FGFR TYROSINE KINASE INHIBITORS AND ANTI-PD1 AGENTS FOR THE TREATMENT OF UROTHELIAL CARCINOMA

TECHNICAL FIELD

Disclosed herein are methods of treating urothelial carcinoma. In particular, the disclosed methods include combination therapies for the treatment of urothelial carcinoma comprising administering a fibroblast growth factor receptor (FGFR) inhibitor and an anti-PD1 antibody or antigen binding fragment thereof.

BACKGROUND

Bladder cancer is the most common malignancy involving the urinary system. Urothelial carcinoma (UC) is the predominant histologic type and the fourth most common cancer in men and eleventh most common in women. Cancer Genome Atlas Research Network. *Nature*. 2014 Mar 20;507(7492):315-322. Patients with locally advanced UC or metastatic or surgically unresectable UC (mUC) have poor outcomes with second-line therapies following relapse on cisplatin-based chemotherapy. Yafi FA, *et al. Curr Oncol.* 2011;18:e25-e34.

FGFR alterations are common in patients with mUC, particularly in the luminal I subtype, and can cause constitutive FGFR signaling that may contribute to carcinogenesis. Haugsten EM, et al. Mol Cancer. 2018;8:1439-1452. As many as 20% of patients with mUC have FGFR alterations, and FGFR mutations are even more frequent (37%) in patients with upper tract UC. Knowles MA, *et al. Nat Rev Cancer*. 2015;15:25-41. Li Q, et al. Curr Urol Rep. 2016;17:12; 7.

New cancer treatment methods are needed for FGFR mutation or fusion positive patients with urothelial carcinoma.

SUMMARY

Described herein are methods of treating urothelial carcinoma comprising, for example, administering a 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, in combination with an anti-PD1 antibody or antigen binding fragment thereof, in particular at a dose of about 240 mg every two weeks, in particular cetrelimab, to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration

and/or FGFR3 genetic alteration. In certain embodiments, the urothelial carcinoma is locally advanced or metastatic.

Described herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks, in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In certain embodiments, the urothelial carcinoma is locally advanced or metastatic.

Described herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks. In certain embodiments, the urothelial carcinoma is locally advanced or metastatic.

Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks. In certain embodiments, the urothelial carcinoma is locally advanced or metastatic.

Described herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks. In certain embodiments, the urothelial carcinoma is locally advanced or metastatic.

Described herein is the use of an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with a FGFR inhibitor at a dose of

about 8 mg per day. In certain embodiments, the urothelial carcinoma is locally advanced or metastatic.

Described herein are methods of treating urothelial carcinoma comprising, for example, administering erdafitinib at a dose of about 8 mg per day, in particular orally, in combination with an anti-PD1 antibody or antigen binding fragment thereof, in particular cetrelimab, in particular cetrelimab at a dose of about 240 mg every two weeks, in particular cetrelimab at a dose of about 240 mg every two weeks IV, to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In certain embodiments, the urothelial carcinoma is locally advanced or metastatic.

Described herein is a combination of erdafitinib at a dose of about 8 mg per day, in particular orally, and an anti-PD1 antibody or antigen binding fragment thereof, in particular cetrelimab, in particular cetrelimab at a dose of about 240 mg every two weeks, in particular cetrelimab at a dose of about 240 mg every two weeks IV, in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In certain embodiments, the urothelial carcinoma is locally advanced or metastatic.

Described herein is erdafitinib for use in combination with an anti-PD1 antibody or antigen binding fragment thereof for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein erdafitinib is administered or is to be administered at a dose of about 8 mg per day, in particular orally, and wherein in a particular embodiment the anti-PD1 antibody or antigen binding fragment thereof is cetrelimab, and wherein in a particular embodiment cetrelimab is administered or is to be administered at a dose of about 240 mg every two weeks IV. In certain embodiments, the urothelial carcinoma is locally advanced or metastatic.

Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with erdafitinib for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein erdafitinib is administered or is to be administered at a dose of about 8 mg per day, in particular orally, and wherein in a particular embodiment, the anti-PD1 antibody or antigen binding fragment thereof is cetrelimab, and wherein in a particular embodiment cetrelimab is administered or is to be administered at a dose of about 240 mg every two weeks IV. In certain embodiments, the urothelial carcinoma is locally advanced or metastatic.

Described herein is the use of erdafitinib at a dose of about 8 mg per day, in particular orally, for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein erdafitinib is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof, in particular cetrelimab, in particular cetrelimab at a dose of about 240 mg every two weeks IV. In certain embodiments, the urothelial carcinoma is locally advanced or metastatic.

Described herein is the use of an anti-PD1 antibody or antigen binding fragment thereof, in particular cetrelimab, in particular cetrelimab at a dose of about 240 mg every two weeks IV for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with erdafitinib at a dose of about 8 mg per day, in particular orally. In certain embodiments, the urothelial carcinoma is locally advanced or metastatic. In further embodiments, administration of the FGFR inhibitor in combination with the anti-PD1 antibody or antigen binding fragment thereof provides improved anti-tumor activity as measured by objective response rate relative to a patient that has been diagnosed with urothelial carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof. In some embodiments, administration of the FGFR inhibitor in combination with the anti-PD1 antibody or antigen binding fragment thereof does not result in hematological toxicity, in particular does not result in hematological toxicity of Grade 3 or higher. In still further embodiments, administration of the FGFR inhibitor in combination with the anti-PD1 antibody or antigen binding fragment thereof does not result in non-hematological toxicity of Grade 3 or higher.

In certain embodiments, the patient received at least one systemic therapy for the treatment of urothelial carcinoma prior to administration of said FGFR inhibitor and said anti-PD1 antibody or antigen binding fragment thereof. In some embodiments, the at least one systemic therapy for the treatment of urothelial carcinoma is platinum-containing chemotherapy. In further embodiments, the urothelial carcinoma progressed during or following at least one line of the platinum-containing chemotherapy. In still further embodiments, the platinum-containing chemotherapy is neoadjuvant platinum-containing chemotherapy or adjuvant platinum-containing chemotherapy. In even further embodiments, the urothelial carcinoma progressed within 12 months following at least one line of the

neoadjuvant platinum-containing chemotherapy or adjuvant platinum-containing chemotherapy.

In some embodiments, the patient did not receive systemic therapy for the treatment of urothelial carcinoma prior to said administration of said FGFR inhibitor and said anti-PD1 antibody or antigen binding fragment thereof. In certain embodiments, the patient is cisplatin-ineligible. In further embodiments, the patient has an ECOG performance status of less than or equal to 2.

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

In some embodiments, said methods or uses further comprise evaluating a biological sample from the patient for the presence of one or more FGFR2 or FGFR3 genetic alterations prior to administration of said FGFR inhibitor and said anti-PD1 antibody or antigen binding fragment thereof. In certain embodiments, the biological sample is blood, lymph fluid, bone marrow, a solid tumor sample, or any combination thereof.

In further embodiments, the FGFR inhibitor is erdafitinib. In further embodiments, erdafitinib is administered daily, in particular once daily. In still further embodiments, erdafitinib is administered orally. In certain embodiments, erdafitinib is administered orally on a continuous daily dosing schedule. In some embodiments, erdafitinib is administered orally at a dose of about 8 mg once daily. In some embodiments, erdafitinib is administered orally at a dose of about 8 mg once daily on a continuous daily dosing schedule. In further embodiments, 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 certain embodiments, erdafitinib is present in a solid dosage form. In further embodiments, the solid dosage form is a tablet.

In certain embodiments, the anti-PD1 antibody or antigen binding fragment thereof is cetrelimab. In further embodiments, the cetrelimab is administered by intravenous infusion. In still further embodiments, the cetrelimab is administered at a dose of about 240 mg: (a) once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks; (b) once every two weeks; (c) once every three weeks; (d)

once every four weeks; (e) once every five weeks; or (f) once every six weeks. In further embodiments, the cetrelimab is administered at a dose of about 240 mg, in particular 240 mg once every two weeks in cycle 1 to 4 of treatment. In further embodiments, the cetrelimab is administered at a dose of about 480 mg, in particular 480 mg once every 4 weeks. In further embodiments, the cetrelimab is administered at a dose of about 480 mg, in particular 480 mg once every 4 weeks, as of cycle 5 of treatment and beyond. In further embodiments, the cetrelimab is administered at a dose of about 360 mg, in particular 360 mg once every three weeks.

Also described herein are methods of improving objective response rate in a patient with urothelial carcinoma relative to a patient that has been diagnosed with urothelial carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof, said method comprising administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg (e.g. every two weeks) to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg (e.g. every two weeks) in cycle 1 to 4 of treatment.

Further provided herein are methods of treating urothelial carcinoma comprising: (a) evaluating a biological sample from a patient with urothelial carcinoma for the presence of one or more FGFR gene alterations, in particular FGFR2 or 3 gene alterations; and (b) administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg (e.g. every two weeks) to the patient if one or more FGFR gene alterations, in particular FGFR2 or 3 gene alterations, is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg (e.g. every two weeks) in cycle 1 to 4 of treatment.

Further provided herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg (e.g. every two weeks), in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg (e.g. every two weeks) in cycle 1 to 4 of treatment.

Further provided herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg (e.g. every two weeks), and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg (e.g. every two weeks) in cycle 1 to 4 of treatment.

Further provided herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg (e.g. every two weeks), and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg (e.g. every two weeks) in cycle 1 to 4 of treatment.

Further provided herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg (e.g. every two weeks), and

wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg (e.g. every two weeks) in cycle 1 to 4 of treatment.

Further provided herein is the use of an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg (e.g. every two weeks) for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with a FGFR inhibitor at a dose of about 8 mg per day, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg (e.g. every two weeks) in cycle 1 to 4 of treatment.

Also described herein are methods of improving objective response rate in a patient with urothelial carcinoma relative to a patient that has been diagnosed with urothelial carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof, said method comprising administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg (e.g. every four weeks) to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg (e.g. every four weeks) as of cycle 5 of treatment and beyond.

Further provided herein are methods of treating urothelial carcinoma comprising: (a) evaluating a biological sample from a patient with urothelial carcinoma for the presence of one or more FGFR gene alterations, in particular FGFR2 or 3 gene alterations; and (b) administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg (e.g. every four weeks) to the patient if one or more FGFR gene alterations, in particular FGFR2 or 3 gene

alterations, is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg (e.g. every four weeks) as of cycle 5 of treatment and beyond.

Further provided herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg (e.g. every four weeks), in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg (e.g. every four weeks) as of cycle 5 of treatment and beyond.

Further provided herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg (e.g. every four weeks), and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg (e.g. every four weeks) as of cycle 5 of treatment and beyond.

Further provided herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg (e.g. every four weeks), and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg (e.g. every four weeks) as of cycle 5 of treatment and beyond.

Further provided herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg (e.g. every four weeks), and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg (e.g. every four weeks) as of cycle 5 of treatment and beyond.

Further provided herein is the use of an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg (e.g. every four weeks) for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with a FGFR inhibitor at a dose of about 8 mg per day, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg (e.g. every four weeks) as of cycle 5 of treatment and beyond.

As described herein, a cycle is defined as a 4 week period; or a cycle is defined as a 28 day period.

Also described herein are methods of improving objective response rate in a patient with urothelial carcinoma relative to a patient that has been diagnosed with urothelial carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof, said method comprising administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding

fragment thereof at a dose of about 360 mg (e.g. every three weeks) to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Further provided herein are methods of treating urothelial carcinoma comprising: (a) evaluating a biological sample from a patient with urothelial carcinoma for the presence of one or more FGFR gene alterations, in particular FGFR2 or 3 gene alterations; and (b) administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg (e.g. every three weeks) to the patient if one or more FGFR gene alterations, in particular FGFR2 or 3 gene alterations, is present in the sample. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Further provided herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg (e.g. every three weeks), in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to

be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Further provided herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 360 mg (e.g. every three weeks), and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Further provided herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 360 mg (e.g. every three weeks), and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin

or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Further provided herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg (e.g. every three weeks), and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Further provided herein is the use of an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg (e.g. every three weeks) for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with a FGFR inhibitor at a dose of about 8 mg per day, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum

chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

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

FIG. 1 is a study schematic for the phase 1b/2, multicenter, open-label dose escalation study to evaluate erdafitinib plus cetrelimab. ERDA stands for erdafitinib, CET stands for cetrelimab, UpT stands for uptitration, C1D1 stands for Cycle 1 Day 1, C2D2 stands for Cycle 2 Day 2, R stands for randomized, and DL stands for dose level. Footnote (a): 8 mg with or without uptitration (DL2 and DL2A) may be considered as the same dose level. Footnote (b): No UpT = no uptitration allowed. Footnote (c): UpT = uptitration of ERDA (after RP2D, uptitration of ERDA dose from 8 mg to 9 mg on C1D15 based on phosphate [PO_4] level) was permitted. Footnote (d): The RP2D was originally determined to be 8 mg ERDA UpT + CET, but after an amendment to the protocol, this was revised to 8 mg ERDA no UpT for phase 2 of the study.

FIG. 2 is a graph showing maximal percentage reduction of sum of target lesion diameters from baseline for the safety analysis population. The y-axis is maximal reduction from baseline (%) and the x-axis is patient. For a response to qualify as stable disease (SD), follow-up measurements must have met the stable disease criteria at least once at a minimum interval not less than 6 weeks after first dose of study drug. One patient was not response evaluable as they did not have measurable disease at baseline, and therefore this patient was excluded from the analysis for response. As of the time of data cutoff, 1 other patient did not have a subsequent on-study tumor assessment. To be counted as a PR, a second scan to confirm response was required. Bars are designated uPR (unconfirmed PR), SD (stable disease), PR (partial response) and NE (not evaluable).

FIG. 3 is a graph of percent change of tumor reduction (target lesion) over time from baseline for the safety analysis population. The y-axis is percent tumor reduction from baseline (%), and the x-axis is tumor assessment in days.

FIG. 4A, **FIG. 4B** and **FIG. 4C** illustrate proportions of T cells compared to baseline in a Phase 1b study to evaluate safety, efficacy, pharmacokinetics, and pharmacodynamics of erdafitinib plus cetrelimab.

FIG. 5A, **FIG. 5B** and **FIG. 5C** illustrate proportions of T cells compared to baseline in a Phase 1b study to evaluate safety, efficacy, pharmacokinetics, and pharmacodynamics of erdafitinib plus cetrelimab.

FIG. 6A and **FIG. 6B** illustrate proportions of T cells compared to baseline in a Phase 1b study to evaluate safety, efficacy, pharmacokinetics, and pharmacodynamics of erdafitinib plus cetrelimab.

FIG. 7A, **FIG. 7B** and **FIG. 7C** illustrate proportions of T cells compared to baseline in a Phase 2 study to evaluate safety, efficacy, pharmacokinetics, and pharmacodynamics of erdafitinib plus cetrelimab.

FIG. 8A, **FIG. 8B** and **FIG. 8C** illustrate proportions of T cells compared to baseline in a Phase 2 study to evaluate safety, efficacy, pharmacokinetics, and pharmacodynamics of erdafitinib plus cetrelimab.

FIG. 9A and **FIG. 9B** illustrate proportions of T cells compared to baseline in a Phase 2 study to evaluate safety, efficacy, pharmacokinetics, and pharmacodynamics of erdafitinib plus cetrelimab.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

It is to be appreciated that certain features of the invention which are, for clarity, described herein in the context of separate embodiments may also be provided in combination in a single embodiment. That is, unless obviously incompatible or specifically excluded, each individual embodiment is deemed to be combinable with any other embodiment(s) and such a combination is considered to be another embodiment. Conversely, various features of the invention that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any sub-combination. Finally, although an embodiment may be described as part of a series of steps or part of a more general structure, each said step may also be considered an independent embodiment in itself, combinable with others.

Certain Terminology

The transitional terms "comprising", "consisting essentially of", and "consisting" are intended to connote their generally in accepted meanings in the patent vernacular; that is, (i) "comprising", which is synonymous with "including", "containing", or "characterized by", is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; (ii) "consisting of" excludes any element, step, or ingredient not specified in the claim or embodiment; and (iii) "consisting essentially of" limits the scope of a claim or embodiment to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention or embodiment. More specifically, the basic and novel characteristics relates to the ability of the method to provide at least one of the benefits described herein, including but not limited to the ability to improve the survivability of the human population relative to the survivability of the comparative human population described elsewhere herein. Embodiments described in terms of the phrase "comprising" (or its equivalents), also provide, as embodiments, those which are independently described in terms of "consisting of" and "consisting essentially of".

When a value is expressed as an approximation by use of the descriptor “about”, it will be understood that the particular value forms another embodiment. If not otherwise specified, the term “about” signifies a variance of ±10% of the associated value, but additional embodiments include those where the variance may be ±5%, ±15%, ±20%, ±25%, or ±50%, in particular the term “about” signifies a variance of ±5% or ±10% of the associated value, more in particular ±5%.

When a list is presented, unless stated otherwise, it is to be understood that each individual element of that list, and every combination of that list, is a separate embodiment. For example, a list of embodiments presented as "A, B, or C" is to be interpreted as including the embodiments, "A," "B," "C," "A or B," "A or C," "B or C," or "A, B, or C."

As used herein, the singular forms “a,” “an,” and “the” include the plural.

The following abbreviations are used throughout the disclosure: FGFR (fibroblast growth factor receptor); FGFR3-TACC3 V1 (fusion between genes encoding FGFR3 and transforming acidic coiled-coil containing protein 3 variant 1); FGFR3-TACC3 V3 (fusion between genes encoding FGFR3 and transforming acidic coiled-coil containing protein 3 variant 3); FGFR3-BAIAP2L1 (fusion between genes encoding FGFR3 and brain-specific angiogenesis inhibitor 1-associated protein 2-like protein 1); FGFR2-BICC1 (fusion between genes encoding FGFR2 and bicaudal C homolog 1); FGFR2-CASP7 (fusion between genes encoding FGFR2 and caspase 7).

As used herein, “patient” is intended to mean any animal, in particular, mammals. Thus, the methods are applicable to human and nonhuman animals, although most preferably with humans. The terms “patient” and “subject” and “human” may be used interchangeably.

The terms “treat” and "treatment" refer to the treatment of a patient afflicted with a pathological condition and refers to an effect that alleviates the condition by killing the cancerous cells, but also to an effect that results in the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (*i.e.,* prophylaxis) is also included.

“Therapeutically effective amount” refers to an amount effective, at doses and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount may vary depending on factors such as the disease state, age, sex, and weight of the individual, and the ability of a therapeutic or a combination of therapeutics to elicit a desired response in the individual. Exemplary indicators of an effective therapeutic or combination of therapeutics that include, for example, improved well-being of the patient.

The term “dosage” refers to the information of the amount of the therapeutic to be taken by the subject and the frequency of the number of times the therapeutic is to be taken by the subject.

The term “dose” refers to the amount or quantity of the therapeutic to be taken each time.

The term "cancer" as used herein refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread).

The terms "co-administration" or the like, as used herein, encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

The term "pharmaceutical combination" as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non- fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, *e.g.*, erdafitinib and a co-agent, are both administered to a patient simultaneously in the form of a single unit or single dosage form. The term "non-fixed combination" means that the active ingredients, *e.g.*, erdafitinib and a co-agent, are administered to a patient as separate units or separate dosage forms, either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides therapeutically effective levels of the two active ingredients in the body of the human. The latter also applies to cocktail therapy, *e.g.*, the administration of three or more active ingredients.

The term "continuous daily dosing schedule" refers to the administration of a particular therapeutic agent without any drug holidays from the particular therapeutic agent. In some embodiments, a continuous daily dosing schedule of a particular therapeutic agent comprises administration of a particular therapeutic agent every day at roughly the same time each day.

The term “objective response rate” or “overall response rate” (ORR), which are used interchangeably herein, is defined as the percentage of participants with PR or CR as defined by RECIST 1.1, as assessed by the investigator

The term “disease control rate” (DCR) is defined as the percentage of participants who have achieved SD and confirmed and unconfirmed CR and PR.

The term “dose limiting toxicities” (DLT) is defined as hematological / non hematological toxicity of Grade 3 or higher. Toxicities described herein are graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. The criteria for non-hematological toxicities, as described herein, are provided in the Table 1:

Table 1: Criteria for non-hematological toxicity

Any Grade 3	**Exceptions**
	Asthenia, anorexia, fever, or constipation
	Fatigue that improves to Grade ≤ 2 in ≤ 7 days
	Nausea lasting for ≤ 7 days responding to BSC[a]
	Vomiting and diarrhea that resolves in ≤ 3 with BSC[a]
	Laboratory abnormalities that do not require hospitalization and are not felt to be clinically significant by the investigator
	Tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) that improves to Grade ≤ 2 in ≤ 7 days
	Elevation in AST or ALT for ≤ 7 days
Any Grade 4	None
Any Grade 5	None
Elevation in AST or ALT >3x ULN meeting criteria for Hy's law[b]	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSC = best supportive care; ULN = upper limit of normal. a Best supportive care (including electrolyte and hormone supplementation where clinically applicable) according to institutional standards. b Concurrent elevation of bilirubin >2 times institutional ULN without initial evidence of cholestasis and no alternative etiology for AST/ALT elevation.

The criteria for hematological toxicities, as described herein, are provided in Table 2:

Table 2: Criteria for Hematological Toxicity

Neutrophil count decreased: Grade 4 for >7 days
Febrile neutropenia: Grace ≥ 3 or 4
Platelet count decreased: Grade 3 with clinically significant bleeding or Grade 4
Any Grade 5 toxicity

The term "adverse event" is any untoward medical event that occurs in a participant administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product.

The term "complete response" (CR) is defined in the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, *i.e.*, disappearance of all target lesions, with no remnant present and no viable tumor seen on histopathological examination.

The term “partial response” (PR) is defined in the RECIST Version 1.1, *i.e.* at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

The term “stable disease” (SD) is defined in the RECIST Version 1.1, *i.e.* neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

The term “progressive disease” (PD) is defined in the RECIST Version 1.1, *i.e.* at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

The term “duration of response” (DoR) is defined as the time from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease (or relapse for participants who experience CR during the study) or death.

The term “time to response” (TTR) is defined as the time from the date of randomization to the date of initial documentation of a response (CR or PR).

The term “overall survival” (OS) is defined as the time from the date of randomization to the date of the participant's death resulting from any cause.

The term “progression-free survival” (PFS) is defined as the duration from the date of randomization until the date of first documented evidence of progressive disease (or relapse for participants who experience CR during the study) or death, whichever comes first.

The term “Maximum Observed Analyte Concentration” (Cmax) is defined as is the maximum observed analyte concentration.

The term "placebo" as used herein means administration of a pharmaceutical composition that does not include an FGFR inhibitor, in particular erdafitinib, andanti-PD1 antibody or antigen binding fragment thereof, in particular, cetrelimab.

The term “randomization” as it refers to a clinical trial refers to the time when the patient is confirmed eligible for the clinical trial and gets assigned to a treatment arm.

The terms "kit" and "article of manufacture" are used as synonyms.

The term “biological sample” refers to any sample from a patient in which cancerous cells can be obtained and detection of a FGFR genetic alteration is possible. Suitable biological samples include, but are not limited to, blood, lymph fluid, bone marrow, a solid

tumor sample, or any combination thereof. In some embodiments, the biological sample can be formalin-fixed paraffin-embedded tissue (FFPET).

The term “antagonist” or “antagonistic” refers to an anti-PD1 antibody which upon binding to PD-1 suppresses at least one biological activity mediated by PD-1 ligand PD-L1 or PD-L2. The anti-PD-1 antibody is an antagonist when the at least one biological activity mediated by PD-L1 or PD-L2 is suppressed by at least about 20%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% greater than in the absence of the antagonist (e.g., negative control), or when the suppression is statistically significant when compared to the suppression in the absence of the antagonist. A typical biological activity that is mediated by PD-L1 or PD-L2 binding to PD-1 is inhibition of antigen-specific CD4 + and/or CD8 + T cells. Therefore, antagonistic antibody relieves PD-L1 mediated suppression resulting in enhancement of immune responses.

The term “anti-PD-1 antibody” refers to an antibody that blocks the interaction between PD-1 and PD-L1, e.g., by specifically binding to PD-1. As used here, "block(s) the interaction" refers to the ability of an anti-PD-1 antibody to inhibit or reduce binding of PD-L1 to PD-1, such that signaling/functioning through PD-1 is abolished or diminished.

The term “specifically binds”, “specific binding” or “binds” refer to antibody binding to an antigen (e.g. PD-1) or an epitope within the antigen with greater affinity than for other antigens. Typically, the antibody binds to the antigen or the epitope within the antigen with an equilibrium dissociation constant (KD) of about 1×10^{-8} M or less, for example about 1×10^{-9} M or less, about 1×10^{-10} M or less, about 1×10^{-11} M or less, or about 1×10^{-12} M or less, typically with a KD that is at least one hundred-fold less than its KD for binding to a non-specific antigen (e.g., BSA, casein). The KD may be measured using standard procedures. Antibodies that specifically bind to the antigen or the epitope within the antigen may, however, have cross-reactivity to other related antigens, for example to the same antigen from other species (homologs), such as human or monkey, for example Macacafascicularis (cynomolgus, cyno), Pan troglodytes (chimpanzee, chimp) or Callithrixjacchus (common marmoset, marmoset).

The term “PD-1” refers to human programmed cell death protein 1, PD-1. PD-1 is also known as CD279 or PDCD1. The amino acid sequence of the mature human PD-1 (without signal sequence) is shown in SEQ ID NO: 39. The extracellular domain spans residues 1-150, the transmembrane domain spans residues 151-171 and the cytoplasmic domain spans residues 172-268 of SEQ ID NO: 39 (Table 3)

Table 3

Mature human PD-1 (without signal sequence) (SEQ ID NO:39)	PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTD KLAAFPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGT YLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQFQTLVVGVVGGLL GSLVLLVWVLAVICSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTP EPPVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL

"Antibodies" is meant in a broad sense and includes immunoglobulin molecules belonging to any class, IgA, IgD, IgE, IgG and IgM, or sub-class IgA1, IgA2, IgG1, IgG2, IgG3 and IgG4 and including either kappa (κ) and lambda (λ) light chain. Antibodies include monoclonal antibodies, full length antibodies, antigen binding fragments, bispecific or multispecific antibodies, dimeric, tetrameric or multimeric antibodies, single chain antibodies, domain antibodies and any other modified configuration of the immunoglobulin molecule that comprises an antigen binding fragment of the required specificity. "Full length antibodies" are comprised of two heavy chains (HC) and two light chains (LC) inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region (comprised of domains CH1, hinge, CH2 and CH3). Each light chain is comprised of a light chain variable region (VL) and a light chain constant region (CL). The VH and the VL may be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with framework regions (FR). Each VH and VL is composed of three CDRs and four FR segments, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. Antibodies include antibodies generated using various technologies, including antibodies generated from immunized mice or rat or identified from phage or mammalian display libraries as described herein.

"Complementarity determining regions (CDR)" are antibody regions that bind an antigen. There are three CDRs in the VH (HCDR1, HCDR2, HCDR3) and three CDRs in the VL (LCDR1, LCDR2, LCDR3). CDRs may be defined using various delineations such as Kabat (Wu et al. (1970) *J Exp Med* 132: 211-50) (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991), Chothia (Chothia et al. (1987) J Mol Biol 196: 901-17), IMGT (Lefranc et al. (2003) Dev Comp Immunol 27: 55-77) and AbM (Martin and Thornton (1996) J Bmol Biol 263: 800-15). The correspondence between the various delineations and variable region numbering are described (*see e.g.* Lefranc et al. (2003) Dev Comp Immunol 27: 55-

77; Honegger and Pluckthun, (2001) J Mol Biol 309:657-70; International ImMunoGeneTics (IMGT) database; Web resources, http://www_imgt_org). Available programs such as abYsis by UCL Business PLC may be used to delineate the CDRs. The term "CDR", "HCDR1", "HCDR2", "HCDR3", "LCDR1", "LCDR2" and "LCDR3" as used herein includes CDRs defined by any of the methods described supra, Kabat, Chothia, IMGT or AbM, unless otherwise explicitly stated in the specification.

"Antigen binding fragment" refers to a portion of an immunoglobulin molecule that retains the antigen binding properties of the parental full-length antibody. Exemplary antigen binding fragments are heavy chain complementarity determining regions (HCDR) 1, 2 and/or 3, light chain complementarity determining regions (LCDR) 1, 2 and/or 3, the VH, the VL, the VH and the VL, Fab, F(ab')2, Fd and Fv fragments as well as domain antibodies (dAb) consisting of either one VH domain or one VL domain. The VH and the VL domains may be linked together via a synthetic linker to form various types of single chain antibody designs in which the VH/VL domains pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate chains, to form a monovalent antigen binding site, such as single chain Fv (scFv) or diabody; described for example in Int. Pat. Publ. No. WO1998/44001, Int. Pat. Publ. No. WO1988/01649; Int. Pat. Publ. No. WO1994/13804; Int. Pat. Publ. No. WO1992/01047.

"Humanized antibody" refers to an antibody in which CDR sequences are derived from non-human species and the frameworks are derived from human immunoglobulin sequences. Humanized antibody may include substitutions in the framework so that the framework may not be an exact copy of expressed human immunoglobulin or human immunoglobulin germline gene sequences. Antibodies in which at least one CDR is derived from non-human species and at least one framework is derived from human immunoglobulin sequences are humanized antibodies. Humanized antibody may include substitutions in the frameworks so that the frameworks may not be exact copies of expressed human immunoglobulin or human immunoglobulin germline gene sequences.

"Human antibody" refers to an antibody that is optimized to have minimal immune response when administered to a human subject. Variable regions of human antibody are derived from human germline immunoglobulin sequences. If the antibody contains a constant region or a portion of the constant region, the constant region is also derived from human germline immunoglobulin sequences.

Human antibody comprises heavy or light chain variable regions that are "derived from" human germline immunoglobulin sequences if the variable regions of the antibody are obtained from a system that uses human germline immunoglobulin genes. Such exemplary systems are human immunoglobulin gene libraries displayed on phage or mammalian cells, and transgenic non-human animals such as mice, rats or chicken carrying human immunoglobulin loci. "Human antibody" typically contains amino acid differences when compared to the immunoglobulins expressed in humans due to differences between the systems used to obtain the antibody and human immunoglobulin loci, introduction of naturally occurring somatic mutations, intentional introduction of substitutions into the framework or the CDRs. "Human antibody" is typically about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical in amino acid sequence to an amino acid sequence encoded by human germline immunoglobulin sequences. In some cases, "human antibody" may contain consensus framework sequences derived from human framework sequence analyses, for example as described in (Knappik et al. (2000) J Mol Biol 296: 57-86), or synthetic HCDR3 incorporated into human immunoglobulin gene libraries displayed on phage, for example as described in (Shi et al. (2010) *J Mol Biol* 397: 385-96), and in Int. Patent Publ. No. WO2009/085462. Antibodies in which CDRs are derived from a non-human species are not included in the definition of "human antibody".

"Monoclonal antibody" refers to an antibody population with single amino acid composition in each antibody chain except for possible well-known alterations such as removal of C-terminal lysine from the antibody heavy chain or alterations due to post-translational modification(s) of amino acids, such as methionine oxidation or asparagine or glutamine deamidation. Monoclonal antibodies typically specifically bind one antigenic epitope, except that bispecific or multispecific monoclonal antibodies specifically bind two or more distinct antigenic epitopes. Monoclonal antibodies may have heterogeneous glycosylation within the antibody population. Monoclonal antibody may be monospecific or multispecific, or monovalent, bivalent or multivalent. A bispecific antibody is included in the term monoclonal antibody.

"Isolated" refers to a homogenous population of molecules (such as synthetic polynucleotides or a protein such as an antibody) which have been substantially separated and/or purified away from other components of the system the molecules are produced in, such as a recombinant cell, as well as a protein that has been subjected to at least one

purification or isolation step. "Isolated antibody" refers to an antibody that is substantially free of other cellular material and/or chemicals and encompasses antibodies that are isolated to a higher purity, such as to 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% purity.

FGFR genetic alterations

Described herein are methods of or uses for treating urothelial carcinoma comprising, consisting of, or consisting essentially of administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks to a patient that has been diagnosed with urothelial carcinoma and harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration (*i.e.,* one or more FGFR2 genetic alteration, one or more FGFR3 genetic alteration, or a combination thereof). Described herein are methods of or uses for treating urothelial carcinoma comprising, consisting of, or consisting essentially of administering at least one FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks to a patient that has been diagnosed with urothelial carcinoma and harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. Described herein are methods of or uses for treating urothelial carcinoma comprising, consisting of, or consisting essentially of administering two or more FGFR inhibitors at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks to a patient that has been diagnosed with urothelial carcinoma and harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration.

Described herein are methods of or uses for treating urothelial carcinoma comprising, consisting of, or consisting essentially of administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg every four weeks to a patient that has been diagnosed with urothelial carcinoma and harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration (*i.e.,* one or more FGFR2 genetic alteration, one or more FGFR3 genetic alteration, or a combination thereof). Described herein are methods of or uses for treating urothelial carcinoma comprising, consisting of, or consisting essentially of administering at least one FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg every four weeks to a patient that

has been diagnosed with urothelial carcinoma and harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. Described herein are methods of or uses for treating urothelial carcinoma comprising, consisting of, or consisting essentially of administering two or more FGFR inhibitors at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg every four weeks to a patient that has been diagnosed with urothelial carcinoma and harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration.

Described herein are methods of or uses for treating urothelial carcinoma comprising, consisting of, or consisting essentially of administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg every three weeks to a patient that has been diagnosed with urothelial carcinoma and harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration (*i.e.,* one or more FGFR2 genetic alteration, one or more FGFR3 genetic alteration, or a combination thereof). Described herein are methods of or uses for treating urothelial carcinoma comprising, consisting of, or consisting essentially of administering at least one FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg every three weeks to a patient that has been diagnosed with urothelial carcinoma and harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. Described herein are methods of or uses for treating urothelial carcinoma comprising, consisting of, or consisting essentially of administering two or more FGFR inhibitors at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg every three weeks to a patient that has been diagnosed with urothelial carcinoma and harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

The fibroblast growth factor (FGF) family of protein tyrosine kinase (PTK) receptors regulates a diverse array of physiologic functions including mitogenesis, wound healing, cell differentiation and angiogenesis, and development. Both normal and malignant cell growth as well as proliferation are affected by changes in local concentration of FGFs, extracellular signaling molecules which act as autocrine as well as paracrine factors. Autocrine FGF signaling may be particularly important in the progression of steroid hormone-dependent cancers to a hormone independent state.

FGFs and their receptors are expressed at increased levels in several tissues and cell lines and overexpression is believed to contribute to the malignant phenotype. Furthermore, a number of oncogenes are homologues of genes encoding growth factor receptors, and there is a potential for aberrant activation of FGF-dependent signaling in human pancreatic cancer (Knights et al., *Pharmacology and Therapeutics* 2010 125:1 (105-117); Korc M. et al *Current Cancer Drug Targets* 2009 9:5 (639-651)).

The two prototypic members are acidic fibroblast growth factor (aFGF or FGF1) and basic fibroblast growth factor (bFGF or FGF2), and to date, at least twenty distinct FGF family members have been identified. The cellular response to FGFs is transmitted via four types of high affinity transmembrane protein tyrosine-kinase FGFR numbered 1 to 4 (FGFR1 to FGFR4).

In certain embodiments, the urothelial carcinoma is susceptible to an FGFR2 genetic alteration and/or an FGFR3 genetic alteration.

As used herein, "FGFR genetic alteration" refers to an alteration in the wild type FGFR gene, including, but not limited to, FGFR fusion genes, FGFR mutations, FGFR amplifications, or any combination thereof. The terms "variant" and "alteration" are used interchangeably herein.

In certain embodiments, the FGFR2 or FGFR3 genetic alteration is an FGFR gene fusion. "FGFR fusion" or "FGFR gene fusion" refers to a gene encoding a portion of FGFR (*e.g.,* FGRF2 or FGFR3) and one of the herein disclosed fusion partners, or a portion thereof, created by a translocation between the two genes. The terms "fusion" and "translocation" are used interchangeable herein. The presence of one or more of the following FGFR fusion genes in a biological sample from a patient can be determined using the disclosed methods or uses or by methods known to those of ordinary skill in the art : FGFR3-TACC3, FGFR3-BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7, or any combination thereof. In certain embodiments, FGFR3-TACC3 is FGFR3-TACC3 variant 1 (FGFR3-TACC3 V1) or FGFR3-

TACC3 variant 3 (FGFR3-TACC3 V3). Table 4 provides the FGFR fusion genes and the FGFR and fusion partner exons that are fused. The sequences of the individual FGFR fusion genes are disclosed in Table 7.

Table 4

Fusion Gene	FGFR Exon	Partner Exon
FGFR2		
FGFR2-BICC1	19	3
FGFR2-CASP7	19	4
FGFR3		
FGFR3-BAIAP2L1	18	2
FGFR3-TACC3 V1	18	11
FGFR3-TACC3 V3	18	10

FGFR genetic alterations include FGFR single nucleotide polymorphism (SNP). "FGFR single nucleotide polymorphism" (SNP) refers to a FGFR2 or FGFR3 gene in which a single nucleotide differs among individuals. In certain embodiments, the FGFR2 or FGFR3 genetic alteration is an FGFR3 gene mutation. In particular, FGFR single nucleotide polymorphism" (SNP) refers to a FGFR3 gene in which a single nucleotide differs among individuals. The presence of one or more of the following FGFR SNPs in a biological sample from a patient can be determined by methods known to those of ordinary skill in the art or methods disclosed in WO 2016/048833, FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, FGFR3 Y373C, or any combination thereof. The sequences of the FGFR SNPs are provided in Table 5.

Table 5

FGFR3 mutant	Sequence
FGFR3 R248C	TCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCA TCCGGCAGACGTACACGCTGGACGTGCTGGAG(T)GCTCCCCGCACCGGC CCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCTGGGCAG CGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATC CAGTGGCTCAAGCACGTGGAGGTGAATGGCAGCAAGGTGGGCCCGGACG GCACACCCTACGTTACCGTGCTCA (SEQ ID NO:1)
FGFR3 S249C	GACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCC GGCAGACGTACACGCTGGACGTGCTGGGTGAGGGCCCTGGGGCGGCGCG GGGGTGGGGGCGGCAGTGGCGGTGGTGGTGAGGGAGGGGGTGGCCCCT GAGCGTCATCTGCCCCCACAGAGCGCT(G)CCCGCACCGGCCCATCCTGCA GGCGGGGCTGCCGGCCAACCAGACGGCGGTGCTGGGCAGCGACGTGGAG

FGFR3 mutant	Sequence
	TTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAA GCACGTGGAGGTGAATGGCAGCAAGGTGGGCCCGGACGGCACACCCTAC GTTACCGTGCTCAAGGTGGGCCACCGTGTGCACGT (SEQ ID NO:2)
FGFR3 G370C	GCGGGCAATTCTATTGGGTTTTCTCATCACTCTGCGTGGCTGGTGGTGCT GCCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCG**(T)**GCAGTGTGTA TGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGG TGGCGGCTGTGACGCTCTGCCGCCTGCGCAGCCCCCCCAAGAAAGGCCT GGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCG (SEQ ID NO:3)
FGFR3 Y373C*	CTAGAGGTTCTCTCCTTGCACAACGTCACCTTTGAGGACGCCGGGGAGTA CACCTGCCTGGCGGGCAATTCTATTGGGTTTTCTCATCACTCTGCGTGGCT GGTGGTGCTGCCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGC AGTGTGT**(G)**TGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCCTGTTCA TCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTGCGCAGCCCCCCCAAG AAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAA GC (SEQ ID NO:4)

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

As used herein, "FGFR genetic alteration gene panel" includes one or more of the above listed FGFR genetic alterations. In some embodiments, the FGFR genetic alteration gene panel is dependent upon the patient's cancer type.

The FGFR genetic alteration gene panel that is used in the evaluating step of the disclosed methods is based, in part, on the patient's cancer type. For patients with urothelial carcinoma, in particular locally advanced or metastatic UC, a suitable FGFR genetic alteration gene panel can comprise FGFR3-TACC3 V1, FGFR3-TACC3 V3, FGFR3-BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7, FGFR3 R248C, FGFR3 S249C, FGFR3 G370C, or FGFR3 Y373C, or any combination thereof.

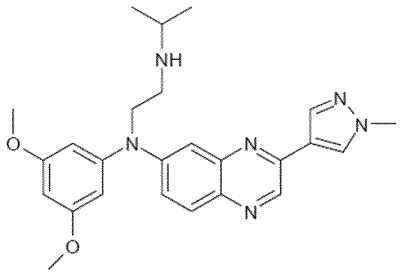
FGFR inhibitors for use in the disclosed methods or uses

Suitable FGFR inhibitors for use in the disclosed methods are provided herein. The FGFR inhibitors may be used alone or in combination with one or more additional FGFR inhibitors in the treatment methods described herein.

In some embodiments, if one or more FGFR genetic alterations are present in the sample, the urothelial carcinoma can be treated with a FGFR inhibitor disclosed in U.S.

Publication No. 2013/0072457 A1 (incorporated herein by reference), including any tautomeric or stereochemically isomeric form thereof, and a *N*-oxide thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof.

In some aspects, for example, the urothelial carcinoma may be treated with N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine (referred to herein as "JNJ-42756493" or "JNJ493" or erdafitinib), including any tautomeric form thereof, N-oxides thereof, pharmaceutically acceptable salts thereof, or solvates thereof. In some embodiments, the FGFR inhibitor can be the compound of formula (I), also referred to as erdafitinib:

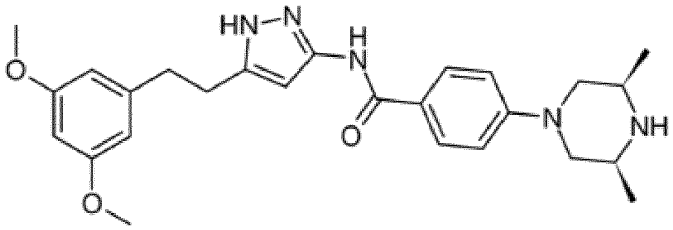


(I)

or a pharmaceutically acceptable salt thereof. In some aspects, the pharmaceutically acceptable salt is a HCl salt. In preferred aspects, erdafitinib base is used.

Erdafitinib (also referred to as ERDA), a once-daily oral pan-FGFR kinase inhibitor, has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult patients who have locally advanced UC or 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, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Loriot Y *et al. NEJM.* 2019;381:338-48. Erdafitinib has shown clinical benefits and tolerability in patients with mUC and alteration in FGFR expressions. Tabernero J, *et al. J Clin Oncol.* 2015;33:3401-3408; Soria J-C, *et al. Ann Oncol.* 2016;27(Suppl 6):vi266-vi295. Abstract 781PD; Siefker-Radtke AO, *et al.* ASCO 2018. Abstract 4503; Siefker-Radtke A, *et al.* ASCO-GU 2018. Abstract 450.

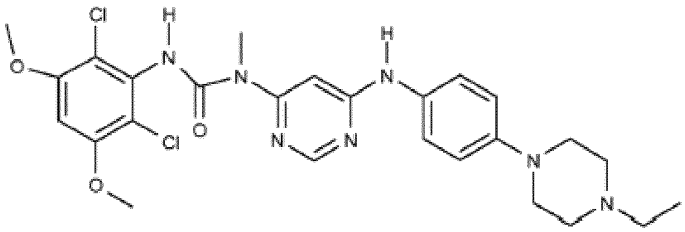
In some embodiments, the urothelial carcinoma can be treated with a FGFR inhibitor wherein the FGFR inhibitor is N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(3,5- diemthylpiperazin-1-yl)benzamide (AZD4547), as described in Gavine, P.R., et al., AZD4547: An Orally Bioavailable, Potent, and Selective Inhibitor of the Fibroblast Growth Factor Receptor Tyrosine Kinase Family, Cancer Res. April 15, 2012 72; 2045:



(II)

including, when chemically possible, any tautomeric or stereochemically isomeric form thereof, and a N-oxide thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof.

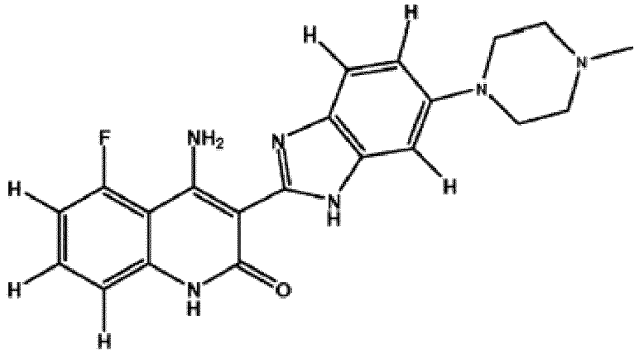
In some embodiments, the urothelial carcinoma can be treated with a FGFR inhibitor wherein the FGFR inhibitor is 3-(2,6- Dichloro-3,5- dimethoxy-phenyl)-l-{6-[4-(4 ethyl-piperazin-l-yl)-phenylamino]-pyrimid-4- yl}-methyl-urea (NVP-BGJ398) as described in Int'l Publ. No. WO2006/000420:



(III)

including, when chemically possible, any tautomeric or stereochemically isomeric form thereof, and a N-oxide thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof.

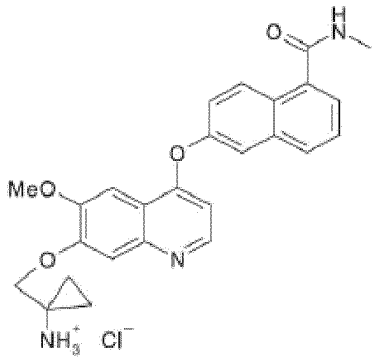
In some embodiments, the urothelial carcinoma can be treated with a FGFR inhibitor wherein the FGFR inhibitor is 4-amino-5-fluoro-3-[6-(4-methylpiperazin-l-yl)-lH-benzimidazol-2-yl]- lH-quinolin-2-one (dovitinib) as described in Int't Publ. No. WO2006/127926:



(IV)

including, when chemically possible, any tautomeric or stereochemically isomeric form thereof, and a N-oxide thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof.

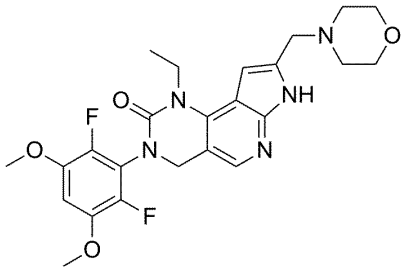
In some embodiments, the urothelial carcinoma can be treated with a FGFR inhibitor wherein the FGFR inhibitor is 6-(7-((l -Aminocyclopropyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide (AL3810) (lucitanib; E-3810), as described in Bello, E. et al., E-3810 Is a Potent Dual Inhibitor of VEGFR and FGFR that Exerts Antitumor Activity in Multiple Preclinical Models, Cancer Res February 15, 2011 71(A)1396-1405 and Int'l Publ. No. WO2008/112408:



(V)

including, when chemically possible, any tautomeric or stereochemically isomeric form thereof, and a N-oxide thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof.

In some embodiments, the urothelial carcinoma can be treated with a FGFR inhibitor wherein the FGFR inhibitor is pemigatinib (11-(2,6-difluoro-3,5-dimethoxyphenyl)-13-ethyl-4-(morpholin-4-ylmethyl)-5,7,11,13-tetrazatricyclo[7.4.0.$0^{2,6}$]trideca-1,3,6,8-tetraen-12-one:



including, when chemically possible, any tautomeric or stereochemically isomeric form thereof, and a N-oxide thereof, a pharmaceutically acceptable salt thereof, or a solvate thereof.

Additional suitable FGFR inhibitors include BAY1163877 (Bayer), BAY1179470 (Bayer), TAS-120 (Taiho), ARQ087 (ArQule), ASP5878 (Astellas), FF284 (Chugai), FP-1039 (GSK/FivePrime), Blueprint, LY-2874455 (Lilly), RG-7444 (Roche), or any combination thereof, including, when chemically possible, any tautomeric or stereochemical isomeric forms thereof, N-oxides thereof, pharmaceutically acceptable salts thereof, or solvates thereof.

In an embodiment the FGFR inhibitor generally, and erdafitinib more specifically, is administered as a pharmaceutically acceptable salt. In a preferred embodiment the FGFR inhibitor generally, and erdafitinib more specifically, is administered in base form. In an embodiment the FGFR inhibitor generally, and erdafitinib more specifically, is administered as a pharmaceutically acceptable salt in an amount corresponding to 8 mg base equivalent or corresponding to 9 mg base equivalent. In an embodiment the FGFR inhibitor generally, and erdafitinib more specifically, is administered in base form in an amount of 8 mg or 9 mg. In an embodiment the FGFR inhibitor generally, and erdafitinib more specifically, is administered in base form in an amount of 8 mg.

The salts can be prepared by for instance reacting the FGFR inhibitor generally, and erdafitinib more specifically, with an appropriate acid in an appropriate solvent.

Acid addition salts may be formed with acids, both inorganic and organic. Examples of acid addition salts include salts formed with an acid selected from the group consisting of acetic, hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic (mesylate), ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids. Another group of acid addition salts includes salts formed from acetic, adipic, ascorbic, aspartic, citric, DL-Lactic, fumaric, gluconic,

glucuronic, hippuric, hydrochloric, glutamic, DL-malic, methanesulphonic, sebacic, stearic, succinic and tartaric acids.

In an embodiment, the FGFR inhibitor generally, and erdafitinib more specifically, is administered in the form of a solvate. As used herein, the term "solvate" means a physical association of erdafitinib with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The term "solvate" is intended to encompass both solution-phase and isolatable solvates. Non-limiting examples of solvents that may form solvates include water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid or ethanolamine and the like.

Solvates are well known in pharmaceutical chemistry. They can be important to the processes for the preparation of a substance (*e.g.* in relation to their purification, the storage of the substance (*e.g.* its stability) and the ease of handling of the substance and are often formed as part of the isolation or purification stages of a chemical synthesis. A person skilled in the art can determine by means of standard and long used techniques whether a hydrate or other solvate has formed by the isolation conditions or purification conditions used to prepare a given compound. Examples of such techniques include thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray crystallography (*e.g.* single crystal X-ray crystallography or X-ray powder diffraction) and Solid-State NMR (SS-NMR, also known as Magic Angle Spinning NMR or MAS-NMR). Such techniques are as much a part of the standard analytical toolkit of the skilled chemist as NMR, IR, HPLC and MS. Alternatively the skilled person can deliberately form a solvate using crystallization conditions that include an amount of the solvent required for the particular solvate. Thereafter the standard methods described above, can be used to establish whether solvates had formed. Also encompassed are any complexes (*e.g.* inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals).

Furthermore, the compound may have one or more polymorph (crystalline) or amorphous forms.

The compounds include compounds with one or more isotopic substitutions, and a reference to a particular element includes within its scope all isotopes of the element. For example, a reference to hydrogen includes within its scope ^{1}H, ^{2}H (D), and ^{3}H (T). Similarly, references to carbon and oxygen include within their scope respectively ^{12}C, ^{13}C and ^{14}C and

^{16}O and ^{18}O. The isotopes may be radioactive or nonradioactive. In one embodiment, the compounds contain no radioactive isotopes. Such compounds are preferred for therapeutic use. In another embodiment, however, the compound may contain one or more radioisotopes. Compounds containing such radioisotopes may be useful in a diagnostic context.

Anti-PD1 antibodies for use in the disclosed methods or uses

Suitable anti-PD1 antibodies or antigen fragments thereof for use in the disclosed methods are provided herein. The anti-PD1 antibodies or antigen fragments thereof may be used alone or in combination for the treatment methods described herein.

In some embodiments, if one or more FGFR genetic alterations are present in the sample, the urothelial carcinoma can be treated with an anti-PD1 antibody or antigen fragment thereof disclosed in U.S. Publication No. 2019/0225689 or U.S. Publication No. 2017/0121409 (incorporated herein by reference in their entireties), such as cetrelimab.

In some embodiments, the antagonistic anti-PD1 antibody or an antigen binding fragment thereof comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 40, a HCDR2 of SEQ ID NO: 41, a HCDR3 of SEQ ID NO: 42, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 43, a LCDR2 of SEQ ID NO: 44 and a LCDR3 of SEQ ID NO: 45.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof comprises a heavy chain variable region (VH) of SEQ ID NO: 46 and a light chain variable region (VL) or SEQ ID NO: 47.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is an IgG1, an IgG2, and IgG3 or an IgG4 isotype. In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is an IgG4 isotype. In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is an IgG4 isotype and comprises proline at position 228, residue numbering according to the EU Index.

In some embodiments, the anti-PD-1 antibody is a nG4m(a) allotype.

In some embodiments, the anti-PD-1 antibody or an antigen binding fragment thereof has at least one substitution in an Fc region to modulate antibody effector functions or antibody half-life.

In some embodiments, the anti-PD-1 antibody comprises a heavy chain of SEQ ID NO: 48 and a light chain of SEQ ID NO: 49.

In some embodiments, the anti-PD-1 antibody is cetrelimab. Cetrelimab is an IgG4/κ antibody characterized by following amino acid sequences: the HCDR1 of SEQ ID NO: 40, the HCDR2 of SEQ ID NO: 41, the HCDR3 of SEQ ID NO: 42, the LCDR1 of SEQ ID NO: 43, the LCDR2 of SEQ ID NO: 44, the LCDR3 of SEQ ID NO: 45, the VH of SEQ ID NO: 46, the VL of SEQ ID NO: 47, the HC of SEQ ID NO: 48 and the LC of SEQ ID NO: 49.

Cetrelimab (JNJ-63723283, CET) is a fully human immunoglobulin (Ig) G4 kappa monoclonal antibody that binds to programmed death receptor-1 (PD-1) with high affinity and specificity. Cetrelimab has shown activity in solid tumors. Rutkowski P, *et al. Journal of Clinical Oncology*. 2019;37(8):31.

Chemotherapeutic agents for use in the disclosed methods or uses

Suitable chemotherapeutic agents for use in the disclosed methods are provided herein. In some embodiments the urothelial carcinoma is treated with the disclosed FGFR inhibitors and anti-PD-1 antibodies in further combination with chemotherapy. In certain embodiments, the chemotherapy is platinum chemotherapy.

Platinum-based chemotherapies and PD-1 therapies in eligible patients remain the mainstay of systemic therapy in metastatic or locally advanced urothelial cancer; however, long-term outcomes are often not adequate. Thus, there remains a need for new combination regimens, such as regimens that include the disclosed FGFR inhibitors with platinum-based chemotherapies and PD-1 therapies.

In certain embodiments, the platinum chemotherapy is cisplatin. Cisplatin is a chemotherapeutic agent that crosslinks with DNA to trigger apoptosis by interfering with mitosis and breakdown of DNA damage repair.

In certain embodiments, the platinum chemotherapy is carboplatin. Carboplatin is an alternate chemotherapeutic agent that inhibits the synthesis of RNA, DNA, and proteins in cells.

Generation of the anti-PD1 antibodies for use in the disclosed methods or uses

Antagonistic anti-PD-1 antibodies or antigen-binding fragments thereof used in the methods of the invention may be generated using various technologies. For example, the hybridoma method of Kohler and Milstein may be used to generate monoclonal antibodies. In the hybridoma method, a mouse or other host animal, such as a hamster, rat or monkey, is immunized with human and/or cyno PD-1 antigens, such as the extracellular domain of PD-1,

followed by fusion of spleen cells from immunized animals with myeloma cells using standard methods to form hybridoma cells. Colonies arising from single immortalized hybridoma cells may be screened for production of antibodies with desired properties, such as specificity of binding, cross-reactivity or lack thereof, affinity for the antigen, and functionality such as antagonistic activity.

Exemplary humanization techniques including selection of human acceptor frameworks include CDR grafting (U.S. Pat. No. 5,225,539), SDR grafting (U.S. Pat. No. 6,818,749), Resurfacing (Padlan, (1991) Mol Immunol 28:489-499), Specificity Determining Residues Resurfacing (U.S. Patent Publ. No. 2010/0261620), human framework adaptation (U.S. Pat. No. 8,748,356) or superhumanization (U.S. Pat. No. 7,709,226). In these methods, CDRs or a subset of CDR residues of parental antibodies are transferred onto human frameworks that may be selected based on their overall homology to the parental frameworks, based on similarity in CDR length, or canonical structure identity, or a combination thereof.

Humanized antibodies may be further optimized to improve their selectivity or affinity to a desired antigen by incorporating altered framework support residues to preserve binding affinity (backmutations) by techniques such as those described in Int. Patent Publ. Nos. WO1990/007861 and WO 1992/22653, or by introducing variation at any of the CDRs for example to improve affinity of the antibody.

Transgenic animals, such as mice or rat carrying human immunoglobulin (Ig) loci in their genome may be used to generate antibodies against PD-1, and are described in for example U.S. Pat. No. 6,150,584, Int. Patent Publ. No. WO1999/45962, Int. Patent Publ. Nos. WO2002/066630, WO2002/43478, WO2002/043478 and WO1990/04036. The endogenous immunoglobulin loci in such animal may be disrupted or deleted, and at least one complete or partial human immunoglobulin locus may be inserted into the genome of the animal using homologous or non-homologous recombination, using transchromosomes, or using minigenes. Companies such as Regeneron (http://_www_regeneron_com), Harbour Antibodies (http://_www_harbourantibodies_com), Open Monoclonal Technology, Inc. (OMT) (http://_www_omtinc_net), KyMab (http://_www_kymab_com), Trianni (http://_www.trianni_com) and Ablexis (http://_www_ablexis_com) may be engaged to provide human antibodies directed against a selected antigen using technologies as described above.

Antibodies may be selected from a phage display library, where the phage is engineered to express human immunoglobulins or portions thereof such as Fabs, single chain

antibodies (scFv), or unpaired or paired antibody variable regions. The antibodies of the invention may be isolated for example from phage display library expressing antibody heavy and light chain variable regions as fusion proteins with bacteriophage pIX coat protein as described in Shi et al., (2010) J Mol Biol 397:385-96, and Int. Patent Publ. No. WO09/085462). The libraries may be screened for phage binding to human and/or cyno PD-1 and the obtained positive clones may be further characterized, the Fabs isolated from the clone lysates, and expressed as full length IgGs.

The CDRs of an antibody may be grafted on any human framework and the functionality of the resulting antibody may be tested. For example, antibody JNJ-63723283 comprises frameworks derived from human germline genes IGHV1-69 and IGKV3-11. Alternatively, JNJ-63723283 HCDRs may be grafted to other IGHV1 germline gene subgroup frameworks and the LCDRs may be grafted to other IGKV3 germline gene subgroup frameworks and the resulting antibodies are tested for desired functionality. The human germline gene sequences are well known and can be retrieved for example from ImMunoGeneTics Information System®.

Preparation of immunogenic antigens and monoclonal antibody production may be performed using any suitable technique, such as recombinant protein production. The immunogenic antigens may be administered to an animal in the form of purified protein, or protein mixtures including whole cells or cell or tissue extracts, or the antigen may be formed de novo in the animal's body from nucleic acids encoding said antigen or a portion thereof.

Methods of producing antibodies at large scales are known. Antibodies may be produced for example in CHO cells cultured using known methods. The antibody may be isolated and/or purified from culture medium by removing solids by centrifugation or filtering as a first step in the purification process. The antibody may be further purified by standard methods including chromatography (e.g., ion exchange, affinity, size exclusion, and hydroxyapatite chromatography), gel filtration, centrifugation, or differential solubility, ethanol precipitation or by any other available technique for the purification of antibodies. Protease inhibitors such as phenyl methyl sulfonyl fluoride (PMSF), leupeptin, pepstatin or aprotinin can be added at any or all stages to reduce or eliminate degradation of the antibody during the purification process. One of ordinary skill in the art will appreciate that the exact purification technique will vary depending on the character of the polypeptide or protein to be purified, the character of the cells from which the polypeptide or protein is expressed, and the composition of the medium in which the cells were grown.

Methods of Treatment and Uses

Described herein are methods of treating urothelial carcinoma comprising, consisting of, or consisting essential of, administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks in cycle 1 to 4 of treatment. According to particular embodiments, the dose of about 240 mg every two weeks of the anti-PD1 antibody or antigen binding fragment thereof refers to a single intravenous (IV) infusion once every two weeks. According to particular embodiments, on days in which both the FGFR inhibitor (e.g., erdafitinib) and the anti-PD1 antibody (e.g., cetrelimab) are administered, the FGFR inhibitor is administered within about 60 minutes, or about 60 minutes ± about 15 minutes before the start of the anti-PD1 antibody IV infusion, e.g., between about 45 minutes to about 75 minutes, before the start of the IV infusion. According to alternative embodiments, the FGFR inhibitor is administered within about 1 hour, or about 2 hours, or about 3 hours, or about 4 hours, or about 5 hours before or after the start of the anti-PD1 antibody IV infusion.

Described herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks, in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks in cycle 1 to 4 of treatment.

Described herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg every three weeks, in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a

AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Described herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg every four weeks, in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks as of cycle 5 of treatment and beyond.

Described herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks in cycle 1 to 4 of treatment.

Described herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 360 mg every three weeks. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Described herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks as of cycle 5 of treatment and beyond.

Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks in cycle 1 to 4 of treatment.

Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 360 mg every three weeks. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor for use in the treatment of urothelial carcinoma in a

patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks as of cycle 5 of treatment and beyond.

Described herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks in cycle 1 to 4 of treatment.

Described herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg every three weeks. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Described herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg every four weeks. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be

administered at a dose of about 480 mg every four weeks as of cycle 5 of treatment and beyond.

Described herein is the use of an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with a FGFR inhibitor at a dose of about 8 mg per day. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks in cycle 1 to 4 of treatment.

Described herein is the use of an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg every three weeks for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with a FGFR inhibitor at a dose of about 8 mg per day. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Described herein is the use of an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg every four weeks for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with a FGFR inhibitor at a dose of about 8 mg per day. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks as of cycle 5 of treatment and beyond.

Further provided herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about

240 mg every two weeks, in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks in cycle 1 to 4 of treatment.

Further provided herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg every three weeks, in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Further provided herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg every four weeks, in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks as of cycle 5 of treatment and beyond.

Further provided herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks in cycle 1 to 4 of treatment.

Further provided herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 360 mg every three weeks, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Further provided herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is

administered or is to be administered at a dose of about 480 mg every four weeks, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks as of cycle 5 of treatment and beyond.

Further provided herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks in cycle 1 to 4 of treatment.

Further provided herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 360 mg every three weeks, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an

embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Further provided herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks as of cycle 5 of treatment and beyond.

Further provided herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks in cycle 1 to 4 of treatment.

Further provided herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg every three weeks, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin.

In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Further provided herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg every four weeks, and wherein the combination 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 3 gene alterations is present in the sample. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks as of cycle 5 of treatment and beyond.

Further provided herein is the use of an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with a FGFR inhibitor at a dose of about 8 mg per day, and wherein the combination 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 3 gene alterations is present in the sample. Described herein are methods of treating urothelial carcinoma comprising, consisting of, or consisting essential of, administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks in further combination with a platinum chemotherapy to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. According to particular embodiments, the dose of about 240 mg every two weeks of the anti-PD1 antibody or antigen

binding fragment thereof refers to a single intravenous (IV) infusion once every two weeks. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks in cycle 1 to 4 of treatment.

Further provided herein is the use of an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg every three weeks for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with a FGFR inhibitor at a dose of about 8 mg per day, and wherein the combination 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 3 gene alterations is present in the sample. Described herein are methods of treating urothelial carcinoma comprising, consisting of, or consisting essential of, administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg every three weeks in further combination with a platinum chemotherapy to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. According to particular embodiments, the dose of about 360 mg every three weeks of the anti-PD1 antibody or antigen binding fragment thereof refers to a single intravenous (IV) infusion once every three weeks. In an embodiment, the platinum chemotherapy is cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Further provided herein is the use of an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg every four weeks for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with a FGFR

inhibitor at a dose of about 8 mg per day, and wherein the combination 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 3 gene alterations is present in the sample. Described herein are methods of treating urothelial carcinoma comprising, consisting of, or consisting essential of, administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg every four weeks in further combination with a platinum chemotherapy to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. According to particular embodiments, the dose of about 480 mg every four weeks of the anti-PD1 antibody or antigen binding fragment thereof refers to a single intravenous (IV) infusion once every four weeks. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks as of cycle 5 of treatment and beyond.

According to particular embodiments, on days in which the FGFR inhibitor (e.g., erdafitinib), the anti-PD1 antibody (e.g., cetrelimab) and the platinum chemotherapy (e.g. cisplatin or carboplatin) are administered, the FGFR inhibitor is administered within about 60 minutes, or about 60 minutes ± about 15 minutes before the start of the anti-PD1 antibody IV infusion, e.g., between about 45 minutes to about 75 minutes, before the start of the IV infusion. According to alternative embodiments, the FGFR inhibitor is administered within about 1 hour, or about 2 hours, or about 3 hours, or about 4 hours, or about 5 hours before or after the start of the anti-PD1 antibody IV infusion.

Described herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and in further combination with a platinum chemotherapy, in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In certain embodiments, described herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and in further combination with a platinum chemotherapy, in particular for use in the

treatment of urothelial carcinoma in a patient who does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration.

Described herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof and in further combination with cisplatin for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the cisplatin is administered at a dose of about 50 mg/m^2 every 3 weeks. Described herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof and in further combination with cisplatin for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the cisplatin is administered at a dose of about 60 mg/m^2 every 3 weeks.

Described herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof and in further combination with carboplatin for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the carboplatin is administered at a dose of about AUC of 4 mg/mL/min every 3 weeks. Described herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof and in further combination with carboplatin for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be

administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the carboplatin is administered at a dose of about AUC 5 mg/mL/min every 3 weeks.

Described herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof and in further combination with cisplatin for use in the treatment of urothelial carcinoma in a patient who does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the cisplatin is administered at a dose of about 50 mg/m^2 every 3 weeks. Described herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof and in further combination with cisplatin for use in the treatment of urothelial carcinoma in a patient who does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the cisplatin is administered at a dose of about 60 mg/m^2 every 3 weeks.

Described herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof and in further combination with carboplatin for use in the treatment of urothelial carcinoma in a patient who does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the carboplatin is administered at a dose of about AUC 4 mg/mL/min every 3 weeks. Described herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof and in further combination with carboplatin for use in the treatment of urothelial carcinoma in a patient who does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg

per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the carboplatin is administered at a dose of about AUC 5 mg/mL/min every 3 weeks.

Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor and in further combination with cisplatin for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks, and wherein the cisplatin is administered at a dose of about 50 mg/m^2 every 3 weeks. Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor and in further combination with cisplatin for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks, and wherein the cisplatin is administered at a dose of about 60 mg/m^2 every 3 weeks.

Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor and in further combination with carboplatin for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks, and wherein the carboplatin is administered at a dose of about AUC 4 mg/mL/min every 3 weeks. Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor and in further combination with cisplatin for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor

is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks, and wherein the cisplatin is administered at a dose of about AUC 5 mg/mL/min every 3 weeks.

Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor and in further combination with cisplatin for use in the treatment of urothelial carcinoma in a patient who does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks, and wherein the cisplatin is administered at a dose of about 50 mg/m^2 every 3 weeks. Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor and in further combination with cisplatin for use in the treatment of urothelial carcinoma in a patient who does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks, and wherein the cisplatin is administered at a dose of about 60 mg/m^2 every 3 weeks.

Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor and in further combination with carboplatin for use in the treatment of urothelial carcinoma in a patient who does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks, and wherein the carboplatin is administered at a dose of about AUC 4 mg/mL/min every 3 weeks. Described herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor and in further combination with cisplatin for use in the treatment of urothelial carcinoma in a patient who

does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day, wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks, and wherein the cisplatin is administered at a dose of about AUC 5 mg/mL/min every 3 weeks.

Described herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the FGFR inhibitor is used or to be used in further combination with cisplatin at a dose of 50 mg/m^2 every 3 weeks. Described herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the FGFR inhibitor is use or to be used in further combination with cisplatin at a dose of 60 mg/m^2 every 3 weeks.

Described herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the FGFR inhibitor is used or to be used in further combination with carboplatin at a dose of AUC 4 mg/mL/min every 3 weeks. Described herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two

weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the FGFR inhibitor is used or to be used in further combination with carboplatin at a dose of AUC 5 mg/mL/min every 3 weeks.

Described herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the FGFR inhibitor is used or to be used in further combination with cisplatin at a dose of 50 mg/m^2 every 3 weeks. Described herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the FGFR inhibitor is used or to be used in further combination with cisplatin at a dose of 60 mg/m^2 every 3 weeks.

Described herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the FGFR inhibitor is used or to be used in further combination with carboplatin at a dose of AUC 4 mg/mL/min every 3 weeks. Described herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who does not harbor at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and wherein the FGFR inhibitor is used or to be used in further combination with carboplatin at a dose of AUC 5 mg/mL/min every 3 weeks.

Described herein is the use of an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with a FGFR inhibitor at a dose of about 8 mg per day and a platinum chemotherapy. In certain embodiments, the platinum chemotherapy is cisplatin. In certain embodiments, the platinum chemotherapy is carboplatin. In certain embodiments, the cisplatin is to be used at a dose of 50 mg/m^2 every 3 weeks. In certain embodiments, the cisplatin is to be used at a dose of 60 mg/m^2 every 3 weeks. In certain embodiments, the carboplatin is to be used at a dose of AUC 4 mg/mL/min every 3 weeks. In certain embodiments, the carboplatin is to be used at a dose of AUC 5 mg/mL/min every 3 weeks.

Further provided herein is a combination of a FGFR inhibitor at a dose of about 8 mg per day and an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and a platinum chemotherapy, in particular for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, and wherein the combination 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 3 gene alterations is present in the sample.

Further provided herein is a FGFR inhibitor for use in combination with an anti-PD1 antibody or antigen binding fragment thereof and a platinum chemotherapy for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks, and wherein the combination 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 3 gene alterations is present in the sample.

Further provided herein is an anti-PD1 antibody or antigen binding fragment thereof for use in combination with a FGFR inhibitor and a platinum chemotherapy for use in the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration, wherein the FGFR inhibitor is administered or is to be administered at a dose of about 8 mg per day and wherein the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks, and wherein the combination 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 3 gene alterations is present in the sample.

Further provided herein is the use of a FGFR inhibitor at a dose of about 8 mg per day for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the FGFR inhibitor is used or is to be used in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks and a platinum chemotherapy, and wherein the combination 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 3 gene alterations is present in the sample.

Further provided herein is the use of an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks for the manufacture of a medicament for the treatment of urothelial carcinoma in a patient who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration wherein the anti-PD1 antibody or antigen binding fragment thereof is used or is to be used in combination with a FGFR inhibitor at a dose of about 8 mg per day and a platinum chemotherapy, and wherein the combination 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 3 gene alterations is present in the sample.

Said methods and uses also encompass administration of at least one, one, two, three or four FGFR inhibitors to a patient that has been diagnosed with urothelial carcinoma.

In certain embodiments, the urothelial carcinoma is locally advanced or metastatic.

In some embodiments, the subject has received one, two, three or more prior therapeutics to treat the urothelial carcinoma prior to said administration of said FGFR inhibitor and said anti-PD1 antibody or antigen binding fragment thereof. In certain embodiments, the patient received at least one systemic therapy for the treatment of urothelial carcinoma prior to administration of said FGFR inhibitor and said anti-PD1 antibody or antigen binding fragment thereof. In some embodiments, the at least one systemic therapy for the treatment of urothelial carcinoma is platinum-containing chemotherapy. Non-limiting examples of platinum-based chemotherapies include cisplatin, carboplatin, oxaliplatin and nedaplatin. In further embodiments, the urothelial carcinoma progressed during or following at least one line of the platinum-containing chemotherapy.

In still further embodiments, the platinum-containing chemotherapy is neoadjuvant platinum-containing chemotherapy or adjuvant platinum-containing chemotherapy. Neoadjuvant therapy, which is given as a first step to shrink a tumor, may be distinguished from adjuvant therapy, which is given after the primary treatment to lower the risk that the cancer will come back. In even further embodiments, the urothelial carcinoma progressed within 12 months following at least one line of the neoadjuvant platinum-containing chemotherapy or adjuvant platinum-containing chemotherapy.

In some embodiments, the subject has not received or is ineligible to receive at least one prior therapeutic to treat the urothelial carcinoma prior to said administration of said FGFR inhibitor and said anti-PD1 antibody or antigen binding fragment thereof. In some embodiments, the patient did not receive systemic therapy for the treatment of urothelial carcinoma prior to said administration of said FGFR inhibitor and said anti-PD1 antibody or antigen binding fragment thereof. In certain embodiments, the patient is cisplatin-ineligible. In certain embodiments, the patient is a first line cisplatin-ineligible mUC patient. The determination of eligibility may be made, for example, by a treating physician.

In certain embodiments, the patient is PD-1 axis naïve. “PD-1 axis naïve” refers to a subject who has not been treated with PD-1, PD-L1 or PD-L2 antagonists. Exemplary PD-1, PD-L1 or PD-L2 antagonists are nivolumab (OPDIVO®), pembrolizumab (KEYTRUDA®), cemiplimab (Libtayo®), sintilimab, tislelizumab, tripolibamab durvalumab (IMFINZI®), atezolizumab (TECENTRIQ®), avelumab (BAVENCIO®) or envafolimab, or any other PD-1, PD-L1 or PD-L2 antagonist. Additional such antagonists are known and include those listed for example at Citeline PharmaIntelligence website.

In further embodiments, the patient has an Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2. In certain embodiments, the patient has an ECOG performance status of 2. In certain embodiments, the patient has an ECOG performance status of 1. In certain embodiments, the patient has an ECOG performance status of 0.

In further embodiments, the combination of an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof as described herein is indicated for adult patients with metastatic or locally advanced urothelial carcinoma that harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration and who have not received prior systemic therapy for metastatic disease. In an embodiment, the patients are ineligible for cisplatin chemotherapy.

In further embodiments, administration of the FGFR inhibitor in combination with the anti-PD1 antibody or antigen binding fragment thereof provides improved anti-tumor activity as measured by objective response rate or disease control rate relative to a patient that has been diagnosed with urothelial carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof. In certain embodiments, administration of the FGFR inhibitor in combination with the anti-PD1 antibody or antigen binding fragment thereof provides improved anti-tumor activity as measured by objective response rate relative to a patient that has been diagnosed with urothelial carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof. In further embodiments, administration of the FGFR inhibitor in combination with the anti-PD1 antibody or antigen binding fragment thereof provides improved anti-tumor activity as measured by disease control rate relative to a patient that has been diagnosed with urothelial carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof.

In certain embodiments, administration of the FGFR inhibitor in combination with the anti-PD1 antibody or antigen binding fragment thereof as described herein, in particular erdafitinib at a dose of 8 mg potentially with uptitration and cetrelimab at a dose of 240 mg as described herein, provides an objective response rate of at least 40%, or at least 44%, or at least 45%, or at least 50%. In an embodiment, erdafitinib is not uptitrated.

In certain embodiments, administration of the FGFR inhibitor in combination with the anti-PD1 antibody or antigen binding fragment thereof as described herein, in particular erdafitinib at a dose of 8 mg potentially with uptitration and cetrelimab at a dose of 240 mg as

described herein, provides a disease control rate of at least 90%, or at least 95% or a disease control rate of 100%. In an embodiment, erdafitinib is not uptitrated.

In certain embodiments, the improvement in anti-tumor activity is relative to treatment with placebo. In certain embodiments, the improvement in anti-tumor activity is relative to no treatment. In certain embodiments, the improvement in anti-tumor activity is relative to standard of care. . In certain embodiments, the improvement in anti-tumor activity is relative to a patient population without urothelial carcinoma.

In some embodiments, administration of the FGFR inhibitor in combination with the anti-PD1 antibody or antigen binding fragment thereof does not result in hematological toxicity, in particular does not result in hematological toxicity of Grade 3 or higher. In still further embodiments, administration of the FGFR inhibitor in combination with the anti-PD1 antibody or antigen binding fragment thereof does not result in non-hematological toxicity of Grade 3 or higher.

Also described herein are methods of improving objective response rate in a patient with urothelial carcinoma relative to a patient that has been diagnosed with urothelial carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof, said method comprising, consisting of, or consisting essential of, administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. Also described herein are methods of improving disease control rate in a patient with urothelial carcinoma relative to a patient that has been diagnosed with urothelial carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof, said method comprising, consisting of, or consisting essential of, administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 240 mg every two weeks in cycle 1 to 4 of treatment.

Also described herein are methods of improving objective response rate in a patient with urothelial carcinoma relative to a patient that has been diagnosed with urothelial

carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof, said method comprising, consisting of, or consisting essential of, administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg every three weeks to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. Also described herein are methods of improving disease control rate in a patient with urothelial carcinoma relative to a patient that has been diagnosed with urothelial carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof, said method comprising, consisting of, or consisting essential of, administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 360 mg every three weeks to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In an embodiment, the treatment further comprises a platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment the platinum chemotherapy is administered or is to be administered every three weeks. In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

Also described herein are methods of improving objective response rate in a patient with urothelial carcinoma relative to a patient that has been diagnosed with urothelial carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof, said method comprising, consisting of, or consisting essential of, administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg every four weeks to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. Also described herein are methods of improving disease control rate in a patient with urothelial carcinoma relative to a patient that has been diagnosed with urothelial carcinoma that has not received treatment with an FGFR inhibitor and an anti-PD1 antibody or antigen binding fragment thereof, said method comprising, consisting of, or consisting essential of, administering a FGFR inhibitor

at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 480 mg every four weeks to a patient that has been diagnosed with urothelial carcinoma who harbors at least one FGFR2 genetic alteration and/or FGFR3 genetic alteration. In an embodiment, the anti-PD1 antibody or antigen binding fragment thereof is administered or is to be administered at a dose of about 480 mg every four weeks as of cycle 5 of treatment and beyond.

In certain embodiments, the improvement is relative to treatment with placebo. In certain embodiments, the improvement is relative to no treatment. In certain embodiments, the improvement is relative to standard of care.

Evaluating a sample for the presence of one or more FGFR genetic alterations

Also described herein are methods of treating urothelial carcinoma comprising, consisting of, or consisting essential of: (a) evaluating a biological sample from a patient with urothelial carcinoma for the presence of one or more FGFR gene alterations, in particular one or more FGFR2 or FGFR3 gene alterations; and (b) administering a FGFR inhibitor at a dose of about 8 mg per day in combination with an anti-PD1 antibody or antigen binding fragment thereof at a dose of about 240 mg every two weeks or at a dose of about 360 mg every three weeks or at a dose of about 480 mg every four weeks to the patient if one or more FGFR gene alterations, in particular one or more FGFR2 or FGFR3 gene alterations, is present in the sample.

The following methods for evaluating a biological sample for the presence of one or more FGFR genetic alterations apply equally to any of the above disclosed methods of treatment and uses.

The disclosed methods are suitable for treating urothelial carcinoma in a patient if one or more FGFR genetic alterations are present in a biological sample from the patient. In some embodiments, the FGFR genetic alteration can be one or more FGFR fusion genes. In some embodiments, the FGFR genetic alteration can be one or more FGFR mutations. In some embodiments, the FGFR genetic alteration can be one or more FGFR amplifications. In some embodiments, a combination of the one or more FGFR genetic alterations can be present in the biological sample from the patient. For example, in some embodiments, the FGFR genetic alterations can be one or more FGFR fusion genes and one or more FGFR mutations. In some embodiments, the FGFR genetic alterations can be one or more FGFR fusion genes and one or more FGFR amplifications. In some embodiments, the FGFR

genetic alterations can be one or more FGFR mutations and one or more FGFR amplifications. In yet other embodiments, the FGFR genetic alterations can be one or more FGFR fusion genes, mutations, and amplifications. Exemplary FGFR fusion genes are provided in Table 4 and include but are not limited to: FGFR2-BICC1; FGFR2-CASP7; FGFR3-BAIAP2L1; FGFR3-TACC3 V1; FGFR3-TACC3 V3; or a combination thereof.

Suitable methods for evaluating a biological sample for the presence of one or more FGFR genetic alterations are described in the methods section herein and in WO 2016/048833 and U.S. Patent Application Serial No. 16/723,975, which are incorporated herein in their entireties. For example, and without intent to be limiting, evaluating a biological sample for the presence of one or more FGFR genetic alterations can comprise any combination of the following steps: isolating RNA from the biological sample; synthesizing cDNA from the RNA; and amplifying the cDNA (preamplified or non-preamplified). In some embodiments, evaluating a biological sample for the presence of one or more FGFR genetic alterations can comprise: amplifying cDNA from the patient with a pair of primers that bind to and amplify one or more FGFR genetic alterations; and determining whether the one or more FGFR genetic alterations are present in the sample. In some aspects, the cDNA can be pre-amplified. In some aspects, the evaluating step can comprise isolating RNA from the sample, synthesizing cDNA from the isolated RNA, and pre-amplifying the cDNA.

Suitable primer pairs for performing an amplification step include, but are not limited to, those disclosed in WO 2016/048833, as exemplified below in Table 6:

Table 6

Target	Forward Primer	Reverse Primer 5'-3'
FGFR3-TACC3 V1	GACCTGGACCGTGTCCTTACC (SEQ ID NO:5)	CTTCCCCAGTTCCAGGTTCTT (SEQ ID NO:6)
FGFR3-TACC3 V3	AGGACCTGGACCGTGTCCTT (SEQ ID NO:7)	TATAGGTCCGGTGGACAGGG (SEQ ID NO:8)
FGFR3-BAIAP2L1	CTGGACCGTGTCCTTACCGT (SEQ ID NO:9)	GCAGCCCAGGATTGAACTGT (SEQ ID NO:10)
FGFR2-BICC1	TGGATCGAATTCTCACTCTCACA (SEQ ID NO:11)	GCCAAGCAATCTGCGTATTTG (SEQ ID NO:12)
FGFR2-CASP7	GCTCTTCAATACAGCCCTGATCA (SEQ ID NO:13)	ACTTGGATCGAATTCTCACTCTCA (SEQ ID NO:14)
FGFR2-CCDC6	TGGATCGAATTCTCACTCTCACA (SEQ ID NO:15)	GCAAAGCCTGAATTTTCTTGAATAA (SEQ ID NO:16)

Target	Forward Primer	Reverse Primer 5'-3'
FGFR3 R248C	GCATCCGGCAGACGTACA (SEQ ID NO:17)	CCCCGCCTGCAGGAT (SEQ ID NO:18)
FGFR3 S249C	GCATCCGGCAGACGTACA (SEQ ID NO:19)	CCCCGCCTGCAGGAT (SEQ ID NO:20)
FGFR3 G370C	AGGAGCTGGTGGAGGCTGA (SEQ ID NO:21)	CCGTAGCTGAGGATGCCTG (SEQ ID NO:22)
FGFR3 Y373C	CTGGTGGAGGCTGACGAG (SEQ ID NO:23)	AGCCCACCCCGTAGCT (SEQ ID NO:24)
FGFR3 R248C	GTCGTGGAGAACAAGTTTGGC (SEQ ID NO:25)	GTCTGGTTGGCCGGCAG (SEQ ID NO:26)
FGFR3 S249C	GTCGTGGAGAACAAGTTTGGC (SEQ ID NO:27)	GTCTGGTTGGCCGGCAG (SEQ ID NO:28)
FGFR3 G370C	AGGAGCTGGTGGAGGCTGA (SEQ ID NO:29)	CCGTAGCTGAGGATGCCTG (SEQ ID NO:30)
FGFR3 Y373C	GACGAGGCGGGCAGTG (SEQ ID NO:31)	GAAGAAGCCCACCCCGTAG (SEQ ID NO:32)

The presence of one or more FGFR genetic alterations can be evaluated at any suitable time point including upon diagnosis, following tumor resection, following first-line therapy, during clinical treatment, or any combination thereof

For example, a biological sample taken from a patient may be analyzed to determine whether a condition or disease, such as cancer, that the patient is or may be suffering from is one which is characterized by a genetic abnormality or abnormal protein expression which leads to up-regulation of the levels or activity of FGFR or to sensitization of a pathway to normal FGFR activity, or to upregulation of these growth factor signaling pathways such as growth factor ligand levels or growth factor ligand activity or to upregulation of a biochemical pathway downstream of FGFR activation.

Examples of such abnormalities that result in activation or sensitization of the FGFR signal include loss of, or inhibition of apoptotic pathways, up-regulation of the receptors or ligands, or presence of genetic alterations of the receptors or ligands *e.g.* PTK variants. Tumors with genetic alterations of FGFR1, FGFR2 or FGFR3 or FGFR4 or up-regulation, in particular over-expression of FGFR1, or gain-of-function genetic alterations of FGFR2 or FGFR3 may be particularly sensitive to FGFR inhibitors.

The methods, approved drug products, and uses can further comprise evaluating the presence of one or more FGFR genetic alterations in the biological sample before the administering step.

The diagnostic tests and screens are typically conducted on a biological sample selected from tumor biopsy samples, blood samples (isolation and enrichment of shed tumor cells), stool biopsies, sputum, chromosome analysis, pleural fluid, peritoneal fluid, buccal spears, biopsy, circulating DNA, or urine. In certain embodiments, the biological sample is blood, lymph fluid, bone marrow, a solid tumor sample, or any combination thereof. In certain embodiments, the biological sample is a solid tumor sample. In certain embodiments, the biological sample is a blood sample. In certain embodiments, the biological sample is a urine sample.

Methods of identification and analysis of genetic alterations and up-regulation of proteins are known to a person skilled in the art. Screening methods could include, but are not limited to, standard methods such as reverse-transcriptase polymerase chain reaction (RT PCR) or in-situ hybridization such as fluorescence in situ hybridization (FISH).

Identification of an individual carrying a genetic alteration in FGFR, in particular an FGFR genetic alteration as described herein, may mean that the patient would be particularly suitable for treatment with erdafitinib. Tumors may preferentially be screened for presence of a FGFR variant prior to treatment. The screening process will typically involve direct sequencing, oligonucleotide microarray analysis, or a mutant specific antibody. In addition, diagnosis of tumor with such genetic alteration could be performed using techniques known to a person skilled in the art and as described herein such as RT-PCR and FISH.

In addition, genetic alterations of, for example FGFR, can be identified by direct sequencing of, for example, tumor biopsies using PCR and methods to sequence PCR products directly as hereinbefore described. The skilled artisan will recognize that all such well-known techniques for detection of the over expression, activation or mutations of the aforementioned proteins could be applicable in the present case.

In screening by RT-PCR, the level of mRNA in the tumor is assessed by creating a cDNA copy of the mRNA followed by amplification of the cDNA by PCR. Methods of PCR amplification, the selection of primers, and conditions for amplification, are known to a person skilled in the art. Nucleic acid manipulations and PCR are carried out by standard methods, as described for example in Ausubel, F.M. et al., eds. (2004) Current Protocols in Molecular Biology, John Wiley & Sons Inc., or Innis, M.A. et al., eds. (1990) PCR Protocols: a guide to methods and applications, Academic Press, San Diego. Reactions and manipulations involving nucleic acid techniques are also described in Sambrook et al., (2001), 3rd Ed, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory

Press. Alternatively, a commercially available kit for RT-PCR (for example Roche Molecular Biochemicals) may be used, or methodology as set forth in United States patents 4,666,828; 4,683,202; 4,801,531; 5,192,659, 5,272,057, 5,882,864, and 6,218,529 and incorporated herein by reference. An example of an in-situ hybridization technique for assessing mRNA expression would be fluorescence in-situ hybridization (FISH) (see Angerer (1987) Meth. Enzymol., 152: 649).

Generally, in situ hybridization comprises the following major steps: (1) fixation of tissue to be analyzed; (2) prehybridization treatment of the sample to increase accessibility of target nucleic acid, and to reduce nonspecific binding; (3) hybridization of the mixture of nucleic acids to the nucleic acid in the biological structure or tissue; (4) post-hybridization washes to remove nucleic acid fragments not bound in the hybridization, and (5) detection of the hybridized nucleic acid fragments. The probes used in such applications are typically labelled, for example, with radioisotopes or fluorescent reporters. Preferred probes are sufficiently long, for example, from about 50, 100, or 200 nucleotides to about 1000 or more nucleotides, to enable specific hybridization with the target nucleic acid(s) under stringent conditions. Standard methods for carrying out FISH are described in Ausubel, F.M. et al., eds. (2004) Current Protocols in Molecular Biology, John Wiley & Sons Inc and Fluorescence In Situ Hybridization: Technical Overview by John M. S. Bartlett in Molecular Diagnosis of Cancer, Methods and Protocols, 2nd ed.; ISBN: 1-59259-760-2; March 2004, pps. 077-088; Series: Methods in Molecular Medicine.

Methods for gene expression profiling are described by (DePrimo et al. (2003), *BMC Cancer*, 3:3). Briefly, the protocol is as follows: double-stranded cDNA is synthesized from total RNA Using a (dT)24 oligomer (SEQ ID NO: 38 : ttttttttt ttttttttt tttt) for priming first-strand cDNA synthesis, followed by second strand cDNA synthesis with random hexamer primers. The double-stranded cDNA is used as a template for in vitro transcription of cRNA using biotinylated ribonucleotides. cRNA is chemically fragmented according to protocols described by Affymetrix (Santa Clara, CA, USA), and then hybridized overnight on Human Genome Arrays.

Alternatively, the protein products expressed from the mRNAs may be assayed by immunohistochemistry of tumor samples, solid phase immunoassay with microtitre plates, Western blotting, 2-dimensional SDS-polyacrylamide gel electrophoresis, ELISA, flow cytometry and other methods known in the art for detection of specific proteins. Detection methods would include the use of site-specific antibodies. The skilled person will recognize

that all such well-known techniques for detection of upregulation of FGFR or detection of FGFR variants or mutants could be applicable in the present case.

Abnormal levels of proteins such as FGFR can be measured using standard enzyme assays, for example, those assays described herein. Activation or overexpression could also be detected in a tissue sample, for example, a tumor tissue. By measuring the tyrosine kinase activity with an assay such as that from Chemicon International. The tyrosine kinase of interest would be immunoprecipitated from the sample lysate and its activity measured.

Alternative methods for the measurement of the over expression or activation of FGFR including the isoforms thereof, include the measurement of microvessel density. This can for example be measured using methods described by Orre and Rogers (Int J Cancer (1999), 84(2) 101-8). Assay methods also include the use of markers.

Therefore, all of these techniques could also be used to identify tumors particularly suitable for treatment with the compounds of the invention.

Erdafitinib is in particular useful in treatment of a patient having a genetic altered FGFR, in particular a mutated FGFR. In certain embodiments, the urothelial carcinoma is susceptible to an FGFR2 genetic alteration and/or an FGFR3 genetic alteration. In certain embodiments, the FGFR2 or FGFR3 genetic alteration is an FGFR3 gene mutation or an FGFR2 or FGFR3 gene fusion. In some embodiments, the FGFR3 gene mutation is R248C, S249C, G370C, Y373C, or any combination thereof. In further embodiments, the FGFR2 or FGFR3 gene fusion is FGFR3-TACC3, in particular FGFR3-TACC3 V1 or V3, FGFR3-BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7, or any combination thereof.

According to certain embodiments, FGFR2 and/or FGFR3 genetic alterations can be identified using commercially available kits including, but not limiting to, a QIAGEN *therascreen*® FGFR RGQ RT-PCR kit.

FGFR Inhibitor Pharmaceutical Compositions and Routes of Administration

In view of its useful pharmacological properties, the FGFR inhibitor generally, and erdafitinib more specifically, may be formulated into various pharmaceutical forms for administration purposes.

In one embodiment the pharmaceutical composition (*e.g.* formulation) comprises at least one active compound of the invention together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives,

lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents.

To prepare the pharmaceutical compositions, an effective amount of the FGFR inhibitor generally, and erdafitinib more specifically, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets.

The pharmaceutical compositions of the invention, in particular capsules and/or tablets, may include one or more pharmaceutically acceptable excipients (pharmaceutically acceptable carrier) such as disintegrants, diluents, fillers, binders, buffering agents, lubricants, glidants, thickening agents, sweetening agents, flavors, colorants, preservatives and the like. Some excipients can serve multiple purposes.

Suitable disintegrants are those that have a large coefficient of expansion. Examples thereof are hydrophilic, insoluble or poorly water-soluble crosslinked polymers such as crospovidone (crosslinked polyvinylpyrrolidone) and croscarmellose sodium (crosslinked sodium carboxymethylcellulose). The amount of disintegrant in the tablets according to the present invention may conveniently range from about 2.5 to about 15 % w/w and preferably range from about 2.5 to 7 % w/w, in particular range from about 2.5 to 5 % w/w. Because disintegrants by their nature yield sustained release formulations when employed in bulk, it is advantageous to dilute them with an inert substance called a diluent or filler.

A variety of materials may be used as diluents or fillers. Examples are lactose monohydrate, anhydrous lactose, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (*e.g.* micro-crystalline cellulose (Avicel™), silicified microcrystalline cellulose), dihydrated or anhydrous dibasic calcium phosphate, and others known in the art, and mixtures thereof (*e.g.* spray-dried mixture of lactose monohydrate (75 %) with microcrystalline cellulose (25 %)

which is commercially available as Microcelac™). Preferred are microcrystalline cellulose and mannitol. The total amount of diluent or filler in the pharmaceutical compositions of the present invention may conveniently range from about 20 % to about 95 % w/w and preferably ranges from about 55 % to about 95 % w/w, or from about 70 % to about 95 % w/w, or from about 80% to about 95% w/w, or from about 85 % to about 95%.

Lubricants and glidants can be employed in the manufacture of certain dosage forms and will usually be employed when producing tablets. Examples of lubricants and glidants are hydrogenated vegetable oils, e.g hydrogenated Cottonseed oil, magnesium stearate, stearic acid, sodium lauryl sulfate, magnesium lauryl sulfate, colloidal silica, colloidal anhydrous silica talc, mixtures thereof, and others known in the art. Interesting lubricants are magnesium stearate, and mixtures of magnesium stearate with colloidal silica, magnesium stearate being preferred. A preferred glidant is colloidal anhydrous silica.

If present, glidants generally comprise 0.2 to 7.0 % w/w of the total composition weight, in particular 0.5 to 1.5% w/w, more in particular 1 to 1.5% w/w .

If present, lubricants generally comprise 0.2 to 7.0 % w/w of the total composition weight, in particular 0.2 to 2 % w/w, or 0.5 to 2% w/w, or 0.5 to 1.75% w/w, or 0.5 to 1.5% w/w.

Binders can optionally be employed in the pharmaceutical compositions of the present invention. Suitable binders are water-soluble polymers, such as alkylcelluloses such as methylcellulose ; hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose ; hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose ; carboxyalkylcelluloses such as carboxymethylcellulose ; alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose ; carboxyalkylalkylcelluloses such as carboxymethylethylcellulose ; carboxyalkylcellulose esters ; starches ; pectines such as sodium carboxymethylamylopectine ; chitin derivates such as chitosan ; di-, oligo- and polysaccharides such as trehalose, cyclodextrins and derivatives thereof, alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar agar, gummi arabicum, guar gummi and xanthan gummi ; polyacrylic acids and the salts thereof ; polymethacrylic acids, the salts and esters thereof, methacrylate copolymers ; polyvinylpyrrolidone (PVP), polyvinylalcohol (PVA) and copolymers thereof, *e.g.* PVP-VA. Preferably, the water-soluble polymer is a hydroxyalkyl alkylcelluloses, such as for example hydroxypropylmethyl cellulose, *e.g.* hydroxypropylmethyl cellulose 15 cps.

Other excipients such as coloring agents and pigments may also be added to the compositions of the invention. Coloring agents and pigments include titanium dioxide and dyes suitable for food. A coloring agent or a pigment is an optional ingredient in the formulation of the invention, but when used the coloring agent can be present in an amount up to 3.5 % w/w based on the total composition weight.

Flavors are optional in the composition and may be chosen from synthetic flavor oils and flavoring aromatics or natural oils, extracts from plants leaves, flowers, fruits and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, bay oil, anise oil, eucalyptus, thyme oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth, the amount of flavor may depend on a number of factors including the organoleptic effect desired. Generally, the flavor will be present in an amount from about 0 % to about 3 % (w/w).

Formaldehyde scavengers are compounds that are capable of absorbing formaldehyde. They include compounds comprising a nitrogen center that is reactive with formaldehyde, such as to form one or more reversible or irreversible bonds between the formaldehyde scavenger and formaldehyde. For example, the formaldehyde scavenger comprises one or more nitrogen atoms/centers that are reactive with formaldehyde to form a schiff base imine that is capable of subsequently binding with formaldehyde. For example, the formaldehyde scavenger comprises one or more nitrogen centers that are reactive with formaldehyde to form one or more 5-8 membered cyclic rings. The formaldehyde scavenger preferably comprises one or more amine or amide groups. For example, the formaldehyde scavenger can be an amino acid, an amino sugar, an alpha amine compound, or a conjugate or derivative thereof, or a mixture thereof. The formaldehyde scavenger may comprise two or more amines and/or amides.

Formaldehyde scavengers include, for example, glycine, alanine, serine, threonine, cysteine, valine, lecuine, isoleucine, methionine, phenylalanine, tyrosine, aspartic acid, glutamic acid, arginine, lysine, ornithine, citrulline, taurine pyrrolysine, meglumine, histidine, aspartame, proline, tryptophan, citrulline, pyrrolysine, asparagine, glutamine, or a conjugate or mixture thereof; or, whenever possible, pharmaceutically acceptable salts thereof.

In an aspect of the invention, the formaldehyde scavenger is meglumine or a pharmaceutically acceptable salt thereof, in particular meglumine base.

In an embodiment, in the methods and uses as described herein, erdafitinib is administered or is to be administered as a pharmaceutical composition, in particular a tablet or capsule, comprising erdafitinib or a pharmaceutically acceptable salt thereof, in particular erdafitinib base; a formaldehyde scavenger, in particular meglumine or a pharmaceutically acceptable salt thereof, in particular meglumine base; and a pharmaceutically acceptable carrier.

It is another object of the invention to provide a process of preparing a pharmaceutical composition as described herein, in particular in the form of a tablet or a capsule, characterized by blending a formaldehyde scavenger, in particular meglumine, and erdafitinib, a pharmaceutically acceptable salt thereof or a solvate thereof, in particular erdafitinib base, with a pharmaceutically acceptable carrier and compressing said blend into tablets or filling said blend in capsules.

Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, *e.g.*, as a transdermal patch, as a spot-on, as an ointment. It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers,

injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient, calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof. Preferred forms are tablets and capsules.

In certain embodiments, the FGFR inhibitor is present in a solid unit dosage form, and a solid unit dosage form suitable for oral administration. The unit dosage form may contain about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg of the FGFR inhibitor per unit dose form or an amount in a range bounded by two of these values, in particular 3, 4 or 5 mg per unit dose.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight, even more preferably from 0.1 to 50 % by weight of the compound of the present invention, and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 % by weight, even more preferably from 50 to 99.9 % by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the composition.

Tablets or capsules of the present invention may further be film-coated *e.g.* to improve taste, to provide ease of swallowing and an elegant appearance. Polymeric film-coating materials are known in the art. Preferred film coatings are water-based film coatings opposed to solvent based film coatings because the latter may contain more traces of aldehydes. A preferred film-coating material is Opadry® II aqueous film coating system, *e.g.* Opadry® II 85F, such as Opadry® II 85F92209. Further preferred film coatings are water-based film coatings that protects from environmental moisture, such as Readilycoat® (*e.g.* Readilycoat® D), AquaPolish® MS, Opadry® amb, Opadry® amb II, which are aqueous moisture barrier film coating systems. A preferred film-coating is Opadry® amb II, a high-performance moisture barrier film coating which is a PVA-based immediate release system, without polyethylene glycol.

In tablets according to the invention, the film coat in terms of weight preferably accounts for about 4 % (w/w) or less of the total tablet weight.

For capsules according to the present invention, hypromellose (HPMC) capsules are preferred over gelatin capsules.

In an aspect of the invention, the pharmaceutical compositions as described herein, in particular in the form of a capsule or a tablet, comprise from 0.5 mg to 20 mg base equivalent, or from 2 mg to 20 mg base equivalent, or from 0.5 mg to 12 mg base equivalent, or from 2 mg to 12 mg base equivalent, or from 2 mg to 10 mg base equivalent, or from 2 mg to 6 mg base equivalent, or 2 mg base equivalent, 3 mg base equivalent, 4 mg base equivalent, 5 mg base equivalent, 6 mg base equivalent, 7 mg base equivalent, 8 mg base equivalent, 9 mg base equivalent, 10 mg base equivalent, 11 mg base equivalent or 12 mg base equivalent of erdafitinib, a pharmaceutically acceptable salt thereof or a solvate thereof. In particular, the pharmaceutical compositions as described herein comprise 3mg base equivalent, 4 mg base equivalent or 5 mg base equivalent of erdafitinib, a pharmaceutically acceptable salt thereof or a solvate thereof, in particular 3 mg or 4 mg or 5 mg of erdafitinib base.

In an aspect of the invention, the pharmaceutical compositions as described herein, in particular in the form of a capsule or a tablet, comprise from 0.5 mg to 20 mg, or from 2 mg to 20 mg, or from 0.5 mg to 12 mg, or from 2 mg to 12 mg, or from 2 mg to 10 mg, or from 2 mg to 6 mg, or 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg or 12 mg of erdafitinib base. In particular, the pharmaceutical compositions as described herein comprise 3mg, 4 mg or 5 mg of erdafitinib base. In particular, the pharmaceutical compositions as described herein comprise 3mg, 4 mg or 5 mg of erdafitinib base and from about 0.5 to about 5 % w/w, from about 0.5 to about 3 % w/w, from about 0.5 to about 2% w/w, from about 0.5 to about 1.5% w/w, or from about 0.5 to about 1% w/w of a formaldehyde scavenger, in particular meglumine. In particular, the pharmaceutical compositions as described herein comprise 3mg, 4 mg or 5 mg of erdafitinib base and from about 0.5 to about 1.5% w/w or from about 0.5 to about 1% w/w of a formaldehyde scavenger, in particular meglumine.

In an aspect of the invention, more than one, *e.g.* two, pharmaceutical compositions as described herein can be administered in order to obtain a desired dose, *e.g.* a daily dose. For example, for a daily dose of 8 mg base equivalent of erdafitinib, 2 tablets or capsules of 4 mg erdafitinib base equivalent each may be administered; or a tablet or a capsule of 3 mg erdafitinib base equivalent and a tablet or capsule of 5 mg base equivalent may be administered. For example, for a daily dose of 9 mg base equivalent of erdafitinib, 3 tablets

or capsules of 3 mg erdafitinib base equivalent each may be administered; or a tablet or a capsule of 4 mg erdafitinib base equivalent and a tablet or capsule of 5 mg base equivalent may be administered.

The amount of formaldehyde scavenger, in particular meglumine, in the pharmaceutical compositions according to the present invention may range from about 0.1 to about 10 % w/w, about 0.1 to about 5 % w/w, from about 0.1 to about 3 % w/w, from about 0.1 to about 2% w/w, from about 0.1 to about 1.5% w/w, from about 0.1 to about 1% w/w, from about 0.5 to about 5 % w/w, from about 0.5 to about 3 % w/w, from about 0.5 to about 2% w/w, from about 0.5 to about 1.5% w/w, from about 0.5 to about 1% w/w.

According to particular embodiments, erdafitinib is supplied as 3 mg, 4 mg or 5 mg film-coated tablets for oral administration and contains the following inactive ingredients or equivalents thereof: Tablet Core: croscarmellose sodium, magnesium stearate, mannitol, meglumine, and microcrystalline cellulose; and Film Coating: Opadry amb II: Glycerol monocaprylocaprate Type I, polyvinyl alcohol-partially hydrolyzed, sodium lauryl sulfate, talc, titanium dioxide, iron oxide yellow, iron oxide red (for orange and brown tablets), ferrosoferric oxide/iron oxide black (for brown tablets).

Studies that look at safety seek to identify any potential adverse effects that may result from exposure to the drug. Efficacy is often measured by determining whether an active pharmaceutical ingredient demonstrates a health benefit over a placebo or other intervention when tested in an appropriate situation, such as a tightly controlled clinical trial.

The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means that the beneficial effects of that formulation, composition or ingredient on the general health of the human being treated substantially outweigh its detrimental effects, to the extent any exist.

All formulations for oral administration are in dosage form suitable for such administration.

Anti-PD1 Antibody Pharmaceutical Compositions and Routes of Administration

In view of its useful pharmacological properties, the anti-PD1 antibody or antigen fragment thereof generally, and cetrelimab more specifically, may be formulated into various pharmaceutical forms for administration purposes.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration in a pharmaceutical composition comprising

between about 10 mg/ml to about 30 mg/ml of the anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients.

Exemplary buffers that may be used are acetic acid, citric acid, formic acid, succinic acid, phosphoric acid, carbonic acid, malic acid, aspartic acid, histidine, boric acid, Tris buffers, HEPPSO and HEPES.

Exemplary antioxidants that may be used are ascorbic acid, methionine, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite, lecithin, citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol and tartaric acid.

Exemplary amino acids that may be used are histidine, isoleucine, methionine, glycine, arginine, lysine, L-leucine, tri-leucine, alanine, glutamic acid, L-threonine, and 2-phenylamine.

Exemplary surfactants that may be used are polysorbates (e.g., polysorbate-20 or polysorbate-80); polyoxamers (e.g., poloxamer 188); Triton; sodium octyl glycoside; lauryl-, myristyl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl- or stearyl-sarcosine; linoleyl-, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (e.g., lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl oleyl-taurate; and the MONAQUA™ series (Mona Industries, Inc., Paterson, N.J.), polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol (e.g., PLURONICS™, PF68, etc).

Exemplary preservatives that may be used are phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof.

Exemplary saccharides that may be used are monosaccharides, disaccharides, trisaccharides, polysaccharides, sugar alcohols, reducing sugars, nonreducing sugars such as glucose, sucrose, trehalose, lactose, fructose, maltose, dextran, glycerin, dextran, erythritol, glycerol, arabitol, sylitol, sorbitol, mannitol, mellibiose, melezitose, raffinose, mannotriose, stachyose, maltose, lactulose, maltulose, glucitol, maltitol, lactitol or iso-maltulose.

Exemplary salts that may be used are acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as

from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N′-dibenzylethylenediamine, N-methylglucamine, chloroprocaine, choline, diethanolamine, ethylenediamine, procaine and the like. An exemplary salt is sodium chloride.

The amounts of pharmaceutically acceptable carrier(s) in the pharmaceutical compositions may be determined experimentally based on the activities of the carrier(s) and the desired characteristics of the formulation, such as stability and/or minimal oxidation.

In some embodiments, the pharmaceutical composition comprises histidine. In some embodiments, the pharmaceutical composition comprises histidine at a concentration of from about 1 mM to about 50 mM. In some embodiments, the pharmaceutical composition comprises histidine at a concentration of from about 5 mM to about 50 mM. In some embodiments, the pharmaceutical composition comprises histidine at a concentration of from about 5 mM to about 30 mM. In some embodiments, the pharmaceutical composition comprises histidine at a concentration of from about 5 mM to about 20 mM. In some embodiments, the pharmaceutical composition comprises histidine at a concentration of from about 5 mM to about 15 mM. In some embodiments, the pharmaceutical composition comprises histidine at a concentration of from about 5 mM to about 10 mM.

In some embodiments, the pharmaceutical composition comprises histidine at a concentration of about 1 mM, about 2 mM, about 3 mM, about 4 mM, about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, about 20 mM, about 21 mM, about 22 mM, about 23 mM, about 24 mM, about 25 mM, about 26 mM, about 27 mM, about 28 mM, about 29 mM, about 30 mM, about 31 mM, about 32 mM, about 33 mM, about 34 mM, about 35 mM, about 36 mM, about 37 mM, about 38 mM, about 39 mM, about 40 mM, about 41 mM, about 42 mM, about 43 mM, about 44 mM, about 45 mM, about 46 mM, about 47 mM, about 48 mM, about 49 mM or about 50 mM.

In some embodiments, the pharmaceutical composition comprises histidine at a concentration of about 10 mM.

In some embodiments, the pharmaceutical composition comprises sucrose. In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of from about 1% (w/v) to about 20% (w/v). In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of from about 2% (w/v) to about 18% (w/v). In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of from about 4% (w/v) to about 16% (w/v). In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of from about 6% (w/v) to about 14% (w/v). In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of from about 6% (w/v) to about 12% (w/v). In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of from about 6% (w/v) to about 10% (w/v).

In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of about 1% (w/v), about 2% (w/v), about 3% (w/v), about 4% (w/v), about 5% (w/v), about 6% (w/v), about 7% (w/v), about 8% (w/v), about 9% (w/v), about 10% (w/v), about 11% (w/v), about 12% (w/v), about 13% (w/v), about 14% (w/v), about 15% (w/v), about 16% (w/v), about 17% (w/v), about 18% (w/v), about 19% (w/v) or about 20% (w/v), In some embodiments, the pharmaceutical composition comprises sucrose at a concentration of about 8% (w/v).

In some embodiments, the pharmaceutical composition comprises polysorbate-20. In some embodiments, the pharmaceutical composition comprises polysorbate-20 (PS-20) at a concentration of from about 0.01% (w/v) to about 0.1% (w/v). In some embodiments, the pharmaceutical composition comprises polysorbate-20 (PS-20) at a concentration of from about 0.01% (w/v) to about 0.08% (w/v). In some embodiments, the pharmaceutical composition comprises polysorbate-20 (PS-20) at a concentration of from about 0.02% (w/v) to about 0.06% (w/v).

In some embodiments, the pharmaceutical composition comprises polysorbate-20 (PS-20) at a concentration of about 0.01% (w/v), about 0.02% (w/v), about 0.03% (w/v), about 0.04% (w/v), about 0.05% (w/v), about 0.06% (w/v), about 0.07% (w/v), about 0.08% (w/v), about 0.09% (w/v) or about 0.1% (w/v).

In some embodiments, the pharmaceutical composition comprises polysorbate-20 (PS-20) at a concentration of about 0.04% (w/v).

In some embodiments, the pharmaceutical composition comprises EDTA. In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of from about 1 μg/ml to about 50 μg/ml. In some embodiments, the pharmaceutical composition

comprises EDTA at a concentration of from about 5 μg/ml to about 50 μg/ml. In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of from about 5 μg/ml to about 30 μg/ml. In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of from about 5 μg/ml to about 20 μg/ml. In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of from about 5 μg/ml to about 15 μg/ml. In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of from about 5 μg/ml to about 10 μg/ml.

In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of about 1 μg/ml, about 2 μg/ml, about 3 μg/ml, about 4 μg/ml, about 5 μg/ml, about 6 μg/ml, about 7 μg/ml, about 8 μg/ml, about 9 μg/ml, about 10 μg/ml, about 11 μg/ml, about 12 μg/ml, about 13 μg/ml, about 14 μg/ml, about 15 μg/ml, about 16 μg/ml, about 17 μg/ml, about 18 μg/ml, about 19 μg/ml, about 20 μg/ml, about 21 μg/ml, about 22 μg/ml, about 23 μg/ml, about 24 μg/ml, about 25 μg/ml, about 26 μg/ml, about 27 μg/ml, about 28 μg/ml, about 29 μg/ml, about 30 μg/ml, about 31 μg/ml, about 32 μg/ml, about 33 μg/ml, about 34 μg/ml, about 35 μg/ml, about 36 μg/ml, about 37 μg/ml, about 38 μg/ml, about 39 μg/ml, about μg/ml, about 41 μg/ml, about 42 μg/ml, about 43 μg/ml, about 44 μg/ml, about 45 μg/ml, about 46 μg/ml, about 47 μg/ml, about 48 μg/ml, about 49 μg/ml or about 50 μg/ml.

In some embodiments, the pharmaceutical composition comprises EDTA at a concentration of about 20 μg/ml.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration in a pharmaceutical composition comprising between about 10 mg/ml to about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, histidine, sucrose, polysorbate-20 and EDTA.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration in a pharmaceutical composition comprising between about 10 mg/ml to about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 μg/ml EDTA at pH 6.5.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration in a pharmaceutical composition comprising about 10 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment

thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 μg/ml EDTA at pH 6.5.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered or provided for administration in a pharmaceutical composition comprising about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 μg/ml EDTA at pH 6.5.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is provided for administration as a lyophilized formulation comprising between about 90 mg and about 240 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is provided for administration as a lyophilized formulation comprising about 90 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is provided for administration as a lyophilized formulation comprising about 240 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is provided for administration as a lyophilized formulation comprising about 360 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is provided for administration as a lyophilized formulation comprising about 480 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients.

In some embodiments, the lyophilized formulation, once reconstituted, comprises about 30 mg/ml of the anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 μg/ml EDTA at pH 6.5.

In some embodiments, the pharmaceutical composition is a liquid. In some embodiments, the pharmaceutical composition is a frozen liquid. In some embodiments, the pharmaceutical composition is a lyophilized powder.

"Lyophilization," "lyophilized," and "freeze-dried" refer to a process by which the material to be dried is first frozen and then the ice or frozen solvent is removed by sublimation in a vacuum environment. An excipient may be included in pre-lyophilized formulations to enhance stability of the lyophilized product upon storage.

In some embodiments, the pharmaceutical composition is provided in a volume of between about 1 ml to about 20 ml. In some embodiments, the pharmaceutical composition is provided in a volume of about 1 ml, about 2 ml, about 3 ml, about 4 ml, about 5 ml, about 6 ml, about 7 ml, about 8 ml, about 9 ml, about 10 ml, about 11 ml, about 12 ml, about 13 ml, about 14 ml, about 15 ml, about 16 ml, about 17 ml, about 18 ml, about 19 ml or about 20 ml. In some embodiments, the pharmaceutical composition is provided or reconstituted in a volume of about 3 ml. In some embodiments, the pharmaceutical composition is provided or reconstituted in a volume of about 3.3 ml. In some embodiments, the pharmaceutical composition is provided or reconstituted in a volume of about 8 ml. In some embodiments, the pharmaceutical composition is provided or reconstituted in a volume of about 8.6 ml. In some embodiments, the pharmaceutical composition is provided or reconstituted in a volume of about 8.8 ml.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof generally, or cetrelimab specifically, is administered or provided for administration in a pharmaceutical composition comprising about 10 mg/ml of the anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 μg/ml EDTA at pH 6.5 in a volume of about 3.3 ml.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof generally, or cetrelimab specifically, is administered or provided for administration as a lyophilized formulation comprising about 90 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients that upon reconstitution into about 3.3 ml comprises about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 μg/ml EDTA at pH 6.5.

In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof generally, or cetrelimab specifically, is administered or provided for administration as a lyophilized formulation comprising about 240 mg of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof and one or more pharmaceutically acceptable excipients that upon reconstitution into about 8.6 ml comprises about 30 mg/ml of the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof, about 10 mM histidine, about 8.0% (w/v) sucrose, about 0.04% (w/v) polysorbate-20 and about 20 μg/ml EDTA at pH 6.5.

In some embodiments, the lyophilized formulation is reconstituted into sterile water for injection (sWFI).

"Reconstitute", "reconstituted" or "reconstitution" refers to dissolving the lyophilized formulation in a diluent so that the protein in the lyophilized formulation is dispersed in the reconstituted formulation. The reconstituted formulation is suitable for administration, e.g. parenteral administration), and may optionally be suitable for subcutaneous administration. In some embodiments, the diluent is sterile water for injection (sWFI).

"Pharmaceutical composition", "pharmaceutical formulation" or "formulation" as used in this section refers to a combination of an active ingredient (*e.g.* the anti-PD-1 antibody) and one or more excipients in either liquid or solid (*e.g.* lyophilized) form.

All formulations for intravenous or subcutaneous administration are in dosage form suitable for such administration.

Methods of Dosing and Treatment Regimens

In one aspect, described herein are methods of treating urothelial carcinoma comprising, consisting of, or consisting essentially of administering a therapeutically effective amount of an FGFR inhibitor to a patient that has been diagnosed with urothelial carcinoma, wherein the FGFR inhibitor is administered orally. In some embodiments, the FGFR inhibitor generally, and erdafitinib specifically is administered daily, in particular once daily. In some embodiments, the FGFR inhibitor generally, and erdafitinib specifically is administered twice-a-day. In some embodiments, the FGFR inhibitor generally, and erdafitinib specifically is administered three times a day. In some embodiments, the FGFR inhibitor generally, and erdafitinib specifically is administered four times a day. In some embodiments, the FGFR inhibitor generally, and erdafitinib specifically is administered every other day. In some embodiments, the FGFR inhibitor generally, and erdafitinib specifically is

administered weekly. In some embodiments, the FGFR inhibitor generally, and erdafitinib specifically is administered twice a week. In some embodiments, the FGFR inhibitor generally, and erdafitinib specifically is administered every other week. In some embodiments, the FGFR inhibitor generally, and erdafitinib specifically is administered orally on a continuous daily dosage schedule.

In general, doses of the FGFR inhibitor, and erdafitinib specifically, employed for treatment of the diseases or conditions described herein in humans are typically in the range of about 1 to 20 mg per day. In some embodiments, the FGFR inhibitor, and erdafitinib specifically, is administered orally to the human at a dose of about 1 mg per day, about 2 mg per day, about 3 mg per day, about 4 mg per day, about 5 mg per day, about 6 mg per day, about 7 mg per day, about 8 mg per day, about 9 mg per day, about 10 mg per day, about 11 mg per day, about 12 mg per day, about 13 mg per day, about 14 mg per day, about 15 mg per day, about 16 mg per day, about 17 mg per day, about 18 mg per day, about 19 mg per day or about 20 mg per day. In an embodiment, erdafitinib is administered at a dose of 8 mg per day.

In some embodiments, erdafitinib is administered orally. In certain embodiments, erdafitinib is administered orally at a dose of about 8 mg once daily. In further embodiments, the dose of erdafitinib is increased from 8 mg once daily to 9 mg once daily. In still further embodiments, 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 administration of erdafitinib at 8 mg once daily resulted in no ocular disorder; or (b) administration of erdafitinib at 8 mg once daily resulted in no Grade 2 or greater adverse reaction.

In certain embodiments, the dose of erdafitinib is increased from 8 mg once daily to 9 mg once daily at 14 days after initiating treatment. In certain embodiments, the dose of erdafitinib is increased from 8 mg once daily to 9 mg once daily at 15 days after initiating treatment. In certain embodiments, the dose of erdafitinib is increased from 8 mg once daily to 9 mg once daily at 16 days after initiating treatment. In certain embodiments, the dose of erdafitinib is increased from 8 mg once daily to 9 mg once daily at 17 days after initiating treatment. In certain embodiments, the dose of erdafitinib is increased from 8 mg once daily to 9 mg once daily at 18 days after initiating treatment. In certain embodiments, the dose of erdafitinib is increased from 8 mg once daily to 9 mg once daily at 19 days after initiating

treatment. In certain embodiments, the dose of erdafitinib is increased from 8 mg once daily to 9 mg once daily at 20 days after initiating treatment. In certain embodiments, the dose of erdafitinib is increased from 8 mg once daily to 9 mg once daily at 21 days after initiating treatment

In an embodiment, erdafitinib is administered at a dose of 8 mg, in particular 8 mg once daily. In an embodiment, erdafitinib is administered at a dose of 8 mg, in particular 8 mg once daily, with an option to uptitrate to 9 mg depending on serum phosphate levels (*e.g.* serum phosphate levels are < 5.5 mg/dL, or are < 7 mg/dL or range from and include 7 mg/dL to ≤9 mg/dL or are ≤9 mg/dL), and depending on treatment-related adverse events observed. In an embodiment, the levels of serum phosphate for determining whether or not to up-titrate are measured on a treatment day during the first cycle of erdafitinib treatment, in particular on day 14 ± 2 days, more in particular on day 14, of erdafitinib administration.

In an embodiment, the treatment cycle as used herein is a 28-day cycle. In certain embodiments, the treatment cycle is a 28-day cycle for up to two years. In certain embodiments, the treatment cycle is four weeks.

In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day. In some embodiments, the FGFR inhibitor is conveniently presented in divided doses that are administered simultaneously (or over a short period of time) once a day. In some embodiments, the FGFR inhibitor generally, and erdafitinib specifically, is conveniently presented in divided doses that are administered in equal portions twice-a-day. In some embodiments, the FGFR inhibitor generally, and erdafitinib specifically, is conveniently presented in divided doses that are administered in equal portions three times a day. In some embodiments, the FGFR inhibitor is conveniently presented in divided doses that are administered in equal portions four times a day.

In certain embodiments, the desired dose may be delivered in 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fractional unit dosages throughout the course of the day, such that the total amount of FGFR inhibitor generally, and erdafitinib specifically, delivered by the fractional unit dosages over the course of the day provides the total daily dosages.

In some embodiments, the amount of the FGFR inhibitor generally, and erdafitinib specifically, that is given to the human varies depending upon factors such as, but not limited

to, condition and severity of the disease or condition, and the identity (*e.g.*, weight) of the human, and the particular additional therapeutic agents that are administered (if applicable).

In further embodiments, the anti-PD1 antibody generally, and cetrelimab specifically, is administered by intravenous infusion. In some embodiments, the antagonistic anti-PD-1 antibody or the antigen binding fragment thereof is diluted into a volume of between about 100 ml and 1000 ml prior to administration. In some embodiments, duration of the intravenous infusion is between about 20 minutes and about 80 minutes. In some embodiments, duration of the intravenous infusion is about 20, about 30, about 40, about 50, about 60, about 70 or about 80 minutes.

In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered by one or more subcutaneous injections.

In some embodiments, the anti-PD1 antibody or the antigen binding fragment thereof is administered by an intravenous administration, by a subcutaneous administration, or a combination thereof.

In still further embodiments, the anti-PD1 antibody or the antigen binding fragment thereof generally, and cetrelimab specifically, is administered at a dose of about 240 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks. In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered at the dosage of about 240 mg once every two weeks. In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered at a dose of about 240 mg once every three weeks. In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered at a dose of about 240 mg once every four weeks. In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered at a dose of about 240 mg once every five weeks. In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered at a dose of about 240 mg once every six weeks. In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered at a dose of about 480 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks. In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered at a dose of about 480 mg once every two weeks. In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered at a dose of about 480 mg once every three weeks. In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered

at a dose of about 480 mg once every four weeks. In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered at a dose of about 480 mg once every five weeks. In some embodiments, the anti-PD-1 antibody or the antigen binding fragment thereof is administered at a dose of about 480 mg once every six weeks.

In certain embodiments, the anti-PD1 antibody or the antigen binding fragment thereof generally, and cetrelimab specifically, is administered at a dose of about 240 mg to about 480 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks. In certain embodiments, the anti-PD1 antibody or the antigen binding fragment thereof generally, and cetrelimab specifically, is administered at a dose of about 80 mg to about 1000 mg once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks.

In some embodiments, the anti-PD1 antibody or the antigen binding fragment thereof generally, and cetrelimab specifically, is administered at a dosage of about 240 mg once in two weeks; at a dosage of about 480 mg once in four weeks; or as an initial dose of about 240 mg followed by a second dose of about 480 mg six weeks after the initial dose, and thereafter about 480 mg once in four weeks; or as an initial dose of about 240 mg followed by a second dose of about 480 mg six weeks after the initial dose, and thereafter about 240 mg once in two weeks. In some embodiments, the anti-PD1 antibody or the antigen binding fragment thereof generally, and cetrelimab specifically, is administered at a dosage of about 240 mg once every two weeks in cycle 1 to 4 of treatment followed by a dose of about 480 mg every four weeks as of cycle 5 of treatment and beyond.

In one embodiment, erdafitinib is administered or is to be administered at a dose of 8 mg daily, and cetrelimab is administered or is to be administered at a dose of 240 mg every two weeks starting at cycle 1 day 1 (C1D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 8 mg daily, and cetrelimab is administered or is to be administered intravenously at a dose of 240 mg every two weeks starting at cycle 1 day 1 (C1D1).

In one embodiment, erdafitinib is administered or is to be administered at a dose of 8 mg daily, and cetrelimab is administered or is to be administered at a dose of 480 mg every four weeks, in particular starting at cycle 1 day 1 (C1D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 8 mg daily, and cetrelimab is administered or is to be administered intravenously at a dose of 480 mg every four weeks, in particular starting at cycle 1 day 1 (C1D1).

In one embodiment, erdafitinib is administered or is to be administered at a dose of 8 mg daily, and cetrelimab is administered or is to be administered at a dose of 240 mg every two weeks starting at cycle 1 day 1 (C1D1), and as of cycle 5 cetrelimab is administered or is to be administered at a dose of 480 mg every four weeks starting at cycle 5 day 1 (C5D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 8 mg daily, and cetrelimab is administered or is to be administered at a dose of 240 mg every two weeks starting at cycle 1 day 1 (C1D1), and as of cycle 5 cetrelimab is administered or is to be administered at a dose of 480 mg every four weeks starting at cycle 5 day 1 (C5D1).

In one embodiment, erdafitinib is administered or is to be administered at a dose of 8 mg daily, and cetrelimab is administered or is to be administered at a dose of 360 mg every three weeks starting at cycle 1 day 1 (C1D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 8 mg daily, and cetrelimab is administered or is to be administered at a dose of 360 mg every three weeks starting at cycle 1 day 1 (C1D1). In an embodiment, the treatment further comprises platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment, the platinum chemotherapy, in particular cisplatin or carboplatin, is administered or is to be administered every three weeks starting at cycle 1 day 1 (C1D1). In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

In one embodiment, erdafitinib is administered or is to be administered at a dose of 8 mg daily with an option to uptitrate to 9 mg depending on serum phosphate levels, in particular serum phosphate levels as described herein, at about day 14 of erdafitinib administration, and cetrelimab is administered or is to be administered at a dose of 240 mg every two weeks starting at cycle 1 day 1 (C1D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 8 mg daily with an option to uptitrate to 9 mg depending on serum phosphate levels, in particular serum phosphate levels as described herein, at about day 14 of erdafitinib administration, and cetrelimab is administered or is to be administered intravenously at a dose of 240 mg every two weeks starting at cycle 1 day 1 (C1D1).

In one embodiment, erdafitinib is administered or is to be administered at a dose of 8 mg daily with an option to uptitrate to 9 mg depending on serum phosphate levels, in particular serum phosphate levels as described herein, at about day 14 of erdafitinib administration, and cetrelimab is administered or is to be administered at a dose of 480 mg every four weeks, in particular starting at cycle 1 day 1 (C1D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 8 mg daily with an option to uptitrate to 9 mg depending on serum phosphate levels, in particular serum phosphate levels as described herein, at about day 14 of erdafitinib administration, and cetrelimab is administered or is to be administered intravenously at a dose of 480 mg every four weeks, in particular starting at cycle 1 day 1 (C1D1).

In one embodiment, erdafitinib is administered or is to be administered at a dose of 8 mg daily with an option to uptitrate to 9 mg depending on serum phosphate levels, in particular serum phosphate levels as described herein, at about day 14 of erdafitinib administration, and cetrelimab is administered or is to be administered at a dose of 240 mg every two weeks starting at cycle 1 day 1 (C1D1), and as of cycle 5 cetrelimab is administered or is to be administered at a dose of 480 mg every four weeks starting at cycle 5 day 1 (C5D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 8 mg daily with an option to uptitrate to 9 mg depending on serum phosphate levels, in particular serum phosphate levels as described herein, at about day 14 of erdafitinib administration, and cetrelimab is administered or is to be administered at a dose of 240 mg every two weeks starting at cycle 1 day 1 (C1D1), and as of cycle 5 cetrelimab is administered or is to be administered at a dose of 480 mg every four weeks starting at cycle 5 day 1 (C5D1).

In one embodiment, erdafitinib is administered or is to be administered at a dose of 8 mg daily with an option to uptitrate to 9 mg depending on serum phosphate levels, in particular serum phosphate levels as described herein, at about day 14 of erdafitinib administration, and cetrelimab is administered or is to be administered at a dose of 360 mg every three weeks starting at cycle 1 day 1 (C1D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 8 mg daily with an option to uptitrate to 9 mg depending on serum phosphate levels, in particular serum phosphate levels as described herein, at about day 14 of erdafitinib administration, and cetrelimab is administered or is to be administered at a dose of 360 mg every three weeks starting at cycle 1 day 1 (C1D1). In an embodiment, the treatment further comprises platinum chemotherapy, in

particular cisplatin or carboplatin. In an embodiment, the platinum chemotherapy, in particular cisplatin or carboplatin, is administered or is to be administered every three weeks starting at cycle 1 day 1 (C1D1). In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

In one embodiment, erdafitinib is administered or is to be administered at a dose of 6 mg daily, and cetrelimab is administered or is to be administered at a dose of 240 mg every two weeks starting at cycle 1 day 1 (C1D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 6 mg daily, and cetrelimab is administered or is to be administered intravenously at a dose of 240 mg every two weeks starting at cycle 1 day 1 (C1D1).

In one embodiment, erdafitinib is administered or is to be administered at a dose of 6 mg daily, and cetrelimab is administered or is to be administered at a dose of 480 mg every four weeks, in particular starting at cycle 1 day 1 (C1D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 6 mg daily, and cetrelimab is administered or is to be administered intravenously at a dose of 480 mg every four weeks, in particular starting at cycle 1 day 1 (C1D1).

In one embodiment, erdafitinib is administered or is to be administered at a dose of 6 mg daily, and cetrelimab is administered or is to be administered at a dose of 240 mg every two weeks starting at cycle 1 day 1 (C1D1), and as of cycle 5 cetrelimab is administered or is to be administered at a dose of 480 mg every four weeks starting at cycle 5 day 1 (C5D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 6 mg daily, and cetrelimab is administered or is to be administered at a dose of 240 mg every two weeks starting at cycle 1 day 1 (C1D1), and as of cycle 5 cetrelimab is administered or is to be administered at a dose of 480 mg every four weeks starting at cycle 5 day 1 (C5D1).

In one embodiment, erdafitinib is administered or is to be administered at a dose of 6 mg daily, and cetrelimab is administered or is to be administered at a dose of 360 mg every three weeks, in particular starting at cycle 1 day 1 (C1D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 6 mg daily, and cetrelimab is administered or is to be administered intravenously at a dose of 360 mg every

three weeks, in particular starting at cycle 1 day 1 (C1D1). In an embodiment, the treatment further comprises platinum chemotherapy, in particular cisplatin or carboplatin. In an embodiment, the platinum chemotherapy, in particular cisplatin or carboplatin, is administered or is to be administered every three weeks starting at cycle 1 day 1 (C1D1). In an embodiment, the platinum chemotherapy is administered or is to be administered at a dose of 50 mg/m^2, or 60 mg/m^2, or at a dose for a AUC of 4 mg/mL*min, or at a dose for a AUC of 5 mg/mL*min. In an embodiment, cisplatin is administered or is to be administered at a dose of 50 mg/m^2 or 60 mg/m^2. In an embodiment, carboplatin is administered or is to be administered at a dose for an AUC of 4 mg/mL*min or at a dose for an AUC of 5 mg/mL*min.

In further embodiments, the platinum chemotherapy generally, and cisplatin or carboplatin specifically, is administered by intravenous infusion.

In still further embodiments, the cisplatin is administered at a dose of about 50 mg/m^2 once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks. In some embodiments the cisplatin is administered at the dosage of about 50 mg/m^{2}once every two weeks. In some embodiments, the cisplatin is administered at a dose of about 50 mg/m^2 once every three weeks. In some embodiments, the cisplatin is administered at a dose of about 50 mg/m^2 once every four weeks. In some embodiments, the cisplatin is administered at a dose of about 50 mg/m^{2}once every five weeks. In some embodiments, the cisplatin is administered at a dose of about 50 mg/m^2 once every six weeks. In some embodiments, the cisplatin is administered at a dose of about 60 mg/m^2 once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks. In some embodiments, the cisplatin is administered at a dose of about 60 mg/m^2 once every two weeks. In some embodiments, the cisplatin is administered at a dose of about 60 mg/m^2 once every three weeks. In some embodiments, the cisplatin is administered at a dose of about 60 mg/m^2 once every four weeks. In some embodiments, the cisplatin is administered at a dose of about 60 mg/m^2 once every five weeks. In some embodiments, the cisplatin is administered at a dose of about 60 mg/m^2 once every six weeks.

In still further embodiments, the carboplatin is administered at a dose of about AUC 4 mg/mL/min once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks. In some embodiments the carboplatin is administered at the dosage of about AUC 4 mg/mL/min once every two weeks. In some

embodiments, the carboplatin is administered at a dose of about AUC 4 mg/mL/min once every three weeks. In some embodiments, the carboplatin is administered at a dose of about AUC 4 mg/mL/min once every four weeks. In some embodiments, the carboplatin is administered at a dose of about AUC 4 mg/mL/min once every five weeks. In some embodiments, the carboplatin is administered at a dose of about AUC 4 mg/mL/min once every six weeks. In some embodiments, the carboplatin is administered at a dose of about AUC 5 mg/mL/min once every two weeks, once every three weeks, once every four weeks, once every five weeks or once every six weeks. In some embodiments, the carboplatin is administered at a dose of about AUC 5 mg/mL/min once every two weeks. In some embodiments, the carboplatin is administered at a dose of about AUC 5 mg/mL/min once every three weeks. In some embodiments, the carboplatin is administered at a dose of about AUC 5 mg/mL/min once every four weeks. In some embodiments, the carboplatin is administered at a dose of about AUC 5 mg/mL/min once every five weeks. In some embodiments, the cisplatin is administered at a dose of about AUC 5 mg/mL/min once every six weeks.

In one embodiment, erdafitinib is administered or is to be administered at a dose of 8 mg daily, and cetrelimab is administered or is to be administered at a dose of 360 mg every three weeks starting at cycle 1 day 1 (C1D1), and cisplatin or carboplatin is administered or is to be administered every three weeks, in particular starting at cycle 1 day 1 (C1D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 8 mg daily, and cetrelimab is administered or is to be administered intravenously at a dose of 360 mg every three weeks starting at cycle 1 day 1 (C1D1), and cisplatin or carboplatin is administered or is to be administered every three weeks, in particular starting at cycle 1 day 1 (C1D1). In an embodiment, cisplatin is administered or is to be administered every three weeks at a dose of 50 mg/m^2 Q3W, in particular starting at cycle 1 day 1 (C1D1). In an embodiment, cisplatin is administered or is to be administered every three weeks at a dose of 60 mg/m^2 Q3W, in particular starting at cycle 1 day 1 (C1D1). In an embodiment, carboplatin is administered or is to be administered every three weeks at a dose of AUC 4 mg/mL/min Q3W (not to exceed 600 mg), in particular starting at cycle 1 day 1 (C1D1). In an embodiment, carboplatin is administered or is to be administered every three weeks at a dose of AUC 5 mg/mL/min Q3W (not to exceed 750 mg), in particular starting at cycle 1 day 1 (C1D1).

In one embodiment, erdafitinib is administered or is to be administered at a dose of 8 mg daily with an option to uptitrate to 9 mg depending on serum phosphate levels, in particular serum phosphate levels as described herein, at about day 14 of erdafitinib administration, and cetrelimab is administered or is to be administered at a dose of 360 mg every three weeks starting at cycle 1 day 1 (C1D1), and cisplatin or carboplatin is administered or is to be administered every three weeks, in particular starting at cycle 1 day 1 (C1D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 8 mg daily with an option to uptitrate to 9 mg depending on serum phosphate levels, in particular serum phosphate levels as described herein, at about day 14 of erdafitinib administration, and cetrelimab is administered or is to be administered intravenously at a dose of 360 mg every three weeks starting at cycle 1 day 1 (C1D1), and cisplatin or carboplatin is administered or is to be administered every three weeks, in particular starting at cycle 1 day 1 (C1D1). In an embodiment, cisplatin is administered or is to be administered every three weeks at a dose of 50 mg/m^2 Q3W, in particular starting at cycle 1 day 1 (C1D1). In an embodiment, cisplatin is administered or is to be administered every three weeks at a dose of 60 mg/m^2 Q3W, in particular starting at cycle 1 day 1 (C1D1). In an embodiment, carboplatin is administered or is to be administered every three weeks at a dose of AUC 4 mg/mL/min Q3W (not to exceed 600 mg), in particular starting at cycle 1 day 1 (C1D1). In an embodiment, carboplatin is administered or is to be administered every three weeks at a dose of AUC 5 mg/mL/min Q3W (not to exceed 750 mg), in particular starting at cycle 1 day 1 (C1D1).

In one embodiment, erdafitinib is administered or is to be administered at a dose of 6 mg daily, and cetrelimab is administered or is to be administered at a dose of 360 mg every three weeks starting at cycle 1 day 1 (C1D1), and cisplatin or carboplatin is administered or is to be administered every three weeks, in particular starting at cycle 1 day 1 (C1D1). In certain embodiments, erdafitinib is administered or is to be administered orally at a dose of 6 mg daily, and cetrelimab is administered or is to be administered intravenously at a dose of 360 mg every three weeks starting at cycle 1 day 1 (C1D1), and cisplatin or carboplatin is administered or is to be administered every three weeks, in particular starting at cycle 1 day 1 (C1D1). In an embodiment, cisplatin is administered or is to be administered every three weeks at a dose of 50 mg/m^2 Q3W, in particular starting at cycle 1 day 1 (C1D1). In an embodiment, cisplatin is administered or is to be administered every three weeks at a dose of 60 mg/m^2 Q3W, in particular starting at cycle 1 day 1 (C1D1). In an embodiment,

carboplatin is administered or is to be administered every three weeks at a dose of AUC 4 mg/mL/min Q3W (not to exceed 600 mg), in particular starting at cycle 1 day 1 (C1D1). In an embodiment, carboplatin is administered or is to be administered every three weeks at a dose of AUC 5 mg/mL/min Q3W (not to exceed 750 mg), in particular starting at cycle 1 day 1 (C1D1).

In one specific embodiment, the FGFR inhibitor is administered in combination with the anti-PD-1 antibody or the antigen binding fragment thereof, wherein the FGFR inhibitor and the anti-PD-1 antibody or the antigen binding fragment thereof modulate different aspects of the urothelial carcinoma, thereby providing a greater overall benefit than administration of either therapeutic agent alone. Without wishing to be being bound by any theory, the FGFR inhibitor, in particular erdafitinib, in combination with the anti-PD1 antibody or the antigen binding fragment thereof, in particular cetrelimab, may demonstrate complementary mechanisms as neoantigen release by erdafitinib may prime the tumor microenvironment for response to the anti-PD1 antibody or the antigen binding fragment thereof. Given the potentially complementary mechanisms of action of erdafitinib and cetrelimab (PD-1 inhibitor), it is hypothesized that this combination will provide increased efficacy relative to either agent alone in patients with urothelial cancer. In certain embodiments, the FGFR inhibitor and anti-PD-1 antibody are further administered in combination with platinum chemotherapy generally, and cisplatin or carboplatin specifically.

The overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

The overall benefit experienced by the patient may simply be additive of the three therapeutic agents or the patient may experience a synergistic benefit.

In combination therapies, the multiple therapeutic agents (one of which is one of the compounds described herein) are administered in any order or even simultaneously. In one embodiment, the FGFR inhibitor is co-administered with the anti PD-1 antibody or antigen binding fragment thereof on day 1 of treatment, and thereafter only the FGFR inhibitor is administered on subsequent days of treatment. In another embodiment, the FGFR inhibitor is co-administered with the anti PD-1 antibody or antigen binding fragment thereof and the platinum chemotherapy on day 1 of treatment, and thereafter only the FGFR inhibitor is administered on subsequent days of treatment.

In an embodiment, on days that the FGFR inhibitor, the anti PD-1 antibody or antigen binding fragment thereof and platinum chemotherapy are administered or are to be

administered, the sequence of administration is the FGFR inhibitor first, followed by the anti PD-1 antibody or antigen binding fragment thereof and then platinum chemotherapy.

In an embodiment, on days that erdafitinib, cetrelimab and cisplatin or carboplatin are administered or are to be administered, the sequence of administration is erdafitinib first, followed by cetrelimab and then cisplatin or carboplatin.

In an embodiment, on days that the FGFR inhibitor and the anti PD-1 antibody or antigen binding fragment thereof are administered or are to be administered, the sequence of administration is the FGFR inhibitor first, followed by the anti PD-1 antibody or antigen binding fragment thereof.

In an embodiment, on days that erdafitinib and cetrelimab are administered or are to be administered, the sequence of administration is erdafitinib first, followed by cetrelimab.

In an embodiment, the treatment with the FGFR inhibitor is started prior to the first administration of the anti PD-1 antibody or antigen binding fragment thereof. In an embodiment, the treatment with the FGFR inhibitor is started four weeks or 28 days prior to the first administration of the anti PD-1 antibody or antigen binding fragment thereof.

In an embodiment, the treatment with erdafitinib is started prior to the first administration of cetrelimab. In an embodiment, the treatment with erdafitinib is started four weeks or 28 days prior to the first administration of cetrelimab.

Kits/Articles of Manufacture

For use in the methods or uses described herein, kits and articles of manufacture are also described. Such kits include a package or container that is compartmentalized to receive one or more dosages of the pharmaceutical compositions disclosed herein. Suitable containers include, for example, bottles. In one embodiment, the containers are formed from a variety of materials such as glass or plastic.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products include, *e.g.*, U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, bags, containers, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

A kit typically includes labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

In one embodiment, a label is on or associated with the container. In one embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, *e.g.*, as a package insert.

In one embodiment, a label is used to indicate that the contents are to be used for a specific therapeutic application. The label also indicates directions for use of the contents, such as in the methods described herein.

In certain embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack, for example, contains metal or plastic foil, such as a blister pack. In one embodiment, the pack or dispenser device is accompanied by instructions for administration. In one embodiment, the pack or dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In one embodiment, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Nucleotide Sequences of FGFR fusion genes

The nucleotide sequences for the FGFR fusion cDNA are provided in Table 7. The underlined sequences correspond to either FGFR3 or FGFR2, the sequences in black represent the fusion partners.

Table 7

FGFR3-TACC3 V1 (2850 base pairs) (SEQ ID NO:33)	>ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCC GGCGCCTCCTCGGAGTCCTTGGGGACGGAGCAGCGCGTCGTGGGGCGAGCGGCA GAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCGGG GATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTG TCTGGGTCAAGGATGGCACAGGGCTGGTGCCCTCGGAGCGTGTCCTGGTGGGGC CCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTACAGCT GCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAG

	ACGCTCCATCCTCGGGAGATGACGAAGACGGGGAGGACGAGGCTGAGGACACA GGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGACAAGAAG CTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCA ACCCCACTCCCTCCATCTCCTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGC ACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGGTCATGGAAA GCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTG GCAGCATCCGGCAGACGTACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGC CCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCTGGGCAGCGACG TGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCA AGCACGTGGAGGTGAATGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTA CCGTGCTCAAGACGGCGGGCGCTAACACCACCGACAAGGAGCTAGAGGTTCTCT CCTTGCACAACGTCACCTTTGAGGACGCCGGGGAGTACACCTGCCTGGCGGGCA ATTCTATTGGGTTTTCTCATCACTCTGCGTGGCTGGTGGTGCTGCCAGCCGAGGA GGAGCTGGTGGAGGCTGACGAGGCGGGCAGTGTGTATGCAGGCATCCTCAGCTA CGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGC CTGCGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCC GCTTCCCGCTCAAGCGACAGGTGTCCCTGGAGTCCAACGCGTCCATGAGCTCCAA CACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGGC CAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCC CGGCTGACCCTGGGCAAGCCCCTTGGGGAGGGCTGCTTCGGCCAGGTGGTCATG GCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGTAGCC GTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCT GAGATGGAGATGATGAAGATGATCGGGAAACACAAAAACATCATCAACCTGCTG GGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCGGCCAAG GGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCT TCGACACCTGCAAGCCGCCCGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTG TGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGAAGTGCATCCAC AGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATC GCAGACTTCGGGCTGGCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACG ACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGCCTTGTTTGACCGA GTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCT TCACGCTGGGGGGCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCT GCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAACTGCACACACGACCTGTA CATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAG CAGCTGGTGGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGTAAAG GCGACACAGGAGGAGAACCGGGAGCTGAGGAGCAGGTGTGAGGAGCTCCACGG GAAGAACCTGGAACTGGGGAAGATCATGGACAGGTTCGAAGAGGTTGTGTACCA GGCCATGGAGGAAGTTCAGAAGCAGAAGGAACTTTCCAAAGCTGAAATCCAGAA AGTTCTAAAAGAAAAAGACCAACTTACCACAGATCTGAACTCCATGGAGAAGTC CTTCTCCGACCTCTTCAAGCGTTTTGAGAAACAGAAAGAGGTGATCGAGGGCTAC CGCAAGAACGAAGAGTCACTGAAGAAGTGCGTGGAGGATTACCTGGCAAGGATC ACCCAGGAGGGCCAGAGGTACCAAGCCCTGAAGGCCCACGCGGAGGAGAAGCT GCAGCTGGCAAACGAGGAGATCGCCCAGGTCCGGAGCAAGGCCCAGGCGGAAG

	CGTTGGCCCTCCAGGCCAGCCTGAGGAAGGAGCAGATGCGCATCCAGTCGCTGG AGAAGACAGTGGAGCAGAAGACTAAAGAGAACGAGGAGCTGACCAGGATCTGC GACGACCTCATCTCCAAGATGGAGAAGATCTGA
FGFR3-TACC3 V3 (2955 base pairs) (SEQ ID NO:34	>ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCC GGCGCCTCCTCGGAGTCCTTGGGGACGGAGCAGCGCGTCGTGGGGCGAGCGGCA GAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCGGG GATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTG TCTGGGTCAAGGATGGCACAGGGCTGGTGCCCTCGGAGCGTGTCCTGGTGGGGC CCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTACAGCT GCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAG ACGCTCCATCCTCGGGAGATGACGAAGACGGGGAGGACGAGGCTGAGGACACA GGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGACAAGAAG CTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCA ACCCCACTCCCTCCATCTCCTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGC ACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGGTCATGGAAA GCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTG GCAGCATCCGGCAGACGTACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGC CCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCTGGGCAGCGACG TGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCA AGCACGTGGAGGTGAATGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTA CCGTGCTCAAGACGGCGGGCGCTAACACCACCGACAAGGAGCTAGAGGTTCTCT CCTTGCACAACGTCACCTTTGAGGACGCCGGGGAGTACACCTGCCTGGCGGGCA ATTCTATTGGGTTTTCTCATCACTCTGCGTGGCTGGTGGTGCTGCCAGCCGAGGA GGAGCTGGTGGAGGCTGACGAGGCGGGCAGTGTGTATGCAGGCATCCTCAGCTA CGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGC CTGCGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCC GCTTCCCGCTCAAGCGACAGGTGTCCCTGGAGTCCAACGCGTCCATGAGCTCCAA CACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCACGCTGGC CAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCC CGGCTGACCCTGGGCAAGCCCCTTGGGGAGGGCTGCTTCGGCCAGGTGGTCATG GCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGTAGCC GTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCT GAGATGGAGATGATGAAGATGATCGGGAAACACAAAAACATCATCAACCTGCTG GGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGCGGCCAAG GGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGACTACTCCT TCGACACCTGCAAGCCGCCCGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCCTG TGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGAAGTGCATCCAC AGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATC GCAGACTTCGGGCTGGCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACG ACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGCCTTGTTTGACCGA GTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTGGGAGATCT TCACGCTGGGGGGCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCT GCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAACTGCACACACGACCTGTA

	CATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCCACCTTCAAG CAGCTGGTGGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCGACGTGCCAG GCCCACCCCCAGGTGTTCCCGCGCCTGGGGGCCCACCCCTGTCCACCGGACCTAT AGTGGACCTGCTCCAGTACAGCCAGAAGGACCTGGATGCAGTGGTAAAGGCGAC ACAGGAGGAGAACCGGGAGCTGAGGAGCAGGTGTGAGGAGCTCCACGGGAAGA ACCTGGAACTGGGGAAGATCATGGACAGGTTCGAAGAGGTTGTGTACCAGGCCA TGGAGGAAGTTCAGAAGCAGAAGGAACTTTCCAAAGCTGAAATCCAGAAAGTTC TAAAAGAAAAAGACCAACTTACCACAGATCTGAACTCCATGGAGAAGTCCTTCT CCGACCTCTTCAAGCGTTTTGAGAAACAGAAAGAGGTGATCGAGGGCTACCGCA AGAACGAAGAGTCACTGAAGAAGTGCGTGGAGGATTACCTGGCAAGGATCACCC AGGAGGGCCAGAGGTACCAAGCCCTGAAGGCCCACGCGGAGGAGAAGCTGCAG CTGGCAAACGAGGAGATCGCCCAGGTCCGGAGCAAGGCCCAGGCGGAAGCGTTG GCCCTCCAGGCCAGCCTGAGGAAGGAGCAGATGCGCATCCAGTCGCTGGAGAAG ACAGTGGAGCAGAAGACTAAAGAGAACGAGGAGCTGACCAGGATCTGCGACGA CCTCATCTCCAAGATGGAGAAGATCTGA
FGFR3-BAIAP2L1 (3765 base pairs) (SEQ ID NO:35)	>ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCC GGCGCCTCCTCGGAGTCCTTGGGGACGGAGCAGCGCGTCGTGGGGCGAGCGGCA GAAGTCCCGGGCCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCGGG GATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTG TCTGGGTCAAGGATGGCACAGGGCTGGTGCCCTCGGAGCGTGTCCTGGTGGGGC CCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTACAGCT GCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAG ACGCTCCATCCTCGGGAGATGACGAAGACGGGGAGGACGAGGCTGAGGACACA GGTGTGGACACAGGGGCCCCTTACTGGACACGGCCCGAGCGGATGGACAAGAAG CTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCA ACCCCACTCCCTCCATCTCCTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGC ACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGGTCATGGAAA GCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTG GCAGCATCCGGCAGACGTACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGC CCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCTGGGCAGCGACG TGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCA AGCACGTGGAGGTGAATGGCAGCAAGGTGGGCCCGGACGGCACACCCTACGTTA CCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGACGTGCGCCTCCGCCT GGCCAATGTGTCGGAGCGGGACGGGGGCGAGTACCTCTGTCGAGCCACCAATTT CATAGGCGTGGCCGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGC CGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTGTGTATGCAGGCATCCT CAGCTACGGGGTGGGCTTCTTCCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTC TGCCGCCTGCGCAGCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAG ATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCTGGAGTCCAACGCGTCCATGA GCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCCTCAGGGGAGGGCCCCA CGCTGGCCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTC TCGGGCCCGGCTGACCCTGGGCAAGCCCCTTGGGGAGGGCTGCTTCGGCCAGGT GGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCAC

	CGTAGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCT GGTGTCTGAGATGGAGATGATGAAGATGATCGGGAAACACAAAAACATCATCAA CCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCTGTACGTGCTGGTGGAGTACGC GGCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCCCGGGCCTGGA CTACTCCTTCGACACCTGCAAGCCGCCCGAGGAGCAGCTCACCTTCAAGGACCTG GTGTCCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGAAGT GCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGA TGAAGATCGCAGACTTCGGGCTGGCCCGGGACGTGCACAACCTCGACTACTACA AGAAGACGACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGCCTTGT TTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCCTTTGGGGTCCTGCTCTG GGAGATCTTCACGCTGGGGGGCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTC TTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAACTGCACACAC GACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCCAGAGGCCC ACCTTCAAGCAGCTGGTGGAGGACCTGGACCGTGTCCTTACCGTGACGTCCACCG ACAATGTTATGGAACAGTTCAATCCTGGGCTGCGAAATTTAATAAACCTGGGGA AAAATTATGAGAAAGCTGTAAACGCTATGATCCTGGCAGGAAAAGCCTACTACG ATGGAGTGGCCAAGATCGGTGAGATTGCCACTGGGTCCCCCGTGTCAACTGAACT GGGACATGTCCTCATAGAGATTTCAAGTACCCACAAGAAACTCAACGAGAGTCT TGATGAAAATTTTAAAAAATTCCACAAAGAGATTATCCATGAGCTGGAGAAGAA GATAGAACTTGACGTGAAATATATGAACGCAACTCTAAAAAGATACCAAACAGA ACACAAGAATAAATTAGAGTCTTTGGAGAAATCCCAAGCTGAGTTGAAGAAGAT CAGAAGGAAAAGCCAAGGAAGCCGAAACGCACTCAAATATGAACACAAAGAAA TTGAGTATGTGGAGACCGTTACTTCTCGTCAGAGTGAAATCCAGAAATTCATTGC AGATGGTTGCAAAGAGGCTCTGCTTGAAGAGAAGAGGCGCTTCTGCTTTCTGGTT GATAAGCACTGTGGCTTTGCAAACCACATACATTATTATCACTTACAGTCTGCAG AACTACTGAATTCCAAGCTGCCTCGGTGGCAGGAGACCTGTGTTGATGCCATCAA AGTGCCAGAGAAAATCATGAATATGATCGAAGAAATAAAGACCCCAGCCTCTAC CCCCGTGTCTGGAACTCCTCAGGCTTCACCCATGATCGAGAGAAGCAATGTGGTT AGGAAAGATTACGACACCCTTTCTAAATGCTCACCAAAGATGCCCCCCGCTCCTT CAGGCAGAGCATATACCAGTCCCTTGATCGATATGTTTAATAACCCAGCCACGGC TGCCCCGAATTCACAAAGGGTAAATAATTCAACAGGTACTTCCGAAGATCCCAGT TTACAGCGATCAGTTTCGGTTGCAACGGGACTGAACATGATGAAGAAGCAGAAA GTGAAGACCATCTTCCCGCACACTGCGGGCTCCAACAAGACCTTACTCAGCTTTG CACAGGGAGATGTCATCACGCTGCTCATCCCCGAGGAGAAGGATGGCTGGCTCT ATGGAGAACACGACGTGTCCAAGGCGAGGGGTTGGTTCCCGTCGTCGTACACGA AGTTGCTGGAAGAAAATGAGACAGAAGCAGTGACCGTGCCCACGCCAAGCCCCA CACCAGTGAGAAGCATCAGCACCGTGAACTTGTCTGAGAATAGCAGTGTTGTCAT CCCCCCACCCGACTACTTGGAATGCTTGTCCATGGGGGCAGCTGCCGACAGGAG AGCAGATTCGGCCAGGACGACATCCACCTTTAAGGCCCCAGCGTCCAAGCCCGA GACCGCGGCTCCTAACGATGCCAACGGGACTGCAAAGCCGCCTTTTCTCAGCGG AGAAAACCCCTTTGCCACTGTGAAACTCCGCCCGACTGTGACGAATGATCGCTCG GCACCCATCATTCGATGA

FGFR2-BICC1 (4989 base pairs) (SEQ ID NO:36)	>ATGGTCAGCTGGGGTCGTTTCATCTGCCTGGTCGTGGTCACCATGGCAACCTTGT CCCTGGCCCGGCCCTCCTTCAGTTTAGTTGAGGATACCACATTAGAGCCAGAAGA GCCACCAACCAAATACCAAATCTCTCAACCAGAAGTGTACGTGGCTGCGCCAGG GGAGTCGCTAGAGGTGCGCTGCCTGTTGAAAGATGCCGCCGTGATCAGTTGGACT AAGGATGGGGTGCACTTGGGGCCCAACAATAGGACAGTGCTTATTGGGGAGTAC TTGCAGATAAAGGGCGCCACGCCTAGAGACTCCGGCCTCTATGCTTGTACTGCCA GTAGGACTGTAGACAGTGAAACTTGGTACTTCATGGTGAATGTCACAGATGCCAT CTCATCCGGAGATGATGAGGATGACACCGATGGTGCGGAAGATTTTGTCAGTGA GAACAGTAACAACAAGAGAGCACCATACTGGACCAACACAGAAAAGATGGAAA AGCGGCTCCATGCTGTGCCTGCGGCCAACACTGTCAAGTTTCGCTGCCCAGCCGG GGGGAACCCAATGCCAACCATGCGGTGGCTGAAAAACGGGAAGGAGTTTAAGCA GGAGCATCGCATTGGAGGCTACAAGGTACGAAACCAGCACTGGAGCCTCATTAT GGAAAGTGTGGTCCCATCTGACAAGGGAAATTATACCTGTGTAGTGGAGAATGA ATACGGGTCCATCAATCACACGTACCACCTGGATGTTGTGGAGCGATCGCCTCAC CGGCCCATCCTCCAAGCCGGACTGCCGGCAAATGCCTCCACAGTGGTCGGAGGA GACGTAGAGTTTGTCTGCAAGGTTTACAGTGATGCCCAGCCCCACATCCAGTGGA TCAAGCACGTGGAAAAGAACGGCAGTAAATACGGGCCCGACGGGCTGCCCTACC TCAAGGTTCTCAAGGCCGCCGGTGTTAACACCACGGACAAAGAGATTGAGGTTC TCTATATTCGGAATGTAACTTTTGAGGACGCTGGGGAATATACGTGCTTGGCGGG TAATTCTATTGGGATATCCTTTCACTCTGCATGGTTGACAGTTCTGCCAGCGCCTG GAAGAGAAAAGGAGATTACAGCTTCCCCAGACTACCTGGAGATAGCCATTTACT GCATAGGGGTCTTCTTAATCGCCTGTATGGTGGTAACAGTCATCCTGTGCCGAAT GAAGAACACGACCAAGAAGCCAGACTTCAGCAGCCAGCCGGCTGTGCACAAGCT GACCAAACGTATCCCCCTGCGGAGACAGGTAACAGTTTCGGCTGAGTCCAGCTCC TCCATGAACTCCAACACCCCGCTGGTGAGGATAACAACACGCCTCTCTTCAACGG CAGACACCCCCATGCTGGCAGGGGTCTCCGAGTATGAACTTCCAGAGGACCCAA AATGGGAGTTTCCAAGAGATAAGCTGACACTGGGCAAGCCCCTGGGAGAAGGTT GCTTTGGGCAAGTGGTCATGGCGGAAGCAGTGGGAATTGACAAAGACAAGCCCA AGGAGGCGGTCACCGTGGCCGTGAAGATGTTGAAAGATGATGCCACAGAGAAAG ACCTTTCTGATCTGGTGTCAGAGATGGAGATGATGAAGATGATTGGGAAACACA AGAATATCATAAATCTTCTTGGAGCCTGCACACAGGATGGGCCTCTCTATGTCAT AGTTGAGTATGCCTCTAAAGGCAACCTCCGAGAATACCTCCGAGCCCGGAGGCC ACCCGGGATGGAGTACTCCTATGACATTAACCGTGTTCCTGAGGAGCAGATGACC TTCAAGGACTTGGTGTCATGCACCTACCAGCTGGCCAGAGGCATGGAGTACTTGG CTTCCCAAAAATGTATTCATCGAGATTTAGCAGCCAGAAATGTTTTGGTAACAGA AAACAATGTGATGAAAATAGCAGACTTTGGACTCGCCAGAGATATCAACAATAT AGACTATTACAAAAAGACCACCAATGGGCGGCTTCCAGTCAAGTGGATGGCTCC AGAAGCCCTGTTTGATAGAGTATACACTCATCAGAGTGATGTCTGGTCCTTCGGG GTGTTAATGTGGGAGATCTTCACTTTAGGGGGCTCGCCCTACCCAGGGATTCCCG TGGAGGAACTTTTTAAGCTGCTGAAGGAAGGACACAGAATGGATAAGCCAGCCA ACTGCACCAACGAACTGTACATGATGATGAGGGACTGTTGGCATGCAGTGCCCTC CCAGAGACCAACGTTCAAGCAGTTGGTAGAAGACTTGGATCGAATTCTCACTCTC ACAACCAATGAGATCATGGAGGAAACAAATACGCAGATTGCTTGGCCATCAAAA

	CTGAAGATCGGAGCCAAATCCAAGAAAGATCCCCATATTAAGGTTTCTGGAAAG AAAGAAGATGTTAAAGAAGCCAAGGAAATGATCATGTCTGTCTTAGACACAAAA AGCAATCGAGTCACACTGAAGATGGATGTTTCACATACAGAACATTCACATGTA ATCGGCAAAGGTGGCAACAATATTAAAAAAGTGATGGAAGAAACCGGATGCCAT ATCCACTTTCCAGATTCCAACAGGAATAACCAAGCAGAAAAAAGCAACCAGGTA TCTATAGCGGGACAACCAGCAGGAGTAGAATCTGCCCGAGTTAGAATTCGGGAG CTGCTTCCTTTGGTGCTGATGTTTGAGCTACCAATTGCTGGAATTCTTCAACCGGT TCCTGATCCTAATTCCCCCTCTATTCAGCATATATCACAAACGTACAATATTTCAG TATCATTTAAACAGCGTTCCCGAATGTATGGTGCTACTGTCATAGTACGAGGGTC TCAGAATAACACTAGTGCTGTGAAGGAAGGAACTGCCATGCTGTTAGAACATCTT GCTGGGAGCTTAGCATCAGCTATTCCTGTGAGCACACAACTAGATATTGCAGCTC AACATCATCTCTTTATGATGGGTCGAAATGGGAGCAACATCAAACATATCATGCA GAGAACAGGTGCTCAGATCCACTTTCCTGATCCCAGTAATCCACAAAAGAAATCT ACCGTCTACCTCCAGGGCACCATTGAGTCTGTCTGTCTTGCAAGGCAATATCTCA TGGGTTGTCTTCCTCTTGTGTTGATGTTTGATATGAAGGAAGAAATTGAAGTAGA TCCACAATTCATTGCGCAGTTGATGGAACAGCTTGATGTCTTCATCAGTATTAAA CCAAAGCCCAAACAGCCAAGCAAGTCTGTGATTGTGAAAAGTGTTGAGCGAAAT GCCTTAAATATGTATGAAGCAAGGAAATGTCTCCTCGGACTTGAAAGCAGTGGG GTTACCATAGCAACCAGTCCATCCCCAGCATCCTGCCCTGCCGGCCTGGCATGTC CCAGCCTGGATATCTTAGCTTCAGCAGGCCTTGGACTCACTGGACTAGGTCTTTT GGGACCCACCACCTTATCTCTGAACACTTCAACAACCCCAAACTCACTCTTGAAT GCTCTTAATAGCTCAGTCAGTCCTTTGCAAAGTCCAAGTTCTGGTACACCCAGCC CCACATTATGGGCACCCCCACTTGCTAATACTTCAAGTGCCACAGGTTTTTCTGCT ATACCACACCTTATGATTCCATCTACTGCCCAAGCCACATTAACTAATATTTTGTT GTCTGGAGTGCCCACCTATGGGCACACAGCTCCATCTCCCCCTCCTGGCTTGACT CCTGTTGATGTCCATATCAACAGTATGCAGACCGAAGGCAAAAAAATCTCTGCTG CTTTAAATGGACATGCACAGTCTCCAGATATAAAATATGGTGCAATATCCACTTC ATCACTTGGAGAAAAAGTGCTGAGTGCAAATCACGGGGATCCGTCCATCCAGAC AAGTGGGTCTGAGCAGACATCTCCCAAATCAAGCCCCACTGAAGGTTGTAATGA TGCTTTTGTTGAAGTAGGCATGCCTCGAAGTCCTTCCCATTCTGGGAATGCTGGT GACTTGAAACAGATGATGTGTCCCTCCAAGGTTTCCTGTGCCAAAAGGCAGACA GTGGAACTATTGCAAGGCACGAAAAACTCACACTTACACAGCACTGACAGGTTG CTCTCAGACCCTGAACTGAGTGCTACCGAAAGCCCTTTGGCTGACAAGAAGGCTC CAGGGAGTGAGCGCGCTGCAGAGAGGGCAGCAGCTGCCCAGCAAAACTCCGAA AGGGCCCACCTTGCTCCACGGTCATCATATGTCAACATGCAGGCATTTGACTATG AACAGAAGAAGCTATTAGCCACCAAAGCTATGTTAAAGAAACCAGTGGTGACGG AGGTCAGAACGCCCACAAATACCTGGAGTGGCCTGGGTTTTTCTAAATCCATGCC AGCTGAAACTATCAAGGAGTTGAGAAGGGCCAATCATGTGTCCTATAAGCCCAC AATGACAACCACTTATGAGGGCTCATCCATGTCCCTTTCACGGTCCAACAGTCGT GAGCACTTGGGAGGTGGAAGCGAATCTGATAACTGGAGAGACCGAAATGGAATT GGACCTGGAAGTCATAGTGAATTTGCAGCTTCTATTGGCAGCCCTAAGCGTAAAC AAAACAAATCAACGGAACACTATCTCAGCAGTAGCAATTACATGGACTGCATTT CCTCGCTGACAGGAAGCAATGGCTGTAACTTAAATAGCTCTTTCAAAGGTTCTGA

	CCTCCCTGAGCTCTTCAGCAAACTGGGCCTGGGCAAATACACAGATGTTTTCCAG CAACAAGAGATCGATCTTCAGACATTCCTCACTCTCACAGATCAGGATCTGAAGG AGCTGGGAATAACTACTTTTGGTGCCAGGAGGAAAATGCTGCTTGCAATTTCAGA ACTAAATAAAAACCGAAGAAAGCTTTTTGAATCGCCAAATGCACGCACCTCTTTC CTGGAAGGTGGAGCGAGTGGAAGGCTACCCCGTCAGTATCACTCAGACATTGCT AGTGTCAGTGGCCGCTGGTAG
FGFR2-CASP7 (3213 base pairs) (SEQ ID NO:37)	>ATGGTCAGCTGGGGTCGTTTCATCTGCCTGGTCGTGGTCACCATGGCAACCTTGT CCCTGGCCCGGCCCTCCTTCAGTTTAGTTGAGGATACCACATTAGAGCCAGAAGA GCCACCAACCAAATACCAAATCTCTCAACCAGAAGTGTACGTGGCTGCGCCAGG GGAGTCGCTAGAGGTGCGCTGCCTGTTGAAAGATGCCGCCGTGATCAGTTGGACT AAGGATGGGGTGCACTTGGGGCCCAACAATAGGACAGTGCTTATTGGGGAGTAC TTGCAGATAAAGGGCGCCACGCCTAGAGACTCCGGCCTCTATGCTTGTACTGCCA GTAGGACTGTAGACAGTGAAACTTGGTACTTCATGGTGAATGTCACAGATGCCAT CTCATCCGGAGATGATGAGGATGACACCGATGGTGCGGAAGATTTTGTCAGTGA GAACAGTAACAACAAGAGAGCACCATACTGGACCAACACAGAAAAGATGGAAA AGCGGCTCCATGCTGTGCCTGCGGCCAACACTGTCAAGTTTCGCTGCCCAGCCGG GGGGAACCCAATGCCAACCATGCGGTGGCTGAAAAACGGGAAGGAGTTTAAGCA GGAGCATCGCATTGGAGGCTACAAGGTACGAAACCAGCACTGGAGCCTCATTAT GGAAAGTGTGGTCCCATCTGACAAGGGAAATTATACCTGTGTAGTGGAGAATGA ATACGGGTCCATCAATCACACGTACCACCTGGATGTTGTGGAGCGATCGCCTCAC CGGCCCATCCTCCAAGCCGGACTGCCGGCAAATGCCTCCACAGTGGTCGGAGGA GACGTAGAGTTTGTCTGCAAGGTTTACAGTGATGCCCAGCCCCACATCCAGTGGA TCAAGCACGTGGAAAAGAACGGCAGTAAATACGGGCCCGACGGGCTGCCCTACC TCAAGGTTCTCAAGGCCGCCGGTGTTAACACCACGGACAAAGAGATTGAGGTTC TCTATATTCGGAATGTAACTTTTGAGGACGCTGGGGAATATACGTGCTTGGCGGG TAATTCTATTGGGATATCCTTTCACTCTGCATGGTTGACAGTTCTGCCAGCGCCTG GAAGAGAAAAGGAGATTACAGCTTCCCCAGACTACCTGGAGATAGCCATTTACT GCATAGGGGTCTTCTTAATCGCCTGTATGGTGGTAACAGTCATCCTGTGCCGAAT GAAGAACACGACCAAGAAGCCAGACTTCAGCAGCCAGCCGGCTGTGCACAAGCT GACCAAACGTATCCCCCTGCGGAGACAGGTAACAGTTTCGGCTGAGTCCAGCTCC TCCATGAACTCCAACACCCCGCTGGTGAGGATAACAACACGCCTCTCTTCAACGG CAGACACCCCCATGCTGGCAGGGGTCTCCGAGTATGAACTTCCAGAGGACCCAA AATGGGAGTTTCCAAGAGATAAGCTGACACTGGGCAAGCCCCTGGGAGAAGGTT GCTTTGGGCAAGTGGTCATGGCGGAAGCAGTGGGAATTGACAAAGACAAGCCCA AGGAGGCGGTCACCGTGGCCGTGAAGATGTTGAAAGATGATGCCACAGAGAAAG ACCTTTCTGATCTGGTGTCAGAGATGGAGATGATGAAGATGATTGGGAAACACA AGAATATCATAAATCTTCTTGGAGCCTGCACACAGGATGGGCCTCTCTATGTCAT AGTTGAGTATGCCTCTAAAGGCAACCTCCGAGAATACCTCCGAGCCCGGAGGCC ACCCGGGATGGAGTACTCCTATGACATTAACCGTGTTCCTGAGGAGCAGATGACC TTCAAGGACTTGGTGTCATGCACCTACCAGCTGGCCAGAGGCATGGAGTACTTGG CTTCCCAAAAATGTATTCATCGAGATTTAGCAGCCAGAAATGTTTTGGTAACAGA AAACAATGTGATGAAAATAGCAGACTTTGGACTCGCCAGAGATATCAACAATAT AGACTATTACAAAAAGACCACCAATGGGCGGCTTCCAGTCAAGTGGATGGCTCC

	AGAAGCCCTGTTTGATAGAGTATACACTCATCAGAGTGATGTCTGGTCCTTCGGG GTGTTAATGTGGGAGATCTTCACTTTAGGGGGCTCGCCCTACCCAGGGATTCCCG TGGAGGAACTTTTTAAGCTGCTGAAGGAAGGACACAGAATGGATAAGCCAGCCA ACTGCACCAACGAACTGTACATGATGATGAGGGACTGTTGGCATGCAGTGCCCTC CCAGAGACCAACGTTCAAGCAGTTGGTAGAAGACTTGGATCGAATTCTCACTCTC ACAACCAATGAGATGGCAGATGATCAGGGCTGTATTGAAGAGCAGGGGGTTGAG GATTCAGCAAATGAAGATTCAGTGGATGCTAAGCCAGACCGGTCCTCGTTTGTAC CGTCCCTCTTCAGTAAGAAGAAGAAAAATGTCACCATGCGATCCATCAAGACCA CCCGGGACCGAGTGCCTACATATCAGTACAACATGAATTTTGAAAAGCTGGGCA AATGCATCATAATAAACAACAAGAACTTTGATAAAGTGACAGGTATGGGCGTTC GAAACGGAACAGACAAAGATGCCGAGGCGCTCTTCAAGTGCTTCCGAAGCCTGG GTTTTGACGTGATTGTCTATAATGACTGCTCTTGTGCCAAGATGCAAGATCTGCTT AAAAAAGCTTCTGAAGAGGACCATACAAATGCCGCCTGCTTCGCCTGCATCCTCT TAAGCCATGGAGAAGAAAATGTAATTTATGGGAAAGATGGTGTCACACCAATAA AGGATTTGACAGCCCACTTTAGGGGGGATAGATGCAAAACCCTTTTAGAGAAAC CCAAACTCTTCTTCATTCAGGCTTGCCGAGGGACCGAGCTTGATGATGGCATCCA GGCCGACTCGGGGCCCATCAATGACACAGATGCTAATCCTCGATACAAGATCCC AGTGGAAGCTGACTTCCTCTTCGCCTATTCCACGGTTCCAGGCTATTACTCGTGG AGGAGCCCAGGAAGAGGCTCCTGGTTTGTGCAAGCCCTCTGCTCCATCCTGGAGG AGCACGGAAAAGACCTGGAAATCATGCAGATCCTCACCAGGGTGAATGACAGAG TTGCCAGGCACTTTGAGTCTCAGTCTGATGACCCACACTTCCATGAGAAGAAGCA GATCCCCTGTGTGGTCTCCATGCTCACCAAGGAACTCTACTTCAGTCAATAG

Amino Acid Sequences of anti-PD1 antibody

The amino acid sequences for the anti-PD1 antibody cetrelimab are provided in Table 8.

Table 8

HCDR1 (SEQ ID NO:40)	SYAIS
HCDR2 (SEQ ID NO:41)	GIIPIFDTANYAQKFQG
HCDR3 (SEQ ID NO:42)	PGLAAAYDTGSLDY
LCDR1 (SEQ ID NO:43)	RASQSVRSYLA
LCDR2 (SEQ ID NO:44)	DASNRAT
LCDR3 (SEQ ID NO:45)	QQRNYWPLT
VH (SEQ ID NO:46)	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFDT ANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARPGLAAAYDTGSLDYW GQGTLVTVSS

VL (SEQ ID NO:47)	EIVLTQSPATLSLSPGERATLSCRASQSVRSYLAWYQQKPGQAPRLLIYDASNRATGI PARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRNYWPLTFGQGTKVEIK
HC (SEQ ID NO:48)	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFDT ANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARPGLAAAYDTGSLDYW GQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPP CPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
LC (SEQ ID NO:49)	EIVLTQSPATLSLSPGERATLSCRASQSVRSYLAWYQQKPGQAPRLLIYDASNRATGI PARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRNYWPLTFGQGTKVEIKRTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

EXAMPLES

These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

EXAMPLE 1: Phase 1b/2, multicenter, open-label study, erdafitinib plus cetrelimab cohort (NCT03473743)

A non-limiting example of a phase 1b/2, multicenter, open-label dose-escalation study to evaluate erdafitinib plus cetrelimab is described below.

Objective

The primary objective of the study is to assess safety, characterize PK and identify the recommended phase 2 dose (RP2D) and schedule of erdafitinib in combination with cetrelimab.

Methods

Study Overview

Subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations with any number of prior lines of systemic therapy are eligible for enrollment in this part of the study. Subjects must have select FGFR gene alterations in tumor or blood. Subjects must be 18 years or older and have ECOG performance status (PS) Grade of 0-2

Three dosing levels (DL1, DL2 or DL2A) of erdafitinib were explored in phase 1b (as defined in **FIG. 1**), while CET intravenous (IV) dose was fixed at 240 mg every two weeks. In DL1, DL2 and DL2A, concurrent daily dosing of oral erdafitinib plus the fixed IV dose of

CET were started at Cycle 1 Day 1 (C1D1) (240 mg IV every 2 weeks). Dose-limiting toxicity (DLT) evaluation period is 1 cycle (4 weeks). The starting dose was DL1 (6 mg erdafitinib + 240 mg CET). Dose escalation was permitted if no patient in a dose cohort experienced a DLT and continued until RP2D was identified.

Alternative dosing regimens (DL1B and DL2B) are currently under exploration. Without wishing to be bound by any theory, it is hypothesized that sequential administration (starting with the FGFR inhibitor erdafitinib for 1 cycle of 4 weeks [28 days] prior to first administration of anti-PD-1 cetrelimab) might mitigate potential toxicities or lead to increased clinical benefit compared with concurrent administration. The Alternative Dose Level regime starts with a 4-week run-in of erdafitinib with subsequent concurrent dosing of erdafitinib and cetrelimab. Dose Level 1B (DL1B) will receive erdafitinib (6 mg) and cetrelimab 240 mg administered intravenously on Day 1 and Day 15 of a 4-week cycle. Dose Level 2B (DL2B) will receive erdafitinib (8 mg with up-titration to 9 mg after RP2D) and cetrelimab 240 mg administered intravenously on Day 1 and Day 15 of a 4-week cycle. At Cycle 5, the dose regimen for cetrelimab for all Alternative Dose Levels changes to 480 mg every 4 weeks. The Alternative Dose Levels will have a DLT period of 2 cycles (8 weeks). In these Alternative dose levels, the administration of cetrelimab is initiated on Cycle 2 Day 1 (C2D1), while the dose and schedule of erdafitinib is unchanged.

Inclusion and Exclusion Criteria

Inclusion criteria

- Adult mUC patients aged 18 years or older with specific FGFR alterations (FGFRa) (see Table 9) based on evaluation of tumor tissue and blood;ECOG performance status of less than or equal to 2, and who have progressed on or after one or more prior line of systemic therapy.

Exclusion criteria

- Prior FGFR or PD-1/PD(L)-1 inhibitor treatment;
- Adequate bone marrow liver and renal (CrC greater than or equal to 40ml/min) function;
- Uncontrolled cardiovascular disease, symptomatic brain metastases, active autoimmune disease, known hepatitis B or C, or known HIV;
- Chemotherapy within 3 weeks of cycle 1, day 1 (C1D1).

Table 9: Molecular Eligibility Based Upon the Following FGFR Alterations

1 of the following fusions:			1 of the following *FGFR3* gene mutations:	
FGFR2-BICC1	FGFR2-CASP7	**OR**	R248C	S249C
FGFR3-TACC3	FGFR3-BAIAP2L1		G370C	Y373C

Outcome Measures

The outcome measures were: incidences of DLT; safety (adverse events (AEs) were monitored throughout the study); and pharmacokinetic (PK) parameters and metrics of systemic exposure of erdafitinib.

Assessments

Safety was assessed continuously by the investigator according to the NCI CTCAE v4.03 and based on medical review of AE reports and the results of vital sign measurements, physical examinations, clinical laboratory tests, ophthalmology examinations, and other safety evaluations. Patients were assessed for efficacy using radiographic imaging performed during screening, once every 6 weeks for the first 12 months, then every 12 weeks until disease progression. Tumor responses were assessed by investigators according to RECIST 1.1 criteria.

Dose-Limiting Toxicity

The DLTs were based on drug-related AEs. DLT evaluation period is 1 full cycle (4 weeks) of erdafitinib and cetrelimab. Patients were evaluable, if they received more than 75% of any of the study drugs in the DLT evaluation period. Patients receiving <75% of each assigned dose due to reasons other than toxicities were replaced with a new patient. Only toxicities that occurred during the DLT evaluation period were considered as DLTs for dose escalation decisions, but toxicities that occurred during the entire treatment period were considered in decisions regarding the RP2D.

Pharmacokinetics (PK)

The PK of erdafitinib and cetrelimab in combination was assessed at different timepoints, following the administration of each compound. Pre- and post-dose plasma samples (C1D1 [pre- and post-dose], C1D15 [pre- and post-dose], C2D1 [pre-dose], C3D1 [pre-dose]) were collected for erdafitinib. Serum samples were also analyzed for cetrelimab concentrations 24 hours before infusion and at end of infusion on C1D1 and C1D15.

Statistical assessments

A modified toxicity probability interval method (mTPI)-2 guided the dose escalation and RP2D recommendation. In the mTPI-2 method, a decision theoretical framework links the dose-finding decisions of "Stay", "De-escalation", and "Escalation" with the equivalence interval, over-dosing interval(s), and under-dosing interval(s), respectively.

Results

Patients

At the time of data cut off, 22 patients were enrolled in the dose-escalation (phase 1b) study. Baseline disease characteristics and demographics are provided in Table 10.

Table 10: Baseline disease characteristics and demographics

n (%)	ERDA 6mg + CET 240 mg (n=4)	ERDA 8 mg no Upt + CET 240 mg (n=3)	ERDA 8 mg with Upt + CET 240 mg at C2D1 (n=3)	ERDA 8 mg with Upt + CET 240 mg (n=12)	Total (N=22)
Treatment exposure, mos, median (range)	5.3 (3-7)	8.3 (0-9)	5.1 (5-5)	5.5 (0-9)	5.5 (0-9)
Age, yrs, median (range)	74 (64-79)	68 (57-75)	58 (51-65)	67 (31-73)	67 (31-79)
Sex, n (%)					
Men	4 (100)	2 (67)	3 (100)	7 (58)	16 (73)
Female	0	1 (33)	0	5 (42)	6 (27)
ECOG, n (%)					
0	2 (50)	1 (33)	3 (100)	8 (67)	14 (64)
1	2 (50)	2 (67)	0	4 (33)	8 (36)
Presence of visceral metastases[a]	2 (50)	3 (100)	2 (67)	5 (2)	12 (55)
No. of prior therapy lines[b]					
0	0	0	0	1 (8)	1 (5)
1	4 (100)	2 (67)	3 (100)	7 (58)	16 (73)
2	0	1 (33)	0	4 (33)	5 (23)
Primary tumor location					
Lower tract	3 (75)	3 (100)	2 (67)	6 (50)	14 (64)
Upper tract	1 (25)	0	1 (33)	6 (50)	8 (36)
PD-L1 positive status[c]					
Yes	0	0	0	4 (33)	4 (18)
No	1 (25)	1 (33)	0	2 (17)	4 (18)
Not available	3 (75)	2 (67)	3 (100)	6 (50)	14 (64)
Any FGFR alteration[d]	4 (100)		1 (33)	10 (83)	17 (77)
Mutations (excluding fusions)*, n (%)	3 (75)	2 (67)	1 (33)	9 (75)	15 (68)
Fusions (excluding mutations)*, n (%)	1 (25)	0	0	1 (8)	2 (9)

Values are n (%) unless otherwise noted.

[a]Lung, liver, bone.

[b]In phase 2, prior lines were for neo/adjuvant therapy. cPD-L1 expression level was assessed by immunohistochemistry in tumor tissue provided at screening (PD-L1 positivity if Tumor Proportion Score ≥ 1%).

[d]Based on central laboratory tissue testing, FGFR alteration status was not available for 3 patients at the time of this analysis; 2 patients enrolled using local and blood-based testing, respectively, but did not have FGFR alterations according to central laboratory tissue testing.

DLT and Safety

RP2D was established as 8 mg UpT + 240 mg CET (DL2). At data cutoff, 13 of 22 patients were currently on active treatment; all 4 patients treated with DL1 have discontinued the study. Overall (across all dose cohorts), treatment-emergent AEs (TEAEs) and treatment-related AEs (TRAEs) were reported in most patients (91% each; Table 11)

Table 11

Patients with AEs, n (%)	**Erda 6 mg + CET 240 mg (n=4)**	**Erda 8 mg No-Upt + CET 240 mg (n=3)**	**Erda 8 mg with Upt + CET 240 mg at C2D1 (n=3)**	**Erda 8 mg with Upt + CET 240 mg (n=12)**	**Total (N=22)**
Any TEAEs	4 (100)	3 (100)	2 (67)	11 (92)	20 (91)
Any TRAEs[a]	4 (100)	3 (100)	2 (67)	11 (92)	20 (91)
Grade 3-4 TEAs	3 (75)	2 (67)	1 (33)	5 (42)	11 (50)
Grade 3-4 TRAEs[a]	1 (25)	2 (67)	1 (33)	5 (42)	9 (41)
Serious TEAs	3 (75)	0	0	4 (33)	7 (32)
Serious TRAEs[a]	0	0	0	3 (25)	3 (14)
TRAEs leading to discontinuation	0	1 (33)	0	3 (25)	4 (18)
Most common grade 3-4 TRAE, *i.e.* stomatitis[b]	1 (25)	0	0	2 (17)	3 (14)
TEAE of special interest, *i.e.* CSR[b]	0	1 (33)	0	2 (17)	3 (14)

[a]An AE was categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b]AEs were coded using MedDRA v22.1
CSR stands for central serous retinopathy.

Grade 3-4 TRAEs occurred in 41% of patients overall and in 42% of patients at the RP2D (Table 11). Only 1 (25%) grade 4 TEAE occurred.

Table 12: Most Common TEAEs (Occurring in >20% of Patients Overall)

Patients with TEAs, n (%)	**Erda 6 mg + CET 240 mg (n=4)**	**Erda 8 mg No-Upt + CET 240 mg (n=3)**	**Erda 8 mg with Upt + CET 240 mg at C2D1 (n=3)**	**Erda 8 mg with Upt + CET 240 mg (n=12)**	**Total (N=22)**
Stomatitis	3 (75)	3 (100)	1 (33)	9 (75)	16 (73)
Diarrhea	1 (25)	1 (33)	1 (33)	9 (75)	12 (55)
Dry mouth	2 (50)	2 (67)	1 (33)	7 (58)	12 (55)
Hyperphophataemia	1 (25)	2 (67)	0	7 (58)	10 (46)
Dysgeusia	2 (50)	2 (67)	0	4 (33)	8 (36)
Dry skin	1 (25)	2 (67)	0	4 (33)	7 (32)
Alopecia	0	2 (67)	0	4 (33)	6 (27)
Asthenia	0	1 (33)	0	7 (58)	8 (36)
Decreased appetite	2 (50)	0	0	5 (33)	6 (27)
Palmar-plantar erythrodysesthesia syndrome	0	2 (67)	1 (33)	2 (17)	5 (23)
Pyrexia	2 (50)	0	0	3 (25)	5 (23)
Pruritus	1 (25)	1 (33)	0	3 (25)	5 (23)
Onycholysis	0	1 (33)	1 (33)	3 (25)	5 (23)

Abbreviations: CET = cetrelimab, ERDA = erdafitinib; Upt = uptitration

Overall, serious TRAEs occurred in 3 patients (Table 11): pneumonia and diarrhea in 1, serous retinal detachment in 1, and herpetic keratitis in 1 patient.

Overall, stomatitis was the most common TEAE, occurring in 73% of patients; grade 3 treatment-related stomatitis occurred in 14% of patients overall and in 17% of patients at the RP2D (Tables 12 and 13). A summary of the most common TEAs (occurring in >20% of patients overall), is provided in Table 12.

Two patients died due to TEAEs: 1 patient due to large intestinal obstruction and 1 patient due to urinary tract infection (both in the DL1 cohort). Overall, 3 patients had central serous retinopathy (CSR) events (a known class effect of FGFR inhibitors) (Table 11); 1 patient had a grade 3 CSR event and 2 patients had grade 2 CSR events; all events improved to grade 1 or resolved. There were no grade 4/5 TRAEs.

Table 13 provides the most common grade ≥ 3 TRAE (treatment related adverse event).

Table 13: Grade ≥ 3 TRAEs[a]

Patients with TRAEs, n (%)	ERDA 6 mg + CET 240 mg (n=4)	ERDA 8 mg No UpT + CET 240 mg (n=3)	ERDA 8 mg UpT + CET 240 mg at C2D1 (n=3)	ERDA 8 mg UpT + CET 240 mg (n=12)	Total (n=22)
Stomatitis	1 (25)	0	0	2 (17)	3 (14)
Nail discoloration	0	0	1 (33)	0	1 (5)
Nail dystrophy	0	1 (33)	0	0	1 (5)
Onycholysis	0	1 (33)	0	0	1 (5)
Hypothyroidism	0	0	0	1 (8)	1 (5)
Serious retinal detachment	0	0	0	1 (8)	1 (5)
Autoimmune hepatitis	0	0	0	1 (8)	1 (5)
Pneumonia	0	0	0	1 (8)	1 (5)
GGT increased	0	0	0	1 (8)	1 (5)
Hyperophosphatemia	0	1 (33)	0	0	1 (5)

[a]No grade 4 or 5 TRAEs were reported. GGT stands for gamma-glutamyltrasferase.

Efficacy

In all response-evaluable patients (n = 21), confirmed ORR was 52%; confirmed ORR in 11 evaluable patients treated at the RP2D was 55% (Table 14, FIG. 2 and FIG. 3). The disease control rate, which included unconfirmed complete responses (CRs) and partial responses (PRs), and stable disease (SD), was 91% overall and 100% at the RP2D.

Table 14: Summary of Best Overall Response for the Response-Evaluable Set[a]

Patients with response, n (%)	ERDA 6 mg + CET 240 mg (n=4)	ERDA 8 mg No UpT + CET 240 mg (n=3)	ERDA 8 mg UpT + CET 240 mg at C2D1 (n=3)	ERDA 8 mg UpT + CET 240 mg (n=11)	Total (n=21)
ORR[b]	2 (50)	2 (67)	1 (33)	6 (55)	11 (52)
Disease control rate[c]	4 (100)	2 (67)	2 (67)	11 (100)	19 (91)
Best overall response					
PR (confirmed)	2 (50)	2 (67)	1 (33)	6 (55)	11 (52)
uPR	0	0	0	2 (18)	2 (10)
SD	2 (50)	0	1 (33)	3 (27)	6 (29)
PD	0	1 (33)	0	0	1 (5)
Not evaluable	0	0	1 (33)	0	1 (5)

[a]Includes all patients in the safety analysis set who have had a baseline and ≥ 1 adequate post-treatment disease evaluation, have had clinical signs or symptoms of disease progression, or died before the first post-treatment disease evaluation; 1 patient was not response evaluable as they did not have measurable disease at baseline, and therefore this patient was excluded from the analysis for response.
[b]Includes only confirmed responses (CR+PR).
[c]CR+PR+uCR+uPR+SD.
CI, confidence interval; PD, progressive disease; uCR, unconfirmed CR; uPR, unconfirmed PR.

The maximal percentage reduction of sum of target lesion diameters from baseline is presented in **FIG. 2**. **FIG. 3** provides data showing percent change of tumor reduction (target lesions) over time from baseline.

Conclusions

Erdafitinib plus cetrelimab is an active and tolerable combination in patients with mUC and specific FGFR alterations. The randomized phase 2 portion of this study is ongoing and continuing to explore erdafitinib plus cetrelimab versus erdafitinib monotherapy as first-line treatment for cisplatin-ineligible patients with mUC. A safety cohort of patients receiving a combination treatment regimen of erdafitinib, cetrelimab, and platinum-based chemotherapy in phase 1 of the NCT03473743 study is being developed. .

EXAMPLE 2: Phase 1b, multicenter, open-label study, erdafitinib plus cetrelimab plus platinum (cisplatin or carboplatin) chemotherapy cohort (NCT03473743)

A non-limiting example of an ongoing phase 1b, multicenter, open-label dose-escalation study to evaluate erdafitinib plus cetrelimab plus platinum (cisplatin or carboplatin) chemotherapy is described below.

Objective

The primary objective of the study is to characterize the safety and tolerability of erdafitinib in combination with cetrelimab and platinum (cisplatin or carboplatin) chemotherapy, and to identify the recommended Phase 2 dose(s) (RP2D) and schedule for erdafitinib with cetrelimab and platinum (cisplatin or carboplatin) chemotherapy. The secondary objective is to characterize the PK of erdafitinib in combination with cetrelimab, and platinum (cisplatin or carboplatin) chemotherapy and to assess the immunogenicity of cetrelimab.

Endpoint

The primary endpoint is frequency and type of dose-limiting toxicity (DLT). The secondary endpoints are concentration and PK parameters of erdafitinib, cetrelimab, and platinum (cisplatin or carboplatin) chemotherapy and detection of antibodies to cetrelimab and effects on serum cetrelimab levels.

Methods

Study Overview

The expected number of subjects to be treated in the Phase 1b erdafitinib plus cetrelimab plus platinum chemotherapy cohort is approximately 40. Three wild-type subjects will be enrolled in the initial erdafitinib plus cetrelimab plus cisplatin dose level (50 mg/m^2). If the starting dose is safe, 3 additional wild-type subjects and 3 additional subjects with select FGFR gene alterations will be enrolled into the escalated dose of cisplatin (60 mg/m^2). Wild-type is defined as subjects without FGFR gene alteration and subjects with FGFR gene alterations other than the select FGFR alterations (see Table 9). Approximately 10 additional subjects with select FGFR gene alterations will be enrolled at the MTD for erdafitinib plus cetrelimab plus cisplatin.

Three wild-type subjects will be enrolled in the initial erdafitinib plus cetrelimab plus carboplatin dose level (AUC 4 mg/mL/min). If the starting dose is safe, 3 additional wild-type subjects and 3 additional subjects with select FGFR gene alterations will be enrolled into

the escalated dose of carboplatin (AUC 5 mg/mL/min). Approximately 10 additional subjects with select FGFR gene alterations will be enrolled at the MTD for erdafitinib plus cetrelimab plus carboplatin.

The dose levels within the platinum chemotherapy cohort are:

Erdafitinib + cetrelimab + cisplatin (DL2C, DL2C1, or DL2C2)

Erdafitinib, cetrelimab and cisplatin start concurrently on C1D1. A maximum of 4 cycles of cisplatin will be administered. The DLT period is 2 cycles (6 weeks).

Erdafitinib + cetrelimab + carboplatin (DL2D or DL2D1)

Erdafitinib, cetrelimab and carboplatin start concurrently on C1D1. A maximum of 4 cycles of carboplatin will be administered. The DLT period is 2 cycles (6 weeks).

Dose-Limiting Toxicity

The DLTs will be based on drug-related AEs. DLT evaluation period is 1 full cycle (4 weeks) of erdafitinib and cetrelimab. Patients are evaluable, if they receive more than 75% of any of the study drugs in the DLT evaluation period. Patients receiving <75% of each assigned dose due to reasons other than toxicities are replaced with a new patient. All available safety data from subjects will be taken into consideration.

Dosage and Administration

Erdafitinib (8 mg) will be given once daily at approximately the same time of the day with or without food. Cetrelimab and platinum chemotherapy intravenous infusions will be administered on Day 1 of a 3-week cycle. Erdafitinib oral dose will be given first, followed by cetrelimab and then platinum chemotherapy. A maximum of 4 cycles of platinum chemotherapy will be administered. If platinum chemotherapy is discontinued, the subject can continue to receive erdafitinib and cetrelimab.

Table 15 provides an overview of the dose levels (in which Q3W refers to once every three weeks and AUC refers to area under the concentration curve).

Table 15: Erdafitinib, Cetrelimab, and Platinum Chemotherapy Administration; Dose Levels

Phase	Dosing Level [a, e]	Cisplatin or Carboplatin (IV infusion) [c, d]	Erdafitinib (oral administration) [c]	Cetrelimab (IV infusion) [b, c]
1b	DL2C	Cisplatin 50 mg/m^2 Q3W	8 mg (no up-titration) once daily	360 mg Q3W
1b	DL2C1	Cisplatin 60 mg/m^2 Q3W		
1b	DL2D	Carboplatin AUC 4 mg/mL/min Q3W (Not to Exceed 600 mg)		
1b	DL2D1	Carboplatin AUC 5 mg/mL/min Q3W (Not to Exceed 750 mg)		

[a] Additional dosing schedules may be explored if recommended and agreed upon by the sponsor.
[b] The cetrelimab dosing schedule can be adjusted if recommended and agreed upon by the sponsor.
[c] On days that all study drugs will be administered, the sequence of administration will be erdafitinib first, followed by cetrelimab and then platinum chemotherapy
[d] Erdafitinib + cetrelimab can continue every 3 weeks after a maximum of 4 cycles of platinum chemotherapy.
[e] Subject to dose escalation criteria

The starting dose is 8 mg erdafitinib (no up titration); 360 mg Q3W cetrelimab, and either 50 mg/m^2 Q3W for cisplatin (DL2C) or AUC 4mg/mL/min Q3W for carboplatin (DL2D).

If based on the rules below, dose escalation for cisplatin is DL2C to DL2C1. If based on the rules below, dose escalation for carboplatin is DL2D to DL2D1.

The following rules for escalation apply:

- At least 3 subjects may be dosed in each dose level that will be explored.
- A staggered enrollment strategy will be applied to the first 3 subjects in a dose level. A minimal interval of 24 hours between a subject's first dose will be required.
- At least 3 subjects per dose level are required to complete the DLT evaluation period or be discontinued for DLT before determination of the dose and schedule for the next dose cohort.
- All available data will be evaluated including, but not limited to, PK, PD, safety, and preliminary anti-tumor activity, and a decision will be made about whether to escalate, stay at the current dose, or de-escalate the dose level based on modified toxicity probability interval (mTPI-2) guidelines.
- Dose escalation may continue until the RP2D is identified.
- The identification of the RP2D will be based on the totality of data from all dose cohorts tested.

- Determination as to whether to modify or terminate dose levels, include additional dose levels, change doses or schedules of either drug, modify the study conduct if deemed necessary, and select the RP2D regimen for Phase 2 based on emerging data.
- Intra-subject dose escalation is not allowed and subjects in Phase 1b erdafitinib + cetrelimab + platinum chemotherapy dose levels will not be entered into Phase 2.

Subject Population

Adult subjects age 18 years and older with metastatic or locally advanced urothelial cancer who meet the molecular eligibility and full-study eligibility are eligible for the study. Screening assessments will be performed as indicated in the Phase 1b erdafitinib + cetrelimab cohort. Molecular eligibility assessment may occur ≥28 days prior to administration of the study drugs.

Inclusion and Exclusion Criteria

Inclusion criteria

- ≥18 years of age;
- Histologic demonstration of transitional cell carcinoma of the urothelium. Variant urothelial carcinoma histologies such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change are acceptable;
- Metastatic or locally advanced urothelial cancer (Stage IV disease per AJCC Staging Guidelines)
- Approximately 6 subjects will be wild-type. Wild-type is defined as subjects without FGFR gene alteration and subjects with FGFR gene alterations other than the select FGFR alterations described in Table 9. All other subjects must have at least one select FGFR alteration as defined in Table 9;
- Must have measurable disease by radiological imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) at baseline;
- No prior systemic therapy for metastatic disease. Note: Subjects who received neoadjuvant or adjuvant chemotherapy and showed disease progression, within 12 months of the last dose are considered to have received systemic chemotherapy in the metastatic setting;

- Renal function for subjects must have a creatinine clearance (CrCl) >50 mL/min as calculated by Cockcroft Gault;
- ECOG 0-1 for cisplatin and ECOG 0-2 for carboplatin;
- Adequate organ function at screening;
- Before the first does of study drug, women of childbearing potential and fertile men who are sexually active must agree to use a highly effective method of contraception (<1%/year failure rate) during the study and for 6 months after the last dose of study drug;
- Women of childbearing potential must have a negative pregnancy test at Screening within ≤7 days of C1D1 (first dose of study drug) using a highly sensitive pregnancy test (serum βhuman chorionic gonadotropin [β-hCG]);

Exclusion criteria

- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 30 days prior to C1D1 and subjects who have received the following nitrosoureas and mitomycin C within 6 weeks;
- Prior neoadjuvant/adjuvant chemotherapy is allowed if the last dose was given >12 months prior to recurrent disease progression and did not result in drug-related toxicity leading to treatment discontinuation;
- Prior anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy. Prior neoadjuvant/adjuvant checkpoint inhibitor therapy is allowed if the last dose was given >12 months prior to recurrent disease progression and did not result in drug-related toxicity leading to treatment discontinuation. PD-1 for non-muscle invasive bladder cancer is also allowed;
- Active malignancies requiring concurrent therapy other than urothelial cancer;
- Symptomatic central nervous system metastases;
- Prior FGFR inhibitor treatment;
- Radiation therapy ≤30 days prior to planned C1D1;
- History of uncontrolled cardiovascular disease including: Unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive heart failure Class III-V within the preceding 3 months; cerebrovascular accident or transient ischemic attack within the preceding 3 months;

- Known to be seropositive for human immunodeficiency virus or acquired immune deficiency syndrome;
- Any of the following:
    - Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection.
    - Active autoimmune disease or a documented history of autoimmune disease that requires systemic steroids or immunosuppressive agents. Note: Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule.
    - Grade 3 or higher toxicity effects from previous treatment with immunotherapy.
    - Psychiatric conditions (*e.g.*, alcohol or drug abuse), dementia, or altered mental status.
    - Any other issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
- Pulmonary compromise requiring supplemental oxygen use to maintain adequate oxygenation.
- Active or chronic hepatitis B or hepatitis C disease as determined by hepatitis B surface antigen (HBsAg), hepatitis B core antibody, or hepatitis C antibody (anti-HCV) positivity at Screening. If positive, further testing of quantitative levels to rule out active infection is required (see Attachment 2).
- Not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are considered by the investigator as not clinically significant, such as alopecia, skin discoloration, or Grade 1 hearing loss or neuropathy).
- Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions;
- Allergies, hypersensitivity, or intolerance to protein-based therapies or with a history of any significant drug allergy (such as anaphylaxis, hepatotoxicity, or

immune-mediated thrombocytopenia or anemia), or to excipients of erdafitinib or cetrelimab (see the Investigator's Brochures for a list of excipients);

- Current central serous retinopathy (CSR) or retinal pigment epithelial detachment (RPED) of any Grade;
- Use of immunosuppressant agents, including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, cyclosporine, azathioprine, and tumor necrosis factor α (TNF-α) blockers, within 2 weeks before the planned first dose of study drug;
- Vaccinated with a live attenuated vaccine within 28 days prior to the first dose of study drug and for 3 months after receiving the last dose of study drug. Annual inactivated influenza vaccine is permitted;
- Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 6 months after receiving the last dose of study drug;
- Plans to father a child while enrolled in this study or within 6 months after receiving the last dose of study drug;
- Major surgery within 4 weeks of enrollment, or inadequate recovery from the toxicity and/or complications from the intervention prior to starting therapy;
- Known sensitivity to any component of cisplatin or carboplatin.

Evaluations

The safety of erdafitinib plus cetrelimab plus platinum chemotherapy will be assessed based on medical review of safety parameters including but not limited to AEs, vital signs, physical examination, ECOG PS, laboratory tests, and electrocardiograms. Corneal or retinal abnormalities for subjects receiving erdafitinib will be considered as AEs of special interest. These occurrences should be reported as AEs or as serious AEs if the severity is a Grade 3 or higher and require enhanced reporting and data collection. Blood samples will be collected to assess the plasma pharmacokinetics (PK) of erdafitinib, platinum (cisplatin or carboplatin) chemotherapy and serum PK and immunogenicity of cetrelimab. Blood and tumor samples will also be assessed for biomarkers that could correlate with response or resistance to erdafitinib alone or in combination with cetrelimab. The evaluation of response will be according to RECIST 1.1.

EXAMPLE 3: Phase 2 (Dose Expansion) (NCT03473743)

A non-limiting example of an ongoing phase 2 dose expansion study is described below.

Objective

The primary objective is to o evaluate the safety and clinical activity of erdafitinib alone and in combination with cetrelimab in cisplatin-ineligible subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations and no prior systemic therapy for metastatic disease. The secondary objectives are to characterize the PK of erdafitinib and cetrelimab, assess the immunogenicity of cetrelimab, further assess safety at the R2PD of erdafitinib alone and in combination with cetrelimab, and further characterize the clinical activity of erdafitinib alone and in combination with cetrelimab.

Endpoints

The primary endpoint is overall response rate (ORR) (partial response [PR] or better) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by investigator assessment and incidence of adverse events (AEs). The secondary endpoints are plasma erdafitinib and serum cetrelimab concentrations, detection of antibodies to cetrelimab and effects on serum cetrelimab levels, incidence of AEs, serious adverse events (SAEs) and laboratory values, duration of response (DoR), time to response (TTR), progression-free survival (PFS) and OS.

Methods

Study Overview

Subjects with metastatic or locally advanced urothelial cancer with select FGFR gene alterations who have had no prior systemic therapy for metastatic disease and are ineligible for cisplatin are eligible for enrollment in this part of the study. Subjects must have select FGFR gene alterations in tumor or blood. Subjects must be 18 years or older and have ECOG PS Grade of 0-2.

Two dosing arms may be explored: Arm A and Arm B.

Subjects who have not received prior systemic therapy for metastatic disease will be stratified by the Eastern Cooperative Oncology Group (ECOG) PS (0-1 versus 2) and assigned randomly (1:1 ratio) to either the erdafitinib monotherapy treatment at the starting oral dose of 8 mg (Arm A), or the combination treatment of erdafitinib and cetrelimab (Arm B). To further characterize safety and clinical activity of the erdafitinib and cetrelimab (Arm B) combination, the dose of erdafitinib and cetrelimab will be administered at 8 mg (no up-titration) and 240 mg Q2W, respectively for Cycles 1 through 4. At Cycle 5, the dosing

regimen of cetrelimab is changed from 240 mg Q2W to 480 mg Q4W. Subjects in the Phase 2 dose expansion cohort of the study are cisplatin-ineligible. See FIG. 1 for study design of the phase 2 dose exapansion.

Cisplatin-ineligible subjects are defined as meeting at least one of the following criteria:

- Impaired renal function defined as calculated by Cockcroft-Gault (Galsky MD, et al. *Lancetrelimab Oncol.* 2011 Mar;12(3):211-4).
- Grade 2 or higher peripheral neuropathy per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0.)
- Grade 2 or higher hearing loss per NCI-CTCAE version 5.0.
- ECOG Performance Status 2.

Dosage and Administration

Arm A: erdafitinib monotherapy (8 mg up-titrated to 9 mg) will be given once daily at approximately the same time of the day with or without food.

Arm B: erdafitinib 8 mg will be given once daily at approximately the same time of the day with or without food. Cetrelimab will be administered at doses of 240 mg every 2 weeks (Cycles 1-4) or 480 mg every 4 weeks (starting at Cycle 5). When both drugs are administered on the same day, erdafitinib will be administered before cetrelimab.

All subjects will continue to receive study treatment until disease progression, unacceptable toxicity, or any other treatment discontinuation criteria are met.

Statistical Methods

Approximately 90 subjects will be assigned randomly in a 1:1 ratio to receive either erdafitinib monotherapy (Arm A) or erdafitinib and cetrelimab combination therapy (Arm B). With approximately 45 subjects on Arm A and assuming a true ORR of 45%, the study is designed such that the resulting 95% confidence interval for estimating ORR excludes those less or equal to 30%. Similarly, assuming a true ORR of 55% in Arm B, 45 subjects results in a 95% confidence interval that excludes ORR less or equal to 40%. The objective response rate will be calculated with a 95% confidence interval by each arm in the treated population according to the RECIST 1.1 criteria. Safety data will be summarized descriptively.

EXAMPLE 4. Clinical Study: Analysis of T cell populations

As described above, BLC2002 (NCT03473743) is a Phase 1b-2 Study to Evaluate Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Erdafitinib plus Cetrelimab,

an Anti-PD-1 Monoclonal Antibody, in Subjects with Metastatic or Locally Advanced Urothelial Cancer with Selected FGFR Gene Alterations. Phase 1b is the dose escalation part of the study wherein two dosing cohorts (Standard Cohorts and Alternative Cohorts) of erdafitinib were explored, while cetrelimab intravenous (IV) dose was fixed. In the Standard Cohorts (DL1, DL2 or DL2A), erdafitinib and cetrelimab start concurrently from Cycle 1 Day 1 (C1D1). In the Alternative Cohorts (DL1B or DL2B), administration of erdafitinib starts on C1D1 but cetrelimab is initiated 1 cycle (4 weeks) later, on Cycle 2 Day 1 (C2D1) (also referred to as a 28-day run-in of erdafitinib). In Phase 2, two dosing arms are explored: the erdafitinib monotherapy treatment at the starting oral dose of 8 mg (Arm A), or the combination treatment of erdafitinib and cetrelimab (Arm B).

For phase 1b, blood for immune cell profiling were collected at four time points (C1D1, C1D15, C2D1 and C3D1). For phase 2, blood was collected at six time points (C1D1, C1D15, C2D1, C2D15, C3D1 and C3D15). Blood samples were subjected to flow cytometry analysis on a real time basis. T cell activation is quantified as fold increase in the proportions of 1) CD38+CD3, CD38+CD4, or CD38+CD8 T cells out of lymphocytes or CD3 T cell populations, and 2) CD38+ cells out of CD4+ or CD8+ T cell populations, compared to the baseline proportion levels at C1D1.

Longitudinal blood samples were analyzed from DL2A (E8J cohort: Erda 8 mg+cetrelimab 240 mg), DL2B (E8RJ cohort: Erda 8 mg 28 days run-in + cetrelimab 240 mg), and DL2 (EJ cohort: Erda 8 mg with the potential dose adjustments to 9 mg depending on phosphate levels measured on C1D15+ cetrelimab 240 mg) of phase 1b, and blood samples from Arm A and Arm B of phase 2.

For phase 1b, for E8RJ cohort, a sustained increase was detected in the proportion of CD38+CD3 T cell (**FIG. 4A**) and CD38+CD4 T cell subset (**FIG. 4B**) in the lymphocytes population. Interestingly, the proportion of CD38+CD8 T cells for E8RJ dramatically increased at C1D15 in response to erdafitinib treatment alone, and was further increased at C3D1 when cetrelimab was applied at C2D1 (**FIG. 4C**). Similar findings were observed in the proportion of CD38+CD3 T cell (**FIG. 5A**), CD38+CD4 T cell subset (**FIG. 5B**), and CD38+CD8 T cell subset (**FIG. 5C**) out of CD3 T cell population, as well as in the proportion of CD38+ cells out of CD4+ (**FIG. 6A**) and CD38+ cells out of CD8+ (**FIG. 6B**) T cell population. In contrast, the proportion of CD38+ T cells for E8J and EJ only showed peak increase at C1D15 and then dropped down to the level similar to that of C1D1 at later time points. These findings indicate that sequential administration of erdafitinib followed by

cetrelimab could boost and prolong the T cell activation in the peripheral blood. The C3D15 in Phase 1b figures (cohort EJ) is not part of the scheduled visits based on the protocol dated before June 2020.

For phase 2, for Arm B, a sustained increase was detected in the proportion of CD38+CD3 T cell (Fig 7a) out of the lymphocytes population. The proportion of CD38+CD8 T cells (Fig 7c), but not CD38+CD4 T cells (Fig 7b), dramatically increased at C1D15 in response to erdafitinib and cetrilimab combination treatment, and peaked at C3D1 (Fig 7c). The proportion of CD38+CD8 T cells also increased with time for Arm A of erdafitinib monotherapy, but the extent of increase was less than that observed in Arm B (Fig 7c). Similar findings were observed in the proportion of CD38+CD3 T cell (Fig 8a) and CD38+CD8 T cell subset (Fig 8c) out of CD3 T cell population, as well as in the proportion of CD38+ cells out of CD8+ (Fig 9b) T cell population. These findings indicate that the concurrent combination administration of erdafitinib and cetrelimab could have more and prolonged activation of T cells in the peripheral blood than erdafitinib monotherapy does.

It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications within the spirit and scope of the present invention as defined by the present description.