastatic urothelial cancer.

29. The use ~~method~~ according to any of claims 18-26, wherein the patient has been diagnosed with locally advanced or metastatic urothelial cancer harboring FGFR2 or FGFR3 genetic alterations.

30. The use ~~method~~ according to any of claims 18-26, wherein the patient has been diagnosed with locally advanced or metastatic urothelial cancer harboring FGFR2 or FGFR3 genetic alterations and who progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

31. The use ~~method~~ according to any of claims 18-30, wherein the patient has an FGFR variant selected from the group consisting of FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFD1; FGFR3:BAIAP2L1; FGFR3:TACC3-Intron; FGFR3:TACC3v1; FGFR3:TACC3v3; and a combination thereof.

32. The use ~~method~~ according to any of claims 18-31, wherein the FGFR inhibitor is erdafitinib and is to be administered in an amount of between about 8 mg and about 9 mg daily during said second period of time.

33. The use ~~method~~ according to any of claims 18-32, wherein the method is effective in achieving a complete or partial response in the patient, e.g., in reducing a tumor volume in the patient and/or stopping or reducing disease progression.

~~34. An immune checkpoint inhibitor for use in the treatment of cancer in a patient, wherein the patient has an FGFR variant, and has been pre-treated with an FGFR inhibitor.~~

~~35. An immune checkpoint inhibitor for use according to claim 34, wherein the FGFR inhibitor is erdafitinib or a pharmaceutically acceptable salt thereof.~~

~~36. An immune checkpoint inhibitor for use according to any of claims 34-35, wherein prior to the use of the immune checkpoint inhibitor, the patient exhibited disease progression in response to the FGFR inhibitor.~~

~~37. An immune checkpoint inhibitor for use according to any of claims 34-36, wherein prior to the use of the FGFR inhibitor, the patient was treated with a first immune checkpoint inhibitor and exhibited disease progression in response to said first immune checkpoint inhibitor.~~

~~38. An immune checkpoint inhibitor for use according to any of claims 34-37, wherein the immune checkpoint inhibitor is an antibody that blocks the interaction between PD-1 and PD-L1.~~

~~39. An immune checkpoint inhibitor for use according to any of claims 34-37, wherein the immune checkpoint inhibitor is pembrolizumab, atezolizumab or nivolumab.~~

~~40. An immune checkpoint inhibitor for use according to any of claims 34-37, wherein the immune checkpoint inhibitor is an antibody that blocks the interaction between CTLA-4 and CD80 or CD86.~~

~~41. An immune checkpoint inhibitor for use according to any of claims 34-37, wherein the immune checkpoint inhibitor is selected from the group consisting of atezolizumab, pembrolizumab, nivolumab, durvalumab, avelumab, anti-CSF1R antibody, tremelimumab and ipilimumab.~~

~~42. An immune checkpoint inhibitor for use according to any of claims 34-41, wherein the patient has been diagnosed with an FGFR-genetically altered tumor.~~

~~43. An immune checkpoint inhibitor for use according to any of claims 34-41, wherein the patient has been diagnosed with bladder cancer~~

~~44. An immune checkpoint inhibitor for use according to any of claims 34-41, wherein the patient has been diagnosed with locally advanced or metastatic urothelial cancer.~~

~~45. An immune checkpoint inhibitor for use according to any of claims 34-41, wherein the patient has been diagnosed with locally advanced or metastatic urothelial cancer harboring FGFR2 or FGFR3 genetic alterations.~~

~~46. An immune checkpoint inhibitor for use according to any of claims 34-41, wherein the patient has been diagnosed with locally advanced or metastatic urothelial cancer harboring FGFR2 or FGFR3 genetic alterations and who progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.~~

~~47. An immune checkpoint inhibitor for use according to any of claims 34-46, wherein the FGFR variant is selected from the group consisting of FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFD1; FGFR3:BAIAP2L1; FGFR3:TACC3-Intron; FGFR3:TACC3V1; FGFR3:TACC3V3; and a combination thereof.~~

~~48. An immune checkpoint inhibitor for use according to any of claims 34-47, wherein the FGFR inhibitor is erdafitinib and is administered in an amount of between about 8 mg and about 9 mg daily.~~

~~49. An immune checkpoint inhibitor for use according to any of claims 34-48, wherein the use is effective in achieving a complete or partial response in the patient, e.g., in reducing a tumor volume in the patient and/or stopping or reducing disease progression.~~

~~50. An immune checkpoint inhibitor for use according to any of claims 34-49, wherein the the immune checkpoint inhibitor is cetrelimab.~~

~~51.~~34. Use of a~~A~~ FGFR inhibitor in the manufacture of a medicament for ~~use in~~ sensitizing a cancer patient to an immune checkpoint inhibitor.

~~52.~~35. ~~A FGFR inhibitor for u~~Use according to claim ~~51~~34, wherein the immune checkpoint inhibitor is an antibody that blocks the interaction between PD-1 and PD-L1.

~~53.~~36. ~~A FGFR inhibitor for u~~Use according to claim ~~51~~34, wherein the immune checkpoint inhibitor is pembrolizumab, atezolizumab or nivolumab.

~~54.~~37. ~~A FGFR inhibitor for u~~Use according to claim ~~51~~34, wherein the immune checkpoint inhibitor is an antibody that blocks the interaction between CTLA-4 and CD80 or CD86.

~~55.~~38. ~~A FGFR inhibitor for u~~Use according to claim ~~51~~34, wherein the immune checkpoint inhibitor is selected from the group consisting of atezolizumab, pembrolizumab, nivolumab, durvalumab, avelumab, anti-CSF1R antibody, tremelimumab and ipilimumab.

~~56.~~39. ~~A FGFR inhibitor for u~~Use according to claim ~~51~~34, wherein the immune checkpoint inhibitor is cetrelimab.

~~57.~~40. ~~A FGFR inhibitor for u~~Use according to any of claims ~~51-56~~34 to 39, wherein the patient has an FGFR variant.

~~58.~~41. ~~A FGFR inhibitor for u~~Use according to any of claims ~~51-56~~34 to 39, wherein the patient has been diagnosed with an FGFR-genetically altered tumor.

~~59.~~42. ~~A FGFR inhibitor for u~~Use according to any of claims ~~51-56~~34 to 39, wherein the patient has been diagnosed with bladder cancer

~~60.~~43. ~~A FGFR inhibitor for u~~Use according to any of claims ~~51-56~~34 to 39, wherein the patient has been diagnosed with locally advanced or metastatic urothelial cancer.

~~61.~~44. ~~A FGFR inhibitor for u~~Use according to any of claims ~~51-56~~34 to 39, wherein the patient has been diagnosed with locally advanced or metastatic urothelial cancer harboring FGFR2 or FGFR3 genetic alterations.

~~62.~~45. ~~A FGFR inhibitor for u~~Use according to any of claims ~~51-56~~34 to 39, wherein the patient has been diagnosed with locally advanced or metastatic urothelial cancer harboring FGFR2 or FGFR3 genetic alterations and who progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

~~63.~~46. ~~A FGFR inhibitor for u~~Use according to any of claims ~~51-56~~34 to 39, wherein the FGFR variant is selected from the group consisting of FGFR2:AFF3; FGFR2:BICC1; FGFR2:CASP7; FGFR2:CCDC6; FGFR2:OFD1; FGFR3:BAIAP2L1; FGFR3:TACC3-Intron; FGFR3:TACC3V1; FGFR3:TACC3V3; and a combination thereof.

~~64.~~47. ~~A FGFR inhibitor for u~~Use according to any of claims ~~51-63~~34 to 46, wherein the FGFR inhibitor is erdafitinib.

~~65.~~48. ~~A FGFR inhibitor for u~~Use according to any of claims ~~51-63~~34 to 46, wherein the FGFR inhibitor is erdafitinib and is to be administered in an amount of between about 8 mg and about 9 mg daily.

~~66.~~49. ~~A FGFR inhibitor for u~~Use according to any of claims ~~51-65~~34 to 48, wherein the immune checkpoint inhibitor is cetrelimab.