FGFR TYROSINE KINASE INHIBITORS FOR THE TREATMENT OF UROTHELIAL CARCINOMA

TECHNICAL FIELD

Disclosed herein are methods of treating urothelial carcinoma with an approved drug product containing a fibroblast growth factor receptor (FGFR) inhibitor. Also disclosed are methods of selling or offering for sale an approved drug product containing a fibroblast growth factor receptor (FGFR) inhibitor.

BACKGROUND

The identification of genetic abnormalities can be useful in selecting the appropriate therapeutic(s) for cancer patients. This is also useful for cancer patients failing the main therapeutic option (front-line therapy) for that cancer type, particularly if there is no accepted standard of care for second and subsequent-line therapy. Fibroblast growth factor receptors (FGFRs) are a family of receptor tyrosine kinases involved in regulating cell survival, proliferation, migration and differentiation. FGFR alterations including FGFR mutations and FGFR fusions or translocations have been observed in some cancers. To date, there are no approved therapies with an FGFR inhibitor that are efficacious in patients with FGFR alterations.

SUMMARY

Described herein are methods of treating urothelial carcinoma comprising, consisting of, or consisting essentially of administering an approved drug product containing a fibroblast growth factor receptor (FGFR) inhibitor to a patient with a urothelial carcinoma in an amount that is described in a drug product label for said drug product.

In one aspect, disclosed herein is a use of erdafitinib in the manufacture of a medicament for the treatment of urothelial carcinoma in a patient, wherein the medicament is to be co-administered with a P-glycoprotein (P-gp) substrate and administration of erdafitinib is to be separated by at least 6 hours before or after administration of the P-gp substrate, in particular wherein the P-gp substrate has a narrow therapeutic index.

In another aspect, disclosed herein is a use of erdafitinib in the manufacture of a medicament for the treatment of urothelial carcinoma in a patient, wherein the medicament is to be co-administered with a moderate CYP2C9 or CYP3A4 inducer.

In certain examples, the urothelial carcinoma is locally advanced or metastatic. In further examples, administration of the FGFR inhibitor provides improved anti-tumor activity as measured by objective response rate or duration of response relative to a patient with urothelial carcinoma that is not receiving treatment with an FGFR inhibitor. In some examples, administration of the FGFR inhibitor results in no more than a grade 3 adverse event.

In further examples, the urothelial carcinoma is susceptible to an FGFR2 genetic alteration or an FGFR3 genetic alteration. In certain examples, the FGFR2 or FGFR3 genetic alteration is an FGFR3 gene mutation or an FGFR2 or FGFR3 gene fusion. In some examples, the FGFR3 gene mutation is R248C, S249C, G370C, Y373C, or any combination thereof. In further examples, the FGFR2 or FGFR3 gene fusion is

FGFR3-TACC3, FGFR3-BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7, or any combination thereof.

Also described herein are methods of treating urothelial carcinoma further comprising, consisting of, or consisting essentially of evaluating a biological sample from the patient for the presence of one or more FGFR2 or FGFR3 genetic alterations, in particular, the FGFR2 or FGFR3 genetic alterations as described herein, prior to administration of the FGFR inhibitor. In certain examples, the biological sample is blood, lymph fluid, bone marrow, a solid tumor sample, or any combination thereof.

In further examples, the patient received at least one prior therapy for the treatment of urothelial carcinoma. In some examples, the at least one prior therapy for the treatment of urothelial carcinoma is platinum-containing chemotherapy. In certain examples, the urothelial carcinoma progressed during or following at least one line of the platinum-containing chemotherapy. In further examples, the platinum-containing chemotherapy is neoadjuvant platinum-containing chemotherapy or adjuvant platinum-containing chemotherapy. In still further examples, the urothelial carcinoma progressed during or within 12 months following at least one line of the neoadjuvant platinum-containing chemotherapy or adjuvant platinum-containing chemotherapy.

In some examples, the FGFR inhibitor is erdafitinib. In further examples, erdafitinib is administered daily, in particular once daily. In still further examples, erdafitinib is administered orally. In certain examples, erdafitinib is administered orally on a continuous daily dosing schedule. In some examples, erdafitinib is administered orally at a dose of about 8 mg once daily. In some examples, erdafitinib is administered orally at a dose of about 8 mg once daily on a continuous daily dosing schedule. In further examples, the dose of erdafitinib is increased from 8 mg once daily to 9 mg once daily at 14 to 21 days after initiating treatment if: (a) the patient exhibits a serum phosphate (PO4) level that is less than about 5.5 mg/dL at 14-21 days after initiating treatment; and (b) administration of erdafitinib at 8 mg once daily resulted in no ocular disorder; or (c) administration of erdafitinib at 8 mg once daily resulted in no Grade 2 or greater adverse reaction. In certain examples, erdafitinib is present in a solid dosage form. In further examples, the solid dosage form is a tablet.

In still further examples, erdafitinib is not co-administered with: (a) a medication that is a strong CYP2C9 inhibitor or CYP3A4 inhibitor; (b) a medication that is a strong CYP2C9 inducer or CYP3A4 inducer; (c) a medication that is a moderate CYP2C9 inducer or CYP3A4 inducer; or (d) a medication that is a serum phosphate level-altering agent. In certain examples, erdafitinib is not co-administered with: (a) a medication that is a CYP3A4 substrate; (b) a medication that is a OCT2 substrate; or (c) a medication that is a P-glycotprotein (P-gp) substrate.

Also described herein are methods of treating urothelial carcinoma in a patient comprising, consisting of, or consisting essentially of: (a) evaluating a biological sample from the patient for the presence of one or more fibroblast growth factor receptor (FGFR) gene alterations; and (b) treating the patient with an approved drug product containing an FGFR inhibitor in an amount that is described in a drug product label for said drug product if one or more FGFR gene alterations is present in the sample.

Also provided herein are methods of selling an approved drug product comprising, consisting of, or consisting essentially of erdafitinib, said method comprising, consisting of, or consisting essentially of selling such drug product, wherein a drug product label for a reference listed drug for such drug product includes instructions for treating urothelial carcinoma. In certain examples, the drug product is an ANDA drug product, a supplemental New Drug Application drug product or a 505(b)(2) drug product.

Further provided herein are methods of offering for sale an approved drug product comprising erdafitinib, said method comprising, consisting of, or consisting essentially of offering for sale such drug product, wherein a drug product label for a reference listed drug for such drug product includes instructions for treating urothelial carcinoma. In certain examples, the drug product is an ANDA drug product, a supplemental New Drug Application drug product or a 505(b)(2) drug product.

Also described herein are methods comprising, consisting of, or consisting essentially of selling an approved drug product comprising erdafitinib, wherein the drug product label for a reference listed drug for such drug product comprises objective response rate or duration of response data. In certain examples, the objective response rate data for erdafitinib is about 40.2%, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma. In certain examples, the objective response rate data for erdafitinib is about 32.2%, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma which has progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (chemotherapy-relapsed/refractory disease). In further examples, the duration of response data for erdafitinib is about 5.6 months, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma. In further examples, the duration of response data for erdafitinib is about 5.4 months, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma which has progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (chemotherapy-relapsed/refractory disease).

Still further provided herein are methods of improving objective response rate or duration or response in a patient with urothelial carcinoma, said method comprising, consisting of, or consisting essentially of administering to said patient an approved drug

product comprising erdafitinib. In certain examples, the objective response rate is about 40.2%, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma. In certain examples, the objective response rate for erdafitinib is about 32.2%, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma which has progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (chemotherapy-relapsed/refractory disease). In further examples, the duration of response is about 5.6 months, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma. In further examples, the duration of response for erdafitinib is about 5.4 months, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma which has progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (chemotherapy-relapsed/refractory disease). In still further examples, the approved drug product is an ANDA drug product or a supplemental New Drug Application drug product.

Also provided herein are methods of improving objective response rate or duration of response in a patient with urothelial carcinoma, said method comprising, consisting of, or consisting essentially of providing to said patient an approved drug product comprising erdafitinib. In certain examples, the objective response rate is about 40.2%, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma. In certain examples, the objective response rate for erdafitinib is about 32.2%, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma which has progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (chemotherapy-relapsed/refractory disease). In further examples, the duration of response is about 5.6 months, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma. In further examples, the duration of response for erdafitinib is about 5.4 months, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma which has progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (chemotherapy-relapsed/refractory disease). In certain examples, the approved drug product is an ANDA drug product or a supplemental New Drug Application drug product. In further examples, the drug product label for a reference listed drug for such drug product includes instructions for treating urothelial carcinoma.

Further provided herein are approved drug products with at least one approved indication, wherein said approved drug product comprises erdafitinib. In certain

examples, the approved drug product is an NDA drug product, an ANDA drug product, a supplemental New Drug Application drug product, or a 505(b)(2) drug product. In further examples, a reference listed drug product for the approved drug product includes a drug product label. In still further examples, the drug product label comprises objective response rate data. In some examples, the objective response rate data for erdafitinib is about 40.2%, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma. In certain examples, the objective response rate data for erdafitinib is about 32.2%, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma which has progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (chemotherapy-relapsed/refractory disease). In certain examples, the drug product label comprises duration of response data. In further examples, the duration of response data for erdafitinib is about 5.6 months, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma. In further examples, the duration of response data for erdafitinib is about 5.4 months, in particular, wherein the patient has locally advanced or metastatic urothelial carcinoma which has progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy (chemotherapy-relapsed/refractory disease).

Further provided herein are approved pharmaceutical products comprising erdafitinib for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has (a) susceptible FGFR3 or FGFR2 genetic alterations and (b) progressed during or following at least one line of prior platinum containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

BRIEF DESCRIPTION OF THE DRAWINGS

The summary, as well as the following detailed description, is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the disclosed methods, the drawings show exemplary embodiments of the methods; however, the methods are not limited to the specific embodiments disclosed. In the drawings:

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

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

FIG. 3, which comprises **FIGS. 3A-C,** shows waterfall plots of reduction in the sum of target lesion diameters after treatment with erdafitinib. Reductions in patients