COMBINATION OF ENCORAFENIB AND BINIMETINIB AS ADJUVANT TREATMENT FOR RESECTED STAGE II MELANOMA

INTRODUCTION

Melanoma is one of the most aggressive skin cancers. Epidemiologic data reveals the increasing incidence of melanoma over time in both United States (USA) and Europe with more than 100.000 new cases expected in 2020 in both USA and Europe. The increase in incidence of melanoma has led to an increased number of patients with early stage being diagnosed each year, across the globe, but especially in the western world (Ref. 1-3).

Current staging criteria are based on melanoma progression from an early stage lesion, confined to the epidermis (stage 0) followed by a series of early stages of local invasion (I and II) before moving to the regional lymph nodes (stage III) and finally metastasising to distal sites (stage IV). High-risk cancers are usually considered those that are ulcerated, involve lymph nodes, demonstrate microsatellitosis, or in-transit disease (stage III). Immunotherapy (immune checkpoint inhibitors) and several BRAF and MEK inhibitor combinations (encorafenib plus binimetinib, dabrafenib plus trametinib, vemurafenib plus cobimetinib) have been approved for treating metastatic melanoma (Ref. 5).

Although sometimes described to be at "low-risk," patients with stage IIA through IIC melanoma carry a melanoma-specific mortality rate of 12% to 25% over the course of 10 years. Indeed, early stage tumours (I-IIA) appear to make a significant contribution to the overall melanoma contribution (Ref. 6). According to the most recent edition of the AJCC (American Joint Committee on Cancer) melanoma staging manual (8th edition, Gershenwald et al. 2018), melanoma specific survival (MSS) at 5 and 10 years for N0M0 is 93% and 88% for pT2b, 94% and 88% for pT3a, 86% and 81% for pT3b, 90% and 83% for pT4a, 82% and 75% for pT4b, respectively (Ref. 4). These numbers may be somewhat overestimated due to the methodological shortcomings of the study, including the fact that some patients may have died due to melanoma without having the cause of death correctly recorded due to being lost to follow-up from the tertiary cancer centre.

Thus, a significant and ongoing unmet need exists for patients with earlier stage melanoma.

Surgical resection is the treatment of choice for localised melanoma. For stage II patients, the current standard of care is wide local excision (WLE) and sentinel node (SN) staging, which is per definition negative. Thereafter, these patients do not receive further treatment, but proceed into surveillance follow-up, which differs between countries in terms of whether it only includes physical examinations or also periodic imaging.

However, after surgical removal of melanoma, some patients will relapse; then, the goal of adjuvant systemic therapy is to minimise that risk of relapse. There are currently two phase 3 trials examining adjuvant systemic therapy with immunotherapy in stage IIB-IIC melanoma. Previous studies with the BRAF inhibitor vemurafenib single-agent did not yield a significant result in stage IIC-IIIB.

Thus, there is a need for therapies with an acceptable safety profile in the adjuvant settings for stage II melanoma.

SUMMARY OF THE INVENTION

The present description provides a method of providing adjuvant treatment to a patient after resection of a melanoma, wherein the melanoma which has been resected is stage II melanoma. This method comprises the administration to the patient of a pharmaceutical combination, wherein the pharmaceutical combination comprises therapeutically effective amounts, independently, of:

a) encorafenib or a pharmaceutically acceptable salt thereof and
b) binimetinib or a pharmaceutically acceptable salt thereof.

The pharmaceutical combination may also optionally comprise at least one pharmaceutically acceptable carrier.

Thus, the present description relates to a pharmaceutical combination for use as adjuvant treatment after resection of a melanoma, wherein the melanoma which has been resected is stage II melanoma, and wherein the pharmaceutical combination comprises therapeutically effective amounts, independently, of:

a) encorafenib or a pharmaceutically acceptable salt thereof;

b) binimetinib or a pharmaceutically acceptable salt thereof; and

optionally at least one pharmaceutically acceptable carrier.

The present description relates also to the use of a pharmaceutical combination for the manufacture of a medicinal product intended to be used as adjuvant treatment after resection of a melanoma, wherein the melanoma which has been resected is stage II melanoma, and wherein the pharmaceutical combination comprises therapeutically effective amounts, independently, of:

a) encorafenib or a pharmaceutically acceptable salt thereof;
b) binimetinib or a pharmaceutically acceptable salt thereof; and

optionally at least one pharmaceutically acceptable carrier.

In another embodiment, the present description relates to a pharmaceutical combination for use in preventing melanoma recurrence after melanoma resection, wherein the melanoma which has been resected is stage II melanoma, and wherein the pharmaceutical combination comprises therapeutically effective amounts, independently, of:

a) encorafenib or a pharmaceutically acceptable salt thereof;
b) binimetinib or a pharmaceutically acceptable salt thereof; and

optionally at least one pharmaceutically acceptable carrier.

The present description also relates to a method of preventing melanoma recurrence after melanoma resection, the method comprising administering a pharmaceutical combination to a patient in need thereof, wherein the melanoma which has been resected is stage II melanoma, and wherein the pharmaceutical combination comprises therapeutically effective amounts, independently, of:

a) encorafenib or a pharmaceutically acceptable salt thereof;
b) binimetinib or a pharmaceutically acceptable salt thereof; and

optionally at least one pharmaceutically acceptable carrier.

The present description relates also to the use of a pharmaceutical combination for the manufacture of a medicinal product intended to prevent melanoma recurrence after melanoma resection, wherein the melanoma which has been resected is stage II

melanoma, and wherein the pharmaceutical combination comprises therapeutically effective amounts, independently, of:

a) encorafenib or a pharmaceutically acceptable salt thereof;
b) binimetinib or a pharmaceutically acceptable salt thereof; and

optionally at least one pharmaceutically acceptable carrier.

In an embodiment, the stage II melanoma is a BRAF-V600 positive melanoma. More preferably, the melanoma is a BRAF V600E positive melanoma or a BRAF V600K positive melanoma. Even more preferably, the BRAF genotype is determined after resection.

In an embodiment, the stage II melanoma is a stage IIA (i.e. pT2b or pT3a), IIB (i.e. pT3b or pT4a) or IIC (i.e. pT4b) melanoma, preferably with a BRAF V600 mutation, and more preferably with a BRAF V600K or BRAF V600E mutation. Even more preferably, the BRAF genotype is determined after resection.

In an embodiment, the stage II melanoma is a stage IIA (i.e. pT2b or pT3a) melanoma, preferably with a BRAF V600 mutation, and more preferably with a BRAF V600K or BRAF V600E mutation. Even more preferably, the BRAF genotype is determined after resection.

In an embodiment, the stage II melanoma is a IIB (i.e. pT3b or pT4a) or IIC (i.e. pT4b) melanoma, preferably with a BRAF V600 mutation, and more preferably with a BRAF V600K or BRAF V600E mutation. Even more preferably, the BRAF genotype is determined after resection.

In another embodiment, encorafenib and binimetinib, or their respective pharmaceutically acceptable salts, are formulated as separate unit dosages for simultaneous, separate or sequential administration.

In another embodiment, encorafenib, or a pharmaceutically acceptable salt thereof, and binimetinib, or a pharmaceutically acceptable salt thereof, are administered simultaneously, separately or sequentially over time.

In another embodiment, encorafenib is administered at an amount of 450 mg once a day.

In another embodiment, binimetinib is administered at an amount of 45 mg twice a day.

In another embodiment, encorafenib is administered at an amount of 450 mg once a day and binimetinib is administered at an amount of 45 mg twice a day.

In another embodiment, encorafenib, or a pharmaceutically acceptable salt thereof, and binimetinib, or a pharmaceutically acceptable salt thereof, are administered during 6 months.

In another embodiment, encorafenib, or a pharmaceutically acceptable salt thereof, and binimetinib, or a pharmaceutically acceptable salt thereof, are administered during 6 months, the treatment being renewable once of 6 months.

In another embodiment, encorafenib, or a pharmaceutically acceptable salt thereof, and binimetinib, or a pharmaceutically acceptable salt thereof, are administered during 12 months.

In an embodiment, the stage II melanoma is a stage IIA (i.e. pT2b or pT3a), IIB (i.e. pT3b or pT4a) or IIC (i.e. pT4b) melanoma, preferably with a BRAF V600 mutation, and more preferably with a BRAF V600K or BRAF V600E mutation; and encorafenib, or a pharmaceutically acceptable salt thereof, and binimetinib, or a pharmaceutically acceptable salt thereof, are administered during 6 months; 6 months with a possible prolongation of 6 months; or 12 months. Even more preferably, the BRAF genotype is determined after resection.

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In an embodiment, the stage II melanoma is a stage IIB (i.e. pT3b or pT4a) or IIC (i.e. pT4b) melanoma, preferably with a BRAF V600 mutation, and more preferably with a BRAF V600K or BRAF V600E mutation; and encorafenib, or a pharmaceutically acceptable salt thereof, and binimetinib, or a pharmaceutically acceptable salt thereof, are administered during 6 months; 6 months with a possible prolongation of 6

months; or 12 months. Even more preferably, the BRAF genotype is determined after resection.

In an embodiment, the stage II melanoma is a stage IIA (i.e. pT2b or pT3a) melanoma, preferably with a BRAF V600 mutation, and more preferably with a BRAF V600K or BRAF V600E mutation; and encorafenib, or a pharmaceutically acceptable salt thereof, and binimetinib, or a pharmaceutically acceptable salt thereof, are administered during 6 months. Even more preferably, the BRAF genotype is determined after resection.

In another embodiment, the methods described herein result in increasing relapse-free survival (RFS) (also called recurrence free survival) compare to no treatment.

DETAILED DESCRIPTION

The essential role and the position of RAF in many signalling pathways has been demonstrated from studies using deregulated and dominant inhibitory RAF mutants in mammalian cells as well as from studies employing biochemical and genetic techniques to model organisms. Certain oncogenic mutations, including the BRAF V600 mutations, lead to constitutive activation of the RAS / RAF / MEK / ERK pathway (also known as the MAPK pathway). The frequency of BRAF V600 mutations is approximately 40-50% in melanomas (Ref. 7). The most commonly observed BRAFV600 mutation is the BRAF V600E mutation representing over 90% of the mutations. The second most common mutation is BRAF V600K representing ~5%-6% of the mutations. Data demonstrate that RAF kinase inhibitors can significantly inhibit signalling through the MAPK pathway, leading to dramatic shrinkage in BRAF (V600E) melanoma.

Encorafenib is an ATP-competitive BRAF serine and threonine kinase inhibitor selectively exhibiting anti-proliferative effects in BRAF V600-mutated cells, and in particular in BRAF V600E-mutated cells, and inhibiting signalling of RAS/MEK/ERK pathway. Importantly, encorafenib is characterised by a significantly increased dissociation half-life of more than 30 hours, as compared with the 2 and 0.5 hours reported for dabrafenib and vemurafenib, respectively. This results in increased efficacy and reduced toxicity, thereby improving the overall benefit-risk ratio of the drug (Ref. 8).

Binimetinib is a reversible inhibitor of the activation of protein kinases MEK1 and MEK2, which are responsible for phosphorylating the ERK1 and ERK2 proteins. Activated ERKs interact with and phosphorylate numerous cytoplasmic substrates and ultimately modulate transcription factors, thereby activating involved in one of the main proliferation pathways of cell survival.

The addition of a MEK inhibitor in combination with a RAF inhibitor leads to a significant inhibition of ERK signalling and consequently a decrease in cellular proliferation and transformation. In particular, encorafenib and binimetinib in combination show enhanced efficacy and reduced toxicity against BRAF-dependent tumours, such as unresectable or metastatic melanoma. Moreover, the rapid onset and sustained efficacy observed in these settings shows that the pharmaceutical combination of encorafenib and binimetinib is particularly advantageous over the combinations of BRAF and MEK inhibitors of the prior art (Ref. 9-12). The specific combination of encorafenib and binimetinib allows for a shorter adjuvant treatment duration than comparable combinations of RAF and MAK inhibitors.

For the purpose of the invention, the term “pharmaceutically acceptable” is intended to mean what is useful to the preparation of a pharmaceutical composition, and what is generally safe and non-toxic, for a pharmaceutical use.

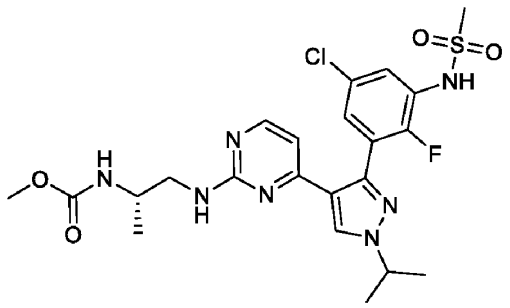
The term “pharmaceutically acceptable salt” is intended to mean, in the framework of the present invention, a salt of a compound which is pharmaceutically acceptable, as defined above, and which possesses the pharmacological activity of the corresponding compound.

For example, the pharmaceutically acceptable salts comprise:

(1) acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric and phosphoric acid and the like; or formed with organic acids such as formic, acetic, benzoic, benzenesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxynaphthoic, 2-hydroxyethanesulfonic, lactic, maleic, malic, mandelic, oxalic, salicylic, methanesulfonic, muconic, 2-naphthalenesulfonic, propionic, succinic, dibenzoyl-L-citric, tartaric, tartaric, p-toluenesulfonic, trimethylacetic, and trifluoroacetic acid and the like, and

(2) salts formed when an acid proton present in the compound is either replaced by a metal ion, such as an alkali metal ion, an alkaline-earth metal ion, or an aluminium ion; or coordinated with an organic or inorganic base. Acceptable organic bases comprise diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, tromethamine and the like. Acceptable inorganic bases comprise aluminium hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

By "encorafenib", it is herein referred to the compound of Formula (I):



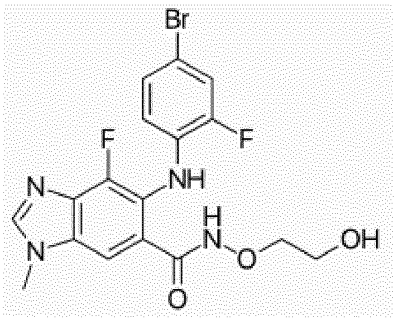
(I).

Encorafenib is also known as methyl N-[(2S)-1-({4-[3-(2-chloro-5-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate, LGX818 or NVP-LGX818. Encorafenib and methods of preparation thereof are described in e.g., PCT application No. WO 2011/025927. In particular, the synthesis of encorafenib is described in Examples 5 and 6 of PCT application No. WO 2011/025927. In one embodiment, encorafenib is in an amorphous form.

When referring to encorafenib, the term "salt" or "salts" is understood to be a salt of encorafenib that can be present alone or in mixture with the free compound of Formula (I) and are preferably pharmaceutically acceptable salts. Such salts are formed, for example, as acid addition salts by reacting the free base form of encorafenib with a pharmaceutically acceptable inorganic acid such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric or phosphoric acid and the like; or with a pharmaceutically acceptable organic acid such as formic, acetic, benzoic, benzenesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxynaphthoic, 2-hydroxyethanesulfonic, lactic, maleic, malic, mandelic, oxalic, salicylic, methanesulfonic, muconic, 2-naphthalenesulfonic, propionic, succinic, dibenzoyl-L-citric, tartaric, tartaric, p-toluenesulfonic, trimethylacetic, or

trifluoroacetic acid and the like. The salts of encorafenib are preferably pharmaceutically acceptable salts. Pharmaceutically acceptable salts of encorafenib are also described in e.g. PCT application No. WO 2011/025927.

By "binimetinib", it is herein referred to 6-(4-bromo-2-fluoro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide which is the compound of Formula (II):



(II).

Binimetinib is described in e.g., PCT application No. WO 2003/077914A1. This PCT application describes methods for its preparation, for example, in Example 18 (compound 29lll). Binimetinib is also known as 5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide, ARRY-162, and MEK 162. In one embodiment, 6-(4-bromo-2-fluoro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide is crystallised 6-(4-bromo-2-fluoro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide. Crystallised 6-(4-bromo-2-fluoro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide and methods of preparing crystallised 6-(4-bromo-2-fluoro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide are described in PCT Publication No. WO 2014/063024.

As related to binimetinib, the term "salt" or "salts", unless otherwise indicated, includes salts of acidic and basic groups which may be present in the compounds of the present invention. Thus, it can be a pharmaceutically salt as defined above formed with an organic or inorganic acid or formed with an organic or inorganic base. In particular, binimetinib is capable of forming salts with various inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric or phosphoric acid and the like; and with various organic acids such as formic, acetic, benzoic,

benzenesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxynaphthoic, 2-hydroxyethanesulfonic, lactic, maleic, malic, mandelic, oxalic, salicylic, methanesulfonic, muconic, 2-naphthalenesulfonic, propionic, succinic, dibenzoyl-L-citric, tartaric, tartaric, p-toluenesulfonic, trimethylacetic, or trifluoroacetic acid and the like. In particular, the acids that may be used to prepare pharmaceutically acceptable acid addition salts of binimetinib are those that form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, such as the acetate, benzoate, citrate, fumarate, hydrobromide, hydrochloride, hydroiodide, lactate, maleate, mandelate, nitrate, oxalate, salicylate, succinate, and tartrate salts. An example of a salt of this type is a hydrochloride or sulfate salt of binimetinib as described herein. Additional pharmaceutically acceptable salts of binimetinib suitable for the present invention include the salts disclosed in PCT Application No. WO 03/077914.

As used herein, the terms "subject" or "patient," used interchangeably, refer to any animal, including mammals such as humans, primates, mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep and horses. In some embodiments, the subject is a human. In some embodiments, the subject has been identified or diagnosed as having stage II melanoma with dysregulation of a BRAF gene, a BRAF protein, or expression or activity, or level of the same (e.g., as determined using a validated assay or kit or a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a stage II melanoma that is positive for dysregulation of a BRAF gene, a BRAF protein, or expression or activity, or level of the same (e.g., as determined using a validated assay or kit or a regulatory agency-approved assay or kit). In some embodiments, the subject has a stage II melanoma that is positive for a BRAF mutation which results in dysregulation of a BRAF gene, a BRAF protein, or expression or activity, or level of the same (e.g., as determined using a validated assay or kit or a regulatory agency-approved assay or kit). In some embodiments, this mutation is a BRAF V600 mutation, preferably V600K or V600E. In some embodiments, the genotype of the stage II melanoma has been determined after this melanoma has been resected.

The term "resection" is used herein to refer to the surgical removal of a tissue or part or all of an organ. More specifically, in the context of the present disclosure, resection consists in the surgical removal of malignant tissue characteristic of melanoma from the patient. Preferably, after resection, the presence of remaining

malignant tissue is undetectable with the available methods. In another preferred embodiment, after resection, the presence of remaining melanoma disease is undetectable with the available methods. Advantageously, surrounding healthy tissue is removed in addition to malignant tissue by resection. In another embodiment, surrounding non-cancerous tissue is removed in addition to melanoma by resection. For example, stage II melanoma are usually removed by wide local excision (WLE), i.e., a margin of healthy tissue is removed in addition to the melanoma.

The terms "treating" or "treatment" refer to administering or the administration of a drug or drugs (e.g. a pharmaceutical combination described herein) in an amount, manner, and/or mode effective to improve a condition, symptom, or parameter associated with a disorder or to prevent progression or exacerbation of the disorder (including secondary damage caused by the disorder) to either a statistically significant degree or to a degree detectable to one skilled in the art.

"Adjuvant therapy" herein refers to therapy given after surgery, where no evidence of residual disease can be detected, so as to reduce the risk of disease recurrence or to delay the onset of the biological, radiological or clinical manifestations of the reoccurrence of the disease. The goal of adjuvant therapy is to prevent recurrence of the cancer, and therefore to reduce the risk of cancer-related death. More specifically, the goal of adjuvant therapy is to prevent recurrence of melanoma, and therefore to reduce the risk of melanoma-related death. In other words, the goal of adjuvant therapy is to increase relapse-free survival (RFS). One particular advantage of the present pharmaceutical combination disclosed herein is that such an increase in RFS is obtained with a shorter treatment duration than for other targeted therapy. Another advantage of the present pharmaceutical combination disclosed herein is that its safety profile confers a favourable benefit-risk ratio compared to other targeted therapies available.

"Recurrence" herein refers to a local recurrence, a regional recurrence, a distant metastasis, a new melanoma which is ulcerated, or thick (Breslow thickness > 1 mm), or which requires a treatment other than surgery, or a combination thereof. A "local cutaneous recurrence" is a regrowth of melanoma occuring in close proximity to the anatomic site from which the primary tumor was excised, in particular within 2 cm of the tumor bed. A "regional recurrence" is either a nodal recurrence defined as regrowth of melanoma into lymph nodes at the periphery of the prior surgical

procedure, or an occurrence of "in transit metastases" defined as any skin or subcutaneous metastases that are more than 2 cm from the primary lesion but are not beyond the regional nodal basin. The local and regional recurrences are also named locoregional recurrences. A "distant metastasis" is once melanoma spreads to distant locations: non-visceral (as the skin, subcutaneous tissue, and lymph nodes), or visceral locations (lung, brain, liver, gastrointestinal tract), or bone.

As used herein, an "effective amount" refers to an amount of a drug or a pharmaceutical agent which is effective, at dosages and for periods of time necessary, to achieve the result desired by a researcher or a clinician. A "therapeutically effective amount" means an amount sufficient to influence the therapeutic course of a particular disease state. A therapeutically effective amount is also one in which any toxic or detrimental effects of the agent are outweighed by the therapeutically beneficial effects.

While it is possible to administer encorafenib and binimetinib as the raw chemical for use in therapy, they are commonly used as part of pharmaceutical compositions. Accordingly, the present disclosure also relates to one or more pharmaceutical composition comprising a) encorafenib or a pharmaceutically acceptable salt thereof, b) binimetinib or a pharmaceutically acceptable salt thereof, or c) encorafenib or a pharmaceutically acceptable salt thereof and binimetinib or a pharmaceutically acceptable salt thereof, with optional pharmaceutically-acceptable carriers, excipients or stabilisers typically employed in the art (all of which are referred to herein as "carriers"), *i.e.*, buffering agents, stabilising agents, preservatives, isotonifiers, non-ionic detergents, antioxidants, and other miscellaneous additives. *See*, The Handbook of Pharmaceutical Excipients, 4th edition, Rowe et al., Eds., American Pharmaceuticals Association (2003); and Remington: The Science and Practice of Pharmacy, 20th edition, Gennaro, Ed., Lippincott Williams & Wilkins (2003). The carrier(s) must be acceptable in the sense of being compatible with the other ingredient(s) of the composition and not deleterious to the recipient thereof. The type of carrier can be selected based upon the intended route of administration. The amount of each carriers used may vary within ranges conventional in the art.

Encorafenib and binimetinib or their pharmaceutically acceptable salts may be administered as pharmaceutical compositions by any conventional route, in particular

enterally, e.g., orally, e.g., in the form of tablets or capsules, parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Preferably, encorafenib and binimetinib or their pharmaceutically acceptable salts are administered, as pharmaceutical compositions, enterally, e.g., orally, e.g., in the form of tablets or capsules. Pharmaceutical compositions comprising encorafenib and/or binimetinib in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatine capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, e.g., magnesium aluminium silicate, starch paste, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavours and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions may be sterilised and/or contain adjuvants, such as preserving, stabilising, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. It will be appreciated that the preferred route may vary with, for example, the condition of the subject receiving the combination disclosed herein. It will also be appreciated that each of the agents administered may be administered by the same or different routes and that the compounds may be formulated separately or compounded together in a pharmaceutical composition.

Preferably, encorafenib is formulated for oral administration. In one embodiment, encorafenib is formulated as a tablet or capsule, e.g. a capsule. Methods of preparing oral formulations of encorafenib are described in PCT publication No. WO 2013/078264.

Binimetinib is preferably formulated for oral administration. In one embodiment, the binimetinib is formulated as a tablet or capsule. In one embodiment,

binimetinib is formulated as a tablet, e.g. a coated tablet. Methods of preparing oral formulations of binimetinib are described in PCT publication No. WO 2014/063024.

In one aspect of the disclosure, the administration of encorafenib is performed with binimetinib, either simultaneously, separately or sequentially over time. When the administration is performed simultaneously, the two active principles may be combined in a single pharmaceutical composition, comprising the two compositions, such as a tablet or a hard capsule. On the other hand, the two active principles may, whether or not they are administered simultaneously, be present in separate pharmaceutical compositions. The two compounds may be administered by the same or different routes, e.g., they can be both administered enterally, e.g., orally, or one can be administered enterally and the other parenterally or topically. Preferably, both encorafenib and binimetinib are administered enterally, more preferably orally. Thus, in one embodiment, one or more doses of encorafenib is administered simultaneously, separately or sequentially over time with one or more doses of binimetinib.

The effective dosage of each of the compounds employed in the present pharmaceutical combination may vary depending on the particular compound or pharmaceutical composition employed, the mode of administration, the condition being treated, and the severity of the condition being treated. The optimum ratios, individual and combined dosages, and concentrations of the combination partners (encorafenib and binimetinib) of a pharmaceutical combination that yield efficacy without toxicity are based on the kinetics of the therapeutic agents' availability to target sites, and may be determined using methods known to those of skill in the art.

Encorafenib may be administered to a suitable subject daily in single or divided doses at an effective dosage in the range of about 0.05 to about 50 mg per kg body weight per day, (e.g., about 0.10 mg/kg/day, 0.30 mg/kg/day, 0.50 mg/kg/day, 0.80 mg/kg/day, 1 mg/kg/day, 5 mg/kg/day, 10 mg/kg/day, 15 mg/kg/day, 20 mg/kg/day, 25 mg/kg/day, 30 mg/kg/day, 35 mg/kg/day, 40 mg/kg/day, 50 mg/kg/day, 0.1-25 mg/kg/day, or 0.5-10 mg/kg/day). For example, doses may be about 35 mg to about 700 mg (e.g., about 50 mg, about 75 mg, about 100 mg, about 120 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, or about 650 mg), in single or divided doses. For a 70 kg human, this would amount to a preferable dosage range of about 35-700 mg

per day, for example 450 mg per day. In one embodiment, encorafenib is orally administered. In one embodiment, encorafenib is in a capsule form. In one embodiment, a capsule formulation of encorafenib comprises 50 mg of encorafenib. In one embodiment, a capsule formulation of encorafenib comprises 75 mg of encorafenib. In one embodiment, a capsule formulation of encorafenib comprises 100 mg of encorafenib. In one embodiment, a capsule formulation of encorafenib comprises amorphous encorafenib. In one embodiment, 450 mg of encorafenib is orally administered once daily. In one embodiment, 375 mg of encorafenib is orally administered once daily. In one embodiment, 300 mg of encorafenib is orally administered once daily. In one embodiment, 225 mg of encorafenib is orally administered once daily. In one embodiment, 150 mg of encorafenib is orally administered once daily.

Binimetinib may be administered to a suitable subject daily in single or divided doses at an effective dosage in the range of about 0.001 to about 100 mg per kg body weight per day, (e.g., about 0.01 mg/kg/day, about 0.10 mg/kg/day, 0.30 mg/kg/day, 0.50 mg/kg/day, 0.80 mg/kg/day, 1 mg/kg/day, 5 mg/kg/day, 10 mg/kg/day, 15 mg/kg/day, 20 mg/kg/day, 25 mg/kg/day, 30 mg/kg/day, 35 mg/kg/day, 40 mg/kg/day, 50 mg/kg/day, 60 mg/kg/day, 70 mg/kg/day, 80 mg/kg/day, 90 mg/kg/day, 100 mg/kg/day, 0.1-25 mg/kg/day, 0.5-10 mg/kg/day, or 1-35 mg/kg/day). For example, doses may be about 10 mg to about 85 mg (e.g., about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, or about 85 mg). For a 70 kg human, this would amount to a preferable dosage range of about 0.05 to 7 g/day, preferably about 0.05 to about 2.5 g/day, notably 0.9 g/day. In one embodiment, binimetinib is orally administered. In one embodiment, binimetinib is formulated as a tablet. In one embodiment, a tablet formulation of binimetinib comprises 15 mg of binimetinib. In one embodiment, binimetinib is orally administered twice daily. In one embodiment, binimetinib is orally administered twice daily, wherein the second dose of binimetinib is administered about 12 hours after the first dose of binimetinib. In one embodiment, 45 mg of binimetinib is orally administered twice daily. In one embodiment, binimetinib is 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide or a pharmaceutically acceptable salt thereof. In one embodiment, binimetinib is crystallised 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-

methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide. In one embodiment, a tablet formulation of binimetinib comprises 15 mg of crystallised 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2- hydroxyethoxy)-amide.

EXAMPLE 1

Study design

This is a randomised triple-blind placebo-controlled phase III superiority clinical trial.

Patients and investigators are blinded to the treatment allocations until the first recurrence or a safety concern affecting an individual patient. The study team remains blinded until the date of the database lock for the final analysis of the primary endpoint RFS.

Patients will undergo BRAF-mutation screening after definitive surgery. Those with a BRAF V600E/K mutation will be offered to be randomised 1:1 to receive either treatment with encorafenib and binimetinib or placebo. In total, around 900 patients will be randomised. Not more than 300 stage IIA (pT2b or pT3a) patients will be randomized.

Approximately 45% of the patients are expected to have a BRAF V600E/K mutation. In addition, some BRAF-positive patients may eventually not be randomised, for example due to a lack of consent or a disease recurrence in the period of time between surgery and randomisation. Hence, approximately 2400 patients need to be screened in order to randomise 900 patients.

The primary objective of the study is to prospectively assess whether treatment with encorafenib and binimetinib prolongs recurrence-free survival (RFS) as compared to placebo in resected pT2b-4bN0 (corresponding to stage IIA, B and C melanoma) BRAF V600E/K melanoma patients. Secondary efficacy objectives include:

- To prospectively assess whether treatment with encorafenib and binimetinib prolongs distant metastasis-free survival (DMFS) as compared to placebo;
- To assess the incidence of adverse events in the two arms;
- To compare the quality of life between the two arms up to 62 weeks from randomisation;

- To prospectively assess whether treatment with encorafenib and binimetinib prolongs overall survival (OS) as compared to placebo;
- To prospectively assess whether treatment with encorafenib and binimetinib prolongs progression/recurrence-free survival 2 (PFS2) as compared to placebo; and
- To investigate the prognostic and predictive value of clinicopathological and gene expression profile (CP-GEP).

Rationale of the study design

The goal of adjuvant therapy is to reduce the rate of recurrent melanoma and therefore to prolong overall survival (OS).

pT2b-pT4b melanoma patients are chosen because they have a large risk of relapse and considerably high 5-year death rate due to melanoma. Therefore, assuming a similar relative risk reduction with adjuvant therapy as seen in stage III melanoma, the absolute benefit of adjuvant therapies is justifiable versus the associated costs in terms of toxicity and the cost of the treatment.

Recently, encorafenib and binimetinib have been proven to be safe and effective treatment for unresectable or metastatic BRAF V600-mutated melanomas.

The rate of treatment discontinuation that were suspected to be related to adverse events on the combination treatment was only 6% (Ref. 13). Although one cannot simply extrapolate this rate to the adjuvant situation, where there is less incentive to persist through adverse events and continue treatment, we expect less treatment discontinuation on this specific BRAF/MEK inhibitor combination due to a better safety profile compared to others such as dabrafenib & trametinib (in the COMBI-AD trial, 26% of the patients discontinued the treatment due to adverse events). Moreover, there is more incentive to continue, as the maximum duration in this trial will be only 6 months (vs. 12 months in the other adjuvant studies) and a smaller risk for long-lasting toxicities.

Subject Selection

About 900 patients with a BRAF V600E/K mutation will be randomised 1:1 to receive either treatment with encorafenib and binimetinib (n = 450) or placebo (n = 450).

The patients will undergo a histopathological examination (including TIL's (tumor infiltrating lymphocytes), mitosis/mm^2, vertical grow phase, ulceration/Breslow thickness, etc. - review of ulceration / Breslow thickness will be done on the 100 first cases to assess concordance) before the beginning of the treatment.

Inclusion criteria

- At least 18 years of age;
- ECOG (Eastern Cooperative Oncology Group) performance status of 0 or 1;
- Surgically resected, with tumor free margins, and histologically/pathologically confirmed new diagnosis of pT2b-pT4b cutaneous melanoma within 26 weeks of the first diagnosis of a primary melanoma;
- Sentinel node (SN): staged node negative (pN0) and within 12 weeks from SN biopsy surgery;
- No clinically apparent metastases (N0/M0);
- No (micro)satellites or in-transit metastases;
- No local (scar) recurrences;
- Melanoma determined locally to be V600E/K mutation-positive (Note: only PCR (Polymerase Chain Reaction) and NGS (Next-Generation Sequencing)-based local assays results will be acceptable);
- Able to provide a sufficient amount of representative tumor specimen (diagnostic biopsy) for retrospective central testing of BRAFV600E/K mutation status. FFPE (Formalin-Fixed, Paraffin-Embedded) tumor tissue block or a minimum of 10 slides, optimally up to 15 slides;
- Recovered from definitive surgery (e.g. no uncontrolled wound infections or indwelling drains);
- Adequate bone marrow function:
  i. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
  ii. Platelets $\geq 100 \times 10^9$/L
  iii. Hemoglobin ≥ 9.0 g/dL
- Adequate renal function:
  Serum creatinine $\leq$ 1.5 × ULN; or calculated creatinine clearance $\geq$ 50 mL/min by Cockcroft-Gault formula; or estimated glomerular filtration rate > 50 mL/min/1.73m^2

- Adequate electrolytes, defined as serum potassium and magnesium levels within institutional normal limits.
- Adequate hepatic function:
  i. Serum total bilirubin ≤ 1.5 x ULN and < 2 mg/dL
  ii. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 x ULN
- Adequate cardiac function:
  i. Left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram (ECHO)
  ii. Mean triplicate QT interval corrected for heart rate according to Fridericia's formula (QTcF) value ≤ 480 msec and no history of QT syndrome
- Able to swallow oral medications;
- Negative serum ß-HCG (human chorionic gonadotropin) test (female patient of childbearing potential only) performed within 72 hours prior to first dose;
- Patients of childbearing/reproductive potential should use adequate birth control measures.

Exclusion criteria

- Unknown ulceration status;
- Uveal and mucosal melanoma;
- Surgery > 26 weeks of the first diagnosis of a primary melanoma;
- SNB (sentinel node biopsy) procedure > 12 weeks from SN biopsy surgery;
- No access to sufficient tumor tissue of primary tumor;
- History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes);
- History of thromboembolic or cerebrovascular events ≤ 12 weeks prior to starting study treatment, including stroke, transient ischemic attacks, cerebrovascular accidents, hemodynamically significant (i.e. massive or sub-massive) deep vein thrombosis, pulmonary emboli, aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis (Note: Patients with thromboembolic events related to indwelling catheters or other procedures may be enrolled);

- Previous or concurrent malignancy for the past 5 years (must be free from disease for at least 5 years). Except for non-melanoma skin cancer (Basal Cell Carcinomas or Squamous Cell Carcinomas) and any in situ cancer;
- Previous treatment for melanoma beyond complete surgical resection (any prior systemic therapy; prior radiotherapy);
- Hypersensitivity to the study drugs or to any of the excipients;
- Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:
  - History of acute myocardial infarction, acute coronary syndromes (including unstable angina, coronary artery bypass graft, coronary angioplasty or stenting) ≤ 6 months prior to start of study treatment;
  - Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2);
  - LVEF < 50% as determined by MUGA or ECHO;
  - Uncontrolled hypertension defined as persistent systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite optimal therapy;
  - History or presence of clinically significant cardiac arrhythmias (including uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);
  - Triplicate average baseline QTcF interval ≥ 480 ms or a history of prolonged QT syndrome.
- Patients with neuromuscular disorders that are associated with CK (creatine kinase) > ULN (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy);
- Non-infectious pneumonitis;
- Impaired gastrointestinal function or disease (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection) which may significantly alter the absorption of encorafenib or binimetinib or recent changes in bowel function suggesting current or impending bowel obstruction.

Study Treatment and Follow up

The experimental arm will receive encorafenib 450 mg (6 × 75 mg oral capsule) QD (daily) *per os* and binimetinib 45 mg (3 × 15 mg oral tablet) BID (twice a day) *per os* for 26 weeks.

The control arm will receive the relevant placebos of encorafenib and binimetinib, respectively.

Patients will regularly undergo clinical examination (including dermatological skin assessment) and imaging (such as chest/abdomen/pelvis computed tomography and/or Magnetic Resonance Imaging (MRI)) while treatment is ongoing, at the end of treatment, and during follow up in order to detect a possible disease recurrence.

Frequency for evaluation is about every 3 months during the treatment period, then about every 6 months until occurrence of relapse.

The study treatment can be discontinued during the treatment period in the case of an unacceptable toxicity or a recurrence of disease.

The study can be discontinued in the following cases: consent withdrawal, loss of follow up, or death.

Blinding

Study treatment will be triple-blinded.

Stratification

Patients are randomised 1:1 using minimisation with a random component stratified for stage with three categories: 1) stage IIA (i.e., pT2b or pT3a), 2) stage IIB (i.e., pT3b or pT4a), and 3) stage IIC (i.e., pT4b).

Endpoints

- Primary endpoint

The primary endpoint of the study is Recurrence Free Survival (RFS), defined as the time from random assignment until first recurrence (loco-regional or distant metastasis) or death due to any cause, whichever is observed first.

Statistical design for the primary endpoint RFS

H_0: HR=1, H_A: HR<1

For the primary endpoint RFS, a target HR (hazard ratio) of 0.55 was used for the power calculations.

The hazard ratio stratified by the stratification factor stage will be used to describe the treatment effect and the log-rank stratified by stage will be used for statistical testing.

Using the formula of Schoenfeld (Ref. 14), 166 RFS events are needed to have a power of 97% to detect a HR of 0.55 in the whole study population with a one-sided alpha of 0.025 using the non-stratified log-rank test.

- Secondary endpoints

The secondary endpoints are:

- Distant metastasis-free survival (DMFS), defined as the time from random assignment until first distant metastasis or death due to any cause, whichever is observed first;
- Incidence of adverse events; and
- Health Related Quality of life (HRQoL).

Distant metastasis-free survival (DMFS)

A hierarchical approach will be used to deal with multiple testing related to the existence of two endpoints (RFS and DMFS) for which the study is powered. In case the study concludes superiority of the experimental treatment regarding RFS, the effect on DMFS will be formally tested. Otherwise, the DMFS analysis will have an exploratory character. A target HR of 0.6 is used in the power calculations for DMFS.

Using the formula of Schoenfeld, 162 DMFS events are needed to have a power of 90% to detect a HR of 0.60 in the whole study population with a one-sided alpha of 0.025 using the non-stratified log-rank test.

In case 5 years from the accrual end 162 DMFS events are not available, the clinical cut-off time for the DMFS analysis will be 5 years from the accrual end, irrespective of the number of DMFS events present at that time.

Health Related Quality of life (HRQoL)

The objective of the HRQoL component is twofold:

- Assess the difference between the two treatment groups during the treatment duration: it is expected that, while on treatment, patients in the experimental arm will have slightly poorer HRQoL due to the additional toxicities;

- Assess the difference between the two treatment groups after treatment completion: long-term toxicities are expected to be minimal and due to the increased efficacy, fewer relapses should occur in the experimental arm. Therefore, self-reported quality of life at 1 year (i.e. 6 months after treatment completion) should be better in the experimental arm.

HRQoL questionnaires will consist of the QLQ-C30 complemented with selected questions to cover any additional relevant issues (such as arthralgia). The questionnaires will be collected at baseline, week 6, 12, 24, 36, 48, and 60 regardless of treatment status or progression status.

Two primary tests will be conducted.

(1) The average HRQoL while on treatment, relative to the baseline score, will be derived per patient and compared across the two treatment arms using a non-parametric test. As supportive analysis, the worst change from baseline observed during treatment will be derived as well per patient and patients will be categorized according to MID (Minimal Importance Difference). The latter approach will allow to identify the proportion of patients suffering from impaired HRQoL during the treatment.

(2) HRQoL at week 48 will be compared across the two treatment arms cross-sectionally using a non-parametric test. As supportive analysis, the scores at the week 36 and week 60 will be used to assess the stability of the scores collected after treatment. Care will be taken to impute scores that are missing after recurrence as these are expected to be decreased and therefore cause informative missingness.

Observed differences will be compared to the relevant MID magnitude in order to asses clinical relevance on top of statistical significance. Descriptive statistics for all scales will include estimates at each time point and overall graphical profiles, adjusted for missing data.

- <u>Exploratory endpoints</u>

The exploratory endpoints are:

- Overall survival (OS), defined as the time from random assignment until death due to any cause.
- Progression/recurrence-free survival 2 (PFS2), defined as time from initial study randomisation to second disease progression or death from any cause.

EXAMPLE 2

Study design

This is a randomised triple-blind placebo-controlled phase III superiority clinical trial.

Patients and investigators are blinded to the treatment allocations until the first recurrence or a safety concern affecting an individual patient. The study team remains blinded until the date of the database lock for the final analysis of the primary endpoint RFS.

Patients will undergo BRAF-mutation screening after definitive surgery. Those with a BRAF V600E/K mutation will be offered to be randomised 1:1 to receive either treatment with encorafenib and binimetinib or placebo. In total, around 815 patients will be randomised

Approximately 45% of the patients are expected to have a BRAF V600E/K mutation. In addition, some BRAF-positive patients may eventually not be randomised, for example due to a lack of consent or a disease recurrence in the period of time between surgery and randomisation. Hence, approximately 2200 patients need to be screened in order to randomise about 815 patients.

The primary objective of the study is to prospectively assess whether treatment with encorafenib and binimetinib prolongs recurrence-free survival (RFS) as compared to placebo in resected stage II melanoma (especially in melanoma of (1) stage pT3b, pT4a, or pT4b, or of (2) stage pT2b or pT3a or of (3) stage pT2b, pT3a, pT3b, pT4a, or pT4b depending on the selected patients) BRAF V600E/K melanoma patients. Secondary efficacy objectives include:

- To prospectively assess whether treatment with encorafenib and binimetinib prolongs distant metastasis-free survival (DMFS) as compared to placebo;
- To assess the incidence of adverse events in the two arms;
- To compare the quality of life between the two arms

- To prospectively assess whether treatment with encorafenib and binimetinib prolongs overall survival (OS) as compared to placebo; and
- To provide additional pharmacokinetic (PK) data to support PK modelling and exposure response (efficacy and safety) relationship developments in this indication.

Rationale of the study design

The goal of adjuvant therapy is to reduce the rate of recurrent melanoma and therefore to prolong overall survival (OS).

pT2b-pT4b (e.g. pT2b-pT3a and/or pT3b-pT4b) melanoma patients are chosen because they have a high risk of relapse and considerably high 5-year death rate due to melanoma. Therefore, assuming a similar relative risk reduction with adjuvant therapy as seen in stage III melanoma, the absolute benefit of adjuvant therapies is justifiable versus the associated costs in terms of toxicity and the cost of the treatment.

Recently, encorafenib and binimetinib have been proven to be safe and effective treatment for unresectable or metastatic BRAF V600-mutated melanomas.

The rate of treatment discontinuation that were suspected to be related to adverse events on the combination treatment was only 6% (Ref. 13). Although one cannot simply extrapolate this rate to the adjuvant situation, where there is less incentive to persist through adverse events and continue treatment, we expect less treatment discontinuation on this specific BRAF/MEK inhibitor combination due to a better safety profile compared to others such as dabrafenib & trametinib (in the COMBI-AD trial, 26% of the patients discontinued the treatment due to adverse events).

Subject Selection

About 800-900 patients (e.g. about 815 patients) with a BRAF V600E/K mutation will be randomised 1:1 to receive either treatment with encorafenib and binimetinib or placebo).

The patients will undergo a histopathological examination (including TIL's (tumor infiltrating lymphocytes), mitosis/mm^2, vertical grow phase, ulceration/Breslow thickness, etc. - review of ulceration / Breslow thickness will be done on the 100 first cases to assess concordance).

Inclusion criteria

- At least 18 years of age;
- ECOG (Eastern Cooperative Oncology Group) performance status of 0 or 1;
- Surgically resected, with tumor free margins, and histologically/pathologically confirmed new diagnosis of pT2b-pT4b cutaneous melanoma, or of pT3b-pT4b cutaneous melanoma, or of pT2b-pT3a cutaneous melanoma (depending if the study relates to stage IIA and/or IIB/IIC melanoma);
- Sentinel node biopsy (SNB) done within 14 weeks from initial diagnosis of melanoma and staged node negative (pN0);
- No clinically apparent metastases (N0/M0);
- No (micro)satellites or in-transit metastases;
- No local (scar) recurrences;
- Melanoma determined locally to be V600E/K mutation-positive;
- Randomization within 12 weeks from SN biopsy;
- Able to provide a sufficient amount of representative tumor specimen (diagnostic biopsy) for retrospective central testing of BRAFV600E/K mutation status. FFPE (Formalin-Fixed, Paraffin-Embedded) tumor tissue block or a minimum of 10 slides, optimally up to 20 slides;
- Recovered from definitive surgery (e.g. no uncontrolled wound infections or indwelling drains);
- Adequate bone marrow function:
  i. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
  ii. Platelets $\geq 100 \times 10^9$/L
  iii. Hemoglobin ≥ 9.0 g/dL
- Adequate renal function:
  Serum creatinine $\leq 1.5 \times$ ULN; or calculated creatinine clearance ≥ 50 mL/min by Cockcroft-Gault formula; or estimated glomerular filtration rate > 50 mL/min/1.73m^2
- Adequate electrolytes, defined as serum potassium and magnesium levels within institutional normal limits.
- Adequate hepatic function:
  i. Serum total bilirubin $\leq 1.5 \times$ ULN and < 2 mg/dL
  ii. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN

- Adequate cardiac function:
  i. Left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram (ECHO)
  ii. Mean triplicate QT interval corrected for heart rate according to Fridericia's formula (QTcF) value ≤ 480 msec and no history of QT syndrome
- Adequate coagulation function, defined as International Normalized Ratio (INR) ≤1.5× ULN unless the patient is receiving anticoagulant therapy as long as Partial Thromboplastin Time (PTT) and activated Partial Thromboplastin Time (aPTT) is within the therapeutic range;
- Negative serum ß-HCG (human chorionic gonadotropin) test (female patient of childbearing potential only) performed within 72 hours prior to first dose;
- Patients of childbearing/reproductive potential should use adequate birth control measures.

Exclusion criteria

- Unknown ulceration status;
- Uveal and mucosal melanoma;
- History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes);
- History of thromboembolic or cerebrovascular events ≤ 12 weeks prior to starting study treatment, including stroke, transient ischemic attacks, cerebrovascular accidents, hemodynamically significant (i.e. massive or sub-massive) deep vein thrombosis, pulmonary emboli, aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis (Note: Patients with thromboembolic events related to indwelling catheters or other procedures may be enrolled);
- Previous or concurrent malignancy for the past 3 years (must be free from disease for at least 3 years). Except for non-melanoma skin cancer (Basal Cell Carcinomas or Squamous Cell Carcinomas) and any in situ cancer;
- Previous treatment for melanoma beyond complete surgical resection (any prior systemic therapy; prior radiotherapy);
- Hypersensitivity to the study drugs or to any of the excipients;
- Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:

- History of acute myocardial infarction, acute coronary syndromes (including unstable angina, coronary artery bypass graft, coronary angioplasty or stenting) ≤ 6 months prior to randomization;
- Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2);
- LVEF < 50% as determined by MUGA or ECHO;
- Uncontrolled hypertension defined as persistent systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite optimal therapy;
- History or presence of clinically significant cardiac arrhythmias (including uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);
- Triplicate average baseline QTcF interval ≥ 480 ms or a history of prolonged QT syndrome.

- Patients with neuromuscular disorders that are associated with CK (creatine kinase) > ULN (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy);
- Patients with a prior cancer associated with RAS mutation;
- Patients with severe lactose intolerance (e.g Rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption);
- Patients with active bacterial, fungal, or viral infection, including, but not limited to: HBV, HCV, and known HIV or AIDS-related illness, or an infection requiring systemic therapeutic treatment within 2 weeks prior to randomization;
- Positive SARs-CoV-2 or variants of SARs-CoV2 RT-PCR test at screening or suspected to be infected with SARs-CoV2 or variants of SARsCoV2 with confirmation pending;
- Non-infectious pneumonitis and Interstitial Lung Disease;
- Impaired gastrointestinal function or disease (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection) which may significantly alter the absorption of encorafenib or binimetinib or recent changes in bowel function suggesting current or impending bowel obstruction;
- Unable to ingest or digest tablets and capsules.

Study Treatment and Follow up

The experimental arm will receive encorafenib 450 mg (6 × 75 mg oral capsule) QD (daily) *per os* and binimetinib 45 mg (3 × 15 mg oral tablet) BID (twice a day) *per os* for a maximum of 12 months, e.g. for 26 weeks or for 12 months.

The control arm will receive the relevant placebos of encorafenib and binimetinib, respectively.

Patients will regularly undergo clinical examination (including dermatological skin assessment) and imaging (such as chest/abdomen/pelvis computed tomography and/or Magnetic Resonance Imaging (MRI)) while treatment is ongoing, at the end of treatment, and during follow up in order to detect a possible disease recurrence.

Frequency for clinical examination is about every 1 months during the treatment period, then about every 3 months until year 3 from the time of random assignment, then about every 6 months until year 5 from the time of random assignment, then about every year until year 10 from the time of random assignment. Frequency for imaging is about every 6 months for the first 3 years from the time of random assignment, and thereafter about every year until 10 years from the time of random assignment.

The study treatment can be discontinued during the treatment period in the case of an unacceptable toxicity or a recurrence of disease (defined as any local, loco-regional recurrence; new melanoma which is ulcerated or thick (Breslow thickness > 1 mm) or which requires a treatment other than surgery; or distant metastases).

The study can be discontinued in the following cases: consent withdrawal, loss of follow up, or death.

Blinding

Study treatment will be triple-blinded.

Stratification

Patients are randomised 1:1 using minimisation with a random component stratified for stage with the following categories: 1) stage IIA (i.e., pT2b or pT3a), 2) stage IIB (i.e., pT3b or pT4a), and 3) stage IIC (i.e., pT4b).

Endpoints

- Primary endpoint

The primary endpoint of the study is Recurrence Free Survival (RFS), defined as the time from random assignment (also called randomization) until first recurrence (local, loco-regional recurrence; new melanoma which is ulcerated or thick (Breslow thickness > 1 mm) or which requires a treatment other than surgery; or distant metastasis), or death due to any cause, whichever is observed first.

Statistical design for the primary endpoint RFS

H_0: HR=1, H_A: HR<1

For the primary endpoint RFS, a target HR (hazard ratio) of 0.55 was used for the power calculations.

The hazard ratio stratified by the stratification factor stage will be used to describe the treatment effect and the log-rank stratified by stage will be used for statistical testing.

Using the formula of Schoenfeld (Ref. 14), 166 RFS events are needed to have a power of 97% to detect a HR of 0.55 in the whole study population with a one-sided alpha of 0.025 using the non-stratified log-rank test.

- Secondary endpoints

The secondary endpoints are:

- Distant metastasis-free survival (DMFS), defined as the time from random assignment until first distant metastasis or death due to any cause, whichever is observed first;
- Overall survival (OS), defined as the time from random assignment until death due to any cause;
- Incidence and severity of adverse events; and
- Health Related Quality of life (HRQoL).

Distant metastasis-free survival (DMFS)

A hierarchical approach will be used to deal with multiple testing related to the existence of two endpoints (RFS and DMFS) for which the study is powered. In case the study concludes superiority of the experimental treatment regarding RFS, the

effect on DMFS will be formally tested. Otherwise, the DMFS analysis will have an exploratory character. A target HR of 0.6 is used in the power calculations for DMFS.

Using the formula of Schoenfeld, 162 DMFS events are needed to have a power of 90% to detect a HR of 0.60 in the whole study population with a one-sided alpha of 0.025 using the non-stratified log-rank test.

In case 5 years from the accrual end 162 DMFS events are not available, the clinical cut-off time for the DMFS analysis will be 5 years from the accrual end, irrespective of the number of DMFS events present at that time.

Overall survival (OS)

This allows prospectively assessing whether the treatment prolongs overall survival as compared to placebo.

Incidence and severity of adverse events

The incidence and severity of advert events (AEs) and serious advert events (SAEs) are graded according to the NCI CTCAE V5.0 and aim to assess the safety and tolerability of the treatment.

Health Related Quality of life (HRQoL)

The objective of the HRQoL component is twofold:

- Assess the difference between the two treatment groups during the treatment duration: it is expected that, while on treatment, patients in the experimental arm will have slightly poorer HRQoL due to the additional toxicities;

- Assess the difference between the two treatment groups after treatment completion: long-term toxicities are expected to be minimal and due to the increased efficacy, fewer relapses should occur in the experimental arm. Therefore, self-reported quality of life at 1 year (i.e. 6 months after treatment completion) should be better in the experimental arm.

HRQoL questionnaires will consist of the QLQ-C30 complemented with selected questions to cover any additional relevant issues (such as arthralgia). The questionnaires will be collected at baseline, and months 3, 6, 9, 12, 18, 24 and 30 (+/- 7 days) regardless of treatment status or progression status.

Analysis of the difference between the two study intervention arms during the treatment period: For each patient, the change from baseline to the average of the scores between randomization and last dose of treatment will be calculated. In the main analysis, the mean of this summary statistic will be compared between the two treatment groups. The difference between the treatment arms in the mean change from baseline will be calculated for each imputed dataset and the Rubin's rules will be used to combine the estimates. A non-inferiority test will be performed for the hypothesis that the difference between the treatment arms is smaller than the threshold of clinical relevance, using a one-sided significance level of 0.025.

Analysis of the difference between the two study intervention arms after treatment completion: For each patient, the change from baseline to the average of the scores at months 18, 24, and 30 will be calculated. In the main analysis, the mean of this summary statistic will be compared between the two treatment groups. The difference between the treatment arms in the mean change from baseline will be calculated for each imputed dataset and the Rubin's rules will be used to combine the estimates. A superiority test will be performed for the hypothesis that the quality of life is better in the experimental arm, using a one-sided significance level of 0.025. In addition, the estimated mean scores and their 95% confidence intervals will be reported separately for all time points including baseline for both treatment arms.

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CLAIMS

1) A pharmaceutical combination for use as adjuvant treatment after resection of a melanoma, wherein the melanoma which has been resected is stage II melanoma, and wherein the pharmaceutical combination comprises therapeutically effective amounts, independently, of:
    a) encorafenib or a pharmaceutically acceptable salt thereof;
    b) binimetinib or a pharmaceutically acceptable salt thereof; and

    optionally at least one pharmaceutically acceptable carrier.

2) The pharmaceutical combination for the use of claim 1, wherein the stage II melanoma has a BRAF V600 mutation.

3) The pharmaceutical combination for the use of claim 2, wherein the stage II melanoma has a BRAF V600K or BRAF V600E mutation.

4) The pharmaceutical combination for the use of any one of claims 1 to 3, wherein the stage II melanoma is a stage IIA melanoma.

5) The pharmaceutical combination for the use of any one of claims 1 to 3, wherein the stage II melanoma is a stage IIB or IIC melanoma.

6) The pharmaceutical combination for the use of any one of claims 1 to 5, wherein encorafenib, or a pharmaceutically acceptable salt thereof, and binimetinib, or a pharmaceutically acceptable salt thereof, are administered simultaneously, separately or sequentially over time.

7) The pharmaceutical combination for the use of any one of claims 1 to 6, wherein encorafenib is administered at an amount of 450 mg once a day.

8) The pharmaceutical combination for the use of any one of claims 1 to 7, wherein binimetinib is administered at an amount of 45 mg twice a day.

9) The pharmaceutical combination for the use of any one of claims 1 to 8, wherein the adjuvant treatment results in increasing relapse-free survival (RFS).