

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

20 August 2020 (20.08.2020)



(10) International Publication Number

WO 2020/164997 A1

(51) International Patent Classification:

A61K 39/395 (2006.01)

A61K 31/5377 (2006.01)

A61K 31/519 (2006.01)

A61P 35/04 (2006.01)

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

(21) International Application Number:

PCT/EP2020/052873

Published:

— with international search report (Art. 21(3))

(22) International Filing Date:

05 February 2020 (05.02.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

19156714.8

12 February 2019 (12.02.2019) EP

(71) Applicants: BAYER AKTIENGESELLSCHAFT

[DE/DE]; Kaiser-Wilhelm-Allee 1, 51373 Leverkusen (DE). EPO - EXPERIMENTELLE PHARMAKOLOGIE & ONKOLOGIE [DE/DE]; Robert-Rössle-Straße 10 Berlin-Buch GmbH, 13122 Berlin (DE).

(72) Inventors: GRÜNEWALD, Sylvia; Kirchstrasse 9, 10557

Berlin (DE). POLITZ, Oliver; Mielenzstr.19, 15537 Grünheide / Mark (DE). SEIDEL, Henrik; Grenobler Ring 16, 13127 Berlin (DE). HOFFMANN, Jens; Rosenow 42, 17268 Boitzenburger Land (DE).

(74) Agent: BIP PATENTS; Alfred-Nobel-Str. 10, 40789 Mon-

heim am Rhein NRW (DE).

(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: COMBINATION OF PI3K-INHIBITORS

(57) Abstract: The present invention relates to combinations of at least two components, component A and component B, component A being an inhibitor of RISK kinase, and component B being cetuximab. Another aspect of the present invention relates to the use of such combinations as described herein for the preparation of a medicament for the treatment or prophylaxis of a disease, particularly for the treatment or prophylaxis of head-and-neck cancer, such as laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer, or head and neck squamous cell carcinoma (abbreviated to "HNSCC").

WO 2020/164997 A1

COMBINATION of PI3K-INHIBITORS

The present invention relates to combinations of at least two components, component A and component B, component A being a PI3K-inhibitor, and component B being
5 cetuximab.

Another aspect of the present invention relates to the use of such combinations as described herein for the preparation of a medicament for the treatment or prophylaxis of a disease, particularly for the treatment of cancer.

10

Yet another aspect of the present invention relates to methods of treatment or prophylaxis of a cancer in a subject, comprising administering to said subject a therapeutically effective amount of a combination as described herein.

15 Further, the present invention relates to a kit comprising a combination of :

- one or more components A, as defined herein, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

20 - a component B, as defined *supraf*; and, optionally

- one or more pharmaceutical agents C ;

in which optionally either or both of said components A and B are in the form of a
25 pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

Component A may be administered by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

30

Component B may be administered by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

BACKGROUND to the INVENTION

Head and neck cancer represents the 6th most common malignancy worldwide, accounting for 6% of cancer incidence and 2% of cancer-related deaths [(1)]. In their efforts of characterizing the genetics of human cancer, TCGA has collected complete genomic characterization of more than 530 HNSCC tumors revealing a number of characteristics for the different forms of HNSCC, e.g. HPV+ versus HPV- and the aberrant activation of specific signalling pathways involved in key processes of tumorigenesis. [(2)]

In 2006, the FDA approved the monoclonal antibody cetuximab supporting EGFR as a therapeutic target in HNSCC. EGFR is a transmembrane tyrosine receptor which activates signalling through RAS and PI3K pathway leading to increased cell proliferation, invasion, angiogenesis and survival of cancer cells. [(3)].

EGFR is a member of the ErbB family of transmembrane receptors, which includes EGFR/ErbB1/human epidermal growth factor receptor (HER)-1, ErbB2/HER-2/neu, ErbB3/HER3, and ErbB4/HER-4. [(4)]. Targeting the ErbB family has been or is currently being evaluated in clinical trials for head and neck cancer for a number of small molecules with reversible or irreversible mode-of-action as well as antibody based therapies [(5)].

The new and promising results for therapies targeting the immune suppressive nature of HNSCC by using immune checkpoint inhibitors such as pembrolizumab or nivolumab were acknowledged by approval of pembrolizumab (accelerated by FDA) or nivolumab (EMA and FDA) for second-line therapy for R/M HNSCC in 2016 by the FDA and EMA. [(6)].

Nevertheless, platinum-based chemotherapy associated with cetuximab is still the first-line treatment for inoperable recurrence or metastatic head and neck squamous cell carcinoma (HNSCC). Despite widespread EGFR expression in HNSCC tumors, only a subset of HNSCC patients benefit from cetuximab therapy. So far, there is no established biomarker for cetuximab efficacy in HNSCC. The PI3K pathway is one of the

most frequently altered pathways in HNSCC. Loss of phosphatase and tensin homolog (PTEN) expression occurs in up to 30 % of cases.

5 The PI3K signaling pathway is one of the prominent pathways that promote tumor cell survival. PI3K is activated by many cancer related receptor tyrosine kinases (e.g. VEGFR, PDGFR, EGFR, HER2/3, or IGF-1R), cell adhesion molecules, GPCR, and oncogenic proteins (such as Ras). The PI3K pathway activation by genetic alteration of PI3K (activation mutation and/or amplification) and/or loss-of-function of the tumour suppressor PTEN are frequently found in many tumors. Furthermore, activation of PI3K
10 is one of the major mechanisms causing the resistance of tumors to radio-, chemo- and targeted therapeutics.

Once PI3K is activated, it catalyzes the generation of PIP3 from PIP2. The biologically active PIP3 binds to the pleckstrin homology (PH) domains of PDK-1, AKT, and other PH-
15 domain containing proteins, such as Rho and PLC. As the consequence of binding to PIP3, these proteins are translocated to the cell membrane and are subsequently activated to induce tumor cell proliferation, survival, invasion and migration.

In addition to the roles in tumor cells, PI3Ks also regulate the activity of the tumor
20 stroma cells (cells that form part of the tumor mass but are not malignantly transformed). The stroma cells include (a) the vasculature, (b) infiltrating immune cells, (c) fibroblasts and (d) other connective tissue. Recent data indicate that the four class I PI3K isoforms have both redundant and distinct roles in regulating PI3K signalling in each of these stromal elements. The complexity and/or difficulty in predicting the final
25 outcomes of PI3K inhibitors have been realized, particularly with regard to different isoform profiles and/or other technical properties of PI3K inhibitors.

The Phosphatidylinositol 3-kinase (PI3Ks) pathway is commonly altered in several human cancer indications including ovarian cancer, gastric cancer, lung cancer,
30 endometrial cancer and breast cancer. [see: (7)]. The PI3K pathway comprises a family of intracellular signal transducer enzymes with three key regulatory nodes: PI3K, AKT,

and mammalian target of rapamycin (mTOR) [see: (8).] Activation of the PI3K pathway including the downstream factor AKT provides a survival signal to tumor cells and has been shown to be associated with resistance to chemotherapy. [see: (9)]. More recently inhibition of PI3K has been shown to enhance the activity of anti-microtubule
5 drugs in human cancer cell lines. [see: (10)].

Copanlisib is a novel intravenous pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor with kinase inhibitory activity predominantly against the PI3K- α and PI3K- δ isoforms, which are expressed in malignant B-cells. The PI3K pathway is involved in cell
10 growth, survival and metabolism, and its dysregulation plays an important role in non-Hodgkin's lymphoma (NHL).

Copanlisib exhibits a broad spectrum of activity against tumors of multiple histologic types, both *in vitro* and *in vivo*.
15

The state of the art does not however disclose the combinations of the present invention comprising the specific PI3K inhibitor copanlisib, or a physiologically acceptable salt thereof, and cetuximab.

20 SUMMARY of the INVENTION

Surprisingly, it was observed that by administering of copanlisib in combination with cetuximab in patient-derived HNSCC xenograft mouse models, an improved tumor response could be achieved compared to the single agent treatments.,
25 Therefore, in accordance with a first aspect, the present invention provides combinations of at least two components, component A and component B, component A being copanlisib, an inhibitor of PI3K-kinase, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, and component B being cetuximab.

In accordance with a second aspect, the present invention covers combinations of at least two components A and B, component A being an inhibitor of PI3K- kinase, and component B being cetuximab.

- 5 In accordance with a third aspect, the present invention comprises combinations of at least two components A and B, component A being an inhibitor of PI3K- kinase or a physiologically acceptable salt thereof, and component B being cetuximab.

The combinations comprising at least two components A and B, as described and
10 defined herein, are also referred to as “combinations of the present invention”.

Further, the present invention relates to :

a kit comprising :

15

- a combination of :

20

Component A: one or more PI3K-kinase inhibitors as described *supra* and *infra*, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

Component B : cetuximab ; and, optionally,

Component C : one or more further pharmaceutical agents ;

25

in which optionally either or both of said components A and B in any of the above-mentioned combinations are in the form of a pharmaceutical formulation/composition which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

30

In accordance with another aspect, the present invention covers the combinations as described *supra* for the treatment or prophylaxis of a disease, in particular cancer, in particular head-and-neck cancers which include, but are not limited to, laryngeal,

hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and head and neck squamous cell carcinoma (herein abbreviated to "HNSCC").

5 In accordance with another aspect, the present invention covers the use of such combinations as described *supra* for the preparation of a medicament for the treatment or prophylaxis of a disease, in particular cancer, in particular head-and-neck cancers which include, but are not limited to, laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and head and neck squamous cell carcinoma (herein abbreviated to "HNSCC").

10

DETAILED DESCRIPTION OF THE INVENTION

Definitions

15 The terms as mentioned in the present text have preferably the following meanings :

The term 'alkyl' refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, such as
20 illustratively, methyl, ethyl, n-propyl 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl).

The term "alkenyl " refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched or branched chain
25 having about 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-and butenyl.

The term "alkynyl" refers to a straight or branched chain hydrocarbonyl radicals
30 having at least one carbon-carbon triple bond, and having in the range of about 2

up to 12 carbon atoms (with radicals having in the range of about 2 up to 10 carbon atoms presently being preferred) e.g., ethynyl.

5 The term "alkoxy" denotes an alkyl group as defined herein attached via oxygen linkage to the rest of the molecule. Representative examples of those groups are methoxy and ethoxy.

10 The term "alkoxyalkyl" denotes an alkoxy group as defined herein attached via oxygen linkage to an alkyl group which is then attached to the main structure at any carbon from alkyl group that results in the creation of a stable structure the rest of the molecule. Representative examples of those groups are $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OC}_2\text{H}_5$.

15 The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of about 3 to 12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and examples of multicyclic cycloalkyl groups include perhydronaphthyl, adamantyl and norbornyl groups bridged cyclic group or spirobicyclic groups e.g. spiro (4,4) non-2-yl.

20 The term "cycloalkylalkyl" refers to cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms directly attached to alkyl group which is then also attached to the main structure at any carbon from the alkyl group that results in the creation of a stable structure such as cyclopropylmethyl, cyclobutylethyl, cyclopentylethyl.

25 The term "aryl" refers to aromatic radicals having in the range of 6 up to 14 carbon atoms such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl.

30 The term "arylalkyl" refers to an aryl group as defined herein directly bonded to an alkyl group as defined herein which is then attached to the main structure at any

carbon from alkyl group that results in the creation of a stable structure the rest of the molecule. e.g., $--CH_2C_6H_5$, $--C_2H_5C_6H_5$.

5 The term "heterocyclic ring" refers to a stable 3- to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated (i.e., heteroaromatic or heteroaryl aromatic). Examples of such heterocyclic ring radicals include, but are not limited to, azetidiny, acridiny, benzodioxoly, benzodioxany, benzofurnyl, carbazoly, cinnoliny, dioxolany, indoliziny, naphthyridiny, perhydroazepiny, phenaziny, phenothiaziny, phenoxaziny, phthalazil, pyridyl, pteridiny, puriny, quinazoliny, quinoxaliny, quinoliny, isoquinoliny, tetrazoyl, imidazolyl, tetrahydroisouinolyl, piperidiny, piperaziny, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, 2-oxoazepiny, azepiny, pyrroly, 4-piperidonyl, pyrrolidiny, pyraziny, pyrimidiny, pyridaziny, oxazolyl, oxazoliny, oxasolidiny, triazolyl, indanyl, isoxazolyl, isoxasolidiny, morpholiny, thiazolyl, thiazoliny, thiazolidiny, isothiazolyl, quinuclidiny, isothiazolidiny, indolyl, isoindolyl, indoliny, isoindoliny, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyrany, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofuryl, tetrahydropyrany, thienyl, benzothienyl, thiamorpholiny, thiamorpholiny, sulfoxide thiamorpholiny, sulfone, dioxaphospholany, oxadiazolyl, chromany, isochromany.

30 The term "heteroaryl" refers to heterocyclic ring radical as defined herein which are aromatic. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

5 The term "heteroarylalkyl" refers to heteroaryl ring radical as defined herein directly bonded to alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from alkyl group that results in the creation of a stable structure.

10 The term "heterocyclyl" refers to a heterocyclic ring radical as defined herein. The heterocyclyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

15 The term "heterocyclylalkyl" refers to a heterocyclic ring radical as defined herein directly bonded to alkyl group. The heterocyclylalkyl radical may be attached to the main structure at carbon atom in the alkyl group that results in the creation of a stable structure.

20 The term "carbonyl" refers to an oxygen atom bound to a carbon atom of the molecule by a double bond.

The term "halogen" refers to radicals of fluorine, chlorine, bromine and iodine.

25 The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

Ring system substituent means a substituent attached to an aromatic or nonaromatic ring system which, for example, replaces an available hydrogen on the ring system.

30 As used herein, the term "one or more times", *e.g.* in the definition of the substituents of the compounds of the present invention (*e.g.* component A, B or C), is understood as

meaning "one, two, three, four or five times, particularly one, two, three or four times, more particularly one, two or three times, even more particularly one or two times".

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates
5 and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

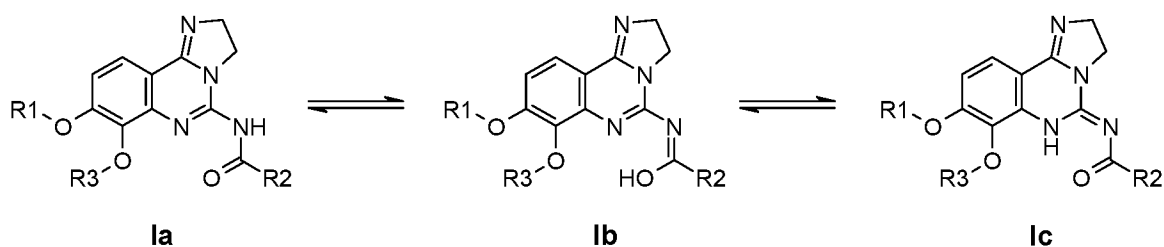
By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and
10 formulation into an efficacious therapeutic agent.

The term "carbonyl" refers to an oxygen atom bound to a carbon atom of the molecule by a double bond.

15 The compounds of this invention may contain one or more asymmetric centers, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (*R*)- and/or (*S*)-configuration, resulting in racemic mixtures in the case of a single asymmetric center, and diastereomeric mixtures in the case of multiple asymmetric centers. In certain instances, asymmetry
20 may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds. Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations (including enantiomers and diastereomers), are included within the scope of the present invention. Preferred compounds are those, which
25 produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

30

Tautomers, sometimes referred to as proton-shift tautomers, are two or more compounds that are related by the migration of a hydrogen atom accompanied by the switch of one or more single bonds and one or more adjacent double bonds. The compounds of this invention may exist in one or more tautomeric forms. For example,
 5 a compound of Formula I may exist in tautomeric form Ia, tautomeric form Ib, or tautomeric form Ic, or may exist as a mixture of any of these forms. It is intended that all such tautomeric forms are included within the scope of the present invention.



10 The present invention also relates to useful forms of the compounds as disclosed herein, such as pharmaceutically acceptable salts, co-precipitates, metabolites, hydrates, solvates and prodrugs of all the compounds of examples. The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M.
 15 Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19. (11) Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically
 20 acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and chlorine salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a
 25 number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, or butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl sulfate, or diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

A solvate for the purpose of this invention is a complex of a solvent and a compound of the invention in the solid state. Exemplary solvates would include, but are not limited to, complexes of a compound of the invention with ethanol or methanol. Hydrates are a specific form of solvate wherein the solvent is water.

Constituents which are optionally substituted as stated herein, may be substituted, unless otherwise noted, one or more times, independently from one another at any possible position. When any variable occurs more than one time in any constituent, each definition is independent.

The heteroaryl, or heterocyclic groups mentioned herein can be substituted by their given substituents or parent molecular groups, unless otherwise noted, at any possible position, such as e.g. at any substitutable ring carbon or ring nitrogen atom. Analogously it is being understood that it is possible for any heteroaryl or heterocycl

5 group to be attached to the rest of the molecule via any suitable atom if chemically suitable. Unless otherwise noted, any heteroatom of a heteroaryl ring with unsatisfied valences mentioned herein is assumed to have the hydrogen atom(s) to satisfy the valences. Unless otherwise noted, rings containing quaternizable amino- or imino-type ring nitrogen atoms (-N=) may be preferably not quaternized on these

10 amino- or imino-type ring nitrogen atoms by the mentioned substituents or parent molecular groups.

Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or

15 diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques already known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using

20 an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The

25 optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (e.g., chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, e.g., Chiracel OD and Chiracel

30 OJ among many others, all routinely selectable. Enzymatic separations, with or without

derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

If in the context of the invention “embodiment” is mentioned it should be understood
5 to include a plurality of possible combinations.

In order to limit different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976) (12).

10 The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually or predominantly found in nature. Examples of isotopes that can be incorporated into a compound of the invention
15 include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine, chlorine, bromine and iodine, such as ^2H (deuterium), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{18}F , ^{36}Cl , ^{82}Br , ^{123}I , ^{124}I , ^{129}I and ^{131}I , respectively. Certain isotopic variations of a compound of the invention, for example, those in which one or more radioactive isotopes such as ^3H or ^{14}C are incorporated, are useful in drug and/or
20 substrate tissue distribution studies. Tritiated and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some
25 circumstances. Isotopic variations of a compound of the invention can generally be prepared by conventional procedures known by a person skilled in the art such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents.

30 The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, in

any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention may be achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

5

The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorphs, or as a mixture of more than one polymorphs, in any ratio.

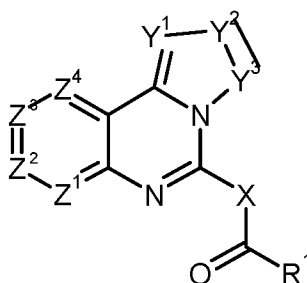
10

Component A of the Combination

Component A can be selected from inhibitors of PI3K-kinase specifically or generically disclosed *e.g.* in the publications as mentioned above which are incorporated herein by reference.

In an embodiment, said component A is a compound of general formula (A) :

20



(A)

in which :

25

X represents CR⁵R⁶ or NH;

Y¹ represents CR³ or N;

the chemical bond between $Y^2 \text{---} Y^3$ represents a single bond or double bond,
 with the proviso that when the $Y^2 \text{---} Y^3$ represents a double bond, Y^2 and Y^3
 independently represent CR^4 or N, and
 when $Y^2 \text{---} Y^3$ represents a single bond, Y^2 and Y^3 independently represent CR^3R^4 or NR^4 ;

5

Z^1 , Z^2 , Z^3 and Z^4 independently represent CH, CR^2 or N;

- R^1 represents aryl optionally having 1 to 3 substituents selected from R^{11} ,
 C_{3-8} cycloalkyl optionally having 1 to 3 substituents selected from R^{11} ,
 C_{1-6} alkyl optionally substituted by aryl, heteroaryl, C_{1-6} alkoxyaryl,
 10 aryloxy, heteroaryloxy or one or more halogen,
 C_{1-6} alkoxy optionally substituted by carboxy, aryl, heteroaryl, C_{1-6}
 alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,
 or
 15 a 3 to 15 membered mono- or bi-cyclic heterocyclic ring that is saturated
 or unsaturated, optionally having 1 to 3 substituents selected from R^{11} ,
 and contains 1 to 3 heteroatoms selected from the group consisting of N,
 O and S,
 20 wherein
 R^{11} represents halogen, nitro, hydroxy, cyano, carboxy, amino, N-
 (C_{1-6} alkyl)amino, N-(hydroxy C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-
 (C_{1-6} acyl)amino, N-(formyl)-N-(C_{1-6} alkyl)amino, N-(C_{1-6} alkanesulfonyl)
 amino, N-(carboxy C_{1-6} alkyl)-N-(C_{1-6} alkyl)amino, N-(C_{1-}
 25 6 alkoxycarbonyl)amino, N-[N,N-di(C_{1-6} alkyl)amino methylene]amino, N-
 [N,N-di(C_{1-6} alkyl)amino (C_{1-6} alkyl)methylene]amino, N-[N,N-di(C_{1-}
 6 alkyl)amino C_{2-6} alkenyl]amino, aminocarbonyl, N-
 (C_{1-6} alkyl)aminocarbonyl, N,N-di(C_{1-6} alkyl)aminocarbonyl, C_{3-8} cycloalkyl,
 C_{1-6} alkylthio, C_{1-6} alkanesulfonyl, sulfamoyl, C_{1-6} alkoxycarbonyl,
 30 N-arylamino wherein said aryl moiety is optionally having 1 to 3 sub-
 stituents selected from R^{101} , N-(aryl C_{1-6} alkyl)amino wherein said aryl

moiety is optionally having 1 to 3 substituents selected from R^{101} , aryl C_{1-6} alkoxycarbonyl wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101} ,

5 C_{1-6} alkyl optionally substituted by mono-, di- or tri- halogen, amino, N-(C_{1-6} alkyl)amino or N,N-di(C_{1-6} alkyl)amino,

C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, N-(C_{1-6} alkyl)sulfonamide, or N-(aryl)sulfonamide,

10 or

a 5 to 7 membered saturated or unsaturated ring having 1 to 3 heteroatoms selected from the group consisting of O, S and N, and optionally having 1 to 3 substituents selected from R^{101}

15 wherein

R^{101} represents halogen, carboxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, aminocarbonyl, N-(C_{1-6} alkyl)aminocarbonyl, N,N-di(C_{1-6} alkyl)aminocarbonyl, pyridyl,

20 C_{1-6} alkyl optionally substituted by cyano or mono- di- or tri-halogen,

and

C_{1-6} alkoxy optionally substituted by cyano, carboxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, aminocarbonyl, N-(C_{1-6} alkyl)aminocarbonyl, N,N-di(C_{1-6} alkyl)aminocarbonyl or mono-,

25 di- or tri- halogen;

R^2 represents hydroxy, halogen, nitro, cyano, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6} alkyl)amino, N-(hydroxy C_{1-6} alkyl)amino, N-(hydroxy C_{1-6} alkyl)-N-(C_{1-6} alkyl)amino, C_{1-6} acyloxy, amino C_{1-6} acyloxy, C_{2-6} alkenyl, aryl,

30

a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by

5 hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, amino C₁₋₆alkyl, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, N-(C₁₋₆alkyl)carbonylamino, phenyl, phenyl C₁₋₆ alkyl, carboxy, C₁₋₆alkoxycarbonyl, aminocarbonyl, N-(C₁₋₆alkyl)aminocarbonyl, or N,N-di(C₁₋₆alkyl)amino, -C(O)- R²⁰

10 wherein

R²⁰ represents C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, or a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N-(C₁₋₆ acyl)amino, phenyl, or benzyl,

C₁₋₆ alkyl optionally substituted by R²¹,

20 or

C₁₋₆ alkoxy optionally substituted by R²¹,

wherein

25 R²¹ represents cyano, mono-, di or tri- halogen, amino, N-(C₁₋₆alkyl)amino, N,N-di(C₁₋₆alkyl)amino, N- (hydroxyC₁₋₆ alkyl) amino, N- (halophenylC₁₋₆ alkyl) amino, amino C₂₋₆ alkylenyl, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkoxy, -C(O)- R²⁰¹, -NHC(O)- R²⁰¹, C₃₋₈cycloalkyl, isoindolino, phthalimidyl, 2-oxo-1,3-oxazolidinyl, aryl or a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and

N, and optionally substituted by hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, aminoC₁₋₆ alkyl, N-(C₁₋₆ alkyl) amino, N,N-di(C₁₋₆ alkyl) amino, N-(C₁₋₆ acyl) amino, or benzyl,

5

wherein

10

R²⁰¹ represents hydroxy, amino, N-(C₁₋₆ alkyl) amino, N,N-di(C₁₋₆ alkyl) amino, N- (halophenylC₁₋₆ alkyl) amino, C₁₋₆ alkyl, aminoC₁₋₆ alkyl, aminoC₂₋₆ alkylenyl, C₁₋₆ alkoxy, a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N, and optionally substituted by hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, hydroxyC₁₋₆ alkoxy, oxo, amino, N-(C₁₋₆ alkyl) amino, N,N-di(C₁₋₆ alkyl) amino, N-(C₁₋₆ acyl) amino or benzyl;

15

20

R³ represents hydrogen, halogen, aminocarbonyl, or C₁₋₆ alkyl optionally substituted by aryl C₁₋₆ alkoxy or mono-, di- or tri- halogen;

R⁴ represents hydrogen or C₁₋₆ alkyl;

25

R⁵ represents hydrogen or C₁₋₆ alkyl; and

R⁶ represents halogen, hydrogen or C₁₋₆ alkyl,

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

30

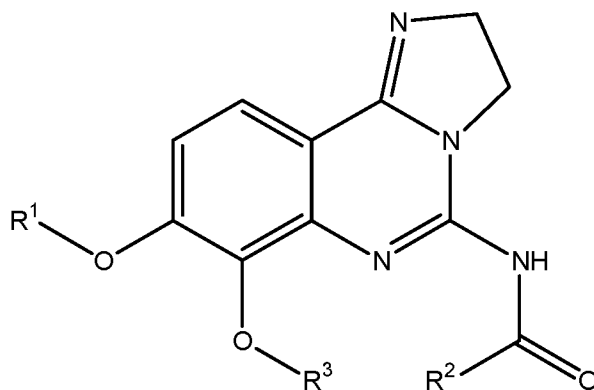
In an embodiment, said component A is a compound of general formula (A), supra, which is selected from the list consisting of :

- N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 2-(7, 8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-pyridin-3-ylethylenol;
- 5 N-(7, 8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
- 6-(acetamido)-N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- N-{5-[2-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide;
- 10 2-({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)-N,N-dimethylacetamide;
- 2-[7-methoxy-8-(tetrahydro-2H-pyran-2-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;
- 15 2-[8-(2-hydroxyethoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;
- ({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)acetic acid;
- 4-({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)butanoic acid;
- 20 ({{5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)acetonitrile;
- 2-[7-methoxy-8-(2H-tetrazol-5-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;
- 25 2-[7-methoxy-8-(4-morpholin-4-yl-4-oxobutoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;
- 5-[1-hydroxy-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)vinyl]pyridin-3-ol ;
- N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;
- 30 6-(acetamido)-N-(7,9-dimethoxy-8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

- N-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;
5-hydroxy-N-(7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-[(4-methoxybenzyl)oxy]nicotinamide;
- 5 N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;
5-hydroxy-N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-{8-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- 10 N-(7-bromo-8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
6-amino-N-(8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
1-(1H-benzimidazol-5-yl)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)ethylenol;
2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2,4-dimethyl-1,3-thiazol-
- 15 5-yl)ethylenol;
N-(9-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
N-(8-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-(8-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-
- 20 carboxamide;
N-(8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
- 25 N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1H-benzimidazole-5-carboxamide;
N-(7-fluoro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
N-(7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 30 N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

- 6-(acetamido)-N-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
 1-(1H-benzimidazol-5-yl)-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)ethylenol;
- 5 N-{5-[1-hydroxy-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)vinyl]pyridin-2-yl}acetamide;
 6-methyl-N-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
 1-(1H-benzimidazol-5-yl)-2-[8-(4-methylpiperazin-1-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]ethylenol;
- 10 N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
 N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
 N-[7-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1H-benzimidazole-5-carboxamide;
- 15 N-(7,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;
 N-{5-[2-(7,9-dimethoxy-8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide;
 N-{5-[2-(7-bromo-9-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide; and
- 20 2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-pyridin-3-ylethylenol;

In an embodiment, said component A is a compound having the formula (I) :



(I)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, in
 5 which :

R^1 represents $-(CH_2)_n-(CHR^4)-(CH_2)_m-N(R^5)(R^{5'})$;

R^2 represents a heteroaryl optionally substituted with 1, 2 or 3 R^6 groups ;

R^3 represents alkyl or cycloalkyl ;

10 R^4 represents hydrogen or alkoxy ; and

R^5 and $R^{5'}$ may be the same or different and represent independently, hydrogen, alkyl, cycloalkylalkyl, or alkoxyalkyl or R^5 and $R^{5'}$ may be taken together with the nitrogen atom to which they are bound to form a 3-7 membered nitrogen containing heterocyclic ring optionally containing at least one additional
 15 heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more $R^{6'}$ groups, or R^4 and R^5 may be taken together with the atoms to which they are bound to form a 5-6 membered nitrogen containing heterocyclic ring optionally containing 1 or more nitrogen, oxygen or sulfur atoms and which may be optionally substituted with 1 or more
 20 $R^{6'}$ groups ;

each occurrence of R^6 may be the same or different and is independently halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclic ring, heterocyclalkyl, alkyl-OR⁷, alkyl-SR⁷, alkyl-N(R⁷)(R^{7'}), alkyl-COR⁷, -CN,
 25 -COOR⁷, -CON(R⁷)(R^{7'}), -OR⁷, -SR⁷, -N(R⁷)(R^{7'}), or -NR⁷COR⁷ each of which may be optionally substituted with 1 or more R^8 groups ;

each occurrence of $R^{6'}$ may be the same or different and is independently alkyl, cycloalkylalkyl, or alkyl-OR⁷;

30

each occurrence of R^7 and $R^{7'}$ may be the same or different and is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heterocyclic ring, heterocyclalkyl, or heteroarylalkyl ;

- 5 each occurrence of R^8 is independently nitro, hydroxy, cyano, formyl, acetyl, halogen, amino, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heterocyclic ring, heterocyclalkyl, or heteroarylalkyl ;

- n is an integer from 1-4 and m is an integer from 0-4 with the proviso that when when
10 R^4 and R^5 are taken together with the atoms to which they are bound to form a 5-6 membered nitrogen containing ring, $n + m \leq 4$;
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

- In an embodiment, said component A is a compound having the formula (I), supra, in
15 which R^2 is a nitrogen containing heteroaryl optionally substituted with 1, 2 or 3 R^6 groups,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

- In an embodiment, said component A is a compound of general formula (I), supra, in
20 which R^5 and $R^{5'}$ are independently alkyl,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

- In an embodiment, said component A is a compound of general formula (I), supra, in
which R^5 and $R^{5'}$ are taken together with the nitrogen atom to which they are bound to
25 form a 5-6 membered nitrogen containing heterocyclic ring containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more $R^{6'}$ groups,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

- 30 In an embodiment, said component A is a compound of formula (I) in which R^4 and R^5 are taken together with the atoms to which they are bound to form a 5-6 membered

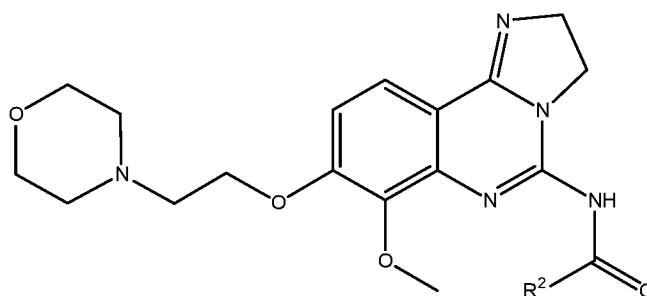
nitrogen containing heterocyclic ring optionally containing 1 or more nitrogen, oxygen or sulfur atoms and which may be optionally substituted with 1 or more R^6 groups, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

- 5 In an embodiment, said component A is a compound of formula (I) in which R^3 is methyl,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

- In an embodiment, said component A is a compound of formula (I), wherein R^2 is
10 pyridine, pyridazine, pyrimidine, pyrazine, pyrrole, oxazole, thiazole, furan or thiophene,
optionally substituted with 1, 2 or 3 R^6 groups; more preferably pyridine, pyridazine,
pyrimidine, pyrazine, pyrrole, oxazole or thiazole, optionally substituted with 1, 2 or 3 R^6
groups,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

15

In an embodiment, said component A is a compound of formula (Ia) :

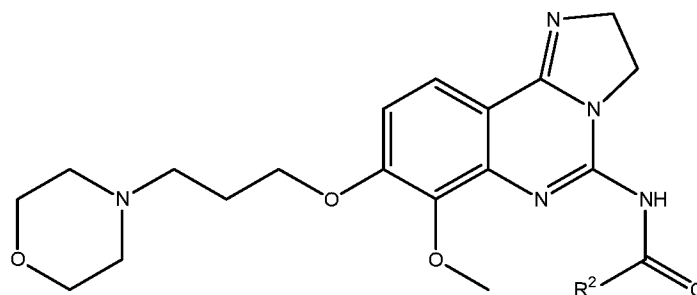


20

(Ia)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein R^2 is as defined above for formula (I).

- 25 In an embodiment, said component A is a compound of formula (Ib) :

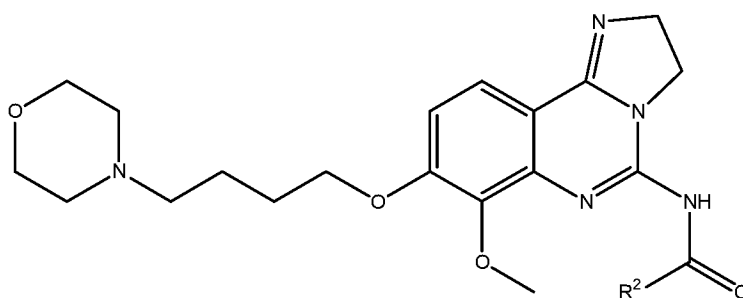


(Ib)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein

5 R^2 is as defined above for formula (I).

In an embodiment, said component A is a compound of formula (Ic) :

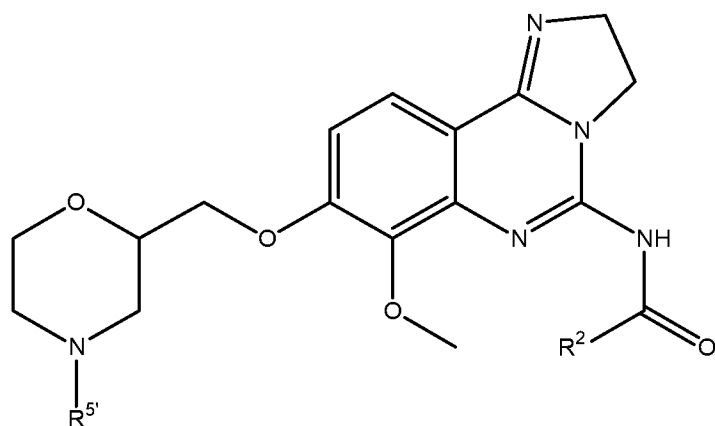


(Ic)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein

R^2 is as defined above for formula (I).

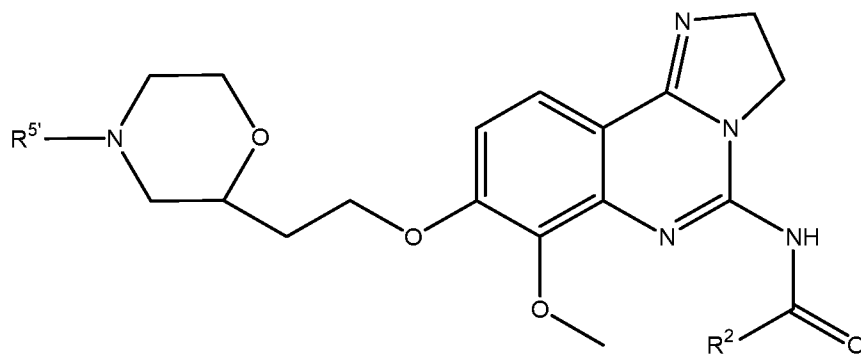
15 In an embodiment, said component A is a compound of the formula (Id) :



(Id)

- 5 or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein R² and R⁴ are as defined above for formula (I).

In an embodiment, said component A is a compound of the formula (Ie) :



10

(Ie)

- or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein
15 R² and R⁴ are as defined above for formula (I).

In an embodiment, said component A is a compound of formula (I) - (Ie), wherein R² is pyridine, pyridazine, pyrimidine, pyrazine, pyrrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R⁶ groups; more preferably wherein R² is pyridine,

pyridazine, pyrimidine, pyrazine, pyrrole, oxazole or thiazole, optionally substituted with 1, 2 or 3 R⁶ groups,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

- 5 In an embodiment, said component A is a compound selected from the list consisting of :

- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
- 10 N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide ;
- N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2,4-dimethyl-1,3-thiazole-5-carboxamide;
- 15 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-5-carboxamide;
- 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide;
- 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methyl-1,3-thiazole-5-carboxamide;
- 20 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-propylpyrimidine-5-carboxamide;
- N-{8-[2-(4-ethylmorpholin-2-yl)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
- 25 N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 30 N-(8-{3-(dimethylamino)propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide 1-oxide;

- 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2-pyrrolidin-1-ylethyl)nicotinamide;
- 5 6-(cyclopentylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- N-[8-(2-hydroxy-3-morpholin-4-ylpropoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 10 N-[7-methoxy-8-[3-(3-methylmorpholin-4-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- N-(8-{2-[4-(cyclobutylmethyl)morpholin-2-yl]ethoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 15 N-(7-methoxy-8-{2-[4-(2-methoxyethyl)morpholin-2-yl]ethoxy}-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- N-{8-[(4-ethylmorpholin-2-yl)methoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- N-(7-methoxy-8-{[4-(2-methoxyethyl)morpholin-2-yl]methoxy}-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 20 N-{7-methoxy-8-[(4-methylmorpholin-2-yl)methoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-4-carboxamide;
- 25 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-4-carboxamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-methyl-1H-imidazole-4-carboxamide;
- rel-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;
- 30

- rel-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-6-methylnicotinamide;
- rel-6-acetamido-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 5 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-methyl-1H-imidazole-5-carboxamide;
- 6-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylnicotinamide;
- 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methylpyrimidine-5-carboxamide;
- 10 6-amino-5-bromo-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-oxazole-5-carboxamide;
- 15 N-[7-methoxy-8-(morpholin-2-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 2-{[2-(dimethylamino)ethyl]amino}-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
- 2-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-1,3-thiazole-5-carboxamide;
- 20 rel-2-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;
- rel-6-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 25 2-[(2-hydroxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-[(3-methoxypropyl)amino]pyrimidine-5-carboxamide;
- 2-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
- 30

- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-[(3-morpholin-4-ylpropyl)amino]pyrimidine-5-carboxamide;
 2-[(2-methoxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
 5 2-[[2-(dimethylamino)ethyl]amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
 6-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
 10 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-pyrrolidin-1-ylpyrimidine-5-carboxamide;
 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxamide;
 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide;
 15 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-piperazin-1-ylnicotinamide hydrochloride;
 6-[(3S)-3-aminopyrrolidin-1-yl]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide hydrochloride hydrate;
 6-[(3R)-3-aminopyrrolidin-1-yl]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide hydrochloride;
 20 6-[(4-fluorobenzyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
 6-[(2-furylmethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
 25 6-[(2-methoxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(1H-pyrrol-1-yl)nicotinamide;
 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-morpholin-4-ylnicotinamide;
 30

- N-[7-methoxy-8-[3-(methylamino)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 6-[(2,2-dimethylpropanoyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 5 6-[(cyclopropylcarbonyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2,2,2-trifluoroethoxy)nicotinamide;
- 10 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(trifluoromethyl)nicotinamide;
- 6-(isobutyrylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- N-[7-methoxy-8-[3-(4-methylpiperazin-1-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 15 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-[[[(methylamino)carbonyl]amino]-1,3-thiazole-4-carboxamide];
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-[[[(methylamino)carbonyl]amino]nicotinamide;
- 20 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylamino)-1,3-thiazole-4-carboxamide;
- N-[7-methoxy-8-(2-morpholin-4-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- N-[8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;
- 25 N-[8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-methylnicotinamide;
- 6-[[[(isopropylamino)carbonyl]amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 30 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-pyrrolidin-1-ylnicotinamide;

- 6-(dimethylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-piperidin-1-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
5 N-[7-methoxy-8-(2-pyrrolidin-1-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(2-piperidin-1-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
6-[[{(ethylamino)carbonyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
10 2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
6-fluoro-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-oxazole-4-carboxamide;
15 2-(ethylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-4-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrazine-2-carboxamide;
N-[8-(2-aminoethoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
20 6-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide;
25 N-[8-[3-(diethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[8-[2-(diisopropylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[8-[2-(diethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
30 5-yl]nicotinamide;

- N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- 5 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylamino)pyrimidine-5-carboxamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylthio)pyrimidine-5-carboxamide;
- 10 N-[8-(3-aminopropoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide trifluoroacetate;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]thiophene-2-carboxamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;
- 15 2-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-3-furamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]thiophene-3-carboxamide;
- 20 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methyl-1,3-thiazole-4-carboxamide;
- 6-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 25 5-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-methylnicotinamide;
- 6-(acetylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-
- 30 dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

- 5 In another embodiment, said component A is a compound selected from the list consisting of :

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

- 10 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-methylnicotinamide;
5-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

- 15 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;
N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

- 20 6-[[[(isopropylamino)carbonyl]amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-2,4-dimethyl-1,3-thiazole-5-carboxamide;
N-[7-methoxy-8-(2-morpholin-4-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

- 25 rel-6-amino-N-{8-[3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
rel-2-amino-N-{8-[3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
30 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

5 or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

In another embodiment, said component A is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

10

In another embodiment, said component A is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide dihydrochloride.

15 Where there is a discrepancy between the chemical name and the chemical structure depicted, the chemical structure depicted takes precedence over the chemical name given.

Without being bound by theory or mechanism, the compounds of the present
20 invention display surprising activity for the inhibition of phosphatidylinositol-3-kinase and chemical and structural stability over those compounds of the prior art. It is believed that this surprising activity is based on the chemical structure of the compounds, in particular the basicity of the compounds as a result of R¹ being amino optionally substituted with R⁵ and R^{5'}. Further, the appropriate choice of R³ and R²
25 provide the necessary activity against the appropriate isoforms to allow for activity in vivo.

The synthesis of the compounds listed above is described in International Patent Application No. PCT/EP2003/010377, published as WO 2004/029055 A1, and in
30 International Patent Application No. PCT/US2007/024985, published as WO

2008/070150, both of which are hereby incorporated herein in their entirety by reference.

Said component A may be in the form of a pharmaceutical formulation which is ready
5 for use to be administered simultaneously, concurrently, separately or sequentially.
The components may be administered independently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

The PI3K-inhibitors mentioned in the prior art as well as in the lists above have been
10 disclosed for the treatment or prophylaxis of different diseases, especially cancer.

The specific compounds of the lists as disclosed above are preferred as being component A of the combination, most preferred is the compound used in the experimental section.

15 The synergistic behavior of a combination of the present invention is demonstrated herein with one of the PI3K inhibitors specifically disclosed in the Examples section as compound A.

20 In addition a combination of the present invention comprising compound A as mentioned above and cetuximab is a preferred aspect of the invention.

In another aspect a combination of the present invention comprises compound A or a pharmaceutically acceptable salt thereof as mentioned above and cetuximab.

25 It is to be understood that the present invention relates also to any combination of the embodiments of component A described above.

Component B of the Combination

30 Component B is cetuximab.

Cetuximab (Erbix[®], Merck Serono) was obtained as sterile injection solution from local pharmacy.

In accordance with an embodiment, the present invention relates to a combination of
5 any component A mentioned herein with any component B mentioned herein, optionally with any component C mentioned herein.

In one embodiment component A of the combination is the compound used in the experimental section and Component B is cetuximab being used in the experimental
10 section.

In a particular embodiment, the present invention relates to a combination of a component A with a component B, optionally with a component C, as mentioned in the Examples Section herein.

15

Further, the present invention relates to :

a kit comprising :

- a combination of :

component A: one or more PI3K-kinase inhibitors, or a physiologically acceptable salt,
20 solvate, hydrate or stereoisomer thereof ;

component B : cetuximab ; and, optionally,

component C : one or more further pharmaceutical agents ;

in which optionally either or both of said components A and B in any of the above-mentioned combinations are in the form of a pharmaceutical formulation which is
25 ready for use to be administered simultaneously, concurrently, separately or sequentially.

The term “component C” being at least one pharmaceutical agent includes the effective compound itself as well as its pharmaceutically acceptable salts, solvates, hydrates or
30 stereoisomers as well as any composition or pharmaceutical formulation comprising

such effective compound or its pharmaceutically acceptable salts, solvates, hydrates or stereoisomers. A list of such readily available agents is being provided further below.

The components may be administered independently of one another by the oral,
5 intravenous, topical, local installations, intraperitoneal or nasal route.

Component A is administered intravenously, intraperitoneally, preferably it is administered orally.

10 Component B is administered intravenously, intraperitoneally, preferably it is administered orally.

Component C being administered as the case may be.

15 The term "pharmaceutically acceptable" is used synonymously to the term "physiologically acceptable".

The term "pharmaceutically or physiologically acceptable salt" of component A refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the
20 present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19. (11) Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid,
25 succinic acid and citric acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and choline salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate
30 inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by

reacting the compounds of the invention with the appropriate base via a variety of known methods.

Representative salts of a component A of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, or butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl sulfate, or diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

A solvate for the purpose of this invention is a complex of a solvent and a compound of the invention in the solid state. Exemplary solvates would include, but are not limited to, complexes of a compound of the invention with ethanol or methanol. Hydrates are a specific form of solvate wherein the solvent is water.

It is possible for the compounds according to the invention to have systemic and/or local activity. For this purpose, they can be administered in a suitable manner, such as,

for example, via the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, vaginal, dermal, transdermal, conjunctival, otic route or as an implant or stent.

For these administration routes, it is possible for the compounds according to the invention to be administered in suitable administration forms.

- 5 For oral administration, it is possible to formulate the compounds according to the invention to dosage forms known in the art that deliver the compounds of the invention rapidly and/or in a modified manner, such as, for example, tablets (uncoated or coated tablets, for example with enteric or controlled release coatings that dissolve with a delay or are insoluble), orally-disintegrating tablets, films/wafers, 10 films/lyophilisates, capsules (for example hard or soft gelatine capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions. It is possible to incorporate the compounds according to the invention in crystalline and/or amorphised and/or dissolved form into said dosage forms.

- Parenteral administration can be effected with avoidance of an absorption step (for 15 example intravenous, intraarterial, intracardial, intraspinal or intralumbal) or with inclusion of absorption (for example intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). Administration forms which are suitable for parenteral administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilisates or sterile powders.

- 20 Examples which are suitable for other administration routes are pharmaceutical forms for inhalation [inter alia powder inhalers, nebulizers], nasal drops, nasal solutions, nasal sprays; tablets/films/wafers/capsules for lingual, sublingual or buccal administration; suppositories; eye drops, eye ointments, eye baths, ocular inserts, ear drops, ear sprays, ear powders, ear-rinses, ear tampons; vaginal capsules, aqueous suspensions 25 (lotions, mixturae agitandae), lipophilic suspensions, emulsions, ointments, creams, transdermal therapeutic systems (such as, for example, patches), milk, pastes, foams, dusting powders, implants or stents.

- The compounds according to the invention can be incorporated into the stated administration forms. This can be effected in a manner known per se by mixing with 30 pharmaceutically suitable excipients. Pharmaceutically suitable excipients include, inter alia,

- fillers and carriers (for example cellulose, microcrystalline cellulose (such as, for example, Avicel®), lactose, mannitol, starch, calcium phosphate (such as, for example, Di-Cafos®)),
- 5 • ointment bases (for example petroleum jelly, paraffins, triglycerides, waxes, wool wax, wool wax alcohols, lanolin, hydrophilic ointment, polyethylene glycols),
- bases for suppositories (for example polyethylene glycols, cacao butter, hard fat),
- 10 • solvents (for example water, ethanol, isopropanol, glycerol, propylene glycol, medium chain-length triglycerides, fatty oils, liquid polyethylene glycols, paraffins),
- surfactants, emulsifiers, dispersants or wetters (for example sodium dodecyl sulfate), lecithin, phospholipids, fatty alcohols (such as, for example, Lanette®), sorbitan fatty acid esters (such as, for example, Span®), polyoxyethylene sorbitan fatty acid esters (such as, for example, Tween®), polyoxyethylene fatty acid glycerides (such as, for example, Cremophor®), polyoxethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, glycerol fatty acid esters, poloxamers (such as, for example, Pluronic®),
- 15 • buffers, acids and bases (for example phosphates, carbonates, citric acid, acetic acid, hydrochloric acid, sodium hydroxide solution, ammonium carbonate, trometamol, triethanolamine),
- 20 • isotonicity agents (for example glucose, sodium chloride),
- adsorbents (for example highly-disperse silicas),
- viscosity-increasing agents, gel formers, thickeners and/or binders (for example polyvinylpyrrolidone, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose-sodium, starch, carbomers, polyacrylic acids (such as, for example, Carbopol®); alginates, gelatine),
- 25

- disintegrants (for example modified starch, carboxymethylcellulose-sodium, sodium starch glycolate (such as, for example, Explotab®), cross-linked polyvinylpyrrolidone, croscarmellose-sodium (such as, for example, AcDiSol®),
- 5 • flow regulators, lubricants, glidants and mould release agents (for example magnesium stearate, stearic acid, talc, highly-disperse silicas (such as, for example, Aerosil®)),
- 10 • coating materials (for example sugar, shellac) and film formers for films or diffusion membranes which dissolve rapidly or in a modified manner (for example polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohol, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, hydroxypropylmethylcellulose phthalate, cellulose acetate, cellulose acetate phthalate, polyacrylates, polymethacrylates such as, for example, Eudragit®)),
- 15 • capsule materials (for example gelatine, hydroxypropylmethylcellulose),
- synthetic polymers (for example polylactides, polyglycolides, polyacrylates, polymethacrylates (such as, for example, Eudragit®), polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohols, polyvinyl acetates, polyethylene oxides, polyethylene glycols and their copolymers and blockcopolymers),
- plasticizers (for example polyethylene glycols, propylene glycol, glycerol, triacetine, triacetyl citrate, dibutyl phthalate),
- 20 • penetration enhancers,
- stabilisers (for example antioxidants such as, for example, ascorbic acid, ascorbyl palmitate, sodium ascorbate, butylhydroxyanisole, butylhydroxytoluene, propyl gallate),
- 25 • preservatives (for example parabens, sorbic acid, thiomersal, benzalkonium chloride, chlorhexidine acetate, sodium benzoate),
- colourants (for example inorganic pigments such as, for example, iron oxides, titanium dioxide),
- flavourings, sweeteners, flavour- and/or odour-masking agents.

The present invention furthermore relates to a pharmaceutical composition which comprise at least one compound according to the invention, conventionally together with one or more pharmaceutically suitable excipient(s), and to their use according to the present invention.

5

Commercial utility

Component A

10 The compounds of formula (A) and (I) and the stereoisomers thereof according to the combination as referred to above are components A. The compounds according to the combination have valuable pharmaceutical properties, which make them commercially utilizable. In particular, they inhibit the PI3K/AKT pathway and exhibit cellular activity. They are expected to be commercially applicable in the therapy of diseases (e.g.
15 diseases dependent on overactivated PI3K/AKT). An abnormal activation of the PI3K/AKT pathway is an essential step towards the initiation and maintenance of human tumors and thus its inhibition, for example with PI3K inhibitors, is understood to be a valid approach for treatment of human tumors. For a recent review see Garcia-Echeverria et al (Oncogene, 2008, 27, 551-5526) (13).

20

Component B

Component B is a monoclonal antibody that binds the extracellular domain of EGFR and exerts its therapeutic effects by blocking ligand binding to the receptor and by
25 promoting ligand-independent internalization and downregulation of EGFR. Additionally, binding of cetuximab to cell surface EGFR has been shown to promote antibody-dependent cell-mediated cytotoxicity. Component B is especially suitable to have effects on tumor diseases, especially those with active EGFR-driven signalling pathways such as the RAS/RAF/ERK and PI3K/AKT pathway but also phospholipase C- γ
30 and signal transducers and activators of transcription pathways, promoting the proliferation and survival of cancer cells and being involved in angiogenesis, invasion

and metastasis. These also include tumors with activated EGFR as a resistance mechanism to former treatments. For a recent review see Moreira et al. (Drugs. 2017 May;77(8):843-857) (14).

5 Combination

The combinations of the present invention thus can be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, such as, for example, haematological tumours and/or metastases thereof, solid tumours, and/or metastases thereof, *e.g.* leukaemias, multiple myeloma thereof and myelodysplastic syndrome, malignant lymphomas, breast tumours including and bone metastases thereof, tumours of the thorax including non-small cell and small cell lung tumours and bone metastases thereof, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours and bone metastases thereof, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

One embodiment relates to the use of a combination as defined herein for the preparation of a medicament for the treatment or prophylaxis of a cancer, in particular head-and-neck cancers which include, but are not limited to, laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and head and neck squamous cell carcinoma (herein abbreviated to "HNSCC").

One embodiment relates to the use of a combination as defined herein in the treatment or prophylaxis of a cancer, in particular particular head-and-neck cancers

which include, but are not limited to, laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and head and neck squamous cell carcinoma.

- 5 In one embodiment the invention relates to combinations comprising component A or a pharmaceutically acceptable salt thereof and Component B being intravenously, intraperitoneally, preferably it is administered orally.

The term “inappropriate” within the context of the present invention, in particular in
10 the context of “inappropriate cellular immune responses, or inappropriate cellular inflammatory responses”, as used herein, is to be understood as preferably meaning a response which is less than, or greater than normal, and which is associated with, responsible for, or results in, the pathology of said diseases.

- 15 Combinations of the present invention might be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis.

This invention includes a method comprising administering to a mammal in need thereof, including a human, an amount of a component A and an amount of component B of this invention, or a pharmaceutically acceptable salt, isomer,
20 polymorph, metabolite, hydrate, solvate or ester thereof ; etc. which is effective to treat the disorder.

Hyper-proliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), as well as malignant neoplasia. Examples of malignant neoplasia treatable with the compounds
25 according to the present invention include solid and hematological tumors. Solid tumors can be exemplified by tumors of the breast, bladder, bone, brain, central and peripheral nervous system, colon, anus, endocrine glands (e.g. thyroid and adrenal cortex), esophagus, endometrium, germ cells, head and neck, kidney, liver, lung, larynx and hypopharynx, mesothelioma, ovary, pancreas, prostate, rectum, renal, small
30 intestine, soft tissue, testis, stomach, skin, ureter, vagina and vulva. Malignant

neoplasias include inherited cancers exemplified by Retinoblastoma and Wilms tumor. In addition, malignant neoplasias include primary tumors in said organs and corresponding secondary tumors in distant organs ("tumor metastases"). Hematological tumors can be exemplified by aggressive and indolent forms of leukemia and lymphoma, namely non-Hodgkins disease, chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins disease, multiple myeloma and T-cell lymphoma. Also included are myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, and cancers of unknown primary site as well as AIDS related malignancies.

10 Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ, particularly with bone metastases.

15 Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophthalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

20 Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

25 Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

5 Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and head and neck squamous cell carcinoma.

10 Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

15 Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

20 The term "treating" or "treatment" as stated throughout this document is used conventionally, *e.g.*, the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, *etc.*, of a disease or disorder, such as a carcinoma.

25 Combinations of the present invention might also be used for treating disorders and diseases associated with excessive and/or abnormal angiogenesis.

Inappropriate and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of

extraneous blood vessels. These include, e.g., diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity [Aiello et al. New Engl. J. Med. 1994, 331, 1480 (15); Pe'er et al. Lab. Invest. 1995, 72, 638 (16)], age-related macular degeneration [AMD ; see, Lopez et al. Invest. Ophthalmol. Vis. Sci. 1996, 37, 855 (17)],

5 neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, etc. In addition, the increased blood supply associated with cancerous and neoplastic tissue, encourages growth, leading to rapid tumor enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumor provides an escape

10 route for renegade cells, encouraging metastasis and the consequence spread of the cancer. Thus, combinations of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, e.g., by inhibiting and/or reducing blood vessel formation ; by inhibiting, blocking, reducing, decreasing, etc. endothelial cell proliferation or other types involved in angiogenesis, as well as causing

15 cell death or apoptosis of such cell types.

Dose and administration

Component A and component B

- Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders and angiogenic disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredients to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular component And dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.
- The total amount of the active ingredients to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules of a compound will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of

from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending
5 diagnostician, the activity of the specific compounds employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in
10 the art using conventional treatment tests.

Combinations of the present invention

The combinations of the present invention can be used in particular in therapy and prevention, *i.e.* prophylaxis, of tumour growth and metastases, including solid and haematological tumours of all indications and stages with or without pre-treatment of
15 the tumour growth.

Methods of testing for a particular pharmacological or pharmaceutical property are well known to persons skilled in the art.

20 The combinations of component A and component B of this invention can be administered as the sole pharmaceutical agent or in combination with one or more further pharmaceutical agents C where the resulting combination of components A, B and C causes no unacceptable adverse effects. For example, the combinations of components A and B of this invention can be combined with component C, *i.e.* one or
25 more further pharmaceutical agents, such as known anti-angiogenesis, anti-hyperproliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and the like, as well as with admixtures and combinations thereof.

Component C, can be one or more pharmaceutical agents such as ¹³¹I-chTNT, abarelix, abemaciclib, abiraterone, acalabrutinib, aclarubicin, adalimumab, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alectinib, alemtuzumab, alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, aneastim, anethole dithiolethione, anetumab, 5 ravtansine, angiotensin II, antithrombin III, apalutamide, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, atezolizumab, avelumab, axicabtagene ciloleucel, axitinib, azacitidine, basiliximab, belotecan, bendamustine, besilesomab, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, blinatumomab, bortezomib, bosutinib, buserelin, brentuximab vedotin, brigatinib, 10 busulfan, cabazitaxel, cabozantinib, calcitonine, calcium folinate, calcium levofolinate, capecitabine, capromab, carbamazepine carboplatin, carboquone, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, cobimetinib, copanlisib , crisantaspase, crizotinib, 15 cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daratumumab, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dianhydrogalactitol, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, dinutuximab, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, 20 durvalumab, eculizumab, edrecolomab, elliptinium acetate, elotuzumab, eltrombopag, enasidenib, endostatin, enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, ethinylestradiol, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic 25 acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, 30 ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron,

incadronic acid, ingenol mebutate, inotuzumab ozogamicin, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, ixazomib, lanreotide, lansoprazole, lapatinib, lasocholine, lenalidomide, lenvatinib, lenograstim, lentinan, letrozole, leuprorelin, 5 levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, lutetium Lu 177 dotatate, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, midostaurin, mifamurtide, miltefosine, miriplatin, 10 mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, mvasi, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, necitumumab, nedaplatin, nelarabine, neratinib, neridronic acid, netupitant/palonosetron, nivolumab, pentetate, nilotinib, nilutamide, nimorazole, 15 nimotuzumab, nimustine, nintedanib, niraparib, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, olaparib, olaratumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotinib, osimertinib, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palbociclib, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, 20 panobinostat, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pembrolizumab, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglucam, polyestradiol phosphate, polyvinylpyrrolidone + sodium 25 hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib, regorafenib, ribociclib, risedronic acid, rhenium-186 etidronate, rituximab, rolapitant, 30 romidepsin, romiplostim, romurtide, rucaparib, samarium (153Sm) lexidronam, sargramostim, sarilumab, satumomab, secretin, siltuximab, sipuleucel-T, sizofiran,

- sobuzoxane, sodium glycididazole, sonidegib, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, talimogene laherparepvec, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide,
- 5 temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tisagenlecleucel, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trametinib, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib ,
- 10 valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin, or combinations thereof.
- 15 Generally, the use of a further pharmaceutical agent as component C in combination with a combination of components A and B of the present invention will serve to:
- (1) yield better efficacy in reducing the growth of a tumor and/or metastasis or even eliminate the tumor and/ or metastasis as compared to administration of
- 20 either agent alone,
- (2) provide for the administration of lesser amounts of the administered chemotherapeutic agents,
- 25 (3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,
- (4) provide for treating a broader spectrum of different cancer types in mammals,
- 30 especially humans,

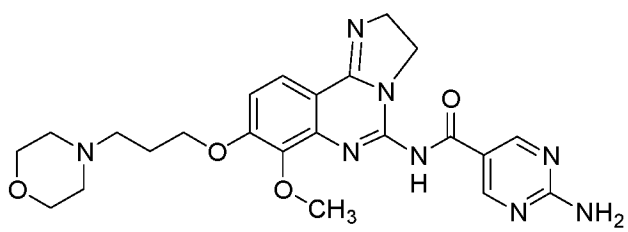
- (5) provide for a higher response rate among treated patients,
- (6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,
- 5 (8) provide a longer time for tumor progression, and/or
- (9) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations
- 10 produce antagonistic effects.

EXPERIMENTAL SECTION

Examples demonstrating the synergistic effect of the combinations of components A and B of the present invention

Component A :

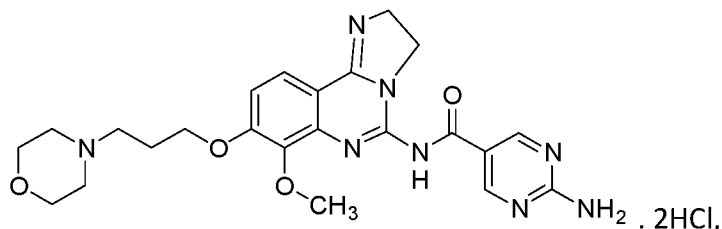
In this Experimental section and in the Figures, the term “compound A” is an example of component A and is compound Example 13 of WO 2008/070150 A1 as shown herein: it is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide, of structure :



compound A

or a solvate, hydrate or stereoisomer thereof.

In this Experimental Section and in the Figures, the term “compound A’ ” refers to 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide dihydrochloride, or “copanlisib” of structure :



compound A'

5 or a solvate, hydrate or stereoisomer thereof.

The synthesis of compound A' is described in European patent application number EP 11 161 111.7, and in PCT application number PCT/EP2012/055600 published under WO 2012/136553, both of which are hereby incorporated herein in their entirety by
 10 reference.

Component B :

In this Experimental Section and in the Figures, the term "compound B" refers to
 15 "cetuximab", which was obtained from Merck Serono (Batch #216878).

Example demonstrating the synergistic effect of the combinations of compound A' and compound B or compound B' of the present invention

20 COMBINATIONS OF COPANLISIB AND CETUXIMAB IN A PANEL OF PATIENT-DERIVED XENOGRAPHS

The efficacy of combination of compound A (copanlisib) and compound B (cetuximab) was evaluated in a mouse-clinical-trial design study in xenografts from 20 patient-derived models of squamous head and neck cancer (HNSCC). Models were selected
 25 from an HNSCC PDX platform available at EPO GmbH, Berlin, based on Pi3K mutational status, with 6 models harboring hot spot mutations, HPV positivity (n=3) and cetuximab resistance based on previous drug screenings (n=12) (Table 1; (18)). For determination of drug response fragments of similar size were transplanted subcutaneously into the left flank of female NMRI nu/nu mice, with one mouse per treatment group and two

mice in the control group. Mice with a tumor size between 0.15-0.5cm³ have been randomized to the control (n=2) and treatment groups (n=1) according to the study design (Table 2, Table 3). Treatment was performed for a period of 3 weeks. Efficacy of the monotherapy as well as the combination treatment was evaluated by

- 5 measurement of two perpendicular diameters of the subcutaneous tumors twice a week. Measurement of body weight of the control and treatment groups was used for assessing the tolerability of the treatments. Animals were sacrificed when the tumour size reached more than 1 cm³ or the intended duration of treatment had been reached. Tumor measurements were used for calculation of tumor volume (TV; formula:
- 10 $V = ([width]^2 \times length)/2$) and relative tumor volume (RTV; change relative to TV at start of treatment). The treatment effects on tumor growth was calculated based on fitting an exponential growth curve into the RTV data and calculation of doubling times (DT) and growth rate (k) (GraphPad Prism 7.0) according to Hafner et.al. 2016 (19). Statistics on treatment effects have been calculated on ranks using Dunn's multiple
- 15 comparisons test, on the relative tumor volumes along the time (GraphPad Prism 7.0).

20

25

Table 1 Patient-derived HNSCC tumor models used for assessment of compound A (copanlisib) and compound B (Cetuximab) in vivo

Tumor model	Site of tumor origin	TNM	UICC stage	Primary/ recurrent	model_passage	Cetuximab Resist.	PI3K mut
HN10980B	Soft palate	T4bN2bM0	IVB	primary	HN10980B_P3		
HN10110	Tongue	T2N2M0 G2	IVA	primary	HN10110_P4		x
HN10309*	Oropharynx	T4N2M0G3	IVA	primary	HN10309_P5	x	
HN10632	Tongue	T2N1M0	III	primary	HN10632_P5	x	
HN10847	Soft palate	T2N1M0	III	recurrent	HN10847_P5	x	x
HN10924	Hypopharynx	T3N2cM0	IVA	primary	HN10924_P6	x	x
HN10960	Tongue	T2N0M0	II	primary	HN10960_P3		x
HN11097	Floor of mouth	T4aN2bM0	IVA	primary	HN11097_P6		x
HN11218	Soft palate	T4N0M0	IVA	primary	HN11218B_P6		x
HN11303*	Oropharynx	T3N1M0	IVA	primary	HN11303_P5	x	
HN11482A	Floor of mouth	T2N2bM0	IVA	primary	HN11482A_P3		x
HN11841	Floor of mouth	T1N0M0	I	recurrent	HN11841B_P2	x	x
HN13869	Oral cavity	T1N2bM0	IVA	recurrent	HN13869_P6	x	
HN9897	Hypopharynx	T2N2M0G3	IVA	recurrent	HN9897_P1		
HN11857B	Oral cavity	-	-	primary (LN metastasis)	HN11857B_P3	x	
HN11437B	Floor of mouth	-	-	primary (LN metastasis)	HN11437B_P5		
HN10621B	Oropharynx	T2N2bM0	IVA	primary (LN metastasis)	HN10621B_P3		
HN11452	Floor of mouth	T2N0M0	II	primary	HN11452_P3	x	
HN11364*	Oropharynx	-	-	primary	HN11364	x	
HN11527A	Floor of mouth	T2N2bM0	IVA	primary	HN11527A_P3	x	

(*) HPV positive HNSCC

Table 2 Test system

Animal	Mice
Strains	NMRI:nu/nu
Gender	Female
Age and body weight at start of studies	6-9 weeks / $29,4 \pm 2,7$ g
Supplier	Janvier Labs, contact@janvier-labs.com, France
Acclimatization	At least 4 days
Environmental Conditions	Strictly controlled and standardized barrier conditions, IVC System Tecniplast DCC (Tecniplast Deutschland GmbH, Hohenpeißenberg, Germany)
Caging	Macrolon Sealsafe 1284L (Tecniplast)
Feed type	Pellets (V1724-300), mail@ssniff.de, ssniff Spezialdiäten GmbH, Soest
Drinking water	Autoclaved tap water in water bottles
Feeding and drinking time	Ad libitum
Room temperature	24 ± 2 °C
Relative humidity	$50 \pm 10\%$
Light period	Artificial; 12 hours dark/12 hours light rhythm (light 06.00 to 18.00 hours)
Health control	At the start of the study and twice daily during the study
Identification	Ear mark and cage labels

All animal experiments were performed in accordance with the Guidelines for the Welfare and Use of Animals in Cancer Research and of the German Animal Protection Law, and approved by the local responsible authorities. Since June 2017, EPO is fully accredited by AAALAC International.

5

10

Table 3 Experimental groups

Group	Animal no	Treatment	Route	Treatment schedule	Dose (mg/kg)
A	2*	Vehicle	p.o.	QDx4weeks	-
C	2*	Copanlisib	i.v.	QD (2on/5off)	10
D	1	Cetuximab		Q7Dx3weeks	50
F	1	Copanlisib &	i.v.	QD (2on/5off)	10
		Cetuximab		Q7Dx3weeks	50
H	5	Transplantation controls			

Example 1. Beneficial combination of PI3K inhibitor compound A (copanlisib) and EGFR inhibitor compound B (cetuximab) observed in a mouse clinical trial setup using patient-derived head and neck cancer models, see Figure 1.

5

Table 4 Overview of response to the treatments by means of RTV and optimal T/C (%)

Study number	Model	Vehicle	Copanlisib (10mg/kg)		Cetuximab (50mg/kg)		Copanlisib & Cetuximab	
	HNSCC	TdT (days)	RTV	T/C	RTV	T/C	RTV	T/C
15181	HN10980B	7	13,1	103,2	0,4	3,8	0,5	4,9
15225	HN10110	14	2,8	77,9	0,4	14,2	0,4	18,3
15226	HN10309	10	1,6	12,3	2,9	26,1	2,2	14,4
15227 ^(a)	HN10632	23	4,4	123,4	3,3	68,0	1,0	17,6
15228	HN10847	22	1,4	20,3	1,0	13,8	0,3	4,1
15229	HN10924	20	3,1	64,6	4,6	104,9	5,9	123,5
15230	HN10960	12	1,6	14,2	0,7	6,2	1,0	7,3
15231 ^(b)	HN11097	12	3,9	65,5	2,1	33,8	1,1	17,2
15232 ^(c)	HN11218	7	1,8	52,4	0,6	13,9	0,0	0,2
15233	HN11303	13	3,5	35,0	2,1	16,1	1,4	16,2
15234 ^(d)	HN11482	12	4,4	116,2	0,9	27,8	0,2	6,4
15235 ^(e)	HN11841	12	14,0	180,1	2,5	31,2	1,9	19,7
15603	HN13869	5	13,1	93,0	0,6	4,2	0,5	3,1
15604 ^(f)	HN9897	11	6,5	75,1	7,7	91,0	10,2	125,9
15657	HN11857B	13	2,9	61,2	6,8	236,4	4,2	118,2
15668	HN11437B	11	5,0	31,5	0,0	0,2	0,0	0,0
15669	HN10621B	82	7,1	580,2	1,8	88,3	3,7	264,0
15721	HN11452	9	1,1	6,5	0,0	0,2	0,6	4,5
15738 ^(g)	HN11364	19	2,1	84,8	2,7	145,5	1,5	79,3
15748 ^(h)	HN11527A	10	7,0	207,7	3,8	84,0	2,8	68,6

Tumor doubling time (TdT) in control group A (vehicle) in days from treatment start. RTV and T/C listed in this table were from the last study day when all experimental groups were complete. Deviations were: (a) RTV and T/C from day 67 of the study. (b) RTV and T/C from day 40 of the study. (c) RTV and T/C from day 41 of the study. (d) RTV and T/C from day 61 of the study. (e) RTV and T/C from day 53 of the study. (f) RTV and T/C from day 68 of the study. (g) RTV and T/C from day 71 of the study. (h) RTV and T/C from day 37 of the study.

Head and neck squamous cell carcinoma (HNSCC) displays multiple ways of activation of PI3K signalling. The PI3K gene *PIK3CA* is frequently mutated in HNSCC and constitutes an attractive targetable oncogene in this indication ((2)).

The benefit of treating HNSCC models with compound A or compound B or a combination of both was tested in a set of 20 patient-derived HNSCC xenograft models on mice. (Table 4) All models have been selected for sensitivity towards standard-of

care treatment with cetuximab as well as the mutational status for *PIK3CA* have been correlated. The respective data for two selected models are shown in Table 4.

5 This model HN10847 showed sensitivity to compound A and B (copanlisib and cetuximab) in monotherapy (**Fehler! Verweisquelle konnte nicht gefunden werden.; Table 4**)). The treatment effects could be further improved by combination of compound A and compound B in this model.

10 In the model HN10632, which is resistant to both monotherapies, there was a significant improvement on the tumor growth rate (**Fehler! Verweisquelle konnte nicht gefunden werden., Table 4**).

15 The combination of a PI3K inhibitor (compound A) and a cetuximab (compound B) showed benefit in inhibition of tumor growth in HNSCC PDX models irrespective of their sensitivity to cetuximab or mutational status for *PIK3CA*. (**Fehler! Verweisquelle konnte nicht gefunden werden.;Table 4**).

20 In summary, our data indicate combination benefits of the PI3K inhibitor copanlisib and cetuximab in inhibiting or controlling tumor growth and warrant further clinical evaluation of this promising combination therapy for the treatment of cancer, in particular head-and-neck cancers which include, but are not limited to, laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and head and neck squamous cell carcinoma (herein abbreviated to “HNSCC”).

REFERENCES

1. McGuire S. World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015. Adv Nutr. 2016 Mar;7(2):418-9.
2. (no-authors). Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015;517.
3. Szabo B, Nelhubel GA, Karpati A, Kenessey I, Jori B, Szekely C, et al. Clinical significance of genetic alterations and expression of epidermal growth factor receptor (EGFR) in head and neck squamous cell carcinomas. Oral Oncol. 2011 Jun;47(6):487-96.
4. Sacco AG, Worden FP. Molecularly targeted therapy for the treatment of head and neck cancer: a review of the ErbB family inhibitors. Onco Targets Ther. 2016;9:1927-43.
5. Lee YS, Johnson DE, Grandis JR. An update: emerging drugs to treat squamous cell carcinomas of the head and neck. Expert Opinion on Emerging Drugs. 2018:null-null.
6. Gillison ML, Blumenschein G, Jr., Fayette J, Guigay J, Colevas AD, Licitra L, et al. CheckMate 141: 1-Year Update and Subgroup Analysis of Nivolumab as First-Line Therapy in Patients with Recurrent/Metastatic Head and Neck Cancer. Oncologist. 2018 Sep;23(9):1079-82.
7. Bader AG, Kang S, Vogt PK. Cancer-specific mutations in PIK3CA are oncogenic in vivo. Proc Natl Acad Sci U S A. 2006 Jan 31;103(5):1475-9.
8. Lux MP, Fasching PA, Schrauder MG, Hein A, Jud SM, Rauh C, et al. The PI3K Pathway: Background and Treatment Approaches. Breast Care. 2016;11(6):398-404.
9. Steelman LS, Navolanic P, Chappell WH, Abrams SL, Wong EW, Martelli AM, et al. Involvement of Akt and mTOR in chemotherapeutic- and hormonal-based drug resistance and response to radiation in breast cancer cells. Cell Cycle. 2011 Sep 1;10(17):3003-15.
10. Morgillo F, Della Corte CM, Diana A, Mauro CD, Ciaramella V, Barra G, et al. Phosphatidylinositol 3-kinase (PI3K α)/AKT axis blockade with taselisib or ipatasertib enhances the efficacy of anti-microtubule drugs in human breast cancer cells. Oncotarget. 2017 Sep 29;8(44):76479-91.
11. Berge SM, Bighley LD, Monkhouse DC. Pharmaceutical salts. J Pharm Sci. 1977 Jan;66(1):1-19.
12. (no-authors). Rules for the Nomenclature of Organic Chemistry. Section E: Stereochemistry. Pure and Applied Chemistry; 1976. p. 11.
13. Garcia-Echeverria C, Sellers WR. Drug discovery approaches targeting the PI3K/Akt pathway in cancer. Oncogene. 2008 Sep 18;27(41):5511-26.
14. Moreira J, Tobias A, O'Brien MP, Agulnik M. Targeted Therapy in Head and Neck Cancer: An Update on Current Clinical Developments in Epidermal

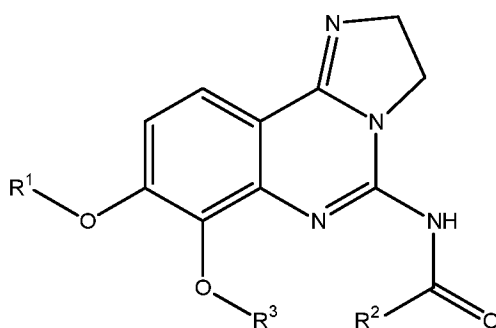
Growth Factor Receptor-Targeted Therapy and Immunotherapies. *Drugs*. 2017 May;77(8):843-57.

15. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *New England Journal of Medicine*. 1994;331(22):1480-7.
16. Pe'er J, Shweiki D, Itin A, Hemo I, Gnessin H, Keshet E. Hypoxia-induced expression of vascular endothelial growth factor by retinal cells is a common factor in neovascularizing ocular diseases. *Lab Invest*. 1995 Jun;72(6):638-45.
- 10 17. Lopez PF, Sippy BD, Lambert HM, Thach AB, Hinton DR. Transdifferentiated retinal pigment epithelial cells are immunoreactive for vascular endothelial growth factor in surgically excised age-related macular degeneration-related choroidal neovascular membranes. *Investigative Ophthalmology and Visual Science*. 1996;37(5):855-68.
- 15 18. Klinghammer K, Raguse J-D, Plath T, Albers AE, Joehrens K, Zakarneh A, et al. A comprehensively characterized large panel of head and neck cancer patient-derived xenografts identifies the mTOR inhibitor everolimus as potential new treatment option. *International Journal of Cancer*. 2014;136:2940-8.
- 20 19. Hafner M, Niepel M, Chung M, Sorger PK. Growth rate inhibition metrics correct for confounders in measuring sensitivity to cancer drugs. *Nat Methods*. 2016 Jun;13(6):521-7.

CLAIMS

1. A combination of at least two components, component A and component B, comprising a component A being an inhibitor of PI3K or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, and component B being cetuximab.

2. The combination of at least two components, component A and component B, according to claim 1, in which said component A is a compound of general formula :



(I)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, in which :

R^1 represents $-(CH_2)_n-(CHR^4)-(CH_2)_m-N(R^5)(R^{5'})$;

R^2 represents a heteroaryl optionally substituted with 1, 2 or 3 R^6 groups ;

R^3 represents alkyl or cycloalkyl ;

R^4 represents hydrogen or alkoxy ;

R^5 and $R^{5'}$ may be the same or different and are independently, hydrogen, alkyl, cycloalkylalkyl, or alkoxyalkyl or R^5 and $R^{5'}$ may be taken together with the nitrogen atom to which they are bound to form a 3-7 membered nitrogen containing heterocyclic ring optionally containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more R^6 groups, or R^4 and R^5 may be taken together with the atoms to which they are bound to form a 5-6 membered nitrogen containing heterocyclic ring optionally containing 1 or more nitrogen,

oxygen or sulfur atoms and which may be optionally substituted with 1 or more R^{6'} groups;

5 each occurrence of R⁶ may be the same or different and is independently halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclic ring, heterocyclalkyl, alkyl-OR⁷, alkyl-SR⁷, alkyl-N(R⁷)(R^{7'}), alkyl-COR⁷, -CN, -COOR⁷, -CON(R⁷)(R^{7'}), -OR⁷, -SR⁷, -N(R⁷)(R^{7'}), or -NR⁷COR⁷ each of which may be optionally substituted with 1 or more R⁸ groups;

10 each occurrence of R^{6'} may be the same or different and is independently alkyl, cycloalkylalkyl, or alkyl-OR⁷;

each occurrence of R⁷ and R^{7'} may be the same or different and is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, 15 aryl, arylalkyl, heteroaryl, heterocyclic ring, heterocyclalkyl, or heteroarylalkyl;

each occurrence of R⁸ is independently nitro, hydroxy, cyano, formyl, acetyl, halogen, amino, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heterocyclic ring, heterocyclalkyl, or heteroarylalkyl;

20

n is an integer from 1-4 and m is an integer from 0-4 with the proviso that when R⁴ and R⁵ are taken together with the atoms to which they are bound to form a 3-7 membered nitrogen containing ring, $n + m \leq 4$;
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

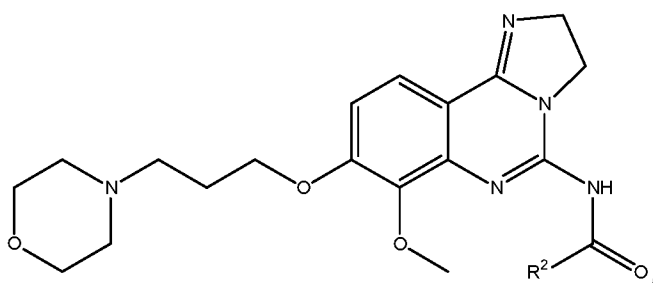
25

3. The combination according to claim 1 or 2, in which said component A is a compound of formula (I) of claim 2, in which R⁴ and R⁵ are taken together with the atoms to which they are bound to form a 5-6 membered nitrogen containing heterocyclic ring optionally containing 1 or more nitrogen, oxygen or sulfur atoms and 30 which may be optionally substituted with 1 or more R^{6'} groups,
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

4. The combination according to any one of claims 1 to 3, in which said component A is a compound of formula (I) of claim 2, in which R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R^6 groups,
 5 or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

5. The combination according to any one of claims 1 to 4, in which said component A is a compound of formula (I), which has the formula :

10



or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

- 15 6. The combination of claim 5, in which, in said compound of formula (I), R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R^6 groups,
 or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

- 20 7. The combination of any one of claims 1 to 6, in which said component A is a compound selected from the list consisting of :

- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
 25 N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide ;
 N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-

- 2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2,4-dimethyl-1,3-thiazole-5-carboxamide;
- 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-5-carboxamide;
- 5 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide;
- 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methyl-1,3-thiazole-5-carboxamide;
- 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-propylpyrimidine-5-carboxamide;
- 10 N-{8-[2-(4-ethylmorpholin-2-yl)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
- 15 N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide 1-oxide;
- 20 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2-pyrrolidin-1-ylethyl)nicotinamide;
- 25 6-(cyclopentylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- N-[8-(2-hydroxy-3-morpholin-4-ylpropoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- N-{7-methoxy-8-[3-(3-methylmorpholin-4-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- 30

- N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- N-(8-{2-[4-(cyclobutylmethyl)morpholin-2-yl]ethoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 5 N-(7-methoxy-8-{2-[4-(2-methoxyethyl)morpholin-2-yl]ethoxy}-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- N-{8-[(4-ethylmorpholin-2-yl)methoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- 10 N-(7-methoxy-8-{[4-(2-methoxyethyl)morpholin-2-yl]methoxy}-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- N-{7-methoxy-8-[(4-methylmorpholin-2-yl)methoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-4-carboxamide;
- 15 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-4-carboxamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-methyl-1H-imidazole-4-carboxamide;
- rel-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;
- 20 rel-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-6-methylnicotinamide;
- rel-6-acetamido-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 25 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-methyl-1H-imidazole-5-carboxamide;
- 6-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylnicotinamide;
- 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methylpyrimidine-5-carboxamide;
- 30

- 6-amino-5-bromo-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-oxazole-5-carboxamide;
- 5 N-[7-methoxy-8-(morpholin-2-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 2-[[2-(dimethylamino)ethyl]amino]-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
- 2-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-1,3-thiazole-5-carboxamide;
- 10 rel-2-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;
- rel-6-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
- 15 2-[(2-hydroxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-[(3-methoxypropyl)amino]pyrimidine-5-carboxamide;
- 2-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
- 20 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-[(3-morpholin-4-ylpropyl)amino]pyrimidine-5-carboxamide;
- 2-[(2-methoxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
- 25 2-[[2-(dimethylamino)ethyl]amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
- 6-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-pyrrolidin-1-ylpyrimidine-5-carboxamide;
- 30

- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide;
5 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-piperazin-1-ylnicotinamide hydrochloride;
6-[(3S)-3-aminopyrrolidin-1-yl]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide hydrochloride hydrate;
6-[(3R)-3-aminopyrrolidin-1-yl]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide hydrochloride;
10 6-[(4-fluorobenzyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
6-[(2-furylmethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
15 6-[(2-methoxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(1H-pyrrol-1-yl)nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-morpholin-4-ylnicotinamide;
20 N-[7-methoxy-8-[3-(methylamino)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
6-[(2,2-dimethylpropanoyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
25 6-[(cyclopropylcarbonyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2,2,2-trifluoroethoxy)nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(trifluoromethyl)nicotinamide;
30

- 6-(isobutyrylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- N-{7-methoxy-8-[3-(4-methylpiperazin-1-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- 5 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-[[{(methylamino)carbonyl]amino}-1,3-thiazole-4-carboxamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-[[{(methylamino)carbonyl]amino}nicotinamide;
- 10 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylamino)-1,3-thiazole-4-carboxamide;
- N-[7-methoxy-8-(2-morpholin-4-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-2,4-dimethyl-1,3-thiazole-5-carboxamide;
- 15 N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-6-methylnicotinamide;
- 6-[[{(isopropylamino)carbonyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 20 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-pyrrolidin-1-ylnicotinamide;
- 6-(dimethylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- N-[7-methoxy-8-(3-piperidin-1-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 25 N-[7-methoxy-8-(2-pyrrolidin-1-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- N-[7-methoxy-8-(2-piperidin-1-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 30 6-[[{(ethylamino)carbonyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

- 6-fluoro-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-oxazole-4-carboxamide;
- 5 2-(ethylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-4-carboxamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrazine-2-carboxamide;
- 10 N-[8-(2-aminoethoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- 6-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide;
- 15 N-{8-[3-(diethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- N-{8-[2-(diisopropylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- N-{8-[2-(diethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- 20 N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
- 25 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylamino)pyrimidine-5-carboxamide;
- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylthio)pyrimidine-5-carboxamide;
- N-[8-(3-aminopropoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide trifluoroacetate;
- 30

- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]thiophene-2-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;
5 2-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-3-furamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]thiophene-3-carboxamide;
10 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methyl-1,3-thiazole-4-carboxamide;
6-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
15 5-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-methylnicotinamide;
6-(acetylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
20 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide ;

preferably,

- 25 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-methylnicotinamide;
30 5-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

- N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;
 N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
 5 N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
 6-[[isopropylamino]carbonyl]amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
 N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;
 10 N-[7-methoxy-8-(2-morpholin-4-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
 rel-6-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
 15 rel-2-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;
 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
 N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
 20 N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
 or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.
- 25 8. The combination of any one of claims 1 to 7, in which said component A is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide,
 or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt, or a mixture of same.

30

9. The combination of any one of claims 1 to 8, in which said component A is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide.
- 5 10. The combination of any one of claims 1 to 8, in which said component A is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide dihydrochloride.
11. The combination of any one of claims 1 to 10, in which component B is cetuximab.
- 10 12. The combination according to any one of claims 1 to 7, wherein said component A is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide and said component B is cetuximab.
- 15 13. The combination according to any one of claims 1 to 7, wherein said component A is 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide dihydrochloride and said component B is cetuximab.
- 20 14. A combination according to any one of claims 1 to 13 for use in the treatment or prophylaxis of a head-and-neck cancer, such as laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer, or head and neck squamous cell carcinoma (abbreviated to "HNSCC").
- 25 15. Use of a combination according to any one of claims 1 to 13 in the treatment or prophylaxis of head-and-neck cancer, such as laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer, or head and neck squamous cell carcinoma (abbreviated to "HNSCC").
- 30 16. Use of a combination according to any one of claims 1 to 13 for the preparation of a medicament for the treatment or prophylaxis of head-and-neck cancer, such as

laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer, or head and neck squamous cell carcinoma (abbreviated to "HNSCC").

17. A method of treatment or prophylaxis of a cancer, particularly head-and-neck
5 cancer, such as laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer, or head and neck squamous cell carcinoma (abbreviated to "HNSCC"), in a subject, comprising administering to said subject a therapeutically effective amount of a combination according to any one of claims 1 to 13.

10 18. A kit comprising a combination of :
one or more components A as defined in any one of the claims 1 to 12;
components B as defined in claims 1 or 12;
and, optionally, one or more further pharmaceutical agents C;
in which optionally both or either of said components A and B are in the form of a
15 pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

19. A composition containing a combination according to claims 1 to 13 together with pharmaceutically acceptable ingredients.

20

Figures

Fig. 1

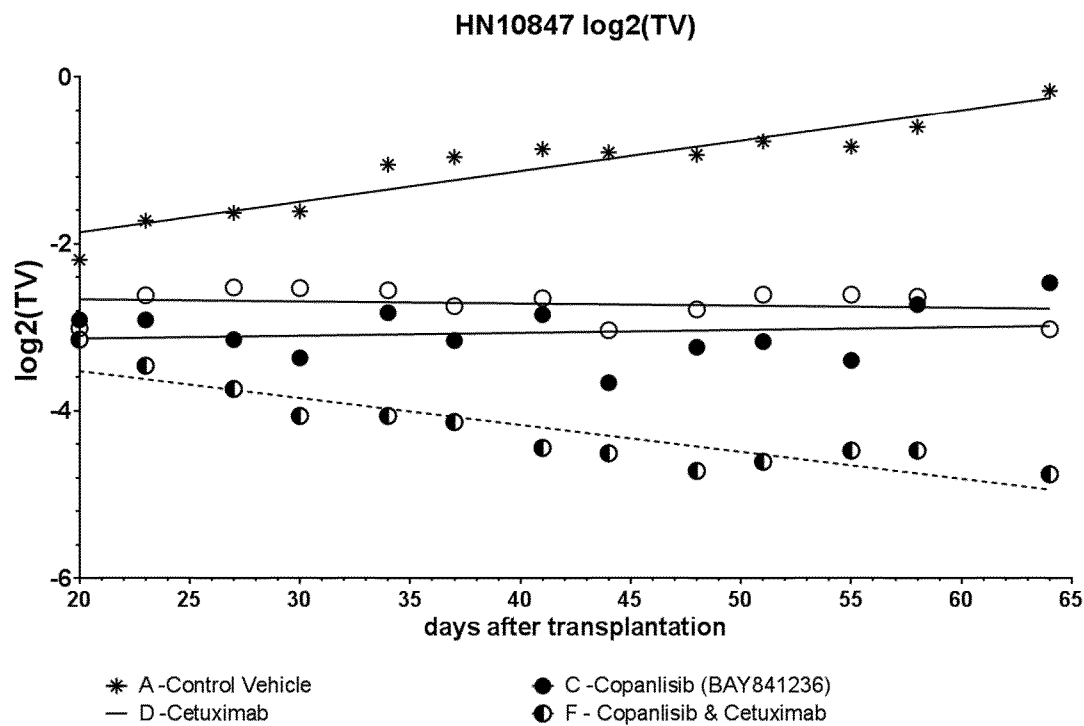


Figure 1: In vivo efficacy of treatment of HNSCC PDX model HN10847 (cetuximab resistant and PIK3CA mutated) with monotherapy of copanlisib and cetuximab respectively and combination thereof. Tumor growth expressed as Log₂ of tumor volume measured over treatment

Fig. 2

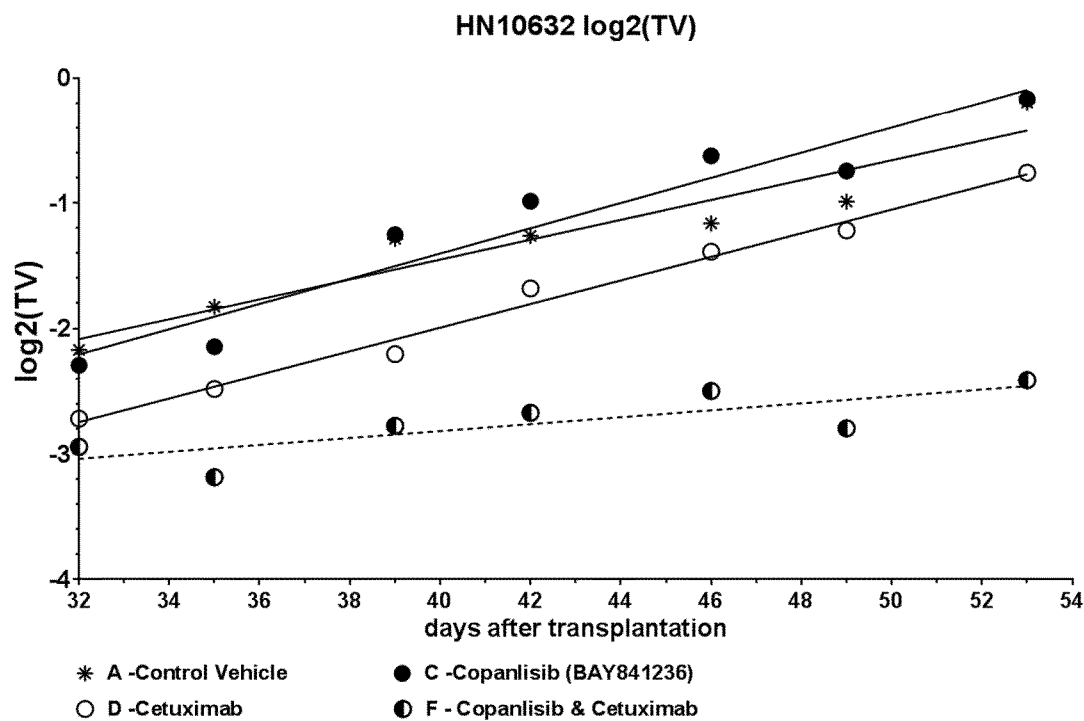


Figure 2: in vivo efficacy of treatment of HNSCC PDX model HN10632 (cetuximab resistant and PIK3CA wild type) with monotherapy of copanlisib and cetuximab respectively and combination thereof. Tumor growth expressed as Log₂ of tumor volume measured over treatment period

Fig 3.

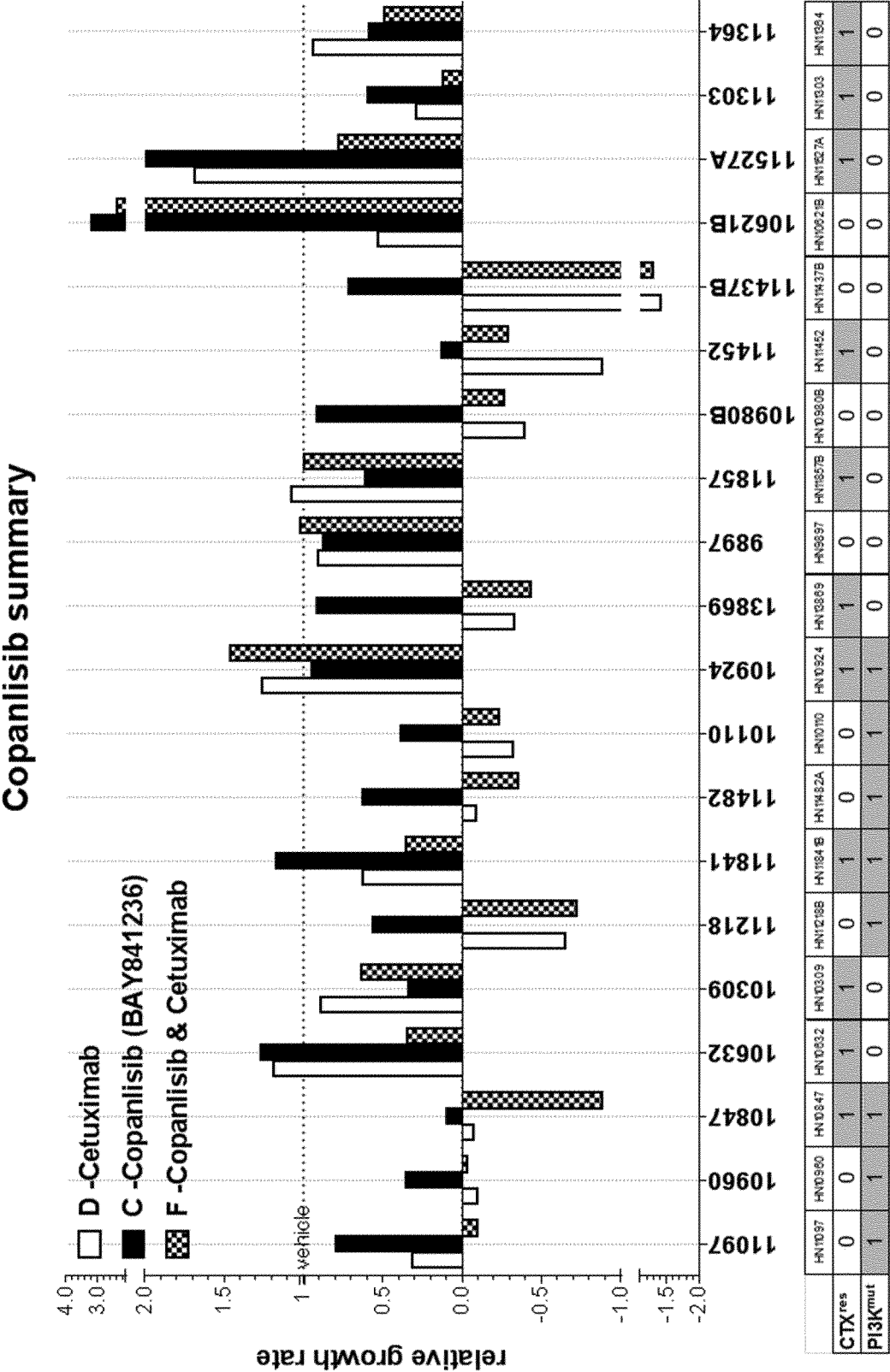


Figure 3: in vivo efficacy of treatment of HNSCC PDX models with monotherapy of copanlisib and cetuximab respectively and combination thereof in comparison to vehicle control. Treatment effects analysed as effects on relative growth rate of respective tumor models (5) (relGR =1 correspondes to same growth rate as vehicle control; $0 < \text{relGR} < 1$ = delay in tumor growth; $\text{relGR} < 0$ = tumor shrinkage)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/052873

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 A61K31/519 A61K31/5377 A61P35/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PAMELA MUNSTER ET AL: "Abstract A46: Inhibition of PIK3CA with BYL719 can overcome resistance to cetuximab in squamous cell carcinoma of the head and neck (SCCHN)", RESISTANCE MECHANISMS, 6 July 2015 (2015-07-06), pages A46-A46, XP055675611, DOI: 10.1158/1538-8514.PI3K14-A46 the whole document ----- -/--	1,14-19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 March 2020

Date of mailing of the international search report

07/04/2020

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Bergkemper, Victoria

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/052873

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anonymous: "Copanlisib in Association With Cetuximab in Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinomas Harboring a PI3KCA Mutation/Amplification and/or a PTEN Loss - Tabular View - ClinicalTrials.gov", 4 July 2016 (2016-07-04), XP055675522, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/show/record/NCT02822482 [retrieved on 2020-03-11] pages 2, 4	1-13, 18, 19
X	----- R GALOT ET AL: "Personalized biomarker-based treatment strategy for patients with squamous cell carcinoma of the head and neck: EORTC position and approach", ANNALS OF ONCOLOGY., vol. 29, no. 12, 11 October 2018 (2018-10-11), pages 2313-2327, XP055552478, NL ISSN: 0923-7534, DOI: 10.1093/annonc/mdy452 page 2320; table 4	1-13
X	----- US 2015/265616 A1 (CAPONIGRO GIORDANO [US] ET AL) 24 September 2015 (2015-09-24) paragraphs [0015] - [0020], [0038], [0064]; claims 1, 4	1, 14-19
X	----- WO 2008/070150 A1 (BAYER PHARMACEUTICALS CORP [US]; HENTEMANN MARTIN [US] ET AL.) 12 June 2008 (2008-06-12) cited in the application claims 28, 33, 43	1-9, 11, 12, 14-18
X	----- WO 2012/136553 A1 (BAYER PHARMA AG [DE]; PETERS JAN GEORG [DE] ET AL.) 11 October 2012 (2012-10-11) cited in the application page 53, lines 23-26; claims 10, 12-14	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2020/052873

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2015265616	A1	24-09-2015	AR 092045 A1 18-03-2015
			AU 2013299841 A1 12-02-2015
			BR 112015002384 A2 04-07-2017
			CA 2879548 A1 13-02-2014
			CL 2015000294 A1 08-05-2015
			CN 104519887 A 15-04-2015
			CO 7200273 A2 27-02-2015
			DK 2882440 T3 06-05-2019
			EA 201590332 A1 30-06-2015
			EC SP15008695 A 29-03-2019
			EP 2882440 A1 17-06-2015
			EP 3574904 A1 04-12-2019
			ES 2717911 T3 26-06-2019
			GT 201500025 A 28-09-2017
			HK 1204976 A1 11-12-2015
			HK 1211831 A1 03-06-2016
			HR P20190537 T1 28-06-2019
			HU E042877 T2 29-07-2019
			IL 236934 A 29-11-2018
			JP 6342396 B2 13-06-2018
			JP 6595024 B2 23-10-2019
			JP 2015524472 A 24-08-2015
			JP 2018109022 A 12-07-2018
			JP 2020019780 A 06-02-2020
			KR 20150040905 A 15-04-2015
			LT 2882440 T 25-04-2019
			MA 37829 A1 31-01-2017
			MX 359403 B 26-09-2018
			NZ 703940 A 27-04-2018
			PE 20150673 A1 20-05-2015
			PH 12015500246 A1 30-03-2015
			PL 2882440 T3 31-07-2019
			PT 2882440 T 23-04-2019
			SG 11201500321Y A 29-04-2015
			SI 2882440 T1 31-05-2019
			TN 2015000027 A1 29-06-2016
			TR 201904980 T4 21-05-2019
			TW 201410247 A 16-03-2014
			UA 115786 C2 26-12-2017
			US 2015265616 A1 24-09-2015
			WO 2014025688 A1 13-02-2014
WO 2008070150	A1	12-06-2008	AR 064106 A1 11-03-2009
			AU 2007328008 A1 12-06-2008
			BR PI0720178 A2 24-12-2013
			CA 2671614 A1 12-06-2008
			CL 2007003508 A1 04-07-2008
			CN 101631464 A 20-01-2010
			CN 105254634 A 20-01-2016
			CN 108774232 A 09-11-2018
			CO 6220908 A2 19-11-2010
			CR 10838 A 05-11-2009
			CU 20090103 A7 28-12-2011
			DK 2096919 T3 17-05-2016
			DO P2009000135 A 30-06-2009
			EA 200900733 A1 30-12-2009
			EC SP099387 A 30-11-2009
			EP 2096919 A1 09-09-2009

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2020/052873

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
		ES 2572189 T3	30-05-2016	
		GT 200900154 A	17-01-2012	
		HK 1217953 A1	27-01-2017	
		HN 2009001131 A	06-02-2012	
		HU E028773 T2	30-01-2017	
		IL 198273 A	30-07-2015	
		JO 3147 B1	20-09-2017	
		JP 5326092 B2	30-10-2013	
		JP 2010511718 A	15-04-2010	
		KR 20090096440 A	10-09-2009	
		MA 31283 B1	01-04-2010	
		MY 157944 A	30-08-2016	
		NO 342348 B1	07-05-2018	
		NZ 577342 A	12-01-2012	
		PA 8759601 A1	09-02-2009	
		PE 20081444 A1	29-11-2008	
		PL 2096919 T3	31-08-2016	
		SG 177170 A1	30-01-2012	
		SV 2009003288 A	02-10-2009	
		TN 2009000137 A1	18-10-2010	
		TW 200840582 A	16-10-2008	
		UA 96965 C2	26-12-2011	
		US RE46856 E	22-05-2018	
		US 2011083984 A1	14-04-2011	
		US 2013261113 A1	03-10-2013	
		UY 30761 A1	03-07-2008	
		WO 2008070150 A1	12-06-2008	
		ZA 200904691 B	29-09-2010	

WO 2012136553	A1	11-10-2012	AP 3709 A	31-05-2016
			AR 085718 A1	23-10-2013
			AU 2012238891 A1	24-10-2013
			BR 112013025549 A2	27-12-2016
			CA 2832123 A1	11-10-2012
			CL 2013002870 A1	20-06-2014
			CN 103649091 A	19-03-2014
			CO 6781534 A2	31-10-2013
			CR 20130511 A	04-12-2013
			CU 20130133 A7	29-01-2014
			CY 1116231 T1	08-02-2017
			DK 2694508 T3	16-02-2015
			DO P2013000223 A	15-11-2013
			EA 201391470 A1	31-03-2014
			EC SP13013006 A	31-12-2013
			EP 2508525 A1	10-10-2012
			EP 2694508 A1	12-02-2014
			ES 2529653 T3	24-02-2015
			GT 201300234 A	16-01-2015
			HK 1195907 A1	26-05-2017
			HR P20150138 T1	08-05-2015
			IL 228561 A	29-10-2015
			JO 2958 B1	15-03-2016
			JP 5763834 B2	12-08-2015
			JP 5826961 B2	02-12-2015
			JP 2014510119 A	24-04-2014
			JP 2015164936 A	17-09-2015
			KR 20140021637 A	20-02-2014
			MA 35014 B1	03-04-2014

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2020/052873

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		ME 02021 B	20-05-2015
		MX 336057 B	07-01-2016
		NZ 616198 A	25-09-2015
		PE 20141038 A1	05-09-2014
		PL 2694508 T3	30-04-2015
		PT 2694508 E	10-02-2015
		SG 193595 A1	30-10-2013
		SI 2694508 T1	31-03-2015
		SM T201500037 B	05-05-2015
		TN 2013000401 A1	30-03-2015
		TW 201249847 A	16-12-2012
		TW 201637656 A	01-11-2016
		UA 111604 C2	25-05-2016
		US 2014072529 A1	13-03-2014
		US 2016193219 A1	07-07-2016
		UY 33985 A	31-10-2012
		WO 2012136553 A1	11-10-2012
		ZA 201307105 B	26-11-2014
