

cancer (mCRC) remains disappointing. Systemic chemotherapy continues to be the main treatment modality for patients with mCRC (James J. Lee, MD, PhD, and Weijing Sun, MD, Clinical Advances in Hematology & Oncology, January 2016, Vol 14, Issue 1). The US Food and Drug Administration (FDA) has approved several cytotoxic agents and targeted agents for mCRC, including irinotecan, oxaliplatin, and capecitabine (S-1 has been approved in Japan and several other countries, but not in the United States). The combination of a fluoropyrimidine (5-fluorouracil [5-FU] or oral capecitabine) with either oxaliplatin or irinotecan has been widely accepted as standard cytotoxic chemotherapy for mCRC, as either first- or second-line therapy. These regimens consist of folinic acid/5-FU/oxaliplatin (FOLFOX), capecitabine/ oxaliplatin (XELOX), folinic acid/5-FU/irinotecan (FOLFIRI), and capecitabine/irinotecan (XELIRI). More recently, in September of 2015, the FDA approved a combination of trifluridine and tipiracil (Lonsurf, Taiho Oncology) for use in refractory mCRC (James J. Lee, MD, PhD, and Weijing Sun, MD, Clinical Advances in Hematology & Oncology, January 2016, Vol 14, Issue 1).

[0006] EGFRs are transmembrane receptors present on cell membranes. They have an extracellular binding component, a transmembrane component and an intracellular tyrosine kinase component. EGFRs play an important role in controlling normal cell growth, apoptosis and other cellular functions. Deregulation of EGFR activity can lead to continual or abnormal activation of the receptors causing unregulated cell division. Epidermal growth factor receptor inhibitors are known in the art. Two categories of drugs affect EGFR: monoclonal antibodies and tyrosine kinase inhibitors (TKIs). Examples of monoclonal antibodies include panitumumab and cetuximab, and their method of action is through extracellular binding with subsequent inhibition of EGFR signaling pathways. Examples of tyrosine kinase inhibitors include erlotinib, gefitinib, and lapatinib, and their method of action is through intracellular binding and subsequent inhibition of EGFR signaling pathways.

[0007] In spite of numerous treatment options for patients with cancer, there remains a need for effective and safe therapeutic agents and a need for new combination therapies that can be administered for the effective long-term treatment of cancer.

SUMMARY

[0007a] In an aspect, there is provided use of a therapeutically effective amount of (a) a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-

yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a proliferative disease, wherein the medicament is to be administered to a patient in need thereof in a combination therapy comprising therapeutically effective amounts, independently, of: (b) at least one MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof, and (c) an anti-EGFR antibody (COMPOUND C).

[0007b] In another aspect, there is provided use of a therapeutically effective amount of (a) a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for increasing the overall survival, objective response rate, time to progression, progression-free survival, time-to-treatment failure, or Duration of Response (DOR) of a patient having a B-Raf mutant cancer, wherein the medicament is to be administered to a patient in need thereof in a combination therapy comprising therapeutically effective amounts, independently, of: (b) at least one MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof, and (c) an anti-EGFR antibody (COMPOUND C).

[0007c] In a further aspect, there is provided use of a therapeutically effective amount of (a) a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a patient in need thereof, wherein the use comprises: (a) detecting a mutant BRAF kinase in the cancer; and (b) wherein the medicament is to be administered to the patient in need thereof in a combination therapy comprising therapeutically effective amounts, independently, of: (b) at least one MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof, and (c) an anti-EGFR antibody (COMPOUND C).

[0007d] In a further aspect, there is provided use of (a) a therapeutically effective amount of a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a patient having colorectal cancer who has been prescribed treatment with cetuximab, wherein the

medicament is to be administered with: (b) a therapeutically effective amount of a MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof.

[0007e] In a further aspect, there is provided use of (a) a therapeutically effective amount of a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a patient having colorectal cancer, wherein: a) a first dose of the medicament, and (b) a therapeutically effective amount of a MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof, are to be administered on a daily basis; b) at least 30 minutes after step a), a first therapeutically effective amount of a dosage amount of cetuximab is to be administered; c) a second dose of said COMPOUND B is to be administered on a daily basis, wherein said second dose is to be administered 10 to 14 hours after administration of said first dose of COMPOUND B; and d) a second therapeutically effective amount of a dosage amount of cetuximab is to be administered on a weekly basis, wherein said administration of said second dosage amount of cetuximab is to be administered one week after administration of said first dosage amount of cetuximab.

[0007f] In a further aspect, there is provided a combination therapy comprising therapeutically effective amounts, independently, of: (a) a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, (b) at least one MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof, and (c) an anti-EGFR antibody (COMPOUND C).

[0008] Provided herein is a pharmaceutical combination comprising therapeutically effective amounts, independently, of (a) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, (b) at least one mitogen activated protein kinase

pharmaceutically acceptable salt thereof, and (c) an anti-EGFR antibody which is cetuximab, and optionally at least one pharmaceutically acceptable carrier. In one embodiment, the BRAF inhibitor, the MEK inhibitor, and the anti-EGFR antibody are formulated as separate unit dosages for simultaneous, separate or sequential administration.

[0013] Also provided are methods of treating a proliferative disease, comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical combination described herein.

[0014] Also provided is a pharmaceutical combination comprising therapeutically effective amounts, independently, of: (a) a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate or a pharmaceutically acceptable salt thereof, (b) at least one MEK inhibitor, and (c) an anti-EGFR-inhibitor antibody, and optionally at least one pharmaceutically acceptable carrier, for use in the treatment of a proliferative disease. In one embodiment, the MEK inhibitor is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof. In one embodiment, the anti-EGFR-inhibitor antibody is cetuximab.

[0015] Also provided is a method of reducing the size of a tumor, comprising contacting the tumor with a pharmaceutical combination of the disclosure.

[0016] Also provided are methods for treating cancer in a patient in need thereof, the method comprising: (a) determining if the cancer in the patient is a BRAF-associated cancer; and (b) if the cancer is determined to be a BRAF-associated cancer, administering to the patient a therapeutically effective amount of a pharmaceutical combination of the disclosure.

[0017] Also provided is a method of treating cancer in a subject in need thereof, the method comprising (a) determining if the cancer has a mutant BRAF kinase, and (b) if the cancer is determined to have a mutant BRAF-kinase, administering to said subject a therapeutically effective amount of a pharmaceutical combination of the disclosure.

[0018] Also provided is a method of treating cancer in a subject in need thereof, the method comprising (a) detecting a mutant BRAF kinase in the cancer, and (b) administering to said subject a therapeutically effective amount of a pharmaceutical combination of the disclosure.

[0019] In one embodiment, provided herein are methods of treating a patient having colorectal cancer who has been prescribed treatment with cetuximab, comprising administering to said patient: (a) a therapeutically effective amount of a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, and (b) a therapeutically effective amount of a MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof.

[0020] In one embodiment, provided herein are methods of treating a patient having colorectal cancer, said method comprising: a) administering on a daily basis a first dose of (a) a therapeutically effective amount of a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, and (b) a therapeutically effective amount of a MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof; b) at least 30 minutes after step a), administering a first therapeutically effective amount of a dosage amount of cetuximab; c) administering on a daily basis a second dose of said COMPOUND B, wherein said second dose is administered 10 to 14 hours after administration of said first dose of COMPOUND B; and d) administering on a weekly basis a second therapeutically effective amount of a dosage amount of cetuximab, wherein said administration of said second dosage amount of cetuximab is administered one week after administration of said first dosage amount of cetuximab.

[0021] Also provided are methods (e.g., in vitro methods) of selecting a treatment for a patient identified or diagnosed as having a BRAF-associated cancer.

[0022] Also provided herein are methods of selecting a treatment for a patient, wherein the methods include a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a *BRAF* gene, a BRAF kinase, or expression or activity or level of any of the same, and identifying or diagnosing a patient determined to have a dysregulation of a *BRAF* gene, a BRAF kinase, or expression or activity or level of any of the same, as having a BRAF-associated cancer.

[0023] Also provided are methods of selecting a patient for treatment, wherein the methods include selecting, identifying, or diagnosing a patient having a BRAF-associated cancer, and selecting the patient for treatment including administration of a therapeutically-effective amount of a pharmaceutical combination of the disclosure.

[0024] Also provided are methods of determining the likelihood that a subject having a cancer will have a positive response to treatment with a pharmaceutical combination of the disclosure that include: determining whether a cancer cell in a sample obtained from the subject has one or more BRAF mutations; and determining that the subject having the cancer cell that has one or more BRAF mutations has a increased likelihood of having a positive response to treatment with a pharmaceutical combination of the disclosure.

[0025] Also provided are methods of predicting the efficacy of treatment with a pharmaceutical combination of the disclosure in a subject having cancer that include: determining whether a cancer cell in a sample obtained from the subject has one or more BRAF mutations; and determining that treatment with a pharmaceutical combination of the disclosure is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more BRAF mutations.

[0026] Also provided is a commercial package comprising as therapeutic agents a combination comprising (a) a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate or a pharmaceutically acceptable salt thereof, (b) at least one MEK inhibitor, and (c) an anti-EGFR antibody, and optionally at least one pharmaceutically acceptable carrier, together with instructions for simultaneous, separate or sequential administration thereof for use in the treatment of a proliferative disease. In one embodiment, the MEK inhibitor is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof. In one embodiment, the anti-EGFR-inhibitor antibody is cetuximab.

[0027] Also provided is commercial package comprising (a) a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate or a pharmaceutically acceptable salt thereof, (b) at least one MEK inhibitor, together with instructions for simultaneous, separate or sequential administration thereof together with (COMPOUND C) in the treatment of a proliferative disease. In one embodiment, the MEK inhibitor is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof. In one embodiment, the anti-EGFR-inhibitor antibody is cetuximab. In some embodiments, provided herein are methods of reducing toxicity (e.g.,

skin toxicity, gastrointestinal toxicity, myelosuppression, cardiac toxicity, neurocerebellar toxicity, or phototoxicity) of a combination of binimetinib and cetuximab in a subject, comprising administering encorafenib in combination with the binimetinib and cetuximab. In certain of these embodiments, the subject is selected as having a BRAF V600 (e.g., V600E) mutation.

[0027a] In yet another aspect, there is provided a combination therapy as disclosed herein for use in the treatment of a proliferative disease.

[0027b] In a further aspect, there is provided a commercial package comprising a combination therapy as defined herein together with instructions for simultaneous, separate or sequential administration thereof for use in the treatment of a proliferative disease.

[0027c] In a further aspect, there is provided a commercial package comprising COMPOUND A and COMPOUND B as disclosed herein together with instructions for simultaneous, separate or sequential administration thereof for use together with an anti-EGFR antibody (COMPOUND C) in the treatment of a proliferative disease.

[0028] In some embodiments, provided herein are methods of reducing toxicity (e.g., skin toxicity, gastrointestinal toxicity, myelosuppression, cardiac toxicity, neurocerebellar toxicity, or phototoxicity) of a combination of encorafenib and cetuximab in a subject, comprising administering binimetinib in combination with the encorafenib and cetuximab. In certain of these embodiments, the subject is selected as having a BRAF V600 (e.g., V600E) mutation.

[0029] In some embodiments, provided herein are methods of reducing adverse effects (e.g., reduction in visual acuity, diarrhea, hand-foot skin reactions, skin irritation (e.g., rash, pruritic lesions, fissuring, desquamation), cardiac arrest, edema, fatigue, asthenia, hypertension, pneumonitis, thrombosis (e.g., pulmonary thrombosis), acute renal failure, facial paresis, headache, or secondary neoplasms) of a first therapeutic agent selected from the group consisting of encorafenib, cetuximab, or binimetinib in a subject, comprising administering the other two therapeutic agents not selected from the group as the first therapeutic agent in combination with the first therapeutic agent. In certain of these embodiments, the first therapeutic agent is encorafenib and the other two therapeutic agents are cetuximab and binimetinib. In certain of these embodiments, the first therapeutic agent is cetuximab and the other two therapeutic agents are encorafenib and binimetinib. In certain of these embodiments, the first therapeutic agent is binimetinib and the other two therapeutic agents are cetuximab and encorafenib. In certain of these embodiments, the subject is selected as having a BRAF V600 (e.g., V600E) mutation.

[0030] In some embodiments, provided herein are methods of reducing one or more adverse events (e.g., skin toxicity, hand-foot-skin rash (HFSR), rash, rash acneiform, dermatitis, retinopathy, or rental detachment) associated with a cancer therapeutic regimen in a subject identified as having a BRAF V600E colorectal cancer comprising: including binimetinib in a cancer treatment regimen which comprises encorafenib and an anti-EGFR antibody. In certain of these embodiments, the anti-EGFR antibody is selected from the group consisting of cetuximab, gefitinib, erlotinib, lapatinib, dacomitinib, neratinib, vanetanib, and panitumumab. In certain of these embodiments, the anti-EGFR antibody is cetuximab. In certain of these embodiments, the subject is selected as having a BRAF V600 (e.g., V600E) mutation.

What is claimed is:

1. Use of a therapeutically effective amount of (a) a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a proliferative disease, wherein the medicament is to be administered to a patient in need thereof in a combination therapy comprising therapeutically effective amounts, independently, of:
 - (b) at least one MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof, and
 - (c) an anti-EGFR antibody (COMPOUND C).
2. The use of claim 1, wherein the BRAF inhibitor is amorphous methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate or a pharmaceutically acceptable salt thereof.
3. The use according to claim 1 or 2, wherein said at least one MEK inhibitor is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof.
4. The use according to any one of claims 1-3, wherein said at least one MEK inhibitor is crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide.
5. The use according to claim 4, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38 and 28.39.
6. The use according to claim 4, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-

hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2θ degrees) at 20.38, 28.39, and 11.18.

7. The use according to claim 4, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2θ degrees) at 20.38, 28.39, 11.18, and 29.18.

8. The use according to claim 4, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, and 22.75.

9. The use according to claim 4, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, 22.75, 25.23, 16.05, and 11.82.

10. The use according to claim 4, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, 22.75, 25.23, 16.05, 11.82, 23.74, 16.33, and 19.00.

11. The use according to claim 4, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having the XRPD diffraction peaks (2θ degrees) listed in Table A.

12. The use according to claim 4, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide has an XRPD pattern substantially as shown in Figure 8.

13. The use according to any one of claims 1-12, wherein the anti-EGFR antibody is cetuximab.

14. The use according to any one of claims 1-13, wherein the proliferative disease is cancer.
15. The use according to claim 14, wherein the cancer is selected from colorectal cancer, melanoma, lung cancer, breast cancer, kidney cancer, liver cancer, endometrial cancer, acute myelogenous leukemia, myelodysplasia syndromes, thyroid cancer, particularly papillary thyroid cancer, pancreatic cancer, neurofibromatosis and hepatocellular carcinoma.
16. The use according to claim 15, wherein the cancer is colorectal cancer.
17. The use according to claim 16, wherein the colorectal cancer is metastatic colorectal cancer.
18. The use according to any one of claims 14-17, wherein the cancer is a BRAF-associated cancer.
19. The use according to claim 18, wherein the cancer is a cancer having a BRAF V600 mutation.
20. The use according to claim 19, wherein the cancer is a cancer having a BRAF V600E mutation.
21. The use according to any one of claims 14-20, wherein the cancer further expresses wild-type KRAS (KRAS^{wt}).
22. The use according to any one of claims 1-21, wherein the therapeutically effective amount of COMPOUND A is to be orally administered once daily.
23. The use according to claim 22 wherein the therapeutically effective amount of compound A is 300 mg, which is to be orally administered once daily.
24. The use according to any one of claims 1-23, wherein the therapeutically effective amount of COMPOUND B is to be orally administered twice daily as first and second

therapeutically effective doses, wherein the first therapeutically effective dose of COMPOUND B is taken together with the therapeutically effective amount of COMPOUND A.

25. The use according to claim 24, wherein said first and second therapeutically effective dose of COMPOUND B each comprises 45 mg of COMPOUND B.

26. The use according to claims 24 or 25, wherein said first therapeutically effective dose of COMPOUND B is to be administered within 30 minutes of administration of the therapeutically effective amount of COMPOUND A.

27. The use according to any one of claims 1-26, wherein the therapeutically effective amount of COMPOUND C is to be administered as an intravenous infusion in the amount of 400 mg/m² of over 120-minute as an initial dose, followed by weekly intravenous infusions in the amount of 250 mg/m² over 60 minutes .

28. The use according to any one of claims 24-27, wherein the therapeutically effective amount of COMPOUND C is to be administered at least 30 to 90 minutes after administration of the therapeutically effective amount of COMPOUND A and the first therapeutically effective dose of COMPOUND B.

29. The use according to any one of claims 1-28, wherein optionally one or more pre-medications is to be administered to said subject prior to treatment with COMPOUND C.

30. The use according to claim 29, wherein said pre-medication is to be administered 30-60 minutes prior to administration of COMPOUND C.

31. The use of claim 30, wherein said one or more pre-medications is selected from one or more of a H¹ antagonist and a systemic corticosteroid.

32. The use according to any one of claims 1-31, wherein said subject was treated with at least one systemic anticancer therapy agent for a period of time prior to treatment with said combination therapy.

33. The use according to claim 32, wherein the systemic anticancer therapy includes treatment with one or more cytotoxic agents.

34. The use according to claim 33, wherein said one or more cytotoxic agents are selected from irinotecan, oxaliplatin, capecitabine, folinic acid and 5-fluorouracil.

35. The use according to any one of claims 1-34, wherein the use further comprises assessing treatment with said combination therapy by determining one or more of inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related symptoms, inhibition of tumor secreted factors, delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To Progression (TTP), increased Progression Free Survival (PFS), increased Overall Survival (OS) or increased Duration of Response (DOR).

36. Use of a therapeutically effective amount of (a) a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for increasing the overall survival, objective response rate, time to progression, progression-free survival, time-to-treatment failure, or Duration of Response (DOR) of a patient having a B-Raf mutant cancer, wherein the medicament is to be administered to a patient in need thereof in a combination therapy comprising therapeutically effective amounts, independently, of:

(b) at least one MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof, and

(c) an anti-EGFR antibody (COMPOUND C).

37. The use of claim 36, wherein the BRAF inhibitor is amorphous methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate or a pharmaceutically acceptable salt thereof.

38. The use according to claim 36 or 37, wherein said at least one MEK inhibitor is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof.

39. The use according to any one of claims 36-38, wherein said at least one MEK inhibitor is crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide.

40. The use according to claim 39, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38 and 28.39.

41. The use according to claim 39, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, and 11.18.

42. The use according to claim 39, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, and 29.18.

43. The use according to claim 39, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, and 22.75.

44. The use according to claim 39, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, 22.75, 25.23, 16.05, and 11.82.

45. The use according to claim 39, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, 22.75, 25.23, 16.05, 11.82, 23.74, 16.33, and 19.00.
46. The use according to claim 39, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having the XRPD diffraction peaks (2θ degrees) listed in Table A.
47. The use according to claim 39, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide has an XRPD pattern substantially as shown in Figure 8.
48. The use according to any one of claims 1-47, wherein the anti-EGFR antibody is cetuximab.
49. The use according to any one of claims 1-48, wherein the proliferative disease is cancer.
50. The use according to claim 49, wherein the cancer is selected from colorectal cancer, melanoma, lung cancer, breast cancer, kidney cancer, liver cancer, endometrial cancer, acute myelogenous leukemia, myelodysplasia syndromes, thyroid cancer, particularly papillary thyroid cancer, pancreatic cancer, neurofibromatosis and hepatocellular carcinoma.
51. The use according to claim 50, wherein the cancer is colorectal cancer.
52. The use according to claim 51, wherein the colorectal cancer is metastatic colorectal cancer.
53. The use according to any one of claims 49-52, wherein the cancer is a BRAF-associated cancer.

54. The use according to claim 53, wherein the cancer is a cancer having a BRAF V600 mutation.
55. The use according to claim 54, wherein the cancer is a cancer having a BRAF V600E mutation.
56. The use according to any one of claims 49-55, wherein the cancer further expresses wild-type KRAS (KRAS^{wt}).
57. The use according to any one of claims 36-56, wherein the therapeutically effective amount of COMPOUND A is to be orally administered once daily.
58. The use according to claim 57 wherein the therapeutically effective amount of compound B is 300 mg, which is to be orally administered once daily .
59. The use according to any one of claims 1-58, wherein the therapeutically effective amount of COMPOUND B is to be orally administered twice daily as first and second therapeutically effective doses, wherein the first therapeutically effective dose of COMPOUND B is taken together with the therapeutically effective amount of COMPOUND A.
60. The use according to claim 59, wherein said first and second therapeutically effective dose of COMPOUND B each comprises 45 mg of COMPOUND B.
61. The use according to claims 59 or 60, wherein said first therapeutically effective dose of COMPOUND B is to be administered within 30 minutes of administration of the therapeutically effective amount of COMPOUND A.
62. The use according to any one of claims 1-61, wherein the therapeutically effective amount of COMPOUND C is to be administered as an intravenous infusion in the amount of 400 mg/m² of over 120-minute as an initial dose, followed by weekly intravenous infusions in the amount of 250 mg/m² over 60 minutes .

63. The use according to any one of claims 59-62, wherein the therapeutically effective amount of COMPOUND C is to be administered at least 30 to 90 minutes after administration of the therapeutically effective amount of COMPOUND A and the first therapeutically effective dose of COMPOUND B.

64. The use according to any one of claims 1-63, wherein optionally one or more pre-medications is to be administered to said subject prior to treatment with COMPOUND C.

65. The use according to claim 64, wherein said pre-medication is to be administered 30-60 minutes prior to administration of COMPOUND C.

66. The use of claim 65, wherein said one or more pre-medications is selected from one or more of a H¹ antagonist and a systemic corticosteroid.

67. The use according to any one of claims 1-66, wherein said subject was treated with at least one systemic anticancer therapy agent for a period of time prior to treatment with said combination therapy.

68. The use according to claim 67, wherein the systemic anticancer therapy includes treatment with one or more cytotoxic agents.

69. The use according to claim 68, wherein said one or more cytotoxic agents are selected from irinotecan, oxaliplatin, capecitabine, folinic acid and 5-fluorouracil.

70. The use according to any one of claims 1-69, wherein the use further comprises assessing treatment with said combination therapy by determining one or more of inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related symptoms, inhibition of tumor secreted factors, delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To Progression (TTP), increased Progression Free Survival (PFS), increased Overall Survival (OS) or increased Duration of Response (DOR).

71. Use of a therapeutically effective amount of (a) a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a patient in need thereof, wherein the use comprises:

(a) detecting a mutant BRAF kinase in the cancer; and

(b) wherein the medicament is to be administered to the patient in need thereof in a combination therapy comprising therapeutically effective amounts, independently, of:

(b) at least one MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof, and

(c) an anti-EGFR antibody (COMPOUND C).

72. The use according to claim 71, wherein said wherein the step of detecting a mutant BRAF kinase in the cancer comprises performing an assay to detect a mutant B-Raf kinase in a sample from the patient.

73. The use according to claim 72, further comprising obtaining a sample from the patient.

74. The use according to claim 73, wherein the sample is a biopsy sample.

75. The use according to any one of claims 72-74, wherein the assay is selected from the group consisting of sequencing, immunohistochemistry, enzyme-linked immunosorbent assay, and fluorescence in situ hybridization (FISH).

76. The use according to claim 75, wherein the sequencing is PCR or next generation sequencing.

77. The use according to any one of claims 71-76, wherein the BRAF inhibitor is amorphous methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate or a pharmaceutically acceptable salt thereof.

78. The use according to claim 76 or 77, wherein said at least one MEK inhibitor is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof.

79. The use according to any one of claims 76-78, wherein said at least one MEK inhibitor is crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide.

80. The use according to claim 79, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38 and 28.39.

81. The use according to claim 79, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, and 11.18.

82. The use according to claim 79, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, and 29.18.

83. The use according to claim 79, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, and 22.75.

84. The use according to claim 79, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, 22.75, 25.23, 16.05, and 11.82.

85. The use according to claim 79, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, 22.75, 25.23, 16.05, 11.82, 23.74, 16.33, and 19.00.
86. The use according to claim 79, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having the XRPD diffraction peaks (2θ degrees) listed in Table A.
87. The use according to claim 79, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide has an XRPD pattern substantially as shown in Figure 8.
88. The use according to any one of claims 1-87, wherein the anti-EGFR antibody is cetuximab.
89. The use according to any one of claims 71-88, wherein the cancer is selected from colorectal cancer, melanoma, lung cancer, breast cancer, kidney cancer, liver cancer, endometrial cancer, acute myelogenous leukemia, myelodysplasia syndromes, thyroid cancer, particularly papillary thyroid cancer, pancreatic cancer, neurofibromatosis and hepatocellular carcinoma.
90. The use according to claim 89, wherein the cancer is colorectal cancer.
91. The use according to claim 90, wherein the colorectal cancer is metastatic colorectal cancer.
92. The use according to any one of claims 71-91, wherein the cancer is a cancer having a BRAF V600 mutation.
93. The use according to claim 92, wherein the cancer is a cancer having a BRAF V600E mutation.

94. The use according to any one of claims 71-93, wherein the cancer further expresses wild-type KRAS (KRAS^{wt}).
95. The use according to any one of claims 71-94, wherein the therapeutically effective amount of COMPOUND A is to be orally administered once daily.
96. The use according to claim 95 wherein the therapeutically effective amount of COMPOUND A is 300 mg, which is to be orally administered once daily.
97. The use according to any one of claims 1-96, wherein the therapeutically effective amount of COMPOUND B is to be orally administered twice daily as first and second therapeutically effective doses, wherein the first therapeutically effective dose of COMPOUND B is taken together with the therapeutically effective amount of COMPOUND A.
98. The use according to claim 97, wherein said first and second therapeutically effective dose of COMPOUND B each comprises 45 mg of COMPOUND B.
99. The use according to claims 97-98, wherein said first therapeutically effective dose of COMPOUND B is to be administered within 30 minutes of administration of the therapeutically effective amount of COMPOUND A.
100. The use according to any one of claims 1-99, wherein the therapeutically effective amount of COMPOUND C is to be administered as an intravenous infusion in the amount of 400 mg/m² of over 120-minute as an initial dose, followed by weekly intravenous infusions in the amount of 250 mg/m² over 60 minutes.
101. The use according to any one of claims 97-100, wherein the therapeutically effective amount of COMPOUND C is to be administered at least 30 to 90 minutes after administration of the therapeutically effective amount of COMPOUND A and the first therapeutically effective dose of COMPOUND B.
102. The use according to any one of claims 1-101, wherein optionally one or more pre-medications is to be administered to said patient prior to treatment with COMPOUND C.

103. The use according to claim 102, wherein said pre-medication is to be administered 30-60 minutes prior to administration of COMPOUND C.

104. The use of claim 103, wherein said one or more pre-medications is selected from one or more of a H¹ antagonist and a systemic corticosteroid.

105. The use according to any one of claims 1-104, wherein said patient was treated with at least one systemic anticancer therapy agent for a period of time prior to treatment with said combination therapy.

106. The use according to claim 105, wherein the systemic anticancer therapy includes treatment with one or more cytotoxic agents.

107. The use according to claim 106, wherein said one or more cytotoxic agents are selected from irinotecan, oxaliplatin, capecitabine, folinic acid and 5-fluorouracil.

108. The use according to any one of claims 1-107, wherein the use further comprises assessing treatment with said combination therapy by determining one or more of inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related symptoms, inhibition of tumor secreted factors, delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To Progression (TTP), increased Progression Free Survival (PFS), increased Overall Survival (OS) or increased Duration of Response (DOR).

109. Use of (a) a therapeutically effective amount of a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a patient having colorectal cancer who has been prescribed treatment with cetuximab, wherein the medicament is to be administered with:

(b) a therapeutically effective amount of a MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof.

110. The use of claim 109, wherein the BRAF inhibitor is amorphous methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate or a pharmaceutically acceptable salt thereof.

111. The use according to claim 109 or 110, wherein said at least one MEK inhibitor is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof.

112. The use according to any one of claims 109-111, wherein said at least one MEK inhibitor is crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide.

113. The use according to claim 112, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2θ degrees) at 20.38 and 28.39.

114. The use according to claim 112, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2θ degrees) at 20.38, 28.39, and 11.18.

115. The use according to claim 112, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2θ degrees) at 20.38, 28.39, 11.18, and 29.18.

116. The use according to claim 112, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-

hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, and 22.75.

117. The use according to claim 112, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, 22.75, 25.23, 16.05, and 11.82.

118. The use according to claim 112, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, 22.75, 25.23, 16.05, 11.82, 23.74, 16.33, and 19.00.

119. The use according to claim 112, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having the XRPD diffraction peaks (2 θ degrees) listed in Table A.

120. The use according to claim 112, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide has an XRPD pattern substantially as shown in Figure 8.

121. The use according to any one of claims 109-120, wherein the colorectal cancer is metastatic colorectal cancer.

122. The use according to any one of claims 109-121, wherein the colorectal cancer is a BRAF-associated colorectal cancer.

123. The use according to claim 122, wherein the colorectal cancer has a BRAF V600 mutation.

124. The use according to claim 123, wherein the colorectal cancer has a BRAF V600E mutation.

125. The use according to any one of claims 109-124, wherein the colorectal cancer further expresses wild-type KRAS (KRAS^{wt}).

126. The use according to any one of claims 109-125, wherein the therapeutically effective amount of COMPOUND A is to be orally administered once daily.

127. The use according to claim 126 wherein the therapeutically effective amount of COMPOUND A is 300 mg, which is to be orally administered once daily.

128. The use according to any one of claims 109-127, wherein the therapeutically effective amount of COMPOUND B is to be orally administered twice daily as first and second therapeutically effective doses, wherein the first therapeutically effective dose of COMPOUND B is taken together with the therapeutically effective amount of COMPOUND A.

129. The use according to claim 128, wherein said first and second therapeutically effective dose of COMPOUND B each comprises 45 mg of COMPOUND B.

130. The use according to claims 128 or 129, wherein said first therapeutically effective dose of COMPOUND B is to be administered within 30 minutes of administration of the therapeutically effective amount of COMPOUND A.

131. The use according to any one of claims 109-130, wherein cetuximab has been prescribed to be administered as an intravenous infusion in the amount of 400 mg/m² of over 120-minute as an initial dose, followed by weekly intravenous infusions in the amount of 250 mg/m² over 60 minutes .

132. The use according to any one of claims 128-131, wherein the cetuximab has been prescribed to be administered at least 30 to 90 minutes after administration of the therapeutically effective amount of COMPOUND A and the first therapeutically effective dose of COMPOUND B.

133. The use according to any one of claims 109-132, wherein optionally one or more pre-medications is to be administered to said patient prior to treatment with cetuximab.

134. The use according to claim 133, wherein said pre-medication is to be administered 30-60 minutes prior to administration of cetuximab.

135. The use of claim 134, wherein said one or more pre-medications is selected from one or more of a H¹ antagonist and a systemic corticosteroid.

136. The use according to any one of claims 109-135, wherein said patient was treated with at least one systemic anticancer therapy agent for a period of time prior to treatment with said combination therapy.

137. The use according to claim 136, wherein the systemic anticancer therapy includes treatment with one or more cytotoxic agents.

138. The use according to claim 137, wherein said one or more cytotoxic agents are selected from irinotecan, oxaliplatin, capecitabine, folinic acid and 5-fluorouracil.

139. The use according to any one of claims 109-138, wherein the use further comprises assessing treatment with said combination therapy by determining one or more of inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related symptoms, inhibition of tumor secreted factors, delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To Progression (TTP), increased Progression Free Survival (PFS), increased Overall Survival (OS) or increased Duration of Response (DOR).

140. Use of (a) a therapeutically effective amount of a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a patient having colorectal cancer, wherein:

a) a first dose of the medicament, and (b) a therapeutically effective amount of a MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof, are to be administered on a daily basis;

b) at least 30 minutes after step a), a first therapeutically effective amount of a dosage amount of cetuximab is to be administered;

c) a second dose of said COMPOUND B is to be administered on a daily basis, wherein said second dose is to be administered 10 to 14 hours after administration of said first dose of COMPOUND B; and

d) a second therapeutically effective amount of a dosage amount of cetuximab is to be administered on a weekly basis, wherein said administration of said second dosage amount of cetuximab is to be administered one week after administration of said first dosage amount of cetuximab.

141. The use of claim 140, wherein the BRAF inhibitor is amorphous methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate or a pharmaceutically acceptable salt thereof.

142. The use according to claim 140 or 141, wherein said at least one MEK inhibitor is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof.

143. The use according to any one of claims 140-142, wherein said at least one MEK inhibitor is crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide.

144. The use according to claim 143, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2θ degrees) at 20.38 and 28.39.

145. The use according to claim 143, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-

hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, and 11.18.

146. The use according to claim 143, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, and 29.18.

147. The use according to claim 143, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, and 22.75.

148. The use according to claim 143, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, 22.75, 25.23, 16.05, and 11.82.

149. The use according to claim 143, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, 22.75, 25.23, 16.05, 11.82, 23.74, 16.33, and 19.00.

150. The use according to claim 143, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having the XRPD diffraction peaks (2 θ degrees) listed in Table A.

151. The use according to claim 143, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide has an XRPD pattern substantially as shown in Figure 8.

152. The use according to any one of claims 140-151, wherein the colorectal cancer is metastatic colorectal cancer.

153. The use according to any one of claims 140-152, wherein the colorectal cancer is a BRAF-associated colorectal cancer.

154. The use according to claim 153, wherein the colorectal cancer has a BRAF V600 mutation.

155. The use according to claim 154, wherein the colorectal cancer has a BRAF V600E mutation.

156. The use according to any one of claims 140-155, wherein the colorectal cancer further expresses wild-type KRAS (KRAS^{wt}).

157. The use according to any one of claims 140-156, wherein the therapeutically effective amount of COMPOUND A is to be orally administered once daily.

158. The use according to claim 157 wherein the therapeutically effective amount of COMPOUND A is 300 mg which is to be orally administered once daily.

159. The use according to any one of claims 140-158, wherein the therapeutically effective amount of COMPOUND B is to be orally administered twice daily as first and second therapeutically effective doses, wherein the first therapeutically effective dose of COMPOUND B is taken together with the therapeutically effective amount of COMPOUND A.

160. The use according to claim 159, wherein said first and second therapeutically effective dose of COMPOUND B each comprises 45 mg of COMPOUND B.

161. The use according to claims 159 or 160, wherein said first therapeutically effective dose of COMPOUND B is to be administered within 30 minutes of administration of the therapeutically effective amount of COMPOUND A.

162. The use according to any one of claims 140-161, the cetuximab is to be administered as an intravenous infusion in the amount of 400 mg/m² of over 120-minute as an initial dose, followed by weekly intravenous infusions in the amount of 250 mg/m² over 60 minutes .

163. The use according to any one of claims 159-162, wherein the cetuximab is to be administered at least 30 to 90 minutes after administration of the therapeutically effective amount of COMPOUND A and the first therapeutically effective dose of COMPOUND B.

164. The use according to any one of claims 140-163, wherein optionally one or more pre-medications is to be administered to said patient prior to treatment with cetuximab.

165. The use according to claim 164, wherein said pre-medication is to be administered 30-60 minutes prior to administration of cetuximab.

166. The use of claim 165, wherein said one or more pre-medications is selected from one or more of a H¹ antagonist and a systemic corticosteroid.

167. The use according to any one of claims 140-166, wherein said patient was treated with at least one systemic anticancer therapy agent for a period of time prior to treatment with said combination therapy.

168. The use according to claim 167, wherein the systemic anticancer therapy includes treatment with one or more cytotoxic agents.

169. The use according to claim 168, wherein said one or more cytotoxic agents are selected from irinotecan, oxaliplatin, capecitabine, folinic acid and 5-fluorouracil.

170. The use according to any one of claims 140-169, wherein the use further comprises assessing treatment with said combination therapy by determining one or more of inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related symptoms, inhibition of tumor secreted factors , delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To

Progression (TTP), increased Progression Free Survival (PFS), increased Overall Survival (OS) or increased Duration of Response (DOR).

171. A combination therapy comprising therapeutically effective amounts, independently, of:

(a) a BRAF inhibitor which is methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof,

(b) at least one MEK inhibitor (COMPOUND B) or a pharmaceutically acceptable salt thereof, and

(c) an anti-EGFR antibody (COMPOUND C).

172. A combination therapy according to claim 171, wherein the BRAF inhibitor is amorphous methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate or a pharmaceutically acceptable salt thereof.

173. A combination therapy according to claim 171 or 172, wherein said at least one MEK inhibitor is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof.

174. A combination therapy according to any one of claims 171-173, wherein said at least one MEK inhibitor is crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide.

175. A combination therapy according to claim 174, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38 and 28.39.

176. A combination therapy according to claim 174, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, and 11.18.

177. A combination therapy according to claim 174, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, and 29.18.

178. A combination therapy according to claim 174, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, and 22.75.

179. A combination therapy according to claim 174, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, 22.75, 25.23, 16.05, and 11.82.

180. A combination therapy according to claim 174, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) at 20.38, 28.39, 11.18, 29.18, 22.43, 22.75, 25.23, 16.05, 11.82, 23.74, 16.33, and 19.00.

181. A combination therapy according to claim 174, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide is characterized by having XRPD diffraction peaks (2 θ degrees) listed in Table A.

182. A combination therapy according to claim 174, wherein said crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide has an XRPD pattern substantially as shown in Figure 8.

183. A combination therapy according to any one of claims 171-182, wherein the anti-EGFR antibody is cetuximab.

184. A combination therapy according to any one of claims 171-183, wherein the BRAF inhibitor (COMPOUND A), the MEK inhibitor (COMPOUND B), and the anti-EGFR antibody (COMPOUND C) are each formulated as single unit dosage forms for simultaneous, separate or sequential administration.

185. A combination therapy according to any one of claims 171-184, wherein the BRAF inhibitor (COMPOUND A) is formulated for oral administration.

186. A combination therapy according to claim 185, wherein the BRAF inhibitor (COMPOUND A) is formulated as a capsule.

187. A combination therapy according to claim 186, wherein said capsule comprises 75 mg of COMPOUND A.

188. A combination therapy according to any one of claims 171-187, wherein the MEK inhibitor (COMPOUND B) is formulated for oral administration.

189. A combination therapy according to claim 188, wherein the MEK inhibitor (COMPOUND B) is formulated as a tablet.

190. A combination therapy according to claim 189, wherein the tablet comprises 15 mg of COMPOUND B.

191. A combination therapy according to any one of claims 171-190, wherein the anti-EGFR antibody (COMPOUND C) is formulated for intravenous administration.

192. A combination therapy according to any one of claims 171-191, for use in the treatment of a proliferative disease.

193. A combination therapy for use according to claim 192, wherein the proliferative disease is cancer.

194. A combination therapy for use according to claim 193, wherein the cancer is selected from colorectal cancer, melanoma, lung cancer, breast cancer, kidney cancer, liver cancer,

endometrial cancer, acute myelogenous leukemia , myelodysplasia syndromes, thyroid cancer, particularly papillary thyroid cancer, pancreatic cancer, neurofibromatosis and hepatocellular carcinoma.

195. A combination therapy for use according to claim 194, wherein the cancer is colorectal cancer.

196. A combination therapy for use according to claim 195, wherein the colorectal cancer is metastatic colorectal cancer.

197. A combination therapy for use according to any one of claims 193-196, wherein the cancer is a B-Raf-associated cancer.

198. A combination therapy for use according to claim 197, wherein the cancer is a cancer having a BRAF V600 mutation.

199. The combination therapy for use according to claim 198, wherein the cancer is a cancer having a BRAF V600E mutation.

200. The combination therapy according to any one of claims 181-199, wherein the cancer further expresses wild-type KRAS (KRAS^{wt}).

201. A commercial package comprising a combination therapy as defined in any one of claims 171-191 together with instructions for simultaneous, separate or sequential administration thereof for use in the treatment of a proliferative disease.

202. A commercial package comprising COMPOUND A and COMPOUND B according to any one of claims 171-182 together with instructions for simultaneous, separate or sequential administration thereof for use together with an anti-EGFR antibody (COMPOUND C) in the treatment of a proliferative disease.

203. The commercial package according to claim 202, wherein the anti-EGFR antibody (COMPOUND C) is cetuximab.