FGFR TYROSINE KINASE INHIBITORS FOR THE TREATMENT OF HIGH-RISK NON-MUSCLE INVASIVE BLADDER CANCER

TECHNICAL FIELD

Disclosed herein are methods of treating high-risk non-muscle invasive bladder cancer (HR-NMIBC) comprising administering a fibroblast growth factor receptor (FGFR) inhibitor. Also disclosed are methods of treating intermediate risk non-muscle invasive bladder cancer (IR-NMIBC) comprising administering an FGFR inhibitor.

BACKGROUND

Early stage non-muscle invasive bladder cancer (NMIBC) is diagnosed in 70% of bladder cancer patients (Isharwal S, Konety B. *Indian J Urol*. 2015;31(4):289-296) of which 25% patients have poorly differentiated, low-stage tumors known as high risk non-muscle invasive bladder cancer (HR-NMIBC). Herr HW, Sogani PC. *J Urol*. 2001;166(4):1296-1299. HR-NMIBC is associated with high rates of recurrence, progression to muscle invasion, and metastasis. Sylvester RJ *et al. Eur Urol*. 2006;49:466-477. The failure rate of treatment with intravesical Bacillus Calmette-Guérin (BCG) therapy is high and recurrence is observed in about 30-40% of patients. Zlotta AR *et al. Can Urol Assoc J*. 2009: S199–S205. Erdafitinib, an oral pan-FGFR kinase inhibitor, is approved by the U.S. FDA for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC) which has susceptible FGFR3 or FGFR2 genetic alterations and who have progressed during or following at least one line of prior platinum-containing chemotherapy (PCC), including within 12 months of neoadjuvant or adjuvant PCC. Loriot Y *et al. N Engl J Med*. 2019; 381:338-348.

New cancer treatment methods are needed for FGFR mutation or fusion positive HR-NMIBC or IR-NMIBC patients, who recurred after BCG therapy.

SUMMARY

Described herein are methods of treating HR-NMIBC comprising, consisting of, or consisting essentially of, for example, administering an FGFR inhibitor, in particular at a dose of about 8 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 8 mg per day, to a patient that has been diagnosed with HR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In one aspect, there is provided use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a

medicament for the treatment of high-risk non-muscle invasive bladder cancer (HR-NMIBC) in a patient that has been diagnosed with HR-NMIBC and who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is erdafitinib.

In certain ~~embodiments~~examples,

the patient received BCG therapy prior to said administration of said FGFR inhibitor. In further examplesembodiments, the BCG therapy is adequate BCG therapy. In some examplesembodiments, the patient is unresponsive to BCG therapy. In still further examplesembodiments, the patient is BCG experienced. In certain examplesembodiments, the patient has a papillary tumor. In further examplesembodiments, the patient has carcinoma *in situ*. In some examplesembodiments, the patient did not previously receive or is ineligible for a cystectomy. In an exampleembodiment, the FGFR inhibitor is administered or is to be administered at a dose of about 6 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 6 mg per day.

Described herein are methods of treating IR-NMIBC comprising, consisting of, or consisting essentially of, for example, administering an FGFR inhibitor, in particular at a dose of about 8 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 8 mg per day, to a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In certain examplesembodiments, the patient received BCG therapy prior to said administration of said FGFR inhibitor. In further examplesembodiments, the BCG therapy is adequate BCG therapy. In some examplesembodiments, the patient is unresponsive to BCG therapy. In still further examplesembodiments, the patient is BCG experienced. In certain examplesembodiments, the patient has a papillary tumor. In further examplesembodiments, the patient has carcinoma *in situ*. In some examplesembodiments, the patient did not previously receive or is ineligible for a cystectomy. In an exampleembodiment, the FGFR inhibitor is administered or is to be administered at a dose of about 6 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 6 mg per day.

Described herein is the use of an FGFR inhibitor, in particular at a dose of about 8 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 8 mg per day, for the manufacture of a medicament for the treatment of a patient that has been diagnosed with HR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In certain examplesembodiments, the patient received BCG therapy prior to said administration of said FGFR inhibitor. In further examplesembodiments, the BCG therapy is adequate BCG therapy. In some examplesembodiments, the patient is unresponsive to BCG therapy. In still further examplesembodiments, the patient is BCG experienced. In certain examplesembodiments, the patient has a papillary tumor. In further examplesembodiments, the patient has carcinoma *in situ*. In some examplesembodiments, the patient did not previously receive or is ineligible for a cystectomy. In an exampleembodiment, the FGFR inhibitor is administered or is to be administered at a dose of

about 6 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 6 mg per day.

Described herein is the use of an FGFR inhibitor for the manufacture of a medicament for the treatment of a patient that has been diagnosed with HR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, in particular wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered at a dose of about 8 mg per day. In certain examples~~embodiments~~, the patient received BCG therapy prior to said administration of said FGFR inhibitor. In further examples~~embodiments~~, the BCG therapy is adequate BCG therapy. In some examples~~embodiments~~, the patient is unresponsive to BCG therapy. In still further examples~~embodiments~~, the patient is BCG experienced. In certain examples~~embodiments~~, the patient has a papillary tumor. In further examples~~embodiments~~, the patient has carcinoma *in situ*. In some examples~~embodiments~~, the patient did not previously receive or is ineligible for a cystectomy. In an example~~embodiment~~, the FGFR inhibitor is administered or is to be administered at a dose of about 6 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 6 mg per day.

Described herein is the use of an FGFR inhibitor, in particular at a dose of about 8 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 8 mg per day, for the manufacture of a medicament for the treatment of a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In certain examples~~embodiments~~, the patient received BCG therapy prior to said administration of said FGFR inhibitor. In further examples~~embodiments~~, the BCG therapy is adequate BCG therapy. In some examples~~embodiments~~, the patient is unresponsive to BCG therapy. In still further examples~~embodiments~~, the patient is BCG experienced. In certain examples~~embodiments~~, the patient has a papillary tumor. In further examples~~embodiments~~, the patient has carcinoma *in situ*. In some examples~~embodiments~~, the patient did not previously receive or is ineligible for a cystectomy. In an example~~embodiment~~, the FGFR inhibitor is administered or is to be administered at a dose of about 6 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 6 mg per day.

Described herein is the use of an FGFR inhibitor for the manufacture of a medicament for the treatment of a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, in particular wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered at a dose of about 8 mg per day. In certain examples~~embodiments~~, the patient received BCG therapy prior to said

administration of said FGFR inhibitor. In further examplesembodiments, the BCG therapy is adequate BCG therapy. In some examplesembodiments, the patient is unresponsive to BCG therapy. In still further examplesembodiments, the patient is BCG experienced. In certain examplesembodiments, the patient has a papillary tumor. In further examplesembodiments, the patient has carcinoma *in situ*. In some examplesembodiments, the patient did not previously receive or is ineligible for a cystectomy. In an exampleembodiment, the FGFR inhibitor is administered or is to be administered at a dose of about 6 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 6 mg per day.

Described herein is an FGFR inhibitor for use in the treatment of a patient that has been diagnosed with HR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, in particular wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered at a dose of about 8 mg per day. In certain examplesembodiments, the patient received BCG therapy prior to said administration of said FGFR inhibitor. In further examplesembodiments, the BCG therapy is adequate BCG therapy. In some examplesembodiments, the patient is unresponsive to BCG therapy. In still further examplesembodiments, the patient is BCG experienced. In certain examplesembodiments, the patient has a papillary tumor. In further examplesembodiments, the patient has carcinoma *in situ*. In some examplesembodiments, the patient did not previously receive or is ineligible for a cystectomy. In an exampleembodiment, the FGFR inhibitor is administered or is to be administered at a dose of about 6 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 6 mg per day.

Described herein is an FGFR inhibitor for use in the treatment of a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, in particular wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered at a dose of about 8 mg per day. In certain examplesembodiments, the patient received BCG therapy prior to said administration of said FGFR inhibitor. In further examplesembodiments, the BCG therapy is adequate BCG therapy. In some examplesembodiments, the patient is unresponsive to BCG therapy. In still further examplesembodiments, the patient is BCG experienced. In certain examplesembodiments, the patient has a papillary tumor. In further examplesembodiments, the patient has carcinoma *in situ*. In some examplesembodiments, the patient did not previously receive or is ineligible for a cystectomy. In an exampleembodiment, the FGFR inhibitor is administered or is to be administered at a dose of about 6 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 6 mg per day.

In further examplesembodiments, said administration of the FGFR inhibitor provides an increase in recurrence-free survival relative to a patient population with HR-NMIBC that has been administered a placebo. In certain examplesembodiments, said administration of the FGFR inhibitor provides an increase in recurrence-free survival relative to a patient population with HR-NMIBC that has been administered intravesical gemcitabine or intravesical Mitomycin C (MMC)/hyperthermic MMC. In some examplesembodiments, the patient exhibits a complete response to the FGFR inhibitor at about 6 months. In some examplesembodiments, said administration of the FGFR inhibitor provides prevention or delay of disease recurrence in the non-muscle invasive bladder cancer (NMIBC) population (HR-NMIBC or IR-NMIBC).

In certain examplesembodiments, the FGFR2 genetic alteration and/or FGFR3 genetic alteration is an FGFR3 gene mutation, FGFR2 gene fusion, or FGFR3 gene fusion. In some examplesembodiments, the FGFR3 gene mutation is R248C, S249C, G370C, Y373C, or any combination thereof. In still further examplesembodiments, the FGFR2 or FGFR3 gene fusion is FGFR3-TACC3, in particular FGFR3-TACC3 V1 or FGFR3-TACC3 V3, FGFR3-BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7, or any combination thereof.

In some examplesembodiments, said methods or uses further comprise evaluating a biological sample from the patient for the presence of at least one of a FGFR2 genetic alteration and/or FGFR3 genetic alteration prior to said administration of the FGFR inhibitor. In certain examplesembodiments, the biological sample is blood, lymph fluid, bone marrow, a solid tumor sample, urine or any combination thereof. In certain examplesembodiments, the biological sample is a blood sample. In certain examplesembodiments, the biological sample is a urine sample.

In some examplesembodiments, the FGFR inhibitor is erdafitinib. In further examplesembodiments, erdafitinib is administered daily, in particular once daily. In still further examplesembodiments, erdafitinib is administered orally. In certain examplesembodiments, erdafitinib is administered orally on a continuous daily dosing schedule. In some examplesembodiments, erdafitinib is administered orally at a dose of about 8 mg once daily. In some examplesembodiments, erdafitinib is administered orally at a dose of about 8 mg once daily on a continuous daily dosing schedule. In further examplesembodiments, the dose of erdafitinib is increased from 8 mg per day to 9 mg per day after initiating treatment if the patient exhibits a serum phosphate (PO_4) level that is less than about 5.5 mg/dL, in particular the dose of erdafitinib is increased from 8 mg per day to 9 mg per day after initiating treatment if 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. In certain examplesembodiments,

erdafitinib is present in a solid dosage form. In further examples~~embodiments~~, the solid dosage form is a tablet.

In some examples~~embodiments~~, in the methods and uses as described herein, the FGFR inhibitor, in particular erdafitinib, is administered at a dose of about 6 mg per day. In further examples~~embodiments~~, erdafitinib is administered at a dose of about 6 mg once daily. In still further examples~~embodiments~~, erdafitinib is administered orally. In certain examples~~embodiments~~, erdafitinib is administered orally on a continuous daily dosing schedule. In some examples~~embodiments~~, erdafitinib is administered orally at a dose of about 6 mg once daily. In some examples~~embodiments~~, erdafitinib is administered orally at a dose of about 6 mg once daily on a continuous daily dosing schedule. In further examples~~embodiments~~, the dose of erdafitinib is increased from 6 mg per day to 8 mg per day after initiating treatment if the patient exhibits a serum phosphate (PO_4) level that is less than about 5.5 mg/dL, in particular the dose of erdafitinib is increased from 6 mg per day to 8 mg per day after initiating treatment if 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. In certain examples~~embodiments~~, erdafitinib is present in a solid dosage form. In further examples~~embodiments~~, the solid dosage form is a tablet.

In another aspect, there is provided use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment of high-risk non-muscle invasive bladder cancer (HR-NMIBC), comprising: (a) evaluating a biological sample from a patient that has been diagnosed with HR-NMIBC for the presence of one or more fibroblast growth factor receptor (FGFR) gene alterations; and (b) wherein the FGFR inhibitor is to be administered to the patient if one or more FGFR gene alterations is present in the sample; and wherein the FGFR inhibitor is erdafitinib.

Also described herein are methods of treating HR-NMIBC comprising (a) evaluating a biological sample from a patient that has been diagnosed with HR-NMIBC for the presence of one or more FGFR gene alterations, in particular one or more FGFR2 or FGFR3 alterations; and (b) administering an FGFR inhibitor, in particular at a dose of about 8 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 8 mg per day, at a dose of about 8 mg per day to the patient if one or more FGFR gene alterations is present in the sample.

Also described herein are methods of treating HR-NMIBC comprising (a) evaluating a biological sample from a patient that has been diagnosed with HR-NMIBC for the presence of one or more FGFR gene alterations, in particular one or more FGFR2 or FGFR3 alterations; and (b) administering an FGFR inhibitor, in particular at a dose of about 6 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 6 mg per day, at a dose of about 6 mg per day to the patient if one or more FGFR gene alterations is present in the sample.

Also described herein are methods of treating IR-NMIBC comprising (a) evaluating a biological sample from a patient that has been diagnosed with IR-NMIBC for the presence of one or more FGFR gene alterations, in particular one or more FGFR2 or FGFR3 alterations;

and (b) administering an FGFR inhibitor, in particular at a dose of about 8 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 8 mg per day, to the patient if one or more FGFR gene alterations is present in the sample.

Also described herein are methods of treating IR-NMIBC comprising (a) evaluating a biological sample from a patient that has been diagnosed with IR-NMIBC for the presence of one or more FGFR gene alterations, in particular one or more FGFR2 or FGFR3 alterations; and (b) administering an FGFR inhibitor, in particular at a dose of about 6 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 6 mg per day, to the patient if one or more FGFR gene alterations is present in the sample.

In another aspect, there is provided use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment of high-risk non-muscle invasive bladder cancer (HR-NMIBC) in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is erdafitinib.

In another aspect, there is provided use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment of a patient that has been diagnosed with high-risk non-muscle invasive bladder cancer (HR-NMIBC) who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is to be administered at a dose of about 8 mg per day.

Described herein is the use of an FGFR inhibitor, in particular at a dose of about 8 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 8 mg per day, for the manufacture of a medicament for the treatment of a patient that has been diagnosed with HR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, and wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered after evaluation of a biological sample from the patient for the presence of one or more FGFR2 or FGFR3 gene alterations and if one or more FGFR2 or FGFR3 gene alterations is present in the sample.

Described herein is the use of an FGFR inhibitor, in particular at a dose of about 6 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 6 mg per day, for the manufacture of a medicament for the treatment of a patient that has been diagnosed with HR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, and wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered after evaluation of a biological sample from the patient for the presence of one or more FGFR2 or FGFR3 gene alterations and if one or more FGFR2 or FGFR3 gene alterations is present in the sample.

Described herein is the use of an FGFR inhibitor for the manufacture of a medicament for the treatment of a patient that has been diagnosed with HR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, in particular wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered at a dose of about 8 mg per day; and wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered after evaluation of a biological sample from the patient for the presence of one or more FGFR2 or FGFR3 gene alterations and if one or more FGFR2 or FGFR3 gene alterations is present in the sample.

Described herein is the use of an FGFR inhibitor for the manufacture of a medicament for the treatment of a patient that has been diagnosed with HR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, in particular wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered at a dose of about 6 mg per day; and wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered after evaluation of a biological sample from the patient for the presence of one or more FGFR2 or FGFR3 gene alterations and if one or more FGFR2 or FGFR3 gene alterations is present in the sample.

In another aspect, there is provided use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment of intermediate risk non-muscle invasive bladder cancer (IR-NMIBC) in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is erdafitinib.

Described herein is the use of an FGFR inhibitor, in particular at a dose of about 8 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 8 mg per day, for the manufacture of a medicament for the treatment of a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, and wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered after evaluation of a biological sample from the patient for the presence of one or more FGFR2 or FGFR3 gene alterations and if one or more FGFR2 or FGFR3 gene alterations is present in the sample.

In another aspect, there is provided use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment of a patient that has been diagnosed with intermediate risk non-muscle invasive bladder cancer (IR-NMIBC) who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is to be administered at a dose of about 8 mg per day.

Described herein is the use of an FGFR inhibitor, in particular at a dose of about 6 mg per day, in particular erdafitinib, more in particular erdafitinib at a dose of about 6 mg per day, for the manufacture of a medicament for the treatment of a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, and wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered after evaluation of a biological sample from the patient for the presence of one or more FGFR2 or FGFR3 gene alterations and if one or more FGFR2 or FGFR3 gene alterations is present in the sample.

Described herein is the use of an FGFR inhibitor for the manufacture of a medicament for the treatment of a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, in particular wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered at a dose of about 8 mg per day, and wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered after evaluation of a biological sample from the patient for the presence of one or more FGFR2 or FGFR3 gene alterations and if one or more FGFR2 or FGFR3 gene alterations is present in the sample.

Described herein is the use of an FGFR inhibitor for the manufacture of a medicament for the treatment of a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, in particular wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered at a dose of about 6 mg per day, and wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered after evaluation of a biological sample from the patient for the presence of one or more FGFR2 or FGFR3 gene alterations and if one or more FGFR2 or FGFR3 gene alterations is present in the sample.

Described herein is an FGFR inhibitor for use in the treatment of a patient that has been diagnosed with HR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, in particular wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered at a dose of about 8 mg per day, and wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered after evaluation of a biological sample from the patient for the presence of one or more FGFR2 or 3 gene alterations and if one or more FGFR2 or FGFR3 gene alterations is present in the sample.

Described herein is an FGFR inhibitor for use in the treatment of a patient that has been diagnosed with HR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, in particular wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered at a dose of about 6 mg per day, and wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered after evaluation of a biological sample from the patient for the presence of one or more FGFR2 or 3 gene alterations and if one or more FGFR2 or FGFR3 gene alterations is present in the sample.

Described herein is an FGFR inhibitor for use in the treatment of a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, in particular wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered at a dose of about 8 mg per day, and wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered after evaluation of a biological sample from the patient for the presence of one or more FGFR2 or 3 gene alterations and if one or more FGFR2 or FGFR3 gene alterations is present in the sample.

Described herein is an FGFR inhibitor for use in the treatment of a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, in particular wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered at a dose of about 6 mg per day, and wherein the FGFR inhibitor, in particular erdafitinib, is administered or is to be administered after evaluation of a biological sample from the patient for the presence of one or more FGFR2 or 3 gene alterations and if one or more FGFR2 or FGFR3 gene alterations is present in the sample.

In another aspect, there is provided use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment of intermediate risk non-muscle invasive bladder cancer (IR-NMIBC) in a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is erdafitinib.

Further provided herein are methods of treating intermediate risk non-muscle invasive bladder cancer (IR-NMIBC) comprising, consisting of, or consisting essentially of, for example, administering an FGFR inhibitor at a dose of about 8 mg per day to a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In certain examples~~embodiments~~, the patient has a papillary tumor. In some examples~~embodiments~~, the patient has an incomplete transurethral resection. In further examples~~embodiments~~, the patient exhibits a complete response to the FGFR inhibitor at about 3 months.

Further provided herein are methods of treating intermediate risk non-muscle invasive bladder cancer (IR-NMIBC) comprising, consisting of, or consisting essentially of, for example, administering an FGFR inhibitor at a dose of about 6 mg per day to a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In certain examples~~embodiments~~, the patient has a papillary tumor. In some examples~~embodiments~~, the patient has an incomplete transurethral resection. In further examples~~embodiments~~, the patient exhibits a complete response to the FGFR inhibitor at about 3 months.

In certain examples~~embodiments~~, the FGFR2 genetic alteration and/or FGFR3 genetic alteration is an FGFR3 gene mutation, FGFR2 gene fusion, or FGFR3 gene fusion. In some examples~~embodiments~~, the FGFR3 gene mutation is R248C, S249C, G370C, Y373C, or any combination thereof. In still further examples~~embodiments~~, the FGFR2 or FGFR3 gene fusion is FGFR3-TACC3, in particular FGFR3-TACC3 V1 or FGFR3-TACC3 V3, FGFR3-BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7, or any combination thereof. In certain examples~~embodiments~~, the FGFR inhibitor is erdafitinib.

What is claimed:

1. Use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment of ~~A method of treating~~ high-risk non-muscle invasive bladder cancer (HR-NMIBC) ~~comprising administering a fibroblast growth factor receptor (FGFR) inhibitor at a dose of about 8 mg per day to~~ in a patient that has been diagnosed with HR-NMIBC and who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is erdafitinib.

2. The use ~~The method~~ of claim 1, wherein the patient received Bacillus Calmette-Guérin (BCG) therapy prior to ~~said~~ administration of said FGFR inhibitor.

3. The use ~~The method~~ of claim 2, wherein the BCG therapy is adequate BCG therapy.

4. The use ~~The method~~ of claim 2 or 3, wherein the patient is unresponsive to BCG therapy.

5. The use ~~The method~~ of claim 2 or 3, wherein the patient is BCG experienced.

6. The use ~~The method~~ of any one of the preceding claims, wherein the patient has a papillary tumor.

7. The use~~The method~~ of any one of the preceding claims, wherein the patient has carcinoma *in situ*.

8. The use ~~The method~~ of any one of the preceding claims, wherein the patient did not previously receive or is ineligible for a cystectomy.

9. The use ~~The method~~ of any one of the preceding claims, wherein ~~said~~ administration of the FGFR inhibitor provides an increase in recurrence-free survival relative to a patient population with HR-NMIBC that has been administered a placebo.

10. The use ~~The method~~ of any one of the claims 1 to 8, wherein ~~said~~ administration of the FGFR inhibitor provides an increase in recurrence-free survival relative to a patient population with HR-NMIBC that has been administered intravesical gemcitabine or intravesical Mitomycin C (MMC)/hyperthermic MMC.

11. The use ~~The method~~ of any one of the preceding claims, wherein the patient exhibits a complete response to the FGFR inhibitor at about 6 months.

12. The use ~~The method~~ of any one of the preceding claims, wherein the FGFR2 genetic alteration and/or FGFR3 genetic alteration is an FGFR3 gene mutation, FGFR2 gene fusion, or FGFR3 gene fusion.

13. The use ~~The method~~ of claim 12, wherein the FGFR3 gene mutation is R248C, S249C, G370C, Y373C, or any combination thereof.

14. The use ~~The method~~ of claim 12, wherein the FGFR2 or FGFR3 gene fusion is FGFR3-TACC3, in particular FGFR3-TACC3 V1 or FGFR3-TACC3 V3, FGFR3-BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7, or any combination thereof.

15. The use ~~The method~~ of any one of the preceding claims, further comprising evaluating a biological sample from the patient for the presence of at least one of a FGFR2 genetic alteration and/or FGFR3 genetic alteration prior to ~~said~~ administration of the FGFR inhibitor.

16. The use ~~The method~~ of claim 15, wherein the biological sample is blood, lymph fluid, bone marrow, a solid tumor sample, or any combination thereof.

17. The use ~~The method~~ of any one of the preceding claims wherein the FGFR inhibitor is to be administered at a dose of about 6 mg per day~~erdafitinib~~.

18. The use ~~The method~~ of claim 17, wherein the FGFR inhibitor~~erdafitinib~~ is to be administered daily.

19. The use ~~The method~~ of claim 17 or 18, wherein the FGFR inhibitor~~erdafitinib~~ is to be administered orally.

20. The use ~~The method~~ of any one of claims 17 to 19, wherein the FGFR inhibitor~~erdafitinib~~ is to be administered orally on a continuous daily dosing schedule.

21. The use ~~The method~~ of any one of claims 17 to 19, wherein the FGFR inhibitor~~erdafitinib~~ is to be administered at a dose of about 6~~8~~ mg once daily.

~~22. The method of any one of claims 17 to 19, wherein the dose of erdafitinib is increased from 8 mg per day to 9 mg per day after initiating treatment if the patient exhibits a serum phosphate (PO_4) level that is less than about 5.5 mg/dL.~~

~~23~~22. The use ~~The method~~ of any one of claims 17 to ~~22~~21, wherein the FGFR inhibitor~~erdafitinib~~ is to be administered in a solid dosage form.

~~24~~23. The use ~~The method~~ of claim ~~23~~22, wherein the solid dosage form is a tablet.

~~25~~24. Use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment of ~~A method of treating~~ high-risk non-muscle invasive bladder cancer (HR-NMIBC), comprising:

(a) evaluating a biological sample from a patient that has been diagnosed with HR-NMIBC for the presence of one or more fibroblast growth factor receptor (FGFR) gene alterations; and

(b) wherein the FGFR inhibitor is to be administered~~administering a fibroblast growth factor receptor (FGFR) inhibitor at a dose of about 8 mg per day~~ to the patient if one or more FGFR gene alterations is present in the sample;
and wherein the FGFR inhibitor is erdafitinib.

~~26~~25. ~~A method of treating intermediate risk non-muscle invasive bladder cancer (IR-NMIBC) comprising administering a fibroblast growth factor receptor (FGFR) inhibitor at a dose of about 8 mg per day to a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration.~~ Use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment of intermediate risk non-muscle invasive bladder cancer (IR-NMIBC) in a patient that has been diagnosed with IR-NMIBC who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is erdafitinib.

~~27~~26. The use ~~The method~~ of claim ~~26~~25, wherein the patient has a papillary tumor.

~~28~~27. The use ~~The method~~ of claim ~~26~~25 or ~~27~~26, wherein the patient has an incomplete transurethral resection.

~~29~~28. The use ~~The method~~ of any one of claims ~~26~~25 to ~~28~~27, wherein the patient exhibits a complete response to the FGFR inhibitor at about 3 months.

~~30~~29. The use ~~The method~~ of any one of claims ~~26~~25 to ~~29~~28, wherein the FGFR2 genetic alteration and/or FGFR3 genetic alteration is an FGFR3 gene mutation, FGFR2 gene fusion, or FGFR3 gene fusion.

~~31~~30. The use ~~The method~~ of claim ~~30~~29, wherein the FGFR3 gene mutation is R248C, S249C, G370C, Y373C, or any combination thereof.

~~32~~31. The use ~~The method~~ of claim ~~30~~29, wherein the FGFR2 or FGFR3 gene fusion is FGFR3-TACC3, in particular FGFR3-TACC3 V1 or FGFR3-TACC3 V3, FGFR3-BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7, or any combination thereof.

~~33~~32. The use ~~The method~~ of any one of the claims ~~26~~25 to ~~32~~31, wherein the FGFR inhibitor is to be administered at a dose of about 6 mg per day~~erdafitinib~~.

~~34~~33. Use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment ~~A fibroblast growth factor receptor (FGFR) inhibitor for use in the treatment~~ of high-risk non-muscle invasive bladder cancer (HR-NMIBC) in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is erdafitinib~~to be administered at a dose of about 8 mg per day~~.

~~35~~34. Use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment ~~A fibroblast growth factor receptor (FGFR) inhibitor for use in the treatment~~ of intermediate risk non-muscle invasive bladder cancer (IR-NMIBC) in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is erdafitinib~~to be administered at a dose of about 8 mg per day~~.

~~36. The use of a fibroblast growth factor receptor (FGFR) inhibitor for the manufacture of a medicament for the treatment of a patient that has been diagnosed with high-risk non-muscle invasive bladder cancer (HR-NMIBC) who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is to be administered at a dose of about 8 mg per day.~~

~~37. The use of a fibroblast growth factor receptor (FGFR) inhibitor for the manufacture of a medicament for the treatment of a patient that has been diagnosed with intermediate risk non-muscle invasive bladder cancer (IR-NMIBC) who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is to be administered at a dose of about 8 mg per day.~~

~~38~~35. The use~~A fibroblast growth factor receptor (FGFR) inhibitor for use or the use of a fibroblast growth factor receptor (FGFR) inhibitor~~ of any one of claims ~~34~~33 to ~~37~~34,

wherein the patient received Bacillus Calmette-Guérin (BCG) therapy prior to ~~said~~ administration of said FGFR inhibitor.

~~39~~36. The use ~~A fibroblast growth factor receptor (FGFR) inhibitor for use or the use of a fibroblast growth factor receptor (FGFR) inhibitor~~ of claim ~~38~~35, wherein the BCG therapy is adequate BCG therapy.

~~40~~37. The use ~~A fibroblast growth factor receptor (FGFR) inhibitor for use or the use of a fibroblast growth factor receptor (FGFR) inhibitor~~ of claim ~~38~~35 or ~~39~~36, wherein the patient is unresponsive to BCG therapy.

~~41~~38. The use ~~A fibroblast growth factor receptor (FGFR) inhibitor for use or the use of a fibroblast growth factor receptor (FGFR) inhibitor~~ of claim ~~38~~35 or ~~39~~36, wherein the patient is BCG experienced.

~~42~~39. The use ~~A fibroblast growth factor receptor (FGFR) inhibitor for use or the use of a fibroblast growth factor receptor (FGFR) inhibitor~~ of any one of claims ~~34~~33 to ~~41~~38, wherein the patient has a papillary tumor.

~~43~~40. The use ~~A fibroblast growth factor receptor (FGFR) inhibitor for use or the use of a fibroblast growth factor receptor (FGFR) inhibitor~~ of any one of claims ~~34~~33 to ~~42~~39, wherein the patient has carcinoma *in situ*.

~~44~~41. The use ~~A fibroblast growth factor receptor (FGFR) inhibitor for use or the use of a fibroblast growth factor receptor (FGFR) inhibitor~~ of any one of claims ~~34~~33 to ~~43~~40, wherein the patient did not previously receive or is ineligible for a cystectomy.

~~45~~42. The use ~~A fibroblast growth factor receptor (FGFR) inhibitor for use or the use of a fibroblast growth factor receptor (FGFR) inhibitor~~ of any one of claims ~~34 33~~ to ~~44~~41, wherein the FGFR2 genetic alteration and/or FGFR3 genetic alteration is an FGFR3 gene mutation, FGFR2 gene fusion, or FGFR3 gene fusion.

~~46~~43. The use ~~A fibroblast growth factor receptor (FGFR) inhibitor for use or the use of a fibroblast growth factor receptor (FGFR) inhibitor~~ of claim ~~45~~42, wherein the FGFR3 gene mutation is R248C, S249C, G370C, Y373C, or any combination thereof.

~~4744~~. The use ~~A fibroblast growth factor receptor (FGFR) inhibitor for use or the use of a fibroblast growth factor receptor (FGFR) inhibitor~~ of claim ~~45~~42, wherein the FGFR2 or FGFR3 gene fusion is FGFR3-TACC3, in particular FGFR3-TACC3 V1 or FGFR3-TACC3 V3, FGFR3-BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7, or any combination thereof.

~~4845~~. The use ~~A fibroblast growth factor receptor (FGFR) inhibitor for use or the use of a fibroblast growth factor receptor (FGFR) inhibitor~~ of any one of claims ~~34~~33 to ~~47~~44, wherein the FGFR inhibitor is ~~erdafitinib~~to be administered at a dose of about 6 mg per day.

46. Use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment of a patient that has been diagnosed with high-risk non-muscle invasive bladder cancer (HR-NMIBC) who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is to be administered at a dose of about 8 mg per day.

47. Use of a fibroblast growth factor receptor (FGFR) inhibitor in the manufacture of a medicament for the treatment of a patient that has been diagnosed with intermediate risk non-muscle invasive bladder cancer (IR-NMIBC) who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is to be administered at a dose of about 8 mg per day.