

yl} amino)propan-2-yl]carbamate (COMPOUND A) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of colorectal cancer having a BRAF mutation, wherein the medicament is to be administered to a patient in need thereof in a combination therapy comprising therapeutically effective amounts, independently, of: (b) a MEK inhibitor (COMPOUND B) which is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof, and (c) an anti-EGFR antibody (COMPOUND C) which is cetuximab.

[0007b] In another aspect, the present disclosure refers to 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 colorectal cancer having a BRAF mutation, wherein the medicament is to be administered to a patient in need thereof in a combination therapy comprising therapeutically effective amounts, independently, of: (b) a MEK inhibitor (COMPOUND B) which is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof, and (c) an anti-EGFR antibody (COMPOUND C) which is cetuximab.

[0007c] In a further aspect, the present disclosure refers to 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 colorectal cancer having a BRAF mutation, 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: (c) at least one MEK inhibitor (COMPOUND B) which is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof, and (d) an anti-EGFR antibody (COMPOUND C) which is cetuximab.

[0007d] In a further aspect, the present disclosure refers to 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 having a BRAF mutation 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) which is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof.

[0007e] In a further aspect, the present disclosure refers to 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) which is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide 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] Disclosed is 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

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 colorectal cancer having a BRAF mutation, wherein the medicament is to be administered to a patient in need thereof in a combination therapy comprising therapeutically effective amounts, independently, of:

(b) a MEK inhibitor (COMPOUND B) which is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof, and

(c) an anti-EGFR antibody (COMPOUND C) which is cetuximab.

2. The use according to claim 1, wherein said MEK inhibitor is crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide.

3. The use according to claim 2, 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.

4. The use according to claim 2, 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.

5. The use according to claim 2, 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.

6. The use according to claim 2, 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.
7. The use according to claim 2, 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.
8. The use according to claim 2, 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.
9. The use according to claim 2, 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 (2 θ degrees) listed in Table A.
10. The use according to claim 4, 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.
11. The use according to any one of claims 1-10, wherein the colorectal cancer is metastatic colorectal cancer.
12. The use according to any one of claims 1-11, wherein the BRAF mutation is a BRAF V600 mutation.
13. The use according to claim 12, wherein the BRAF mutation is a BRAF V600E mutation.

14. The use according to any one of claims 1-13, wherein the cancer further expresses wild-type KRAS (KRAS^{wt}).
15. The use according to any one of claims 1-14, wherein the therapeutically effective amount of COMPOUND A is to be orally administered once daily.
16. The use according to claim 15 wherein the therapeutically effective amount of compound A is 300 mg, which is to be orally administered once daily.
17. The use according to any one of claims 1-16, 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.
18. The use according to claim 17, wherein said first and second therapeutically effective dose of COMPOUND B each comprises 45 mg of COMPOUND B.
19. The use according to claims 17 or 18, 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.
20. The use according to any one of claims 1-19, 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.
21. The use according to any one of claims 17-20, 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.
22. The use according to any one of claims 1-21, wherein optionally one or more pre-medications is to be administered to said subject prior to treatment with COMPOUND C.

23. The use according to claim 22, wherein said pre-medication is to be administered 30-60 minutes prior to administration of COMPOUND C.

24. The use of claim 23, wherein said one or more pre-medications is selected from one or more of a H¹ antagonist and a systemic corticosteroid.

25. The use according to any one of claims 1-24, 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.

26. The use according to claim 25, wherein the systemic anticancer therapy includes treatment with one or more cytotoxic agents.

27. The use according to claim 26, wherein said one or more cytotoxic agents are selected from irinotecan, oxaliplatin, capecitabine, folinic acid and 5-fluorouracil.

28. The use according to any one of claims 1-27, 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).

29. 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 colorectal cancer having a BRAF mutation, wherein the medicament is to be administered to a patient in

need thereof in a combination therapy comprising therapeutically effective amounts, independently, of:

(b) a MEK inhibitor (COMPOUND B) which is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof, and

(c) an anti-EGFR antibody (COMPOUND C) which is cetuximab.

30. The use of claim 29, 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.

31. The use according to any one of claims 29-30, wherein said MEK inhibitor is crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide.

32. The use according to claim 31, 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 and 28.39.

33. The use according to claim 31, 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, and 11.18.

34. The use according to claim 31, 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, and 29.18.

35. The use according to claim 31, 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, and 22.75.

36. The use according to claim 31, 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.

37. The use according to claim 31, 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.

38. The use according to claim 31, 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.

39. The use according to claim 31, 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.

40. The use according to any one of claims 29 to 39, wherein the colorectal cancer is metastatic colorectal cancer.

41. The use according to any one of claims 29 to 39, wherein the cancer is a cancer having a BRAF V600 mutation.

42. The use according to claim 41, wherein the cancer is a cancer having a BRAF V600E mutation.

43. The use according to any one of claims 29 to 42, wherein the cancer further expresses wild-type KRAS (KRAS^{wt}).

44. The use according to any one of claims 29 to 43, wherein the therapeutically effective amount of COMPOUND A is to be orally administered once daily.
45. The use according to claim 44 wherein the therapeutically effective amount of compound B is 300 mg, which is to be orally administered once daily.
46. The use according to any one of claims 29 to 45, 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.
47. The use according to claim 46, wherein said first and second therapeutically effective dose of COMPOUND B each comprises 45 mg of COMPOUND B.
48. The use according to claims 46 or 47, 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.
49. The use according to any one of claims 29 to 48, 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.
50. The use according to any one of claims 46 to 49, 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.
51. The use according to any one of claims 29 to 50, wherein optionally one or more pre-medications is to be administered to said subject prior to treatment with COMPOUND C.
52. The use according to claim 51, wherein said pre-medication is to be administered 30-60 minutes prior to administration of COMPOUND C.

53. The use of claim 52, wherein said one or more pre-medications is selected from one or more of a H¹ antagonist and a systemic corticosteroid.
54. The use according to any one of claims 29 to 53, 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.
55. The use according to claim 54, wherein the systemic anticancer therapy includes treatment with one or more cytotoxic agents.
56. The use according to claim 55, wherein said one or more cytotoxic agents are selected from irinotecan, oxaliplatin, capecitabine, folinic acid and 5-fluorouracil.
57. The use according to any one of claims 29 to 56, 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).
58. 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 colorectal cancer having a BRAF mutation, 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:

(c) a MEK inhibitor (COMPOUND B) which is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof, and

(d) an anti-EGFR antibody (COMPOUND C) which is cetuximab.

59. The use according to claim 58, 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.

60. The use according to claim 59, further comprising obtaining a sample from the patient.

61. The use according to claim 60, wherein the sample is a biopsy sample.

62. The use according to any one of claims 59-61, wherein the assay is selected from the group consisting of sequencing, immunohistochemistry, enzyme-linked immunosorbent assay, and fluorescence in situ hybridization (FISH).

63. The use according to claim 62, wherein the sequencing is PCR or next generation sequencing.

64. The use according to any one of claims 58-63, 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.

65. The use according to any one of claims 58-64, 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.

66. The use according to claim 65, 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 and 28.39.

67. The use according to claim 65, 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.

68. The use according to claim 65, 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.

69. The use according to claim 65, 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.

70. The use according to claim 65, 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.

71. The use according to claim 65, 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.

72. The use according to claim 65, 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.

73. The use according to claim 65, 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.

74. The use according to any one of claims 58 to 73, wherein the colorectal cancer is metastatic colorectal cancer.
75. The use according to any one of claims 58 to 74, BRAF mutation is a BRAF V600 mutation.
76. The use according to claim 75, wherein the BRAF mutation is a BRAF V600E mutation.
77. The use according to any one of claims 58 to 76, wherein the cancer further expresses wild-type KRAS (KRAS^{wt}).
78. The use according to any one of claims 58 to 77, wherein the therapeutically effective amount of COMPOUND A is to be orally administered once daily.
79. The use according to claim 78 wherein the therapeutically effective amount of COMPOUND A is 300 mg, which is to be orally administered once daily.
80. The use according to any one of claims 58 to 79, 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.
81. The use according to claim 80, wherein said first and second therapeutically effective dose of COMPOUND B each comprises 45 mg of COMPOUND B.
82. The use according to claims 80 to 81, 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.
83. The use according to any one of claims 58 to 82, 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.

84. The use according to any one of claims 90 to 83, 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.

85. The use according to any one of claims 58 to 84, wherein optionally one or more pre-medications is to be administered to said patient prior to treatment with COMPOUND C.

86. The use according to claim 85, wherein said pre-medication is to be administered 30-60 minutes prior to administration of COMPOUND C.

87. The use of claim 86, wherein said one or more pre-medications is selected from one or more of a H¹ antagonist and a systemic corticosteroid.

88. The use according to any one of claims 58 to 87, 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.

89. The use according to claim 88, wherein the systemic anticancer therapy includes treatment with one or more cytotoxic agents.

90. The use according to claim 89, wherein said one or more cytotoxic agents are selected from irinotecan, oxaliplatin, capecitabine, folinic acid and 5-fluorouracil.

91. The use according to any one of claims 58 to 90, 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).

92. 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 having a BRAF mutation 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) which is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof.

93. The use of claim 92, 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.

94. The use according to any one of claims 92-93, wherein MEK inhibitor is crystallized 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide.

95. The use according to claim 94, 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 and 28.39.

96. The use according to claim 94, 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, and 11.18.

97. The use according to claim 94, 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, and 29.18.

98. The use according to claim 94, 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.

99. The use according to claim 94, 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.

100. The use according to claim 94, 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.

101. The use according to claim 94, 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.

102. 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.

103. The use according to any one of claims 92-102, wherein the colorectal cancer is metastatic colorectal cancer.

104. The use according to any one of claims 92 to 103, wherein BRAF mutation is a BRAF V600 mutation.

105. The use according to claim 104, wherein the BRAF mutation is a BRAF V600E mutation.

106. The use according to any one of claims 92 to 105, wherein the colorectal cancer further expresses wild-type KRAS (KRAS^{wt}).

107. The use according to any one of claims 92 to 106, wherein the therapeutically effective amount of COMPOUND A is to be orally administered once daily.

108. The use according to claim 107 wherein the therapeutically effective amount of COMPOUND A is 300 mg, which is to be orally administered once daily.

109. The use according to any one of claims 92 to 108, 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.

110. The use according to claim 109, wherein said first and second therapeutically effective dose of COMPOUND B each comprises 45 mg of COMPOUND B.

111. The use according to claims 109 or 110, 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.

112. The use according to any one of claims 92-111, 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.

113. The use according to any one of claims 109-112, 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.

114. The use according to any one of claims 92-113, wherein optionally one or more pre-medications is to be administered to said patient prior to treatment with cetuximab.

115. The use according to claim 114, wherein said pre-medication is to be administered 30-60 minutes prior to administration of cetuximab.

116. The use of claim 115, wherein said one or more pre-medications is selected from one or more of a H¹ antagonist and a systemic corticosteroid.

117. The use according to any one of claims 92-116, 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.

118. The use according to claim 117, wherein the systemic anticancer therapy includes treatment with one or more cytotoxic agents.

119. The use according to claim 118, wherein said one or more cytotoxic agents are selected from irinotecan, oxaliplatin, capecitabine, folinic acid and 5-fluorouracil.

120. The use according to any one of claims 92-119, 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).

121. 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) which is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide 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.

122. The use of claim 121, 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.

123. The use according to any one of claims 121-122, 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.

124. The use according to claim 123, 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.

125. The use according to claim 123, 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.

126. The use according to claim 123, 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.

127. The use according to claim 123, 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.

128. The use according to claim 123, 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.

129. The use according to claim 123, 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.

130. The use according to claim 123, 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.

131. The use according to claim 123, 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.

132. The use according to any one of claims 121-131, wherein the colorectal cancer is metastatic colorectal cancer.

133. The use according to any one of claims 121-132, wherein the BRAF mutation is a BRAF V600 mutation.

134. The use according to claim 133, wherein the BRAF mutation is a BRAF V600E mutation.

135. The use according to any one of claims 121-134, wherein the colorectal cancer further expresses wild-type KRAS (KRAS^{wt}).

136. The use according to any one of claims 121-135, wherein the therapeutically effective amount of COMPOUND A is to be orally administered once daily.

137. The use according to claim 136 wherein the therapeutically effective amount of COMPOUND A is 300 mg which is to be orally administered once daily.

138. The use according to any one of claims 121-137, 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.

139. The use according to claim 138, wherein said first and second therapeutically effective dose of COMPOUND B each comprises 45 mg of COMPOUND B.

140. The use according to claims 138 or 139, 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.

141. The use according to any one of claims 121-140, 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.

142. The use according to any one of claims 138-141, 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.
143. The use according to any one of claims 121-142, wherein optionally one or more pre-medications is to be administered to said patient prior to treatment with cetuximab.
144. The use according to claim 143, wherein said pre-medication is to be administered 30-60 minutes prior to administration of cetuximab.
145. The use of claim 144, wherein said one or more pre-medications is selected from one or more of a H¹ antagonist and a systemic corticosteroid.
146. The use according to any one of claims 121-145, 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.
147. The use according to claim 146, wherein the systemic anticancer therapy includes treatment with one or more cytotoxic agents.
148. The use according to claim 147, wherein said one or more cytotoxic agents are selected from irinotecan, oxaliplatin, capecitabine, folinic acid and 5-fluorouracil.
149. The use according to any one of claims 121-148, 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).