

metastatic melanoma has not been previously treated (e.g., with vemurafenib or with BRAF inhibitor). In some embodiments, the patient's unresectable or metastatic melanoma has been previously treated (in some embodiments, without prior treatment to BRAF inhibitor).

[0012] In some embodiments, BRAF^{V600} mutation is determined using a method comprising (a) performing PCR or sequencing on nucleic acid (e.g., DNA, e.g., genomic DNA) extracted from a sample of the patient's melanoma; and (b) determining expression of BRAF^{V600} in the sample. In some embodiments, the melanoma sample is formalin-fixed paraffin-embedded. In some embodiments, BRAF^{V600} mutation is determined using a method comprising (a) isolating DNA (e.g., genomic DNA) from a sample of the patient's melanoma; (b) performing PCR or sequencing on nucleic acid (e.g., DNA) extracted from a sample of the patient's melanoma; and (c) determining expression of BRAF^{V600} in the sample. In some embodiments, the melanoma sample is formalin-fixed paraffin-embedded.

[0013] The present disclosure provides for methods of extending duration of response to treatment (e.g., therapeutic treatment) in a patient having unresectable or metastatic melanoma (e.g., BRAF^{V600} mutation-positive unresectable or metastatic melanoma) comprising administering to the patient (i) a first composition comprising Compound II, or a pharmaceutically acceptable salt thereof, at a dose of 60 mg, on days 1-21 of a 28 day cycle; and (ii) a second composition comprising Compound I, or a pharmaceutically acceptable salt thereof, at a dose of 960 mg twice daily, each day of the 28 day cycle. ~~In one aspect, provided are pharmaceutical products comprising (i) a first composition comprising Compound II, or a pharmaceutically acceptable salt thereof, at a dose of 60 mg, on days 1-21 of a 28 day cycle; and (ii) a second composition comprising Compound I, or a pharmaceutically acceptable salt thereof, at a dose of 960 mg twice daily, each day of the 28 day cycle, for use in extending duration of response to treatment in a patient having BRAF^{V600} mutation-positive unresectable or metastatic melanoma.~~

[0014] The present disclosure provides for methods of delaying or preventing development of resistance to treatment (e.g., resistance to BRAF inhibitor treatment) in a patient having unresectable or metastatic melanoma (e.g., BRAF^{V600} mutation-positive unresectable or metastatic melanoma) comprising administering to the patient (i) Compound II, or a pharmaceutically acceptable salt thereof,

at a dose of 60 mg, on days 1-21 of a 28 day cycle; and (ii) Compound I, or a pharmaceutically acceptable salt thereof, at a dose of 960 mg twice daily, each day of the 28 day cycle. ~~In another aspect, provided are pharmaceutical product comprising (i) a first composition comprising Compound II, or a pharmaceutically acceptable salt thereof, at a dose of 60 mg, on days 1-21 of a 28 day cycle; and (ii) a second composition comprising Compound I, or a pharmaceutically acceptable salt thereof, at a dose of 960 mg twice daily, each day of the 28 day cycle, for use in delaying or preventing development of resistance to treatment (e.g., resistance to BRAF treatment) in a patient having BRAF^{V600} mutation-positive unresectable or metastatic melanoma.~~

[0015] ~~In another one aspect,~~ provided are pharmaceutical products comprising (i) a first composition comprising [3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl][3-hydroxy-3-[(2S)-2-piperidinyl]-1-azetidiny]methanone (Compound II), or a pharmaceutically acceptable salt thereof; and (ii) a second composition comprising propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4- difluoro-phenyl}-amide

(Compound I), or a pharmaceutically acceptable salt thereof; as a combined preparation for concurrent or sequential use in the treatment of BRAF^{V600} mutation-positive unresectable or metastatic melanoma, wherein the Compound II is administered at a dose of 60 mg, on days 1-21 of a 28 day cycle, and wherein Compound I is administered at a dose of 960 mg, twice daily each day of the 28 day cycle.

[0015a] In another aspect, provided is use of a combination of (i) a first composition comprising [3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl][3-hydroxy-3-[(2S)-2-piperidinyl]-1-azetidiny]methanone (Compound II), or a pharmaceutically acceptable salt thereof; and (ii) a second composition comprising propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (Compound I), or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for the treatment of BRAF^{V600} mutation-positive unresectable or metastatic melanoma, wherein the Compound II is to be administered at a dose of 60 mg, on days 1-21 of a 28 day cycle, concurrently or sequentially with Compound I that is to be administered at a dose of 960 mg, twice daily each day of the 28 day cycle.

[0016] In some embodiments, Compound I, or a pharmaceutically-acceptable salt thereof, is substantially in amorphous form. In some embodiments, Compound I, or a pharmaceutically-acceptable salt thereof, is in amorphous form. In some embodiments, Compound I, or a pharmaceutically-acceptable salt thereof, is contained in a solid molecular complex formed with hydroxypropyl methyl cellulose acetate succinate such that it is immobilized in its amorphous form. In some embodiments, the amounts of Compound I, or a pharmaceutically-acceptable salt thereof, and hydroxypropyl methyl cellulose acetate succinate in said complex are in a ratio of from about 1:9 to about 5:5, respectively. In some embodiments, the amounts of Compound I, or a pharmaceutically-acceptable salt thereof, and hydroxypropyl methyl cellulose acetate succinate in said complex are in a ratio of from about 2:8 to about 4:6, respectively. In some embodiments, the amounts of Compound I, or a pharmaceutically-acceptable salt thereof, and hydroxypropyl methyl cellulose acetate succinate in said complex are in a ratio of about 3:7, respectively. In some embodiments, the second composition comprises a blend wherein about 97% by weight of the blend is the aforementioned solid molecular complex and about 3% by weight of the blend is silicon dioxide. In some embodiments, the second composition comprises a

suspension of the aforementioned solid molecular complex in a pharmaceutically acceptable carrier. In some embodiments, the second composition comprises a tablet comprising a solid molecular complex of Compound I, or a pharmaceutically- acceptable salt thereof, and HPMC-AS. In some embodiments, Compound I is provided as a tablet. In some embodiments, Compound I is provided as a 240 mg tablet (i.e., a tablet comprising 240 mg of Compound I). In some embodiments, compound 1 is provided as a tablet marketed as ZELBORAF®.

[0017] In some embodiments, the first composition comprises one or more of lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In some embodiments, Compound II is provided as a tablet comprising lactose

- [0019] In some embodiments, the unresectable or metastatic melanoma is BRAF^{V600E} mutation-positive melanoma. In some embodiments, the unresectable or metastatic melanoma is metastatic melanoma. In some embodiments, the unresectable or metastatic melanoma is unresectable melanoma. In some embodiments, the patient's unresectable or metastatic melanoma has not been previously treated (e.g., with vemurafenib or with BRAF inhibitor). In some embodiments, the patient's unresectable or metastatic melanoma has been previously treated (in some embodiments, without prior treatment to BRAF inhibitor).
- [0020] In some embodiments, BRAF^{V600} mutation is determined using a method comprising (a) performing PCR or sequencing on nucleic acid (e.g., DNA) extracted from a sample of the patient's melanoma; and (b) determining expression of BRAF^{V600} in the sample. In some embodiments, the melanoma sample is a formalin-fixed paraffin-embedded sample.
- [0021] The present disclosure provides for ~~In another aspect, provided are methods for~~ selecting a therapy for a patient with unresectable or metastatic melanoma comprising determining presence of BRAF^{V600} mutation in the patient's unresectable or metastatic melanoma sample, and selecting a cancer medicament based on the presence of BRAF^{V600} mutation. In some embodiments, sample is shown to express BRAF^{V600} mutation, and treatment with a composition comprising Compound II in combination with a composition comprising Compound I is selected. In some embodiments, the patient is treated for unresectable or metastatic melanoma with a method comprising administering to the patient (i) a first composition comprising Compound II, or a pharmaceutically acceptable salt thereof, at a dose of 60 mg, on days 1-21 of a 28 day cycle; and (ii) a second composition comprising Compound I, or a pharmaceutically acceptable salt thereof, at a dose of 960 mg twice daily, on days 1-28 of the 28 day cycle.
- [0022] The present disclosure provides for ~~In another aspect, provided are methods for~~ optimizing therapeutic efficacy comprising determining presence of BRAF^{V600} mutation in a patient's unresectable or metastatic melanoma sample, and selecting a cancer medicament based on the presence of BRAF^{V600} mutation. In some embodiments, the sample is shown to express BRAF^{V600} mutation, and treatment with a first composition comprising Compound II in combination with a second composition comprising Compound I is selected. In some embodiments, the patient is treated for unresectable or metastatic melanoma with a method comprising administering to the patient (i) a first composition comprising Compound II, or a

tumor. The sample may be obtained when the cancer is first diagnosed and/or, for example, after the tumor has metastasized. In some embodiments, the metastasized tumor sample is of lung, skin, lymph node, bone, liver, colon, thyroid, and/or ovary.

[0024] The methods described herein may further comprise treatment with an additional therapeutic agent. In some embodiments, the additional therapeutic agent is a cancer medicament.

[0025] The present disclosure provides for ~~In another aspect, provided are kits comprising~~ (i) a first composition comprising Compound II, or a pharmaceutically acceptable salt thereof; and (ii) a second composition comprising Compound I, or a pharmaceutically acceptable salt thereof. In some embodiments, the kit comprises instructions for performing any of the methods described herein. In some embodiments, the instructions are for methods of treating (e.g., therapeutically treating) a patient having BRAF^{V600} mutation-positive unresectable or metastatic melanoma comprising administering to the patient (i) a first composition comprising compound II, or a pharmaceutically acceptable salt thereof, at a dose of 60 mg, on days 1-21 of a 28 day cycle; and (ii) a second composition comprising compound I, or a pharmaceutically acceptable salt thereof, at a dose of 960 mg twice daily, on days 1-28 of the 28 day cycle. In some embodiments, the kits are for use in the treatment of BRAF^{V600} mutation-positive unresectable or metastatic melanoma. In some embodiments, the melanoma is BRAF^{V600E} mutation-positive unresectable or metastatic melanoma. In some embodiments, the unresectable or metastatic melanoma has not been previously treated. In some embodiments, the patient's unresectable or metastatic melanoma has been previously treated (in some embodiments, without prior treatment to BRAF inhibitor). In some embodiments, the first composition comprising Compound II is a tablet. In some embodiments, the second composition comprising Compound I is a tablet. In some embodiments, the first composition comprising Compound II and the first composition comprising Compound I are each provided as a tablet. In some embodiments, the first composition comprising Compound I and the second Composition comprising Compound II are provided as a single dosing form. In some embodiments, the first composition comprising Compound II and the second composition comprising Compound I are co-formulated (e.g., as a pharmaceutical formulation).

21. The pharmaceutical product of any one of claims 1-20, wherein the unresectable or metastatic melanoma is BRAF^{V600E} mutation-positive melanoma.

22. The pharmaceutical product of any one of claims 1-21, wherein the unresectable or metastatic melanoma is metastatic melanoma.

23. The pharmaceutical product of any one of claims 1-22, wherein BRAF^{V600} mutation is determined using a method comprising (a) performing PCR or sequencing on nucleic acid (e.g., DNA) extracted from a sample of the patient's melanoma; and (b) determining expression of BRAF^{V600} in the sample.

24. The pharmaceutical product of claim 23, wherein the melanoma sample is a formalin-fixed paraffin-embedded sample.

25. The pharmaceutical product of any of the preceding claims, wherein the patient's unresectable or metastatic melanoma has not been previously treated.

~~26. The pharmaceutical product of any of the preceding claims, for use in the manufacture of a medicament for treatment of BRAF^{V600} mutation-positive unresectable or metastatic melanoma.~~

~~27. The pharmaceutical product of claim 26, wherein the BRAF^{V600} mutation-positive unresectable or metastatic melanoma has not been previously treated.~~

~~28. A kit comprising (i) a first composition comprising Compound II, or a pharmaceutically acceptable salt thereof; and (ii) a second composition comprising Compound I, or a pharmaceutically acceptable salt thereof.~~

~~29. The kit of claim 28, for use in the treatment of BRAF^{V600} mutation-positive unresectable or metastatic melanoma.~~

~~30. The kit of claim 29, wherein the BRAF^{V600} mutation-positive unresectable or metastatic melanoma has not been previously treated.~~

~~31. A pharmaceutical product comprising (i) a first composition comprising Compound II, or a pharmaceutically acceptable salt thereof, at a dose of 60 mg, on days 1-21 of a 28 day cycle; and (ii) a second composition comprising Compound I, or a pharmaceutically acceptable salt thereof, at a dose of 960 mg twice daily, each day of the 28 day cycle, for use in extending duration of response to treatment in a patient having BRAF^{V600} mutation-positive unresectable or metastatic melanoma.~~

~~32. A pharmaceutical product comprising (i) a first composition comprising Compound II, or a pharmaceutically acceptable salt thereof, at a dose of 60 mg, on days 1-21 of a 28 day cycle; and (ii) a second composition comprising Compound I, or a pharmaceutically acceptable salt thereof, at a dose of 960 mg twice daily, each day of the 28 day cycle, for use in delaying or preventing development of resistance to treatment (e.g., resistance to BRAF^{V600} treatment) in a patient having BRAF^{V600} mutation-positive unresectable or metastatic melanoma.~~

~~33. A method for selecting a therapy for a patient with unresectable or metastatic melanoma comprising determining presence of BRAF^{V600} mutation in the patient's unresectable or metastatic melanoma sample, and selecting a cancer medicament based on the presence of BRAF^{V600} mutation.~~

~~34. The method of claim 33, wherein the sample is shown to express BRAF^{V600} mutation, and wherein treatment with Compound II in combination with Compound I is selected.~~

~~35. The method of claim 34, wherein the selected combination treatment comprises (i) a first composition comprising Compound II, or a pharmaceutically acceptable salt thereof, at a dose of 60 mg, on days 1-21 of a 28 day cycle; and (ii) a second composition comprising Compound I, or a pharmaceutically acceptable salt thereof, at a dose of 960 mg twice daily, on days 1-28 of the 28 day cycle.~~

~~36. A method for optimizing therapeutic efficacy comprising determining presence of BRAF^{V600} mutation in a patient's unresectable or metastatic melanoma sample, and selecting a cancer medicament based on the presence of BRAF^{V600} mutation.~~

~~37. The method of claim 36, wherein the sample is shown to express BRAF^{V600} mutation, and wherein treatment with Compound II in combination with Compound I is selected.~~

~~38. The method of claim 37, wherein the selected combination treatment comprises (i) a first composition comprising Compound II, or a pharmaceutically acceptable salt thereof, at a dose of 60 mg, on days 1-21 of a 28 day cycle; and (ii) a second composition comprising Compound I, or a pharmaceutically acceptable salt thereof, at a dose of 960 mg twice daily, on days 1-28 of the 28 day cycle.~~

~~39. The method of any one of claims 33-38, wherein presence of BRAF^{V600} mutation is determined by assessing BRAF nucleic acid.~~

40. The method of any one of claims 33-38, wherein presence of BRAF^{V600}-mutation is determined using a method selected from: polymerase chain reaction (PCR) (including but not limited to quantitative real time PCR and allele-specific PCR), sequencing (including but not limited to Sanger sequencing and/or pyrosequencing), hybridization using allele-specific oligonucleotides, primer extension, allele-specific ligation, or electrophoretic separation techniques (including but not limited to single-stranded conformational polymorphism (SSCP) and heteroduplex analysis), and 5' nuclease assays.

41. The method of any one of claims 33-38, wherein presence of BRAF^{V600}-mutation is determined using PCR or sequencing.

42. The method of any one of claims 33-38, wherein presence of BRAF^{V600}-mutation is determined by a method comprising (a) hybridizing a first and second oligonucleotides to at least one variant of the BRAF target sequence; wherein said first oligonucleotide is at least partially complementary to one or more variants of the target sequence and said second oligonucleotide is at least partially complementary to one or more variants of the target sequence, and has at least one internal selective nucleotide complementary to only one variant of the target sequence; (b) extending the second oligonucleotide with a nucleic acid polymerase; wherein said polymerase is capable of extending said second oligonucleotide preferentially when said selective nucleotide forms a base pair with the target, and substantially less when said selective nucleotide does not form a base pair with the target; and (c) detecting the products of said oligonucleotide extension, wherein the extension signifies the presence of the variant of a target sequence to which the oligonucleotide has a complementary selective nucleotide.

43. The method of claim 42, wherein the sample is a formalin-fixed paraffin-embedded sample.

44. The method of claim 31, 32, 33 or 36, wherein the BRAF^{V600}-mutation-positive unresectable or metastatic melanoma has not been previously treated.

45. The method of any one of claims 33 to 44, further comprising an additional therapeutic agent.

26. Use of a combination of (i) a first composition comprising [3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl][3-hydroxy-3-[(2S)-2-piperidinyl]-1-azetidiny]methanone (Compound II), or a pharmaceutically acceptable salt thereof; and (ii) a second composition comprising propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4- difluoro-phenyl}-amide (Compound I), or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for the treatment of BRAF^{V600} mutation-positive unresectable or metastatic melanoma, wherein the Compound II is to be administered at a dose of 60 mg, on days 1-21 of a 28 day cycle, concurrently or sequentially with Compound I that is to be administered at a dose of 960 mg, twice daily each day of the 28 day cycle.

27. The use of claim 26, wherein the first composition is to be administered sequentially with the second composition.

28. The use of claim 26, wherein the first composition is to be administered concurrently with the second composition.

29. The use of claim 26, wherein the first and second compositions are co-formulated.

30. The use of any one of claims 26-29, wherein Compound I, or a pharmaceutically-acceptable salt thereof, is substantially in amorphous form.

31. The use of any one of claims 26-29, wherein Compound I, or a pharmaceutically-acceptable salt thereof, is in amorphous form.

32. The use of any one of claims 26-31, wherein Compound I, or a pharmaceutically-acceptable salt thereof, is contained in a solid molecular complex formed with hydroxypropyl methyl cellulose acetate succinate such that it is immobilized in its amorphous form.

33. The use of claim 32, wherein the amounts of Compound I, or a pharmaceutically-acceptable salt thereof, and hydroxypropyl methyl cellulose acetate succinate in said complex are in a ratio of from about 1:9 to about 5:5, respectively.

34. The use of claim 32, wherein the amounts of Compound I, or a pharmaceutically-acceptable salt thereof, and hydroxypropyl methyl cellulose acetate succinate in said complex are in a ratio of from about 2.8 to about 4.6, respectively.

35. The use of claim 32, wherein the amounts of Compound I, or a pharmaceutically-acceptable salt thereof, and hydroxypropyl methyl cellulose acetate succinate in said complex are in a ratio of about 3:7, respectively.

36. The use of claim 32, wherein the amounts of Compound I, or a pharmaceutically-acceptable salt thereof, and hydroxypropyl methyl cellulose acetate succinate in said complex are in a ratio of 3:7, respectively.

37. The use of any one of claims 26-32, wherein the second composition comprises a blend wherein about 97% by weight of the blend is the solid molecular complex according to claim 32 and about 3% by weight of the blend is silicon dioxide.

38. The use of any one of claims 26-32, wherein the second composition comprises a suspension of the solid molecular complex according to claim 32 in a pharmaceutically acceptable carrier.

39. The use of any one of claims 26-32, wherein the second composition comprises a tablet comprising a solid molecular complex of Compound I, or a pharmaceutically- acceptable salt thereof, and HPMC-AS.

40. The use of any one of claims 26-29, wherein the first composition comprises one or more of lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

41. The use of any one of claims 26-29, wherein Compound II is provided as a tablet comprising lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

42. The use of claim 41, wherein the tablet comprises a tablet coating comprising polyvinyl alcohol-part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc.

43. The use of any one of claims 26-42, wherein Compound II is provided as a 20 mg tablet, as a 40 mg tablet, or as a 60 mg tablet.

44. The use of any one of claims 26-43, wherein a second 960 mg dose of Compound I, or a pharmaceutically acceptable salt thereof is administered about 12 hours after a first 960 mg dose of Compound I, or a pharmaceutically acceptable salt thereof.

45. The use of any one of claims 26-44, wherein Compound I, or a pharmaceutically acceptable salt thereof, and Compound II, or a pharmaceutically acceptable salt thereof, are each administered orally, with or without food.

46. The use of any one of claims 26-45, wherein the patient's unresectable or metastatic melanoma has not been previously treated.