In one aspect, described herein is use of an FGFR inhibitor in the manufacture of a medicament for the treatment of urothelial carcinoma, wherein said treatment comprises: (a) a biological sample from a patient is to be evaluated for the presence of at least two FGFR genetic alterations, wherein: (i) two or more of the at least two FGFR genetic alterations are FGFR2 fusions; (ii) one or more of the at least two FGFR genetic alterations is an FGFR2 fusion and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion; (iii) two or more of the at least two FGFR genetic alterations are FGFR3 mutations; (iv) one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR2 fusion; or (v) one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion; and (b) the patient is to be administered an FGFR inhibitor if the at least two FGFR genetic alterations are present in the sample.

Also described herein are methods of treating urothelial carcinoma in a patient harboring at least two FGFR genetic alterations comprising, consisting of, or consisting essentially of administering a FGFR inhibitor to the patient, wherein: (a) two or more of the at least two FGFR genetic alterations are FGFR2 fusions; (b) one or more of the at least two FGFR genetic alterations is an FGFR2 fusion and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion; (c) two or more of the at least two FGFR genetic alterations are FGFR3 mutations; (d) one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR2 fusion; or (e) one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion.

In another aspect, described herein is use of an FGFR inhibitor in the manufacture of a medicament for the treatment of urothelial carcinoma in a patient harboring at least two FGFR genetic alterations, wherein said FGFR inhibitor is to be administered to the patient when: (a) two or more of the at least two FGFR genetic alterations are FGFR2 fusions; (b) one or more of the at least two FGFR genetic alterations is an FGFR2 fusion and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion; (c) two or more of the at least two FGFR genetic alterations are FGFR3 mutations; (d) one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR2 fusion; or (e) one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion.

In certain examples, the methods of treating urothelial carcinoma in a patient harboring at least two FGFR genetic alterations further comprise evaluating a biological sample from the patient for the presence of the at least two FGFR genetic alterations prior to administration of the FGFR inhibitor.

In certain examples of the methods of treating urothelial carcinoma disclosed herein, two or more of the at least two FGFR genetic alterations are FGFR2 fusions. In some examples, two or more FGFR genetic alterations comprise FGFR2-BICC1 and FGFR2-CASP7.

In certain examples of the methods of treating urothelial carcinoma disclosed herein, one or more of the at least two FGFR genetic alterations is an FGFR2 fusion and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion. In some examples, two or more FGFR genetic alterations comprise FGFR2-CASP7 and FGFR3-BAIAP2L1; FGFR2-CASP7 and FGFR3-TACC3 V1; or FGFR2-CASP7 and FGFR3-TACC3 V3.

In certain examples of the methods of treating urothelial carcinoma disclosed herein, two or more of the at least two FGFR genetic alterations are FGFR3 mutations. In some embodiments, two or more FGFR genetic alterations comprise FGFR3 G370C and FGFR3 S249C; FGFR3 R248C and FGFR3 Y373C; or FGFR3 S249C and FGFR3 Y373C.

In certain examples of the methods of treating urothelial carcinoma disclosed herein, one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR2 fusion. In some examples, two or more FGFR genetic alterations comprise FGFR3 G370C/FGFR2-BICC1; or FGFR3 S249C, FGFR3 Y373C, FGFR2-CASP7, FGFR3-BAIAP2L1, FGFR3-TACC3 V1 and FGFR3_TACC3 V3.

In certain examples of the methods of treating urothelial carcinoma disclosed herein, one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion. In some

examples, the two or more FGFR genetic alterations are FGFR3 G370C and FGFR3-TACC3 V1; FGFR3 R248C and FGFR3-TACC3 V1; FGFR3 S249C and FGFR3-BAIAP2L1; FGFR3 R248C, FGFR3 S249 and FGFR3-TACC3 V1; or FGFR3 S249C, FGFR3 Y373C, FGFR2-CASP7, FGFR3-BAIAP2L1, FGFR3-TACC3 V1 and FGFR3-TACC3 V3.

In certain examples of the methods of treating urothelial carcinoma disclosed herein, the urothelial carcinoma is locally advanced or metastatic.

In further examples of the methods of treating urothelial carcinoma disclosed herein, the biological sample is blood, lymph fluid, bone marrow, a solid tumor sample, or any combination thereof.

In some examples, the FGFR inhibitor is erdafitinib. In further examples, erdafitinib is administered daily, in particular once daily. In still further examples, erdafitinib is administered orally. In certain examples, erdafitinib is administered orally on a continuous daily dosing schedule. In some examples, erdafitinib is administered orally at a dose of about 8 mg once daily. In some examples, erdafitinib is administered orally at a dose of about 8 mg once daily on a continuous daily dosing schedule. In further examples, the dose of erdafitinib is increased from 8 mg once daily to 9 mg once daily at 14 to 21 days after initiating treatment if: (a) the patient exhibits a serum phosphate (PO_4) level that is less than about 5.5 mg/dL at 14-21 days after initiating treatment; and (b) administration of erdafitinib at 8 mg once daily resulted in no ocular disorder or (c) administration of erdafitinib at 8 mg once daily resulted in no Grade 2 or greater adverse reaction.

In certain examples of the methods of treating urothelial carcinoma disclosed herein, erdafitinib is present in a solid dosage form. In some examples, the solid dosage form is a tablet.

BRIEF DESCRIPTION OF THE DRAWINGS

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, the drawings show exemplary embodiments of the methods; however, the methods are not limited to the specific embodiments disclosed. In the drawings:

FIG. 1 represents the study scheme for the Phase 2, multicenter, open-label study to evaluate the efficacy and safety of erdafitinib in subjects with metastatic or surgically unresectable urothelial cancer harboring selected FGFR (fibroblast growth factor receptor) genetic alterations (FGFR translocations or mutations).

FIG. 2 shows patient responses to treatment with 8 mg per day continuous erdafitinib (Regimen 3) : Objective response rates (ORRs) among patient subgroups.

What is claimed:

1. Use of an FGFR inhibitor in the manufacture of a medicament for the treatment of urothelial carcinoma, wherein said treatment comprises:

(a) a biological sample from a patient is to be evaluated for the presence of at least two FGFR genetic alterations, wherein:

(i) two or more of the at least two FGFR genetic alterations are FGFR2 fusions;

(ii) one or more of the at least two FGFR genetic alterations is an FGFR2 fusion and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion;

(iii) two or more of the at least two FGFR genetic alterations are FGFR3 mutations;

(iv) one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR2 fusion; or

(v) one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion; and

(b) the patient is to be administered an FGFR inhibitor if the at least two FGFR genetic alterations are present in the sample.

2. Use of an FGFR inhibitor in the manufacture of a medicament for the treatment of urothelial carcinoma in a patient harboring at least two FGFR genetic alterations, wherein said FGFR inhibitor is to be administered to the patient when:

(a) two or more of the at least two FGFR genetic alterations are FGFR2 fusions;

(b) one or more of the at least two FGFR genetic alterations is an FGFR2 fusion and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion;

(c) two or more of the at least two FGFR genetic alterations are FGFR3 mutations;

(d) one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR2 fusion; or

(e) one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion.

3. Use of an FGFR inhibitor according to claim 1 or 2 wherein the at least two FGFR genetic alterations comprise FGFR3 G370C and FGFR3 S249C; or FGFR3 R248C and FGFR3 Y373C.

4. Use of an FGFR inhibitor according to claim 1 or 2 wherein the at least two FGFR genetic alterations comprise FGFR3 G370C and FGFR2-BICC1; FGFR3 G370C and FGFR3-TACC3 V1; FGFR3 R248C and FGFR3-TACC3 V1; or FGFR3 R248C, FGFR3 S249 and FGFR3-TACC3 V1.

5. Use of an FGFR inhibitor according to claim 2, wherein a biological sample that had been obtained from the patient is to be evaluated for the presence of the at least two FGFR genetic alterations prior to administration of the FGFR inhibitor.

6. Use of an FGFR inhibitor according to claim 1 or 2, wherein two or more of the at least two FGFR genetic alterations are FGFR2 fusions.

7. Use of an FGFR inhibitor according to claim 6, wherein the two or more FGFR genetic alterations comprise FGFR2-BICC1 and FGFR2-CASP7.

8. Use of an FGFR inhibitor according to claim 1 or 2, wherein one or more of the at least two FGFR genetic alterations is an FGFR2 fusion and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion.

9. Use of an FGFR inhibitor according to claim 8, wherein the two or more FGFR genetic alterations comprise FGFR2-CASP7 and FGFR3-BAIAP2L1; FGFR2-CASP7 and FGFR3-TACC3 V1; or FGFR2-CASP7 and FGFR3-TACC3 V3.

10. Use of an FGFR inhibitor according to claim 1 or 2, wherein two or more of the at least two FGFR genetic alterations are FGFR3 mutations.

11. Use of an FGFR inhibitor according to claim 10, wherein the two or more FGFR genetic alterations comprise FGFR3 G370C and FGFR3 S249C; FGFR3 R248C and FGFR3 Y373C; or FGFR3 S249C and FGFR3 Y373C.

12. Use of an FGFR inhibitor according to claim 1 or 2, wherein one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR2 fusion.

13. Use of an FGFR inhibitor according to claim 12, wherein the two or more FGFR genetic alterations comprise FGFR3 G370C/FGFR2-BICC1; or FGFR3 S249C, FGFR3 Y373C, FGFR2-CASP7, FGFR3-BAIAP2L1, FGFR3-TACC3 V1 and FGFR3-TACC3 V3.

14. Use of an FGFR inhibitor according to claim 1 or 2, wherein one or more of the at least two FGFR genetic alterations is an FGFR3 mutation and one or more of the at least two FGFR genetic alterations is an FGFR3 fusion.

15. Use of an FGFR inhibitor according to claim 14, wherein the two or more FGFR genetic alterations comprise FGFR3 G370C and FGFR3-TACC3 V1; FGFR3 R248C and FGFR3-TACC3 V1; FGFR3 S249C and FGFR3-BAIAP2L1; FGFR3 R248C, FGFR3 S249 and FGFR3-TACC3 V1; or FGFR3 S249C, FGFR3 Y373C, FGFR2-CASP7, FGFR3-BAIAP2L1, FGFR3-TACC3 V1 and FGFR3-TACC3 V3.

16. Use of an FGFR inhibitor according to any one of the preceding claims, wherein the urothelial carcinoma is locally advanced or metastatic.

17. Use of an FGFR inhibitor according to claim 1 or 5, wherein the biological sample is blood, lymph fluid, bone marrow, a solid tumor sample, or any combination thereof.

18. Use of an FGFR inhibitor according to any one of the preceding claims wherein the FGFR inhibitor is erdafitinib.

19. Use of an FGFR inhibitor according to claim 18, wherein erdafitinib is to be administered daily.

20. Use of an FGFR inhibitor according to claim 18 or 19, wherein erdafitinib is to be administered orally.

21. Use of an FGFR inhibitor according to any one of claims 18 to 20, wherein erdafitinib is to be administered orally on a continuous daily dosing schedule.

22. Use of an FGFR inhibitor according to any one of claims 18 to 21, wherein erdafitinib is to be administered orally at a dose of about 8 mg once daily.

23. Use of an FGFR inhibitor according to claim 22, wherein the dose of erdafitinib is to be increased from 8 mg once daily to 9 mg once daily at 14 to 21 days after initiating treatment if:

(a) the patient exhibits a serum phosphate (PO_4) level that is less than about 5.5 mg/dL at 14-21 days after initiating treatment; and

(b) administration of erdafitinib at 8 mg once daily resulted in no ocular disorder; or

(c) administration of erdafitinib at 8 mg once daily resulted in no Grade 2 or greater adverse reaction.

24. Use of an FGFR inhibitor according to any one of claims 18 to 23, wherein erdafitinib is present in a solid dosage form.

25. Use of an FGFR inhibitor according to claim 24, wherein the solid dosage form is a tablet.