It is known that receptor tyrosine kinases of the HER-family like HER-2 and EGFR (HER-1) are frequently aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer (colon, rectal or stomach cancer), thyroid, leukemia and ovarian, bronchial and pancreatic cancer and melanoma. High levels of these receptors correlate with poor prognosis and response to treatment (Wright, C., et al., Br. J. Cancer 65 (1992) 118-121).

Inhibitors of PTKs, and in particular of EGFR, have been developed. Tumors comprising b-Raf having the V600E mutation, however, have been known to be resilient to treatment with EGFR inhibitors. See Prewett et al., *Clin. Cancer Res.* (2002), 8:994-1003 and Ouchi et al., *Cancer Chemother. Pharmacol.* (2006), 57:693-702. Applicants have unexpectedly found, however, that combination therapy with Compound I and an EGFR inhibitor not only is capable of reducing such resilience but also results in improved antineoplastic effects that are significantly superior to the results obtained with each compound alone without a significant increase in toxicity.

In addition to EGFR inhibitors, topoisomerase inhibitors are also antiproliferative agents. Tumors containing the V600E mutation, however, have also been known to be resilient to treatment with topoisomerase inhibtors. See Prewett et al., *Clin. Cancer Res.* (2002), 8:994-1003 and Abal et al., *Oncogene* (2004), 23:1737-44. Applicants have unexpectedly found, however, that the combination of Compound I with an EGFR inhibitor and a topoisomerase inhibitor not only is capable of reducing such resilience but also results in improved antineoplastic effects that are significantly superior to the results obtained with each compound alone or with the aforementioned combination therapy of Compound I and EGFR inhibitor without a significant increase in toxicity.

Summary

The present disclosure relates to a pharmaceutical product comprising (A) a first component which comprises, as an active agent, propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo [2,3-b] pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide, or a pharmaceutically-acceptable salt thereof; and (B) a second component which comprises, as an active agent, an EGFR inhibitor; as a combined preparation for the simultaneous or sequential use in the treatment of a proliferative disorder, in particular cancer, more particularly colorectal cancer, melanoma, and thyroid cancer comprising b-Raf having a V600 mutation, and in particular the V600E mutation.

The present disclosure further relates to a method of treating a patient suffering from a proliferative disorder, comprising administering to the patient the combination as mentioned above

The present disclosure also relates to a kit comprising: (A) a first component which comprises, as an active agent, Compound I, or a pharmaceutically-acceptable salt thereof; and (B) a second component which comprises, as an active agent, an EGFR inhibitor.

The present disclosure further relates to a pharmaceutical product comprising: (A) a first component which comprises, as an active agent, Compound I, or a pharmaceutically-acceptable salt thereof; and (B) a second component which comprises, as an active agent, an EGFR inhibitor; and optionally (C) a third component which comprises a topoisomerase inhibitor or a pharmaceutically acceptable salt thereof; as a combined preparation for the simultaneous or sequential use in the treatment of a proliferative disorder, in particular cancer, more particularly colorectal cancer, melanoma, and thyroid cancer comprising b-Raf having a V600 mutation, and in particular the V600E mutation.

In addition, the present disclosure relates to the use of Compound I, or a pharmaceutically-acceptable salt thereof, and an EGFR inhibitor for the treatment of a proliferative disorder.

Further, the present disclosure relates to the use of Compound I, or a pharmaceutically-acceptable salt thereof, and an EGFR inhibitor for the preparation of a medicament for the treatment of a proliferative disorder.

In one aspect, there is provided use of propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo [2,3-b] pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide , or a pharmaceutically-acceptable salt thereof, and an EGFR inhibitor for the manufacture of medicaments for the treatment of cancer, comprising b-Raf having a V600 mutation, wherein the EGFR inhibitor is selected from erlotinib or a pharmaceutically acceptable salt thereof, or cetuximab.

In another aspect, there is provided use of (A) a first component which comprises, as an active agent, Compound I or a pharmaceutically-acceptable salt thereof; and (B) a second component which comprises, as an active agent, erlotinib or a pharmaceutically acceptable salt thereof for the manufacture of medicaments for simultaneous or sequential use in the treatment of cancer comprising b-Raf having the V600E mutation, wherein

(A) is to be administered in an amount of from about 200 mg/day to about 3000 mg/day, from about 1000 mg/day to about 2500 mg/day, from about 1700 mg/day to about 2100 mg/day or about 1920 mg/day, and

(B) is to be administered in an amount of from about 20 mg/day to about 500 mg/day, from about 100 mg/day to about 400 mg/day, or from about 100 mg/day to about 200 mg/day.

In another aspect, there is provided use of (A) a first component which comprises, as an active agent, Compound I, or a pharmaceutically-acceptable salt thereof; and (B) a second component which comprises, as an active agent, cetuximab; for the manufacture of medicaments for simultaneous or sequential use in the treatment of cancer comprising b-Raf having the V600E mutation, wherein

(A) is to be administered in an amount of from about 200 mg/day to about 3000 mg/day, from about 1000 mg/day to about 2500 mg/day, from about 1700 mg/day to about 2100 mg/day or about 1920 mg/day; and

(B) is to be administered in an amount of from about 50 mg/m^2/week to about 700 mg/m^2/week, from about 100 mg/m^2/week to about 600 mg/m^2/week, or from about 200 mg/m^2/week to about 500 mg/m^2/week.

In another aspect, there is provided use of (A) a first component which comprises, as an active agent, Compound I or a pharmaceutically-acceptable salt thereof; (B) a second component which comprises, as an active agent, cetuximab; and (C) a third component which comprises, as an active agent, irinotecan or a pharmaceutically-acceptable salt thereof; for the manufacture of medicaments for simultaneous or sequential use in the treatment of cancer comprising b-Raf having the V600E mutation, wherein

(A) is to be administered in an amount of from about 200 mg/day to about 3000 mg/day, from about 1000 mg/day to about 2500 mg/day, from about 1700 mg/day to about 2100 mg/day or about 1920 mg/day;

(B) is to be administered in an amount of from about 50 mg/m^2/week to about 700 mg/m^2/week, from about 100 mg/m^2/week to about 600 mg/m^2/week, or from about 200 mg/m^2/week to about 500 mg/m^2/week; and

(C) is to be administered in an amount of from about 1 to about 250 mg/m^2/week, about 50 to about 200 mg/m^2/week, or about 125 mg/m^2/week.

In another aspect, there is provided use of (A) a first component which comprises, as an active agent, propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo [2,3-b] pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide, or a pharmaceutically-acceptable salt thereof; and (B) a second component which comprises, as an active agent, an EGFR inhibitor wherein the EGFR inhibitor is selected from erlotinib or a pharmaceutically acceptable salt thereof, or cetuximab, for the manufacture of a kit for the treatment of cancer comprising b-Raf having a V600 mutation.

Brief Description of the Drawings

Figure 1 illustrates the tolerability, as demonstrated by % body weight change, of Compound I monotherapy at 75 mg/kg bid, erlotinib hydrochloride monotherapy at 67 mg/kg qd, erlotinib hydrochloride monotherapy at 100 mg/kg qd, and Compound I at 75 mg/kg bid and erlotinib hydrochloride at 67 mg/kg qd combination therapy.

Figure 2 illustrates the antitumor activity, as demonstrated by the change in mean tumor volume over time, of Compound I monotherapy at 75 mg/kg bid, erlotinib hydrochloride monotherapy at 67 mg/kg qd, erlotinib hydrochloride monotherapy at 100 mg/kg qd, and Compound I at 75 mg/kg bid and erlotinib hydrochloride at 67 mg/kg qd combination therapy.