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(54) Title: PHARMACEUTICAL COMBINATIONS FOR TREATING CANCER

(57) Abstract: The present invention relates to pharmaceutical combinations comprising a peptidic CXCR4 inhibitor and a phosphatidylinositol-3-kinase (PI3K) inhibitor for use in a method for the prevention, delay of progression or treatment of cancer.

WO 2023/285681 A1

PHARMACEUTICAL COMBINATIONS FOR TREATING CANCER

Field of the invention

The present invention relates to pharmaceutical combinations comprising a peptidic CXCR4 inhibitor and a phosphatidylinositol-3-kinase (PI3K) inhibitor and their use in a method for the prevention, delay of progression or treatment of cancer in a subject.

Background of the invention

Despite the ever increasing number of cancer therapies in general, and combination cancer therapies in particular, cancer is still the third most common cause of death worldwide after cardiovascular diseases and infectious/parasitic diseases; in absolute numbers, this corresponds to 7.6 million deaths (ca. 13% of all deaths) in any given year. The WHO estimates deaths due to cancer to increase to 13.1 million by 2030.

Chemotherapy interferes with cell replication or cell metabolism. Typical chemotherapeutic agents include alkylating agents, nucleotide analogues such as gemcitabine and capecitabine, platinum agents such as cisplatin or oxaliplatin, topoisomerase I inhibitors such as camptothecin or irinotecan, topoisomerase II inhibitors such doxorubicin or mitoxanthrone, vinca alkaloids such as vinorelbine, and modulators of tubulins such as taxanes (I. Ojima et al. *Exp. Opin. Ther. Patents* 2016, *26*, 1-20) and eribulin (U. Swami et al. *Mar. Drugs* 2015, *13*, 5016-5058). Chemotherapy can be effective, however, often there are severe side effects, e.g., vomiting, low white blood cells (WBC), loss of hair, loss of weight and other toxic effects. Because of the extremely toxic side effects, many cancer patients cannot successfully finish a complete chemotherapy therapy. Chemotherapy-induced side effects have a significant impact on the quality of life of patients affected by cancer and may dramatically influence individual compliance with treatment. Adverse side effects associated with chemotherapeutic agents are in many cases the major dose-limiting toxicity (DLT) in the administration of these drugs.

Emerging tumor resistance during or after chemotherapy (N. Vasan et al. *Nature* 2019, *575*, 299-309) and/or inadequate dosing due to dose-limitations in case of pre-existing or acquired

resistance are additional serious limitations of chemotherapeutic treatment. Combination therapy of two chemotherapeutics with different mechanism of action can alleviate the resistance problem only to a certain extent. For all these reasons there is a great need for effective treatments of cancer.

Administration of two or more drugs to treat a given condition, such as cancer, generally raises a number of potential problems due to complex *in vivo* interactions between drugs. The effects of any single drug are related to its absorption, distribution, and elimination. When two drugs are introduced into the body, each drug can affect the absorption, distribution, and elimination of the other and hence, alter the effects of the other. For instance, one drug may inhibit, activate or induce the production of enzymes involved in a metabolic route of elimination of the other drug. Thus, when two drugs are administered to treat the same condition, it is unpredictable whether each will complement, have no effect on, or interfere with, the therapeutic activity of the other in a subject. Not only may the interaction between two drugs affect the intended therapeutic activity of each drug, but the interaction may increase the levels of toxic metabolites. The interaction may also heighten or lessen the side effects of each drug. Hence, upon administration of two drugs to treat a disease, it is unpredictable what change, either deterioration or improvement, will occur in the side effect profile of each drug. Additionally, it is difficult to accurately predict when the effects of the interaction between the two drugs will become manifest. For example, metabolic interactions between drugs may become apparent upon the initial administration of the second drug, after the two have reached a steady-state concentration or upon discontinuation of one of the drugs. Therefore, the effects of a combination therapy of two or more drugs cannot be easily predicted. Nevertheless, there is a distinct need for new treatment modalities such as useful combination therapies for the treatment of cancer.

Summary of the invention

It has now unexpectedly been found that a combination comprising a peptidic CXCR4 inhibitor and a phosphatidylinositol-3-kinase (PI3K) inhibitor is useful for the prevention, delay of progression or treatment of cancer, in particular useful for the prevention, delay of progression or treatment of tumors of the hematopoietic and lymphoid tissues. In a cell-line model, it was unexpectedly found that treatment with said combination provides an increased anti-tumor effect above the effect of either agent alone.

Taking these unexpected findings into account, the inventors herewith provide the present invention in its following aspects.

In a first aspect the present invention provides a pharmaceutical combination comprising:
(a) a peptidic CXCR4 inhibitor;
(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and
(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers.

In a second aspect the present invention provides a pharmaceutical combination as described herein, for use as a medicament.

In a third aspect the present invention provides a pharmaceutical combination as described herein, for use in a method for the prevention, delay of progression or treatment of cancer in a subject.

In a fourth aspect the present invention provides kit of parts comprising a first container, a second container and a package insert, wherein the first container comprises at least one dose of a medicament comprising a peptidic CXCR4 inhibitor; the second container comprises at least one dose of a medicament comprising a phosphatidylinositol-3-kinase (PI3K) inhibitor, and the package insert comprises optionally instructions for treating a subject for cancer using the medicaments.

Brief description of the figures

Figure 1. Combination of the CXCR4 inhibitor POL5551 with PI3K inhibitor idelalisib. Anti-tumor activity of POL5551 was determined in parental lines and resistant lines (IDE-RES) to the PI3K inhibitor idelalisib (Idel). Parental and resistant lines were derived from the VL51 splenic marginal zone lymphoma model. Cells were exposed (72h) to increasing doses of idelalisib alone or in combination with increasing doses of POL5551 followed by MTT assay.

Figure 2. Combination of the CXCR4 inhibitor POL5551 with PI3K inhibitor copanlisib. Anti-tumor activity of POL5551 was determined in parental lines and resistant lines (COP-RES) to the PI3K inhibitor copanlisib (Copa). Parental and resistant lines were derived from the VL51 splenic marginal zone lymphoma model. Cells were exposed (72h) to increasing doses of copanlisib alone or in combination with increasing doses of POL5551 followed by MTT assay.

Figure 3. Combination of the CXCR4 inhibitor POL6326 with PI3K inhibitor idelalisibb. Anti-tumor activity of POL6326 was determined in parental lines and resistant lines (IDE-RES) to the PI3K inhibitor idelalisib (Idel). Parental and resistant lines were derived from the VL51 splenic marginal zone lymphoma model. Cells were exposed (72h) to increasing doses of idelalisib alone or in combination with increasing doses of POL6326 followed by MTT assay.

Figure 4. Combination of the CXCR4 inhibitor POL6326 with PI3K inhibitor copanlisib. Anti-tumor activity of POL6326 was determined in parental lines and resistant lines (COP-RES) to the PI3K inhibitor copanlisib (Copa). Parental and resistant lines were derived from the VL51 splenic marginal zone lymphoma model. Cells were exposed (72h) to increasing doses of copanlisib alone or in combination with increasing doses of POL6326 followed by MTT assay.

Figure 5. Combination with CXCR4 inhibitors overcomes resistance to PI3K inhibitor idelalisib**.** Addition of the CXCR4 inhibitors POL5551 (upper panel) and POL6326 (balixafortide, lower panel), respectively, overcome resistance to the PI3K inhibitor idelalisib (Idel). VL51 cells were exposed (72h) to increasing doses of idelalisib alone or in combination with increasing doses of POL5551/POL6326 followed by MTT assay.

Figure 6. Combination with CXCR4 inhibitors overcomes resistance to PI3K inhibitor copanlisib. Addition of the CXCR4 inhibitors POL5551 (upper panel) and POL6326 (balixafortide, lower panel), respectively, overcome resistance to the PI3K inhibitor copanlisib

(Copa). VL51 cells were exposed (72h) to increasing doses of copanlisib alone or in combination with increasing doses of POL5551/POL6326 followed by MTT assay.

Detailed description of the invention

For the purposes of interpreting this specification, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa. It is to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. The terms "comprising", "having", and "including" are to be construed as open-ended terms (i.e. meaning "including, but not limited to,") unless otherwise noted.

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

The terms "individual," "subject" or "patient" are used herein interchangeably. In certain embodiments, the subject is a mammal. Mammals include, but are not limited to primates (including human and non-human primates). In a preferred embodiment, the subject is a human.

The term "pharmaceutically acceptable diluents, excipients or carriers" as used herein refers to diluents, excipients or carriers that are suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio. "Diluents" are agents which are added to the bulk volume of the active agent making up the solid composition. As a result, the size of the solid composition increases, which makes it easier to handle. Diluents are convenient when the dose of drug per solid composition is low and the solid composition would otherwise be too small. "Excipients" can be binders, lubricants, glidants, coating additives or combinations thereof. Thus, excipients are intended to serve multiple purposes. "Carriers" can be solvents, suspending agents or vehicles, for delivering the instant compounds to a subject.

The term "dose" as used herein refers to the total amount of an active ingredient (e.g., the peptidic CXCR4 inhibitor or phosphatidylinositol-3-kinase (PI3K) inhibitor) to be taken each time by a subject (e.g. a human).

The term "objective response rate" (ORR) as used herein refers to the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period. Response duration usually is measured from the time of initial response until documented tumor progression. Generally, the FDA has defined ORR as the sum of partial responses plus complete responses. When defined in this manner, ORR is a direct measure of drug antitumor activity, which can be evaluated in a single-arm study. The ORR refers to the sum of complete response (CR) and partial response (PR).

The term "clinical benefit rate" (CBR) as used herein refers to the sum of complete response (CR), partial response (PR) and stable disease (SD) $\geq$6 months.

The term "complete response" (CR) as used herein in relation to target lesions refers to disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. The term complete response (CR) as used herein in relation to non-target lesions refers to disappearance of all non-target lesions and

normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

The term "partial response" (PR) as used herein in relation to target lesions refers to at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

The term "progressive disease" (PD) as used herein in relation to target lesions refers to at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progressions. The term progressive disease (PD) as used herein in relation to non-target lesions refers to appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

The term "stable disease" (SD) as used herein in relation to target lesions refers to neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

The term “progression-free survival” (PFS) as used herein relates to the duration of time from start of treatment to time of progression or death, whichever occurs first.

The terms "cancer" and "cancerous" as used herein refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. A "tumor" comprises one or more cancerous cells. Examples of cancer include, but are not limited to, tumors of the hematopoietic and lymphoid tissues such as e.g. small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia), hairy cell leukaemia, Burkitt lymphoma, marginal zone lymphoma (MZL), splenic marginal zone

lymphoma (SMZL), mantle cell lymphoma (MCL), follicle lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL).

The term "tumors of the hematopoietic and lymphoid tissues" which is equivalent to the term "tumours of the haematopoietic and lymphoid malignancies" and is synonymously used herein means tumors that affect the blood, bone marrow, lymph, and lymphatic system.

The term "mature B-cell neoplasm" as used herein refer to or describe biologically and clinically heterogeneous diseases of the B-lymphatic system. Mature B-cell neoplasms comprise over 90% of lymphoid neoplasms worldwide and there are 4% of new cancers each year. The most common types are follicular lymphoma (FL) and diffuse large B-cell lymphoma which make up 50% of the non-Hodgkin's lymphomas.

The terms " drug resistance", "cancer resistant to", "tumor resistant to" "tumor of the hematopoietic and lymphoid tissues resistant to" are used synonymously herein and refer to or describe a well-known phenomenon that results when cancers become tolerant to pharmaceutical treatments. Cancer drug resistance is a complex phenomenon that is influenced by drug inactivation, drug target alteration, drug efflux, DNA damage repair, cell death inhibition, epithelial–mesenchymal transition (EMT), inherent cell heterogeneity, epigenetic effects, or any combination of these mechanisms (G. Housman, et al. *Cancers* 2014, *6*, 1769-1792; doi:10.3390/cancers6031769). Cases of primary and secondary resistance to PI3K inhibitors have emerged and usually resulted in a poor prognosis. The terms "resistant to at least one treatment with a PI3K inhibitor" and "refractory to at least one treatment with a PI3K inhibitor" are used synonymously herein.

The term "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that it possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid,

cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, citric acid, benzoic acid, 3-(4-hydroxy-benzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e. g. an alkaline metal ion, an alkaline earth metal ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

The term "about" as used herein refers to +/- 10% of a given measurement.

Thus, in a first aspect the present invention provides a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers.

Peptidic CXCR4 inhibitors

The term "peptidic CXCR4 inhibitor" as used herein refers to a compound that binds to the CXCR4 receptor and generally antagonizes ligand (CXCL12)-induced signaling and can also act as an inverse agonist or a partial agonist of the CXCR4 receptor (W. Zhang et al., *J Biol Chem.* 2002, *277*(27), 24515-24521).

In one embodiment the peptidic CXCR4 inhibitor is a backbone cyclized peptidic CXCR4 inhibitor.

In a further embodiment the peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues.

In a preferred embodiment the peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Xaa^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^3 is Ala; Tyr; or Tyr(Me);

Xaa^6 is Ala or Acc;

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^\omega$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues; and

wherein the compound of formula Ia has a disulfide bond between Cys^4 and Cys^{11}.

In a more preferred embodiment the peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^{1}-His^{2}-Xaa^{3}-Cys^{4}-Ser^{5}-Xaa^{6}-Xaa^{7}-Xaa^{8}-Arg^{9}-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^{3} is Tyr; or Tyr(Me);

Xaa^{6} is Ala or Acc;

Xaa^{7} is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^{8} is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues; and

wherein the compound of formula Ia has a disulfide bond between Cys^{4} and Cys^{11}.

In an even more preferred embodiment the peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Ala^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(I),

in which

Xaa^3 is Ala; Tyr; or Tyr(Me);

Xaa^7 is ^{D}Pro ; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^\omega$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and wherein the peptidic CXCR4 inhibitor has a disulfide bond between Cys^4 and Cys^{11}.

In a particular preferred embodiment the peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Ala^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(I),

in which

Xaa^3 is Tyr; or Tyr(Me);

Xaa^7 is ^{D}Pro ; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N^{ω}-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and wherein the peptidic CXCR4 inhibitor has a disulfide bond between Cys^{4} and Cys^{11}.

In a more particular preferred embodiment the peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, selected from the group consisting of

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-)

having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-)

having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Lys(iPr)-Pro-)

having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:3**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)

having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:4**),

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Tyr-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)

having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:5**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)

having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:6**),

cyclo(-Tyr-His-Tyr(Me)-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)

having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:7**),

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Tyr(Me)-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)

having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:8**),
cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Tyr-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)
having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:9**),
cyclo(-Tyr-His-Tyr(Me)-Cys-Ser-Ala-^{D}Tyr(Me)-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)
having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:10**),
cyclo(-Tyr-His-Tyr-Cys-Ser-Acc-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)
having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:11**),
or pharmaceutically acceptable salts thereof.

In an even more particular preferred embodiment the peptidic CXCR4 inhibitor is selected from the group consisting of cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:1**), and cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:2**), or pharmaceutically acceptable salts thereof.

In the most particular preferred embodiment the peptidic CXCR4 inhibitor is cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:2**), or pharmaceutically acceptable salts thereof.

Cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:1**), is also referred as POL6326 herein or balixafortide. POL6326 is a cyclic synthetic peptide consisting of 16 amino acids and an antagonist of the highly conserved chemokine receptor CXCR4. In vitro receptor binding studies demonstrated a significant affinity of POL6326 for the human CXCR4 receptor, as well as a general lack of significant binding to other potential target receptors.
Particularly suitable pharmaceutically acceptable salts of the peptidic CXCR4 inhibitor to be useful in the context of the present invention include the acetates, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid,

suberic acid, azelaic acid, malic acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4-methyl-benzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid.

Phosphatidylinositol-3-kinase (PI3K) inhibitors

The phosphatidylinositol-3-kinase (PI3K) family of enzymes is grouped in three main classes, I, II, and III, which differ in structure and substrate specificity and exhibit non-redundant functions.

Class I heterodimeric PI3Ks are further subdivided in class IA and class IB, depending on the structure of regulatory and catalytic subunits and are involved in antigen and receptor signaling. Class IA PI3K comprise the regulatory subunit p85 (or its splice variants p55 and p50) and the distinct catalytic subunits p110α, p110β and p110δ. The class IB PI3K, are composed of the p110γ catalytic subunit and form heterodimers with the regulatory subunits p84 or p101 (S. Jean and A. A. Kiger, *J. Cell Sci.* 2014, *127*, 923-928; J. Yang et al., *Mol. Cancer* 2019, *18*, 26). PI3Kα and PI3Kβ have ubiquitous expression. PI3Kδ and PI3Kγ, however, are primarilly expressed in hematopoietic cells (highlighting their role in leukocyte-mediated diseases) beside cardiomyocytes, fibroblasts, and smooth muscle cells. PI3Kδ inhibtion has been shown to relax human airway smooth muscle cells (E. Jabbour et al., *Haematologica* 2014, *99 (1)*, 7-18; M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814; C. J. Koziol-White et al. *Br. J. Pharmacol.* 2016, *173*, 2726-2738).

Class I PI3Ks are part of PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway, which plays an important role in regulating gene transcription, protein synthesis, cell growth and motility. These PI3Ks transduce upstream signals from (receptor) tyrosine kinases, the B-

cell receptor, or G-protein coupled receptors by phosphorylation of phosphatidylinositol-4,5-diphosphate (PIP_2) into phosphatidylinositol-3,4,5-triphosphate (PIP_3). PIP_3 molecules then recruit the kinase AKT which controls, among others, the mTOR pathway. PI3K is negatively regulated by the phosphatase and tensin homolog (PTEN) (V. Sapon-Cousineau et al., *Curr. Treat. Options in Oncol*. 2020, *21*, 51).

The PI3K/Akt/mTOR pathway is dysregulated almost in all human cancers including solid tumors and hematologic malignancies. In B-cell malignancies like chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) the tonic activation of the B-cell receptor results in continuous activity of PI3Kδ. Therefore, PI3Kδ has become an important therapeutic target for B-cell malignancies (V. Sapon-Cousineau et al., *Curr. Treat. Options in Oncol*. 2020, *21*, 51).

The term "phosphatidylinositol-3-kinase (PI3K) inhibitor" as used herein relates to structurally diverse compounds which target one or several class I PI3K subtypes, or target class I PI3K and other components of the PI3K/Akt/mTOR signaling pathway like for example mTOR.

Based on their target engagement, four categories of PI3K inhibitors can be distinguished:

i. Pan-PI3K inhibitors targeting PI3Kα, PI3Kβ, PI3Kγ and/or PI3Kδ
ii. Isoform-selective PI3K inhibitors
iii. Dual PI3K/mTOR inhibitors
iv. Multikinase inhibitors acting on PI3K and further kinase(s)

Pan-PI3K inhibitors as well as isoform-selective inhibitors have been used to produce various approved chemotherapy drugs and are, as well as dual PI3K/mTOR inhibitors and other multikinase inhibitors with a PI3K component, under clinical evaluation comprising oncology indications as well as respiratory, immunodefiency, inflammatory and autoimmune conditions (M. W. D. Perry et al., *J. Med. Chem.* **2019**, *62*, 4783-4814).

The most well known PI3K inhibitors include Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202) and Alpelisib

(Piqray™, BYL719) which belong to the group of isoform-selective PI3K inhibitors as well as Copanlisib (Aliqopa™, BAY 80-6946) which belongs to the group of pan-PI3K inhibitors.

In one embodiment the PI3K inhibitor is selected from the group consisting of pan-PI3K inhibitors, isoform-selective PI3K inhibitors, dual PI3K/mTOR inhibitors, multikinase inhibitors acting on PI3K and further kinase(s) and PI3K inhibitors with undisclosed target selectivity.

In a particular embodiment the PI3K inhibitor is selected from the group consisting of pan-PI3K inhibitors and isoform-selective PI3K inhibitors, preferably selected from the group consisting of pan-PI3K inhibitors and isoform-selective PI3K inhibitors, wherein the isoform-selective PI3K inhibitors are targeting selectively the PI3Kδ- or PI3Kγ/δ enzyme isoforms.

The group of pan-PI3K inhibitors consists of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866) and TG100-115.

The group of isoform-selective PI3K inhibitors consists of Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244 , Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, Alpelisib (Piqray™, BYL719), Serabelisib (MLN1117, INK1117, TAK-117), CYH33, GDC-0326, WX-037, GSK2636771, SAR-260301, AZD-8835, AZD-8186, KA2237 and VT30.

The group of dual PI3K/mTOR inhibitors consists of Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, and PKI-179.

The group of multikinase inhibitors acting on PI3K and further kinase(s) consists of Puquitinib (XC-302), Fimepinostat (CUDC-907), Rigosertib (ON-01910) and BR101801.

The group of PI3K inhibitors with undisclosed target selectivity consists of HEC89736, CHF-6523 and TL117.

In a preferred embodiment the PI3K inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, Alpelisib (Piqray™, BYL719), Serabelisib (MLN1117, INK1117, TAK-117), CYH33, GDC-0326, WX-037, GSK2636771, SAR-260301, AZD-8835, AZD-8186, KA2237, VT30, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302), Fimepinostat (CUDC-907), Rigosertib (ON-01910), BR101801, HEC89736, CHF-6523 and TL117.

In a more preferred embodiment, the PI3K inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-

8835, AZD-8186, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302) and Fimepinostat (CUDC-907).

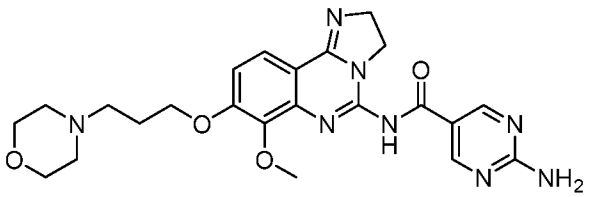
In an even more preferred embodiment, the PI3K inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Taselisib (GDC-0032), Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Puquitinib (XC-302) and Fimepinostat (CUDC-907) .

In a particular embodiment, the PI3K inhibitor is selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Leniolisib (CDZ173-NX), Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120) and Taselisib (GDC-0032).

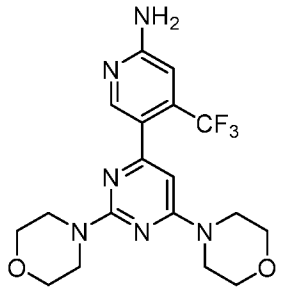
In a more particular embodiment, the PI3K inhibitor is selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202) and Copanlisib (Aliqopa™, BAY 80-6946).

In the most particular embodiment the PI3K inhibitor is selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101) and Copanlisib (Aliqopa™, BAY 80-6946).

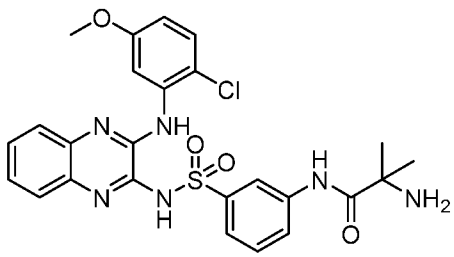
Copanlisib (Aliqopa™, BAY 80-6946) is a pan-PI3K inhibitor (preferential activity against PI3Kα and PI3Kδ) which is described in N. Liu et al., *Mol. Cancer Ther.* 2013, *12 (11)*, 2319- 2330 and R. R. Yadav et al., *Eur. J. Med. Chem.* 2016, *122*, 731-743, and is represented by the structural formula indicated below:



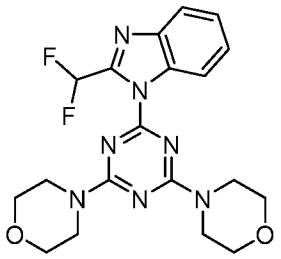
Buparlisib (BKM-120), a pan-PI3K inhibitor, is described in M. C. deGooijer et al., *Sci. Rep.* 2018, *8*, 10784 and G. W. Rewcastle et al., *Oncotarget* 2017, *8*, 47725-47740 https://doi.org/10.18632/oncotarget.17730, and is represented by the structural formula indicated below:



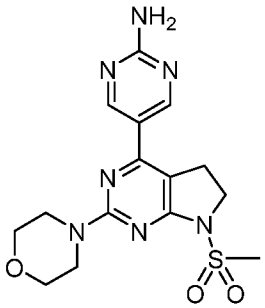
Pilaralisib (XL-147), a pan-PI3K inhibitor, is described in SciFinder (CAS Registry Nr 934526-89-3) and P. Foster et al., *Mol. Cancer Ther.* 2015, *14*, 931-940, and is represented by the structural formula indicated below:



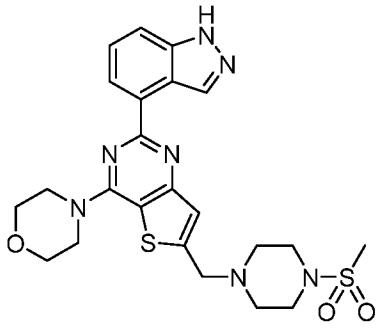
ZSTK474, a pan-PI3K inhibitor, is described in D. Kong et al., *Biol. Pharm. Bull.* 2009, *32 (2)*, 297-300 and G. W. Rewcastle et al., *Oncotarget* 2017, *8*, 47725-47740, https://doi.org/10.18632/oncotarget.17730, and is represented by the structural formula indicated below:



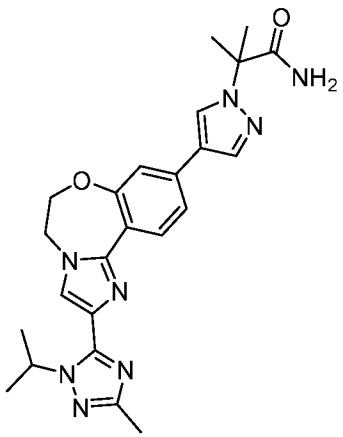
CH5132799 (MEN 1611), a pan-PI3K inhibitor, is described in J. Ohwada et al., *Bioorg. Med. Chem. Lett.* 2011, *21*, 1767-1772, and is represented by the structural formula indicated below:



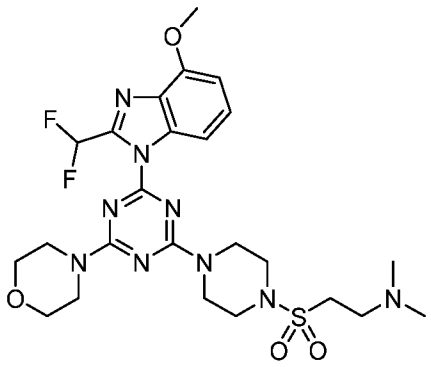
Pictilisib (GDC-0941), a pan-PI3K inhibitor, is described in A. J. Folkes et al., *J. Med. Chem.* 2008, *51*, 5522-5532 and G. W. Rewcastle et al., *Oncotarget* 2017, *8*, 47725-47740 https://doi.org/10.18632/oncotarget.17730, and is represented by the structural formula indicated below:



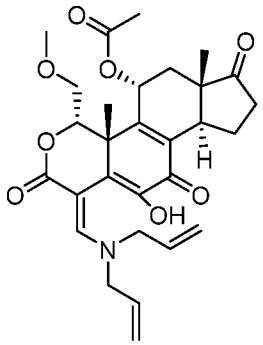
Taselisib (GDC-0032), a pan-PI3K inhibitor, is described in T. P. Heffron et al., *J. Med. Chem.* 2016, *59*, 985-1002 and R. R. Yadav et al., *Eur. J. Med. Chem.* 2016, *122*, 731-743, and is represented by the structural formula indicated below:



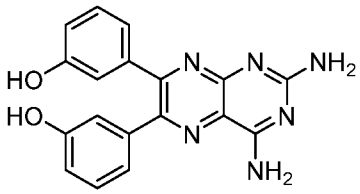
SN32976, a pan-PI3K inhibitor, is described in G. W. Rewcastle et al., *Oncotarget* 2017, *8*, 47725-47740 https://doi.org/10.18632/oncotarget.17730, and is represented by the structural formula indicated below:



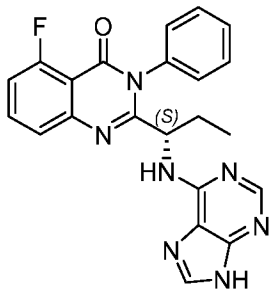
Sonolisib (PX-866), a Wortmannin analogue, is a pan-PI3K inhibitor which is described in N. T. Ihle et al., *Mol. Cancer Ther.* 2004, *3 (7)*, 763-772, and is represented by the structural formula indicated below:



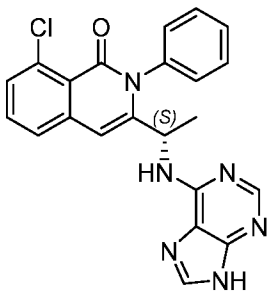
TG100-115, a pan-PI3K inhibitor, is described in Y. Liu et al., *Mol. Med. Rep.* 2013, *8*, 1305-1310, and is represented by the structural formula indicated below:



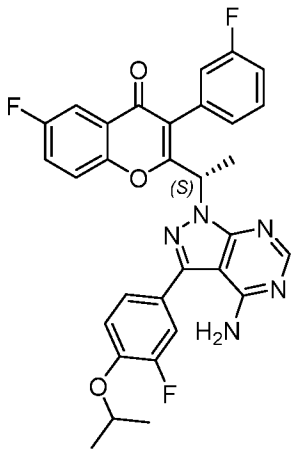
Idelalisib (Zydelig™, GS-1101, CAL-101), is a PI3Kδ-selective inhibitor which is described in M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814 and B. J. Lannutti et al., *Blood* 2011, *117 (2)*, 591-594, and is represented by the structural formula indicated below:



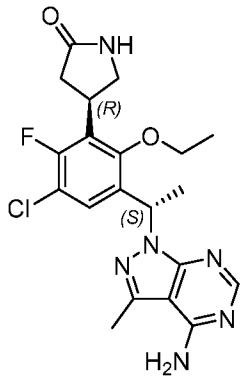
Duvelisib (Copiktra™, IPI-145, INK-1197) is a PI3Kδ/γ-selective inhibitor which is described in SciFinder (CAS Registry Nr 1201438-56-3) and M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814, and is represented by the structural formula indicated below:



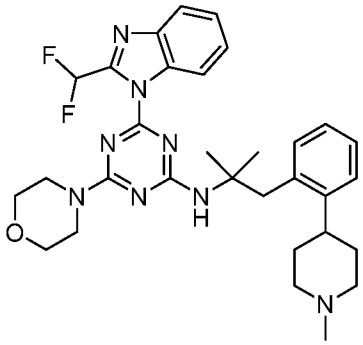
Umbralisib (Ukoniq™, RP5264, TGR-1202) is a PI3Kδ-selective inhibitor which is described in M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814 and H. A. Burris III et al., *Lancet Oncol.* 2018, *19*, 486-496, and is represented by the structural formula indicated below:



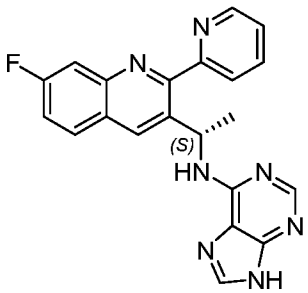
Parsaclisib (INCB050465), a highly PI3Kδ-selective inhibitor, is described in SciFinder (CAS Registry Nr 1426698-88-5) and M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814, and is represented by the structural formula indicated below:



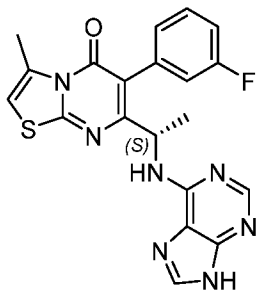
Zandelisib (ME-401, PWT-143), a PI3Kδ-selective inhibitor, is described in SciFinder (CAS Registry Nr 1401436-95-0), and is represented by the structural formula indicated below:



AMG319 (ACP319), a PI3Kδ-selective inhibitor, is described in SciFinder (CAS Registry Nr 1608125-21-8) and M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814 and is represented by the structural formula indicated below:

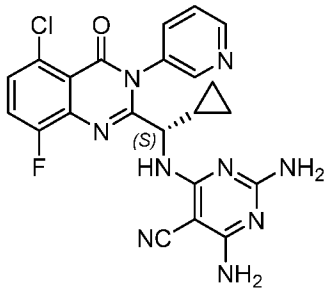


Dezapelisib (INCB040093), a PI3Kδ-selective inhibitor, is described in SciFinder (CAS Registry Nr 1262440-25-4) and M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814, and is represented by the structural formula indicated below:

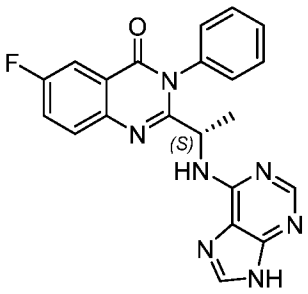


HMPL-689 (Hutchinsson China MediTech) is a PI3Kδ-selective inhibitor and is discussed in M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814.

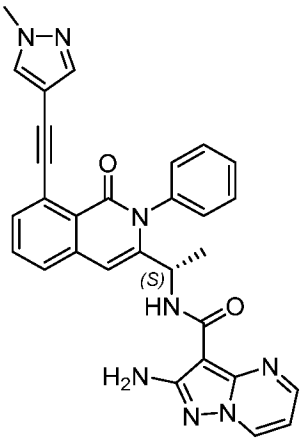
GS9901, a PI3Kδ-selective inhibitor, is described in M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814, and is represented by the structural formula indicated below:



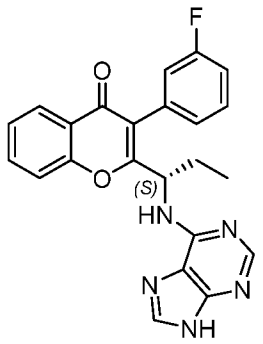
Acalisib (GS-9820), a PI3Kδ-selective inhibitor, is described in M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814 and X. X. Peng et al., *RCS Adv.* 2017, *7*, 56344-56358, and is represented by the structural formula indicated below:



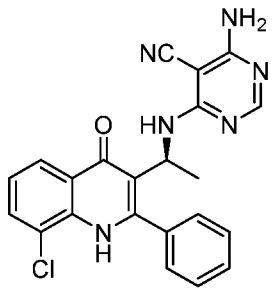
Eganelisib (IPI-549), a PI3Kγ-selective inhibitor, is described in SciFinder (CAS Registry Nr 1693758-51-8) and M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814, and is represented by the structural formula indicated below:



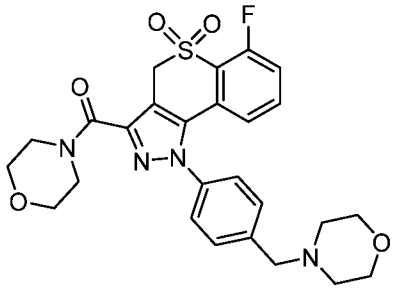
Tenalisib (RP6530), a PI3Kδ/γ-selective inhibitor, is described in SciFinder (CAS Registry Nr 1639417-53-0) and M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814, and is represented by the structural formula indicated below:



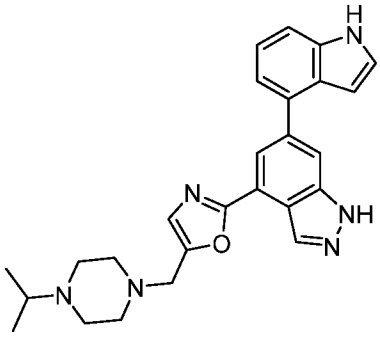
SHC014748M (SH748), a PI3Kδ-selective inhibitor, is described in L. Fan et al., *Neoplasia* 2020, *22 (12)*, 714-724, and is represented by the structural formula indicated below:



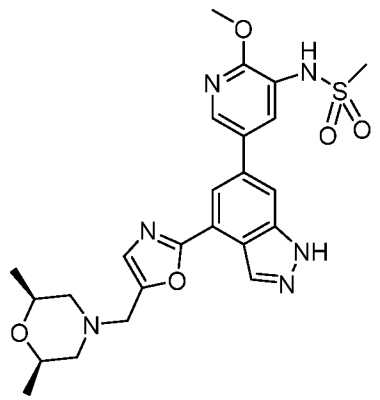
IOA244, a PI3Kδ-selective inhibitor, is described in A. MacQueen et al, AACR 2020, Virtual Annual Meeting II, June 22-24, 2020, Poster #666 and in Z. Johnson et al., *Annals of Oncology*, 2019, *30*, suppl. 7, vii27 (doi.org/10.1093/annonc/mdz413.097), and is represented by the structural formula indicated below:



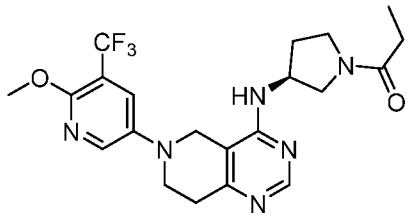
Nemiralisib (GSK-2269557), a PI3Kδ-selective inhibitor, is described in M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814 and X. X. Peng et al., *RCS Adv.* 2017, *7*, 56344-56358, and is represented by the structural formula indicated below:



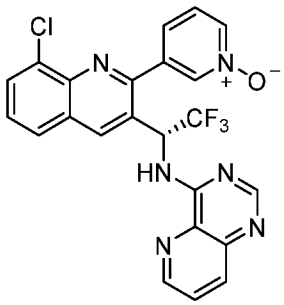
GSK2292767, a PI3Kδ-selective inhibitor, is described in SciFinder (CAS Registry Nr 1254036-66-2) and M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814, and is represented by the structural formula indicated below:



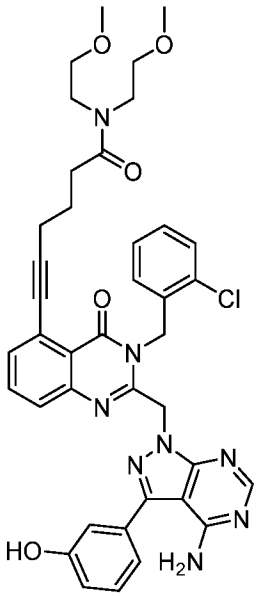
Leniolisib (CDZ173-NX), a PI3Kδ-selective inhibitor, is described in SciFinder (CAS Registry Nr 1354690-24-6) and M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814, and is represented by the structural formula indicated below:



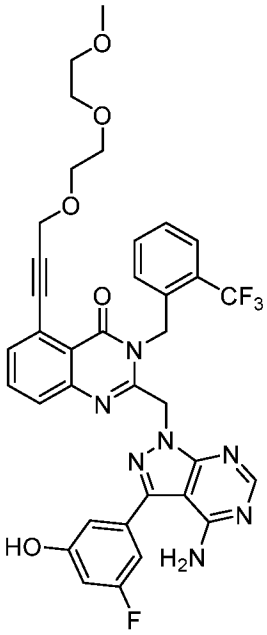
Seletalisib, a PI3Kδ-selective inhibitor, is described in SciFinder (CAS Registry Nr 1362850-20-1) and M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814, and is represented by the structural formula indicated below:



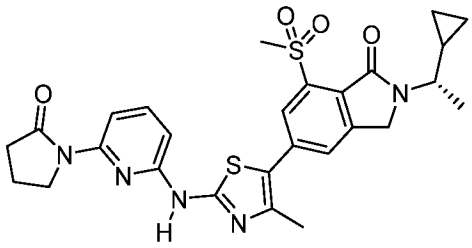
RV1729, a PI3Kδ/γ-selective inhibitor, is described in SciFinder (CAS Registry Nr 1293915-42-0) and M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814, and is represented by the structural formula indicated below:



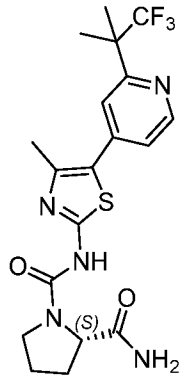
RV6153, a PI3Kδ/γ-selective inhibitor, is described in M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814, and is represented by the structural formula indicated below:



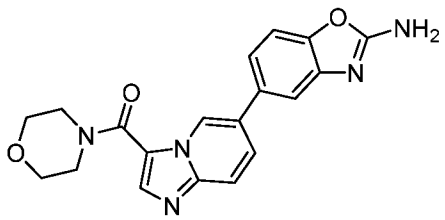
AZD8154, a PI3Kδ/γ-selective inhibitor, is described in M. W. D. Perry et al., *J. Med. Chem.* 2019, *62*, 4783-4814, M. W. D. Perry et al., *J. Med. Chem.* 2021, *64,* 8053-8075 and SciFinder (CAS Registry Nr 2215022-45-8), and is represented by the structural formula indicated below:



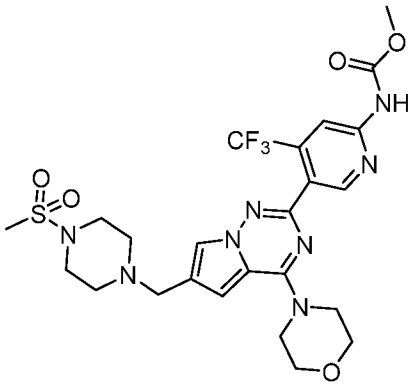
Alpelisib (Piqray™, BYL719) is a PI3Kα-selective inhibitor which is described in SciFinder (CAS Registry Nr 1217486-61-7) and H.-Y. Xiang et al. *Eur. J. Med. Chem.* 2021, *209*, 112913, and is represented by the structural formula indicated below:



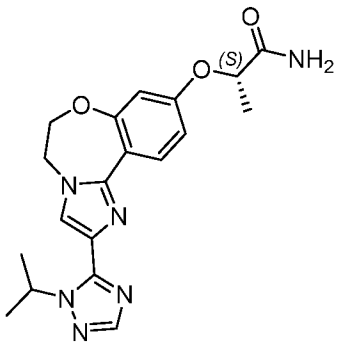
Serabelisib (MLN1117, INK1117, TAK-117), a PI3Kα-selective inhibitor, is described in SciFinder (CAS Registry Nr 1268454-23-4) and H.-Y. Xiang et al. *Eur. J. Med. Chem.* 2021, *209*, 112913, and R. R. Yadav et al., *Eur. J. Med. Chem.* 2016, *122*, 731-743, and is represented by the structural formula indicated below:



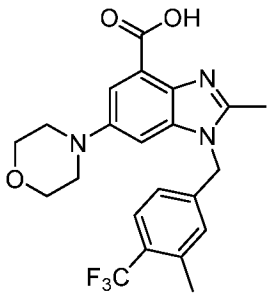
CYH33, a PI3Kα-selective inhibitor, is described in H.-Y. Xiang et al. *Eur. J. Med. Chem.* 2021, *209*, 112913 and SciFinder (CAS Registry Nr 1494684-28-4), and is represented by the structural formula indicated below:



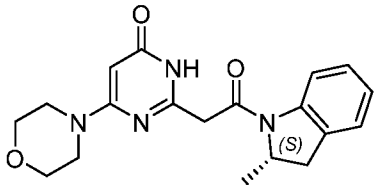
GDC-0326, a PI3Kα-selective inhibitor, is described in T. P. Heffron et al., *J. Med. Chem.* 2016, *59*, 985-1002 and H.-Y. Xiang et al. *Eur. J. Med. Chem.* 2021, *209*, 112913, and is represented by the structural formula indicated below:



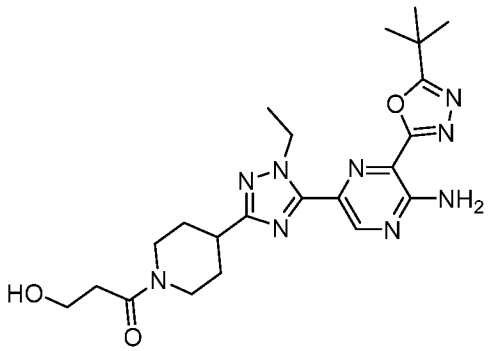
GSK2636771, a PI3Kβ-selective inhibitor, is described in SciFinder (CAS Registry Nr 1421958-41-9) and is represented by the structural formula indicated below:



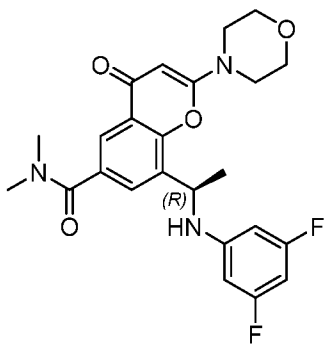
SAR-260301, a PI3Kβ-selective inhibitor, is described in V. Certal et al., *J. Med. Chem*. 2014, *57*, 903-920 and SciFinder (CAS Registry Nr 1260612-13-2), and is represented by the structural formula indicated below:



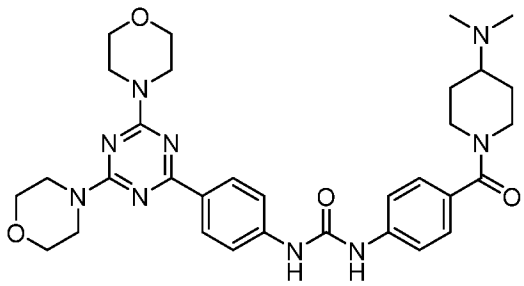
AZD-8835, a PI3Kα/δ-selective inhibitor, is described in K. Hudson et al., *Mol. Cancer Ther.* 2016, *15*, 877-889, doi:10.1158/1535-7163.MCT-15-0687 and SciFinder (CAS Registry Nr 1620576-64-8), and is represented by the structural formula indicated below:



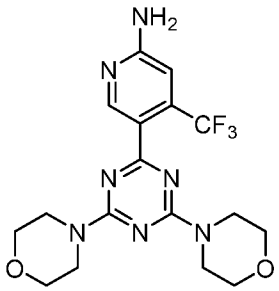
AZD-8186, a PI3Kβ/δ-selective inhibitor, is described in SciFinder (CAS Registry Nr 1627494-13-6), and U. Hancox et al., *Mol. Cancer Ther.* 2015, *14*, 48-58, and is represented by the structural formula indicated below:



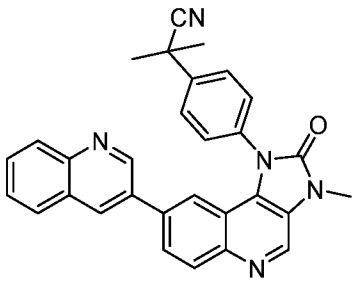
Gedatolisib (PF-05212384, PKI-587) is a dual PI3K/mTOR inhibitor which is described in A. M. Venkatesan et al., *J. Med. Chem.* 2010, *53*, 2636-2645 and L. Mologni et al., *Cancers* 2021, *13*, 119, and is represented by the structural formula indicated below:



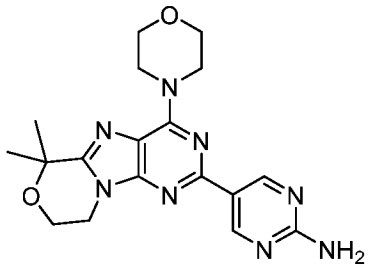
Bimiralisib (PQR309), a dual PI3K/mTOR inhibitor, is described in F. Beaufils et al., *J. Med. Chem.* 2017, *60*, 7524-7538 and L. Mologni et al., *Cancers* 2021, *13*, 119, and is represented by the structural formula indicated below:



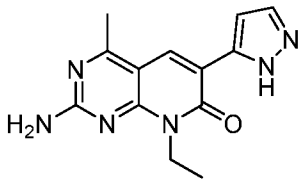
Dactolisib (BEZ235, NVP-BEZ235), a dual PI3K/mTOR inhibitor, is described in L. Mologni et al., *Cancers* 2021, *13*, 119 and G. W. Rewcastle et al., *Oncotarget* 2017, *8*, 47725-47740 https://doi.org/10.18632/oncotarget.17730 and A. Martorana et al., *Molecules* 2020, *25*, 4279; doi:10.3390/molecules25184279 and SciFinder (CAS Registry Nr 915019-65-7), and is represented by the structural formula indicated below:



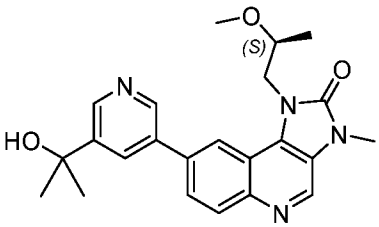
Paxalisib (GDC-0084), a dual PI3K/mTOR inhibitor, is described in T. P. Heffron et al., *ACS Med. Chem. Lett.* 2016, *7*, 351-356, and is represented by the structural formula indicated below:



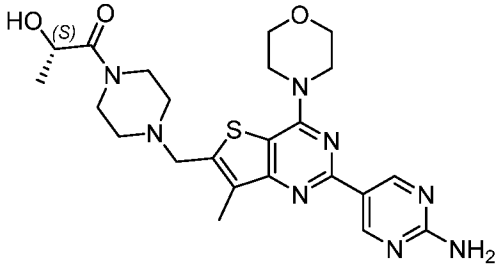
Voxtalisib (XL765, SAR245409), a dual PI3K/mTOR inhibitor, is described in SciFinder (CAS Registry Nr 934493-76-2) and P. Yu et al., *Mol. Cancer Ther.* 2014, *13*, 1078-1091, and is represented by the structural formula indicated below:



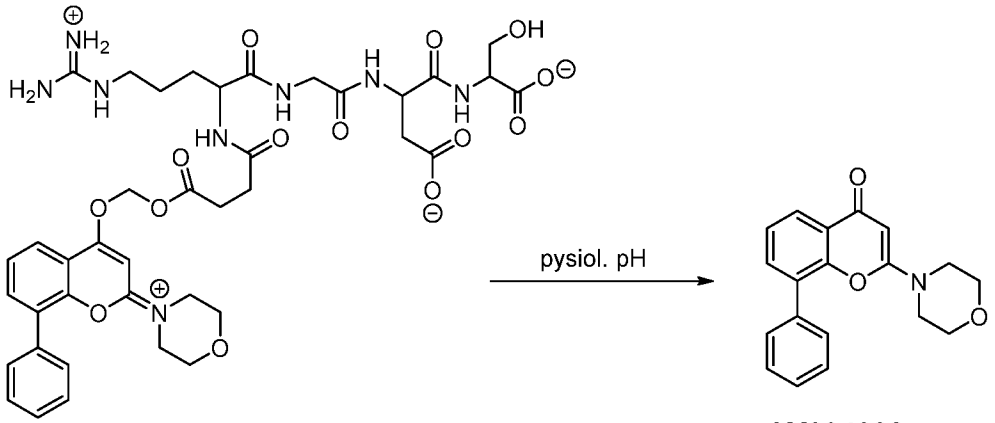
Samotolisib (LY3023414), a dual PI3K/mTOR inhibitor, is described in M. C. Smith et al., *Mol. Cancer Ther.* 2016, *15*, 2344-2356 and A. Martorana et al., *Molecules* 2020, *25*, 4279, doi:10.3390/molecules25184279, and is represented by the structural formula indicated below:



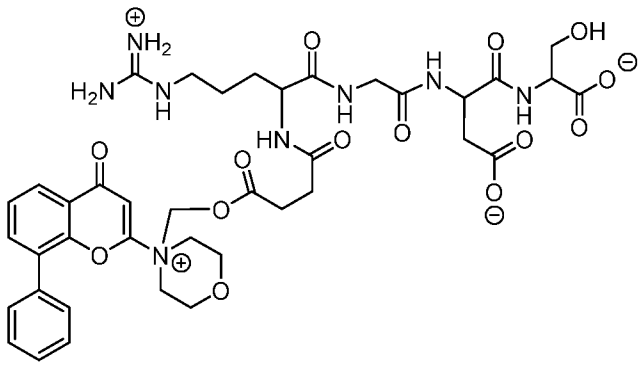
Apitolisib (GDC-0980), a dual PI3K/mTOR inhibitor, is described in J. J. Wallin et al., *Mol. Cancer Ther.* 2011, *10*, 2426-2436, and is represented by the structural formula indicated below:



SF1126 is a prodrug releasing under physiological pH the pan-PI3K/mTOR inhibitor LY294002. It is described in P. De et al., *Cancer Chemother. Pharmacol.* 2013, *71 (4)*, 867-881, doi:10.1007/s00280-013-2078-0 and J. R. Garlich et al., *Cancer Res.* 2008, *68 (1)*, 206- 215, and is represented by the structural formula indicated below:

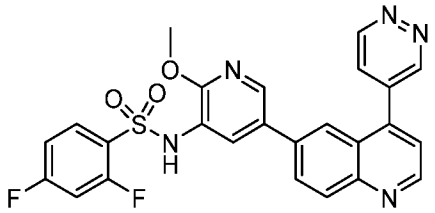


SF1126 **LY294002**

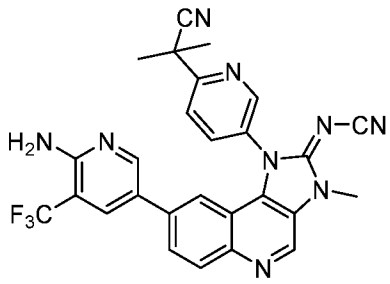


Omipalisib (GSK2126458, GSK458) is a dual PI3K/mTOR inhibitor which is described in S. D. Knight et al., *ACS Med. Chem. Lett.* 2010, *1*, 39-43 and G. W. Rewcastle et al., *Oncotarget* 2017,

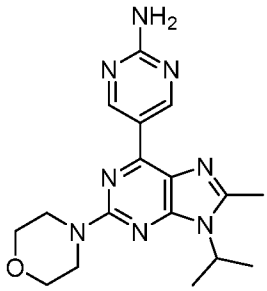
8, 47725-47740, https://doi.org/10.18632/oncotarget.17730, and is represented by the structural formula indicated below:



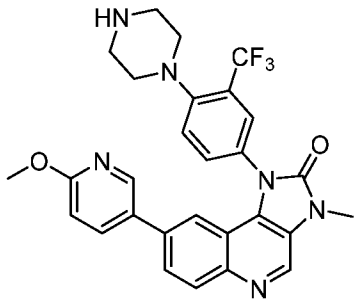
Panulisib (P7170), a dual PI3K/mTOR inhibitor, is described in A. Jalota-Badhwar et al., *Mol. Cancer Ther.* 2015, *14*, 1095-1106 and A. Martorana et al., *Molecules* 2020, *25*, 4279, doi:10.3390/molecules25184279, and is represented by the structural formula indicated below:



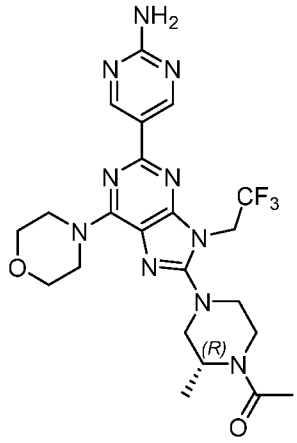
VS-5584 (SB2343), a dual PI3K/mTOR inhibitor, is described in S. Hart et al., *Mol. Cancer Ther.* 2013, *12*, 151-161, and is represented by the structural formula indicated below:



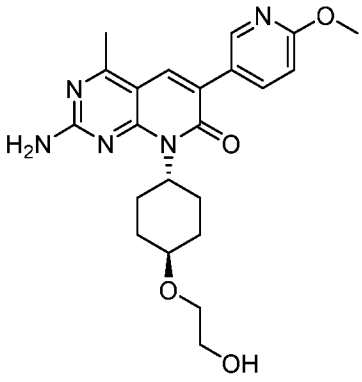
BGT-226 (NVP-BGT226), a dual PI3K/mTOR inhibitor, is described in A. Martorana et al., *Molecules* 2020, *25*, 4279; doi:10.3390/molecules25184279, and is represented by the structural formula indicated below:



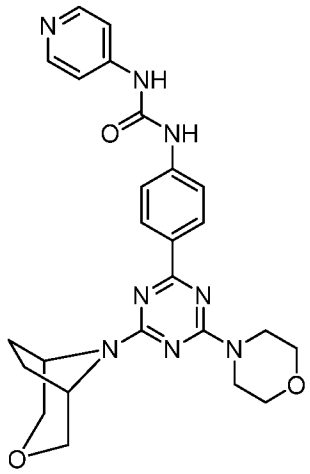
DS-7423, a dual PI3K/mTOR inhibitor, is described in D. Koul et al., *Oncotarget* 2017, *8 (13)*, 21741-21753 and is represented by the structural formula indicated below:



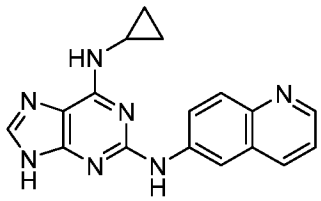
PF-04691502, a dual PI3K/mTOR inhibitor, is described in J. Yuan et al., *Mol. Cancer Ther.* 2011, *10 (11)*, 2189-2199, and is represented by the structural formula indicated below:



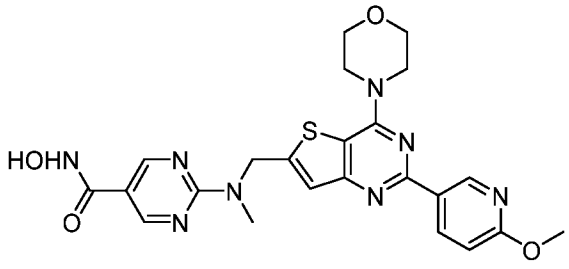
PKI-179, a dual PI3K/mTOR inhibitor, is described in A. M. Venkatesan et al., *Bioorg. Med. Chem. Lett.* 2010, *20*, 5869-5873, and is represented by the structural formula indicated below:



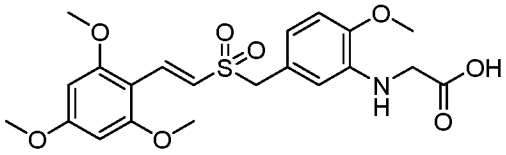
Puquitinib (XC-302) is an isoform-selective PI3Kδ inhibitor which also inhbits AKT phosphorylation mediated by EGFR and the receptor tyrosine kinases KDR and PDGFR. The compound is described in C. Xie et al., *Cancer Sci*. 2017, *108 (7)*, 1476-1484 and H. Yang et al., *Oncotarget* 2015, *6 (41)*, 44049- 44056, and is represented by the structural formula indicated below:



Fimepinostat (CUDC-907) is a dual HDAC/PI3K inhibitor which is described in K. Sun et al., *Mol. Cancer Ther.* 2017, *16 (2)*, 285-299, and is represented by the structural formula indicated below:



Rigosertib (ON-01910) is a multikinase inhibitor capable to bind PI3Kα and β beside other kinases and is described in M. Jost et al., *Mol. Cell* 2017, *68 (1)*, 210 – 223.e.6, and is represented by the structural formula indicated below:



Pharmaceutical combinations

As outlined above, in a first aspect, the present invention provides a pharmaceutical combination comprising:

a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers.

A pharmaceutical combination according to the invention is for example a combined preparation or a pharmaceutical composition, for simultaneous, separate or sequential use.

The term "combined preparation" as used herein defines especially a "kit of parts" in the sense that said peptidic CXCR4 inhibitor and said phosphatidylinositol-3-kinase (PI3K) inhibitor can be dosed independently, either in separate form e.g. as separate tablets or by use of different fixed combinations with distinguished amounts of the active ingredients. The ratio of the amount of peptidic CXCR4 inhibitor to the amount of phosphatidylinositol-3-kinase (PI3K) inhibitor to be administered in the combined preparation can be varied, e.g. in order to cope with the needs of a patient sub-population to be treated or the needs of a single patient, which

needs can be different due to age, sex, body weight, etc. of a patient. The individual parts of the combined preparation (kit of parts) can be administered simultaneously or sequentially, i.e. chronologically staggered, e.g. at different time points and with equal or different time intervals for any part of the kit of parts.

The term "pharmaceutical composition" refers to a fixed-dose combination (FDC) that includes the peptidic CXCR4 inhibitor and the phosphatidylinositol-3-kinase (PI3K) inhibitor combined in a single dosage form, having a predetermined combination of respective dosages. In one embodiment, the pharmaceutical combination of the invention is a pharmaceutical composition and includes other medicinal or pharmaceutical agents, e.g., one or more pharmaceutically acceptable diluents, excipients or carriers.

The pharmaceutical combination further may be used as add-on therapy. As used herein, "add-on" or "add-on therapy" means an assemblage of reagents for use in therapy, the subject receiving the therapy begins a first treatment regimen of one or more reagents prior to beginning a second treatment regimen of one or more different reagents in addition to the first treatment regimen, so that not all of the reagents used in the therapy are started at the same time. For example, adding phosphatidylinositol-3-kinase (PI3K) inhibitor therapy to a patient already receiving peptidic CXCR4 inhibitor therapy and vice versa.
In a preferred embodiment, the pharmaceutical combination according to the invention is a combined preparation.

The amount of the peptidic CXCR4 inhibitor and the phosphatidylinositol-3-kinase (PI3K) inhibitor to be administered will vary depending upon factors such as the particular compound, disease condition and its severity, according to the particular circumstances surrounding the case, including, e.g., the specific peptidic CXCR4 inhibitor being administered, the route of administration, the condition being treated, the target area being treated, and the subject or host being treated.

In one embodiment, the invention provides a pharmaceutical combination comprising a peptidic CXCR4 inhibitor and a phosphatidylinositol-3-kinase (PI3K) inhibitor, wherein said peptidic CXCR4 inhibitor and said phosphatidylinositol-3-kinase (PI3K) inhibitor are present in a therapeutically effective amount.

The expression "effective amount" or "therapeutically effective amount" as used herein refers to an amount capable of invoking one or more of the following effects in a subject receiving the combination of the present invention: (i) increase of objective response rate (ORR); (ii) inhibition or arrest of tumor growth, including, reducing the rate of tumor growth or causing complete growth arrest; (iii) reduction in the number of tumor cells; (iv) reduction in tumor size; (v) reduction in tumor number; (vi) inhibition of metastasis (i.e. reduction, slowing down or complete stopping) of tumor cell infiltration into peripheral organs; (vii) enhancement of antitumor immune response, which may, but does not have to, result in the regression or elimination of the tumor; (viii) relief, to some extent, of one or more symptoms associated with cancer; (ix) increase in progression-free survival (PFS) and/or; overall survival (OS) of the subject receiving the combination.

Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. In some embodiments, a therapeutically effective amount of the peptidic CXCR4 inhibitor may (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow down to some extent, and preferably stop cancer cell infiltration into peripheral organs; (iv) inhibit (e.g., slow to some extent and preferably stop) tumor metastasis; (v) inhibit tumor growth; (vi) delay occurrence and/or recurrence of a tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer. In various embodiments, the amount is sufficient to ameliorate, palliate, lessen, and/or delay one or more of symptoms of cancer.
The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one ordinary skilled in the art.

In a preferred embodiment, the invention provides a pharmaceutical combination comprising a peptidic CXCR4 inhibitor and a phosphatidylinositol-3-kinase (PI3K) inhibitor, wherein said peptidic CXCR4 inhibitor and said phosphatidylinositol-3-kinase (PI3K) inhibitor produce an additive therapeutic effect i.e. wherein said peptidic CXCR4 inhibitor and said phosphatidylinositol-3-kinase (PI3K) inhibitor are present in an amount producing an additive therapeutic effect.

As used herein, the term "additive" means that the effect achieved with the pharmaceutical combinations of this invention is approximately the sum of the effects that result from using the agents, namely the peptidic CXCR4 inhibitor and the phosphatidylinositol-3-kinase (PI3K) inhibitor, as a monotherapy.

In a further preferred embodiment, the invention provides a pharmaceutical combination comprising a peptidic CXCR4 inhibitor and a phosphatidylinositol-3-kinase (PI3K) inhibitor, wherein said peptidic CXCR4 inhibitor and said phosphatidylinositol-3-kinase (PI3K) inhibitor produce a synergistic therapeutic effect, i.e. wherein said peptidic CXCR4 inhibitor and said phosphatidylinositol-3-kinase (PI3K) inhibitor are present in an amount producing a synergistic therapeutic effect.

As used herein, the term "synergistic" means that the effect achieved with the pharmaceutical combinations of this invention is greater than the sum of the effects that result from using the agents, namely the peptidic CXCR4 inhibitor and the phosphatidylinositol-3-kinase (PI3K) inhibitor, as a monotherapy. In particular the synergistic effect of the pharmaceutical combination versus the single agents is referred to in the present application as synergism according to the Chou-Talalay combination index (Chou TC.: Drug combination studies and their synergy quantification using the Chou-Talalay method, *Cancer Res*. 2010, *70*(2), 440-446) and /or according to the MuSyC synergistic efficacy model (Meyer CT, Wooten DJ, Paudel BB, et al.: Quantifying Drug Combination Synergy along Potency and Efficacy Axes, *Cell Syst*. 2019, *8*(2), 97-108 e116).

In one embodiment, the invention provides a pharmaceutical combination comprising a phosphatidylinositol-3-kinase (PI3K) inhibitor and a peptidic CXCR4 inhibitor, wherein the amount of said peptidic CXCR4 inhibitor in the combination is is from about 0.3 to about 3500 mg, or from about 0.3 to about 2500 mg, or from about 0.3 to about 1600 mg, or from about 0.3 to about 1200 mg, or from about 0.3 to about 800 mg, or from about 1 to about 500 mg, preferably from about 1 to about 400 mg. Where said peptidic CXCR4 inhibitor is in the form of a pharmaceutically acceptable salt, the amounts of peptidic CXCR4 inhibitor provided herein are calculated on the basis of the respective free base.

In one embodiment, the invention provides a pharmaceutical combination comprising a phosphatidylinositol-3-kinase (PI3K) inhibitor and a peptidic CXCR4 inhibitor, wherein the amount of said phosphatidylinositol-3-kinase (PI3K) inhibitor in the combination is from about 0.1 to about 3500 mg, or from about 1 to about 1800 mg, or from about 5 to about 1200 mg, or from about 5 to about 1000 mg preferably from about 5 to about 1000mg. Where said phosphatidylinositol-3-kinase (PI3K) inhibitor is in the form of a pharmaceutically acceptable salt, the amounts of phosphatidylinositol-3-kinase (PI3K) inhibitor provided herein are calculated on the basis of the respective free base.

In one embodiment, the invention provides a pharmaceutical combination comprising a phosphatidylinositol-3-kinase (PI3K) inhibitor and a peptidic CXCR4 inhibitor, wherein the amount of said peptidic CXCR4 inhibitor in the combination is from about 0.3 to about 3500 mg, or from about 0.3 to about 2500 mg, or from about 0.3 to about 1600 mg, or from about 0.3 to about 1200 mg, or from about 0.3 to about 800 mg, or from about 1 to about 500 mg, preferably from about 1 to about 400 mg, and wherein the amount of said phosphatidylinositol-3-kinase (PI3K) inhibitor in the combination is from about from about 0.1 to about 3500 mg, or from about 1 to about 1800 mg, or from about 5 to about 1200 mg, or from about 5 to about 1000 mg preferably from about 5 to about 1000mg.

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^{1}-His^{2}-Xaa^{3}-Cys^{4}-Ser^{5}-Xaa^{6}-Xaa^{7}-Xaa^{8}-Arg^{9}-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^{3} is Ala; Tyr; or Tyr(Me);

Xaa^{6} is Ala or Acc;

Xaa^{7} is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^{8} is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula Ia has a disulfide bond between Cys^{4} and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143),

AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, Alpelisib (Piqray™, BYL719), Serabelisib (MLN1117, INK1117, TAK-117), CYH33, GDC-0326, WX-037, GSK2636771, SAR-260301, AZD-8835, AZD-8186, KA2237, VT30, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302), Fimepinostat (CUDC-907), Rigosertib (ON-01910), BR101801, HEC89736, CHF-6523 and TL117.

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Xaa^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^3 is Ala; Tyr; or Tyr(Me);

Xaa^6 is Ala or Acc;

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N^{ω}-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula Ia has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of

Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302) and Fimepinostat (CUDC-907).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Xaa^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^3 is Ala; Tyr; or Tyr(Me);

Xaa^6 is Ala or Acc;

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N^{ω}-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula Ia has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of pan-PI3K inhibitors and isoform-selective PI3K inhibitors.

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^{1}-His^{2}-Xaa^{3}-Cys^{4}-Ser^{5}-Xaa^{6}-Xaa^{7}-Xaa^{8}-Arg^{9}-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^{3} is Ala; Tyr; or Tyr(Me);

Xaa^{6} is Ala or Acc;

Xaa^{7} is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^{8} is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula Ia has a disulfide bond between Cys^{4} and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of

Copanlisib (Aliqopa^{TM}, BAY 80-6946), Buparlisib (BKM-120), Taselisib (GDC-0032), Idelalisib (Zydelig^{TM}, GS-1101, CAL-101), Duvelisib (Copiktra^{TM}, IPI-145, INK-1197), Umbralisib (Ukoniq^{TM}, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Puquitinib (XC-302 and Fimepinostat (CUDC-907).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Xaa^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^3 is Ala; Tyr; or Tyr(Me);

Xaa^6 is Ala or Acc;

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^\omega$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula Ia has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-

1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Leniolisib (CDZ173-NX), Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120) and Taselisib (GDC-0032), wherein the PI3K inhibitor is most preferably selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101) and Copanlisib (Aliqopa™, BAY 80-6946).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^{1}-His^{2}-Xaa^{3}-Cys^{4}-Ser^{5}-Ala^{6}-Xaa^{7}-Xaa^{8}-Arg^{9}-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-) (I),

in which

Xaa^{3} is Ala; Tyr; or Tyr(Me);

Xaa^{7} is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^{8} is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula I has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, Alpelisib (Piqray™, BYL719), Serabelisib (MLN1117, INK1117, TAK-117), CYH33, GDC-0326, WX-037, GSK2636771, SAR-260301, AZD-8835, AZD-8186, KA2237, VT30, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302), Fimepinostat (CUDC-907), Rigosertib (ON-01910), BR101801, HEC89736, CHF-6523 and TL117.

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Ala^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-) (I),

in which

Xaa^3 is Ala; Tyr; or Tyr(Me);

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N^{ω}-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula I has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of

Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186,Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302) and Fimepinostat (CUDC-907).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Ala^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(I),

in which

Xaa^3 is Ala; Tyr; or Tyr(Me);

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^\omega$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula I has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the the PI3K inhibitor is selected from the group consisting of pan-PI3K inhibitors and isoform-selective PI3K inhibitors.

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Ala^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(I),

in which

Xaa^3 is Ala; Tyr; or Tyr(Me);

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^\omega$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula I has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of

Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Taselisib (GDC-0032), Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Puquitinib (XC-302 and Fimepinostat (CUDC-907).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Ala^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-) (I),

in which

Xaa^3 is Ala; Tyr; or Tyr(Me);

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^\omega$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula I has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Leniolisib (CDZ173-NX), Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120) and Taselisib (GDC-0032), wherein the PI3K inhibitor is most

preferably selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101) and Copanlisib (Aliqopa™, BAY 80-6946).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^{1}-His^{2}-Xaa^{3}-Cys^{4}-Ser^{5}-Xaa^{6}-Xaa^{7}-Xaa^{8}-Arg^{9}-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^{3} is Tyr; or Tyr(Me);

Xaa^{6} is Ala or Acc;

Xaa^{7} is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^{8} is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula Ia has a disulfide bond between Cys^4 and Cys^{11}, and wherein the PI3K inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, Alpelisib (Piqray™, BYL719), Serabelisib (MLN1117, INK1117, TAK-117), CYH33, GDC-0326, WX-037, GSK2636771, SAR-260301, AZD-8835, AZD-8186, KA2237, VT30, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302), Fimepinostat (CUDC-907), Rigosertib (ON-01910), BR101801, HEC89736, CHF-6523 and TL117.

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Xaa^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^3 is Tyr; or Tyr(Me);

Xaa^6 is Ala or Acc;

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N^{ω}-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula Ia has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of

Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186,Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302) and Fimepinostat (CUDC-907).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Xaa^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^3 is Tyr; or Tyr(Me);

Xaa^6 is Ala or Acc;

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^\omega$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula Ia has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of pan-PI3K inhibitors and isoform-selective PI3K inhibitors.

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Xaa^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^3 is Tyr; or Tyr(Me);

Xaa^6 is Ala or Acc;

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^\omega$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula Ia has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of

Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Taselisib (GDC-0032), Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143),

AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Puquitinib (XC-302 and Fimepinostat (CUDC-907).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^{1}-His^{2}-Xaa^{3}-Cys^{4}-Ser^{5}-Xaa^{6}-Xaa^{7}-Xaa^{8}-Arg^{9}-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^{3} is Tyr; or Tyr(Me);

Xaa^{6} is Ala or Acc;

Xaa^{7} is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^{8} is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula Ia has a disulfide bond between Cys^{4} and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting Idelalisib (Zydelig^{TM}, GS-1101, CAL-101), Duvelisib (Copiktra^{TM}, IPI-145, INK-1197), Umbralisib (Ukoniq^{TM}, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Leniolisib (CDZ173-NX), Copanlisib (Aliqopa^{TM}, BAY 80-6946), Buparlisib (BKM-120) and Taselisib (GDC-0032), wherein the PI3K inhibitor is most preferably selected from the group consisting of Idelalisib (Zydelig^{TM}, GS-1101, CAL-101) and Copanlisib (Aliqopa^{TM}, BAY 80-6946).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^{1}-His^{2}-Xaa^{3}-Cys^{4}-Ser^{5}-Ala^{6}-Xaa^{7}-Xaa^{8}-Arg^{9}-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-) (I),

in which

Xaa^{3} is Tyr; or Tyr(Me);

Xaa^{7} is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^{8} is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula I has a disulfide bond between Cys^{4} and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, Alpelisib (Piqray™, BYL719), Serabelisib (MLN1117, INK1117, TAK-117), CYH33, GDC-0326, WX-037, GSK2636771, SAR-260301, AZD-8835, AZD-8186, KA2237, VT30, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302), Fimepinostat (CUDC-907), Rigosertib (ON-01910), BR101801, HEC89736, CHF-6523 and TL117.

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Ala^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(I),

in which

Xaa^3 is Tyr; or Tyr(Me);

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula I has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of

Copanlisib (Aliqopa^{TM}, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig^{TM}, GS-1101, CAL-101), Duvelisib (Copiktra^{TM}, IPI-145, INK-1197), Umbralisib (Ukoniq^{TM}, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186,Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302) and Fimepinostat (CUDC-907).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Ala^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(I),

in which

Xaa^3 is Tyr; or Tyr(Me);

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N^{ω}-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula I has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the the PI3K inhibitor is selected from the group consisting of pan-PI3K inhibitors and isoform-selective PI3K inhibitors.

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Ala^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(I),

in which

Xaa^3 is Tyr; or Tyr(Me);

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^\omega$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula I has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of

Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Taselisib (GDC-0032), Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-

8186, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Puquitinib (XC-302 and Fimepinostat (CUDC-907).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Ala^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(I),

in which

Xaa^3 is Tyr; or Tyr(Me);

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N^{ω}-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N^{ω}-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula I has a disulfide bond between Cys^4 and Cys^{11}, and

wherein the PI3K inhibitor is selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-

1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Leniolisib (CDZ173-NX), Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120) and Taselisib (GDC-0032), wherein the PI3K inhibitor is most preferably selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101) and Copanlisib (Aliqopa™, BAY 80-6946).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein the peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, selected from the group consisting of

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Lys(iPr)-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:3**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:4**),

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Tyr-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:5**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:6**),

cyclo(-Tyr-His-Tyr(Me)-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:7**),

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Tyr(Me)-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:8**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Tyr-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:9**),

cyclo(-Tyr-His-Tyr(Me)-Cys-Ser-Ala-^{D}Tyr(Me)-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:10**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Acc-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:11**),

or pharmaceutically acceptable salts thereof, and

wherein the PI3K inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, Alpelisib (Piqray™, BYL719), Serabelisib (MLN1117, INK1117, TAK-117), CYH33, GDC-0326, WX-037, GSK2636771, SAR-260301, AZD-8835, AZD-8186, KA2237, VT30, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302), Fimepinostat (CUDC-907), Rigosertib (ON-01910), BR101801, HEC89736, CHF-6523 and TL117.

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein the peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, selected from the group consisting of

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Lys(iPr)-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:3**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:4**),

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Tyr-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:5**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:6**),

cyclo(-Tyr-His-Tyr(Me)-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:7**),

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Tyr(Me)-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:8**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Tyr-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:9**),

cyclo(-Tyr-His-Tyr(Me)-Cys-Ser-Ala-^{D}Tyr(Me)-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:10**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Acc-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:11**),

or pharmaceutically acceptable salts thereof, and

wherein the PI3K inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557),

GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186,Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302) and Fimepinostat (CUDC-907).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein the peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, selected from the group consisting of

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Lys(iPr)-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:3**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:4**),

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Tyr-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:5**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:6**),

cyclo(-Tyr-His-Tyr(Me)-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:7**),

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Tyr(Me)-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:8**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Tyr-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)

having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:9**),
cyclo(-Tyr-His-Tyr(Me)-Cys-Ser-Ala-^{D}Tyr(Me)-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)
having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:10**),
cyclo(-Tyr-His-Tyr-Cys-Ser-Acc-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)
having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:11**),
or pharmaceutically acceptable salts thereof, and
wherein the PI3K inhibitor is selected from the group consisting of pan-PI3K inhibitors and isoform-selective PI3K inhibitors.

In one embodiment, there is provided a pharmaceutical combination comprising:
(a) a peptidic CXCR4 inhibitor;
(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and
(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,
wherein the peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, selected from the group consisting of
cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-)
having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:1**),
cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-)
having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:2**),
cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Lys(iPr)-Pro-)
having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:3**),
cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)
having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:4**),
cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Tyr-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)
having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:5**),
cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)
having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:6**),
cyclo(-Tyr-His-Tyr(Me)-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-)
having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:7**),

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Tyr(Me)-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:8**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Tyr-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:9**),

cyclo(-Tyr-His-Tyr(Me)-Cys-Ser-Ala-^{D}Tyr(Me)-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:10**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Acc-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:11**),

or pharmaceutically acceptable salts thereof, and

wherein the PI3K inhibitor is selected from the group consisting of

Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Taselisib (GDC-0032), Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Puquitinib (XC-302 and Fimepinostat (CUDC-907).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein the peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, selected from the group consisting of

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Lys(iPr)-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:3**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:4**),

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Tyr-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:5**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:6**),

cyclo(-Tyr-His-Tyr(Me)-Cys-Ser-Ala-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:7**),

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Tyr(Me)-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:8**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Tyr-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:9**),

cyclo(-Tyr-His-Tyr(Me)-Cys-Ser-Ala-^{D}Tyr(Me)-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:10**),

cyclo(-Tyr-His-Tyr-Cys-Ser-Acc-^{D}Pro-Orn(iPr)-Arg-Tyr-Cys-Tyr-Gln-Lys(iPr)-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:11**),

or pharmaceutically acceptable salts thereof, and

wherein the PI3K inhibitor is selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Leniolisib (CDZ173-NX), Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120) and Taselisib (GDC-0032), wherein the PI3K inhibitor is most preferably selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101) and Copanlisib (Aliqopa™, BAY 80-6946).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is selected from the group consisting of cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**), and cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), or pharmaceutically acceptable salts thereof, and

wherein the PI3K inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, Alpelisib (Piqray™, BYL719), Serabelisib (MLN1117, INK1117, TAK-117), CYH33, GDC-0326, WX-037, GSK2636771, SAR-260301, AZD-8835, AZD-8186, KA2237, VT30, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302), Fimepinostat (CUDC-907), Rigosertib (ON-01910), BR101801, HEC89736, CHF-6523 and TL117.

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is selected from the group consisting of cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**), and

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-)
having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**),
or pharmaceutically acceptable salts thereof, and
wherein the PI3K inhibitor is selected from the group consisting of
Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186,Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302) and Fimepinostat (CUDC-907).

In one embodiment, there is provided a pharmaceutical combination comprising:
(a) a peptidic CXCR4 inhibitor;
(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and
(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,
wherein said peptidic CXCR4 inhibitor is selected from the group consisting of
cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-)
having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**), and
cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-)
having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**),
or pharmaceutically acceptable salts thereof, and
wherein the PI3K inhibitor is selected from the group consisting of pan-PI3K inhibitors and isoform-selective PI3K inhibitors.

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is selected from the group consisting of

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**), and

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**),

or pharmaceutically acceptable salts thereof, and

wherein the PI3K inhibitor is selected from the group consisting of

Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Taselisib (GDC-0032), Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Puquitinib (XC-302 and Fimepinostat (CUDC-907).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is selected from the group consisting of

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**), and

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**),

or pharmaceutically acceptable salts thereof, and

wherein the PI3K inhibitor is selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Leniolisib (CDZ173-NX), Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120) and Taselisib (GDC-0032), wherein the PI3K inhibitor is most preferably selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101) and Copanlisib (Aliqopa™, BAY 80-6946).

In one embodiment, there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers, wherein said peptidic CXCR4 inhibitor is cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), or pharmaceutically acceptable sals thereof, and

wherein the PI3K inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, Alpelisib (Piqray™, BYL719), Serabelisib (MLN1117, INK1117, TAK-117), CYH33, GDC-0326, WX-037, GSK2636771, SAR-260301, AZD-8835, AZD-8186, KA2237, VT30, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302), Fimepinostat (CUDC-907), Rigosertib (ON-01910), BR101801, HEC89736, CHF-6523 and TL117.

In a preferred embodiment there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), or pharmaceutically acceptable sals thereof, and the phosphatidylinositol-3-kinase (PI3K) inhibitor is selected from the group consisting of

Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186,Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458), Panulisib (P7170), VS-5584 (SB2343), BGT-226, DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302) and Fimepinostat (CUDC-907).

In a further preferred embodiment there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), or pharmaceutically acceptable sals thereof, and the phosphatidylinositol-3-kinase (PI3K) inhibitor is selected from the group consisting of pan-PI3K inhibitors and isoform-selective PI3K inhibitors.

In a particular preferred embodiment there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), or pharmaceutically acceptable sals thereof, and wherein the phosphatidylinositol-3-kinase (PI3K) inhibitor is selected from the group consisting of

Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Taselisib (GDC-0032), Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M, IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Puquitinib (XC-302 and Fimepinostat (CUDC-907).

In a particular preferred embodiment there is provided a pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers,

wherein said peptidic CXCR4 inhibitor is cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), or pharmaceutically acceptable sals thereof, and wherein the phosphatidylinositol-3-kinase (PI3K) inhibitor is selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530),

SHC014748M, IOA244, Leniolisib (CDZ173-NX), Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120) and Taselisib (GDC-0032, wherein the PI3K inhibitor is most preferably selected from the group consisting of Idelalisib (Zydelig™, GS-1101, CAL-101) and Copanlisib (Aliqopa™, BAY 80-6946).

Formulations and modes of administration

The formulation and route of administration chosen may be tailored to the individual subject, the nature of the condition to be treated in the subject, and generally, the judgment of the attending practitioner.

The pharmaceutical compositions or combined preparations of the invention may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including rectal, buccal, intranasal, transmucosal, transdermal, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, as e.g. an inhalant via pulmonary adminstration, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

One mode for administration is administration by injection, preferably intravenous administration by injection. The forms in which the peptidic CXCR4 inhibitor and/or phosphatidylinositol-3-kinase (PI3K) inhibitor, may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, peanut oil, or castor oil, or chemical modified derivatives of the aforesaid oils thereof, as for example Cremophor EL, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles. Aqueous solutions in saline may also conventionally be used for injection, preferably physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer are used as aqueous solutions. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of

surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

Sterile injectable solutions are prepared by incorporating a compound according to the present disclosure in the required amount in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. In certain embodiments, for parenteral administration, sterile injectable solutions are prepared containing a therapeutically effective amount, e.g., 0.3 to 3500 mg, of the peptidic CXCR4 inhibitor. It will be understood, however, that the amount of the compound actually administered usually will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

A pharmaceutical combination according to the invention is, preferably, suitable for oral administration and/or injection or infusion, e.g. subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, and usually comprises a therapeutically effective amount of the active ingredients and one or more suitable pharmaceutically acceptable diluent, excipient or carrier, e.g. the phosphatidylinositol-3-kinase (PI3K) inhibitor is administered to the subject orally or intravenously by infusion

Pharmaceutical compositions or combined preparations in separate form comprising a peptidic CXCR4 inhibitor and phosphatidylinositol-3-kinase (PI3K) inhibitor may be manufactured by means of conventional mixing, dissolving, granulating, coated tablet-making,

levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions or combined preparations in separate form may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxilliaries which facilitate processing of the active ingredient into preparations which can be used pharmaceutically. Proper formulation depends upon the method of administration chosen.

For topical administration the peptidic CXCR4 inhibitor and/or phosphatidylinositol-3-kinase (PI3K) inhibitor may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation as known in the art.

For oral administration, the compounds can be readily formulated by combining the peptidic CXCR4 inhibitor and/or phosphatidylinositol-3-kinase (PI3K) inhibitor with pharmaceutically acceptable carriers well known in the art. Such carriers enable the peptidic CXCR4 inhibitor and/or phosphatidylinositol-3-kinase (PI3K) inhibitor to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions etc., for oral ingestion by a patient to be treated. For oral formulations such as, for example, powders, capsules and tablets, suitable excipients include fillers such as sugars, e. g. lactose, sucrose, mannitol and sorbitol; cellulose preparations such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethylcellulose; granulating agents; and binding agents. If desired, desintegrating agents may be added, such as cross-linked polyvinylpyrrolidones, agar, or alginic acid or a salt thereof, such as sodium alginate. If desired, solid dosage forms may be sugar-coated or enteric-coated using standard techniques. For oral liquid preparations such as, for example, suspensions, elixirs and solutions, suitable carriers, excipients or diluents include water, glycols, oils, alcohols, etc. In addition, flavoring agents, preservatives, coloring agents and the like may be added.

For buccal administration, the composition may take the form of tablets, lozenges, etc. formulated as usual.

For administration by inhalation, the peptidic CXCR4 inhibitor and/or phosphatidylinositol-3-kinase (PI3K) inhibitor are conveniently delivered in form of an aeorosol spray from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluromethane, carbon dioxide or another suitable gas. In the case of a pressurized aerosol the dose unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compounds of the invention and a suitable powder base such as lactose or starch.

The compounds may also be formulated in rectal or vaginal compositions such as suppositories together with appropriate suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the peptidic CXCR4 inhibitor and/or phosphatidylinositol-3-kinase (PI3K) inhibitor may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (e.g. subcutaneously or intramuscularly) or by intramuscular injection. For the manufacture of such depot preparations the peptidic CXCR4 inhibitor and/or phosphatidylinositol-3-kinase (PI3K) inhibitor may be formulated with suitable polymeric or hydrophobic materials (e.g. as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble salts.

In addition, other pharmaceutical delivery systems may be employed such as liposomes and emulsions well known in the art. Certain organic solvents such as dimethylsulfoxide may also be employed. Additionally, the peptidic CXCR4 inhibitor and/or phosphatidylinositol-3-kinase (PI3K) inhibitor may be delivered using a sustained-release system, such as semipermeable matrices of solid polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-

release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic agent, additional strategies for protein stabilization may be employed.

Using the combinations of the invention to treat cancer

According to a second aspect the present invention provides a pharmaceutical combination as described herein, for use as a medicament.

According to a third aspect the present invention provides a pharmaceutical combination as described herein, for use in a method for the prevention, delay of progression or treatment of cancer in a subject, preferably for use in a method for the delay of progression or treatment of cancer in a subject, more preferably for use in a method for the treatment of cancer in a subject.

Also provided is the use of a pharmaceutical combination as described herein for the manufacture of a medicament for the prevention, delay of progression or treatment of cancer in a subject, preferably for the manufacture of a medicament for the delay of progression or treatment of cancer in a subject, more preferably for the manufacture of a medicament for the treatment of cancer in a subject.

Also provided is the use of a pharmaceutical combination as described herein for the prevention, delay of progression or treatment of cancer in a subject, preferably for the delay of progression or treatment of cancer in a subject, more preferably for the treatment of cancer in a subject.

Also provided is a method for the prevention, delay of progression or treatment of cancer in a subject, preferably a method for the delay of progression or treatment of cancer in a subject, more preferably a method for the treatment of cancer in a subject, comprising administering to said subject a pharmaceutical combination as described herein e.g. administering to said subject a therapeutically effective amount of a pharmaceutical combination as described herein.

As used herein, the term "prevention"/"preventing" e.g. preventive treatments comprise prophylactic treatments. In preventive applications, the pharmaceutical combination of the invention is administered to a subject suspected of having, or at risk for developing cancer.

As used herein, the term "delay of progression"/"delaying of progression" means increasing the time to appearance of a symptom of a cancer or a mark associated with a cancer or slowing the increase in severity of a symptom of a cancer. Further, "delay of progression" as used herein includes reversing or inhibition of disease progression. "Inhibition" of disease progression or disease complication in a subject means preventing or reducing the disease progression and/or disease complication in the subject.

The terms "treatment"/"treating" as used herein includes: (1) delaying the appearance of clinical symptoms of the state, disorder or condition developing in an animal, particularly a mammal and especially a human, that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition; (2) inhibiting the state, disorder or condition (e.g. arresting, reducing or delaying the development of the disease, or a relapse thereof in case of maintenance treatment, of at least one clinical or subclinical symptom thereof; and/or (3) relieving the condition (i.e. causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms). The benefit to a patient to be treated is either statistically significant or at least perceptible to the patient or to the physician. However, it will be appreciated that when a medicament is administered to a patient to treat a disease, the outcome may not always be effective treatment.

In therapeutic applications, the pharmaceutical combination is usually administered to a subject such as a patient already suffering from cancer, in an amount sufficient to cure or at least partially arrest the symptoms of the disease. Amounts effective for this use will depend on the severity and course of the disease, previous therapy, the subject's health status and response to the drugs, and the judgment of the treating physician.

In the case wherein the subject's condition does not improve, the pharmaceutical combination of the invention may be administered chronically, which is, for an extended period of time,

including throughout the duration of the subject's life in order to ameliorate or otherwise control or limit the symptoms of the subject's disease or condition.

In the case wherein the subject's status does improve, the pharmaceutical combination may be administered continuously; alternatively, the dose of drugs being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday").

Once improvement of the patient's condition has occurred, a maintenance dose of the pharmaceutical combination of the invention is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, is optionally reduced, as a function of the symptoms, to a level at which the improved disease is retained.

In one embodiment of the invention, there is provided a pharmaceutical combination according to the invention, for use in a method for the prevention, delay of progression or treatment of cancer in a subject, preferably for use in a method for the delay of progression or treatment of a cancer in a subject, more preferably for use in a method for the treatment of cancer in a subject, wherein the cancer is a tumor of the hematopoietic and lymphoid tissues, even more preferably wherein the cancer is a mature B-cell neoplasm, in particular wherein the cancer is a non-Hodgkin lymphoma, more particular wherein the cancer is preferably selected from the group consisting of small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia), hairy cell leukaemia, Burkitt lymphoma, marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL), more preferably selected from the group consisting of marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL), even more preferably selected from the group consisting of marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL), in particular selected from the group consisting of marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), and chronic

lymphocytic leukemia (CLL), more particular wherein the cancer is marginal zone lymphoma (MZL) or splenic marginal zone lymphoma (SMZL), most particular splenic marginal zone lymphoma (SMZL).

In a preferred embodiment of the invention, there is provided a pharmaceutical combination according to the invention, for use in a method for the prevention, delay of progression or treatment of cancer in a subject, preferably for use in a method for the delay of progression or treatment of a cancer in a subject, more preferably for use in a method for the treatment of cancer in a subject, wherein the cancer is selected from the group consisting of mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) and splenic marginal zone lymphoma (SMZL). In a more preferred embodiment of the invention, there is provided a pharmaceutical combination according to the invention, for use in a method for the prevention, delay of progression or treatment of cancer in a subject, preferably for use in a method for the delay of progression or treatment of a cancer in a subject, more preferably for use in a method for the treatment of cancer in a subject, wherein the cancer is mantle cell lymphoma (MCL) or splenic marginal zone lymphoma (SMZL). In an even more preferred embodiment of the invention, there is provided a pharmaceutical combination according to the invention, for use in a method for the prevention, delay of progression or treatment of cancer in a subject, preferably for use in a method for the delay of progression or treatment of a cancer in a subject, more preferably for use in a method for the treatment of cancer in a subject, wherein the cancer is mantle cell lymphoma (MCL). In an even further more preferred embodiment of the invention, there is provided a pharmaceutical combination according to the invention, for use in a method for the prevention, delay of progression or treatment of cancer in a subject, preferably for use in a method for the delay of progression or treatment of a cancer in a subject, more preferably for use in a method for the treatment of cancer in a subject, wherein the cancer is marginal zone lymphoma (MZL). In an even further more preferred embodiment of the invention, there is provided a pharmaceutical combination according to the invention, for use in a method for the prevention, delay of progression or treatment of cancer in a subject, preferably for use in a method for the delay of progression or treatment of a cancer in a subject, more preferably for use in a method for the treatment of cancer in a subject, wherein the cancer is splenic marginal zone lymphoma (SMZL).

In even a more preferred embodiment of the invention, there is provided a pharmaceutical combination according to the invention, for use in a method for the prevention, delay of progression or treatment of cancer in a subject, preferably for use in a method for the delay of progression or treatment of a cancer in a subject, more preferably for use in a method for the treatment of cancer in a subject, wherein the cancer is mantle cell lymphoma (MCL), wherein the pharmaceutical combination according to the invention comprises POL5551 (cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), and copanlisib; or wherein the cancer is splenic marginal zone lymphoma (SMZL), wherein the pharmaceutical combination according to the invention comprises POL5551 (cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), or POL6326 (cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-), (**SEQ ID NO:1**), having a disulfide bond between Cys^{4} and Cys^{11}) and idelalisib.

Also provided is the use of a pharmaceutical combination as described herein for the manufacture of a medicament for the prevention, delay of progression or treatment of cancer in a subject, preferably for the manufacture of a medicament for the delay of progression or treatment of a cancer in a subject, more preferably for the manufacture of a medicament for the treatment of cancer wherein the cancer is a tumor of the hematopoietic and lymphoid tissues, even more preferably wherein the cancer is a mature B-cell neoplasm, in particular wherein the cancer is a non-Hodgkin lymphoma, more particular wherein the cancer is preferably selected from the group consisting of small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia), hairy cell leukaemia, Burkitt lymphoma, marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), more preferably selected from the group consisting of marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL), even more preferably selected from the group consisting of marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell

lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL), in particular selected from the group consisting of marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), and chronic lymphocytic leukemia (CLL), more particular wherein the cancer is marginal zone lymphoma (MZL) or splenic marginal zone lymphoma (SMZL), most particular splenic marginal zone lymphoma (SMZL).

In a preferred embodiment of the invention, there is provided the use of a pharmaceutical combination as described herein for the manufacture of a medicament for the prevention, delay of progression or treatment of cancer in a subject, preferably for the manufacture of a medicament for the delay of progression or treatment of a cancer in a subject, more preferably for the manufacture of a medicament for the treatment of cancer, wherein the cancer is selected from the group consisting of mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) and splenic marginal zone lymphoma (SMZL). In a more preferred embodiment of the invention, there is provided the use of a pharmaceutical combination as described herein for the manufacture of a medicament for the prevention, delay of progression or treatment of cancer in a subject, preferably for the manufacture of a medicament for the delay of progression or treatment of a cancer in a subject, more preferably for the manufacture of a medicament for the treatment of cancer, wherein the cancer is mantle cell lymphoma (MCL) or splenic marginal zone lymphoma (SMZL). In an even more preferred embodiment of the invention, there is provided the use of a pharmaceutical combination as described herein for the manufacture of a medicament for the prevention, delay of progression or treatment of cancer in a subject, preferably for the manufacture of a medicament for the delay of progression or treatment of a cancer in a subject, more preferably for the manufacture of a medicament for the treatment of cancer, wherein the cancer is mantle cell lymphoma (MCL). In an even further more preferred embodiment of the invention, there is provided the use of a pharmaceutical combination as described herein for the manufacture of a medicament for the prevention, delay of progression or treatment of cancer in a subject, preferably for the manufacture of a medicament for the delay of progression or treatment of a cancer in a subject, more preferably for the manufacture of a medicament for the treatment of cancer, wherein the cancer is marginal zone lymphoma

(MZL). In an even further more preferred embodiment of the invention, there is provided the use of a pharmaceutical combination as described herein for the manufacture of a medicament for the prevention, delay of progression or treatment of cancer in a subject, preferably for the manufacture of a medicament for the delay of progression or treatment of a cancer in a subject, more preferably for the manufacture of a medicament for the treatment of cancer, wherein the cancer is splenic marginal zone lymphoma (SMZL).

In even a more preferred embodiment of the invention, there is provided the use of a pharmaceutical combination as described herein for the manufacture of a medicament for the prevention, delay of progression or treatment of cancer in a subject, preferably for the manufacture of a medicament for the delay of progression or treatment of a cancer in a subject, more preferably for the manufacture of a medicament for the treatment of cancer, wherein the cancer is mantle cell lymphoma (MCL), wherein the pharmaceutical combination according to the invention comprises POL5551 (cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), and copanlisib; or wherein the cancer is splenic marginal zone lymphoma (SMZL), wherein the pharmaceutical combination according to the invention comprises POL5551 (cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), or POL6326 (cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**), and idelalisib.

Also provided is the use of a pharmaceutical combination as described herein for the prevention, delay of progression or treatment of cancer in a subject, preferably for the delay of progression or treatment of a cancer in a subject, more preferably for the treatment of a cancer in a subject, more preferably wherein the cancer is a tumor of the hematopoietic and lymphoid tissues, even more preferably wherein the cancer is a mature B-cell neoplasm, in particular wherein the cancer is a non-Hodgkin lymphoma, more particular wherein the cancer is preferably selected from the group consisting of small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia), hairy cell leukaemia, Burkitt lymphoma, marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL),

mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), more preferably selected from the group consisting of marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL), even more selected from the group consisting of marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL), in particular selected from the group consisting of marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), and chronic lymphocytic leukemia (CLL), more particular wherein the cancer is marginal zone lymphoma (MZL) or splenic marginal zone lymphoma (SMZL), most particular splenic marginal zone lymphoma (SMZL).

In a preferred embodiment of the invention, there is provided the use of a pharmaceutical combination as described herein for the prevention, delay of progression or treatment of cancer in a subject, preferably for the delay of progression or treatment of a cancer in a subject, more preferably for the treatment of a cancer in a subject, wherein the cancer is selected from the group consisting of mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) and splenic marginal zone lymphoma (SMZL). In a more preferred embodiment of the invention, there is provided the use of a pharmaceutical combination as described herein for the prevention, delay of progression or treatment of cancer in a subject, preferably for the delay of progression or treatment of a cancer in a subject, more preferably for the treatment of a cancer in a subject, wherein the cancer is mantle cell lymphoma (MCL) or splenic marginal zone lymphoma (SMZL). In an even more preferred embodiment of the invention, there is provided the use of a pharmaceutical combination as described herein for the prevention, delay of progression or treatment of cancer in a subject, preferably for the delay of progression or treatment of a cancer in a subject, more preferably for the treatment of a cancer in a subject, wherein the cancer is mantle cell lymphoma (MCL). In an even further more preferred embodiment of the invention, there is provided the use of a pharmaceutical combination as described herein for the prevention, delay of progression or treatment of cancer in a subject, preferably for the delay of progression or treatment of a cancer in a subject, more preferably for the treatment of a cancer in a subject, wherein the cancer is

marginal zone lymphoma (MZL). In an even further more preferred embodiment of the invention, there is provided the use of a pharmaceutical combination as described herein for the prevention, delay of progression or treatment of cancer in a subject, preferably for the delay of progression or treatment of a cancer in a subject, more preferably for the treatment of a cancer in a subject, wherein the cancer is splenic marginal zone lymphoma (SMZL).

In even a more preferred embodiment of the invention, there is provided the use of a pharmaceutical combination as described herein for the prevention, delay of progression or treatment of cancer in a subject, preferably for the delay of progression or treatment of a cancer in a subject, more preferably for the treatment of a cancer in a subject, wherein the cancer is mantle cell lymphoma (MCL), wherein the pharmaceutical combination according to the invention comprises POL5551 (cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), and copanlisib; or wherein the cancer is splenic marginal zone lymphoma (SMZL), wherein the pharmaceutical combination according to the invention comprises POL5551 (cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), or POL6326 (cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**), and idelalisib.

Also provided is a method for the prevention, delay of progression or treatment of cancer in a subject, preferably a method for the delay of progression or treatment of cancer in a subject, more preferably a method for the treatment of a cancer in a subject, comprising administering to said subject a pharmaceutical combination as described herein e.g. administering to said subject a therapeutically effective amount of a pharmaceutical combination as described herein, wherein the cancer is a tumor of the hematopoietic and lymphoid tissues, even more preferably wherein the cancer is a mature B-cell neoplasm, in particular, wherein the cancer is a non-Hodgkin lymphoma, more particular, wherein the cancer is preferably selected from the group consisting of small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia), hairy cell leukaemia, Burkitt lymphoma, marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL),

follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), more preferably selected from the group consisting of marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL), even more preferably selected from the group consisting of marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL), in particular selected from the group consisting of marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), and chronic lymphocytic leukemia (CLL), more particular wherein the cancer is marginal zone lymphoma (MZL) or splenic marginal zone lymphoma (SMZL), most particular splenic marginal zone lymphoma (SMZL).

In a preferred embodiment of the invention, there is provided a method for the prevention, delay of progression or treatment of cancer in a subject, preferably a method for the delay of progression or treatment of cancer in a subject, more preferably a method for the treatment of a cancer in a subject, comprising administering to said subject a pharmaceutical combination as described herein e.g. administering to said subject a therapeutically effective amount of a pharmaceutical combination as described herein, wherein the cancer is selected from the group consisting of mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) and splenic marginal zone lymphoma (SMZL). In a more preferred embodiment of the invention, there is provided a method for the prevention, delay of progression or treatment of cancer in a subject, preferably a method for the delay of progression or treatment of cancer in a subject, more preferably a method for the treatment of a cancer in a subject, comprising administering to said subject a pharmaceutical combination as described herein e.g. administering to said subject a therapeutically effective amount of a pharmaceutical combination as described herein, wherein the cancer is mantle cell lymphoma (MCL) or splenic marginal zone lymphoma (SMZL). In an even more preferred embodiment of the invention, there is provided a method for the prevention, delay of progression or treatment of cancer in a subject, preferably a method for the delay of progression or treatment of cancer in a subject, more preferably a method for the treatment of a cancer in a subject, comprising administering to said subject a pharmaceutical combination as described herein e.g. administering to said

subject a therapeutically effective amount of a pharmaceutical combination as described herein, wherein the cancer is mantle cell lymphoma (MCL). In an even further more preferred embodiment of the invention, there is provided a method for the prevention, delay of progression or treatment of cancer in a subject, preferably a method for the delay of progression or treatment of cancer in a subject, more preferably a method for the treatment of a cancer in a subject, comprising administering to said subject a pharmaceutical combination as described herein e.g. administering to said subject a therapeutically effective amount of a pharmaceutical combination as described herein, wherein the cancer is marginal zone lymphoma (MZL). In an even further more preferred embodiment of the invention, there is provided a method for the prevention, delay of progression or treatment of cancer in a subject, preferably a method for the delay of progression or treatment of cancer in a subject, more preferably a method for the treatment of a cancer in a subject, comprising administering to said subject a pharmaceutical combination as described herein e.g. administering to said subject a therapeutically effective amount of a pharmaceutical combination as described herein, wherein the cancer is splenic marginal zone lymphoma (SMZL).

In even a more preferred embodiment of the invention, there is provided a method for the prevention, delay of progression or treatment of cancer in a subject, preferably a method for the delay of progression or treatment of cancer in a subject, more preferably a method for the treatment of a cancer in a subject, comprising administering to said subject a pharmaceutical combination as described herein e.g. administering to said subject a therapeutically effective amount of a pharmaceutical combination as described herein, wherein the cancer is mantle cell lymphoma (MCL), wherein the pharmaceutical combination according to the invention comprises POL5551 (cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), and copanlisib; or wherein the cancer is splenic marginal zone lymphoma (SMZL), wherein the pharmaceutical combination according to the invention comprises POL5551 (cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), or POL6326 (cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**), and idelalisib.

In one embodiment the subject who has cancer e.g. the subject who has a tumor of the hematopoietic and lymphoid tissues is resistant to at least one treatment with a PI3K inhibitor.

In one embodiment the subject who has cancer e.g. the subject who has a tumor of the hematopoietic and lymphoid tissues is (i) refractory to at least one chemotherapy treatment e.g. refractory to at least one treatment with a PI3K inhibitor, or (ii) is in relapse after treatment with chemotherapy, or a combination thereof.

In some embodiments, the subject is refractory to at least two, at least three, or at least four anti-cancer therapy (including, for example, standard or experimental chemotherapies).

A subject who is refractory to at least one anti-cancer therapy and/or is in relapse after treatment with at least one anti-cancer therapy, as described above, may have undergone one or more prior therapies. In some embodiments, such subjects have undergone one, two, three, or four, or five, or at least one, at least two, at least three, at least four, or at least five, or between one and ten, between one and nine, between one and eight, between one and seven, between one and six, between one and five, or between one and four, or between one and three, between four and six or between seven and ten anti-cancer therapies prior to treatment using the methods described herein (e.g., prior to the administration of a peptidic CXCR4 inhibitor and a PI3K inhibitor).

Dosing regimen

The dosing regimen of the peptidic CXCR4 inhibitor in combination with a phosphatidylinositol-3-kinase (PI3K) inhibitor, in the methods provided herein may vary depending upon the indication, route of administration, and severity of the condition, for example. Depending on the route of administration, a suitable dose can be calculated according to body weight, body surface area, or organ size. The final dosing regimen can be determined by the attending physician in view of good medical practice, considering various factors that modify the action of drugs, e.g., the specific activity of the compound, the identity and severity of the disease state, the responsiveness of the patient, the age, condition, body weight, sex, and diet of the patient, and the severity of any infection. Additional factors that can be taken into account include time and frequency of administration, drug combinations,

reaction sensitivities, and tolerance/response to therapy. Further refinement of the doses appropriate for treatment involving any of the formulations mentioned herein is done routinely by the skilled practitioner without undue experimentation, especially in light of the dosing information and assays disclosed, as well as the pharmacokinetic data observed in human clinical trials. Appropriate doses can be ascertained through use of established assays for determining concentration of the agent in a body fluid or other sample together with dose response data.

The amount, e.g. the therapeutically effective amount of the peptidic CXCR4 inhibitor may be provided in a single dose or multiple doses to achieve the desired treatment endpoint.

The frequency of dosing will depend on the pharmacokinetic parameters of the compound administered, the route of administration, and the particular disease treated. The dose and frequency of dosing may also depend on pharmacokinetic and pharmacodynamic, as well as toxicity and therapeutic efficiency data. For example, pharmacokinetic and pharmacodynamic information about a peptidic CXCR4 inhibitor and a phosphatidylinositol-3-kinase (PI3K) inhibitor, can be collected through preclinical in vitro and in vivo studies, later confirmed in humans during the course of clinical trials. Thus, for the peptidic CXCR4 inhibitor and the phosphatidylinositol-3-kinase (PI3K) inhibitor, used in the methods provided herein, a therapeutically effective dose can be estimated initially from biochemical and/or cell-based assays. Then, dosage can be formulated in animal models to achieve a desirable circulating concentration range. As human studies are conducted further information will emerge regarding the appropriate dosage levels and duration of treatment for various diseases and conditions.

Toxicity and therapeutic efficacy of a peptidic CXCR4 inhibitor and a phosphatidylinositol-3-kinase (PI3K) inhibitor, can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the "therapeutic index", which typically is

expressed as the ratio LD50/ED50. Compounds that exhibit large therapeutic indices, i.e. the toxic doses are substantially higher than the effective doses, are preferred. The data obtained from such cell culture assays and additional animal studies can be used in formulating a range of dosage for human use. The doses of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity.

A peptidic CXCR4 inhibitor may be administered to the subject (e.g. a human) within minutes or hours. In some embodiments, a peptidic CXCR4 inhibitor may be administered to the subject (e.g. a human) over about 1 to about 240 minutes, over about 1 to about 180 minutes, or over about 5 to about 150 minutes, or over about 5 to about 120 minutes, or over about 1 to 60 minutes, or over about 1 to 10 minutes, or over about 5 minutes.

A phosphatidylinositol-3-kinase (PI3K) inhibitor may be administered to the subject (e.g. a human) within minutes or hours. In some embodiments, a phosphatidylinositol-3-kinase (PI3K) inhibitor may be administered to the subject (e.g. a human) over about 1 to about 240 minutes, over about 1 to about 180 minutes, or over about 5 to about 150 minutes, or over about 5 to about 120 minutes.

An exemplary treatment regime entails administration once daily, twice daily, three times daily, every day, every second day, every third day, every fourth day, every fifth day, every sixth day, twice per week, once per week. The combination of the invention is usually administered on multiple occasions. Intervals between single dosages can be, for example, less than a day, a day, two days, three days, four days, five days, six days or a week. The combination of the invention may be given as a continous uninterrupted treatment. The combination of the invention may also be given in a regime in which the subject receives cycles of treatment (administration cycles) interrupted by a drug holiday or period of non-treatment. Thus, the combination of the invention may be administered according to the selected intervals above for a continuous period of one week or a part thereof, for two weeks, for three weeks for four weeks, for five weeks or for six weeks and then stopped for a period of one week, or a part thereof, for two weeks, for three weeks, for four weeks, for five weeks, or for

six weeks or for even more weeks. The combination of the treatment interval and the non-treatment interval is called a cycle. The cycle may be repeated one or more times. Two or more different cycles may be used in combination for repeating the treatment one or more times. The administration of the pharmaceutical combination according to the invention may start with a run-in cycle.

Exemplary doses of the peptidic CXCR4 inhibitor for a subject, preferably for a human subject, may be from about 0.1 to about 700 mg/kg, or from about 0.1 to about 500 mg/kg, or from about 0.1 to about 250 mg/kg.

Exemplary doses of phosphatidylinositol-3-kinase (PI3K) inhibitor, for a subject, preferably for a human subject, may be from about 0.05 to about 50 mg/kg or from about 0.05 to about 25 mg/kg or from about 0.05 to about 20 mg/kg or from about 0.05 to about 15 mg/kg or from about 0.5 to about 12 mg/kg.

In one embodiment, the invention provides a pharmaceutical combination comprising a peptidic CXCR4 inhibitor and phosphatidylinositol-3-kinase (PI3K) inhibitor, wherein the dose of said peptidic CXCR4 inhibitor in the combination from about 0.1 to about 700 mg/kg, or from about 0.1 to about 500 mg/kg, or from about 0.1 to about 250 mg kg and wherein the dose of said phosphatidylinositol-3-kinase (PI3K) inhibitor in the combination is from about 0.05 to about 50 mg/kg or from about 0.05 to about 25 mg/kg or from about 0.05 to about 20 mg/kg or from about 0.05 to about 15 mg/kg or from about 0.5 to about 12 mg/kg.

In a preferred embodiment, the invention provides a pharmaceutical combination comprising a peptidic CXCR4 inhibitor and phosphatidylinositol-3-kinase (PI3K) inhibitor, wherein the dose of said peptidic CXCR4 inhibitor in the combination is from about 0.1 to about 250 mg/kg; and wherein the dose of said phosphatidylinositol-3-kinase (PI3K) inhibitor in the combination is from about 0.05 to about 25 mg/kg.

In one embodiment, the invention provides a pharmaceutical combination comprising a peptidic CXCR4 inhibitor and phosphatidylinositol-3-kinase (PI3K) inhibitor, wherein the

peptidic CXCR4 inhibitor is administered to the subject at a dose from about 0.1 to about 700 mg/kg, or from about 0.1 to about 500 mg/kg, or from about 0.1 to about 250 mg/kg.

In one embodiment, the invention provides a pharmaceutical combination comprising a peptidic CXCR4 inhibitor and phosphatidylinositol-3-kinase (PI3K) inhibitor, wherein phosphatidylinositol-3-kinase (PI3K) inhibitor is administered to the subject at a dose from about 0.05 to about 50 mg/kg or from about 0.05 to about 25 mg/kg or from about 0.05 to about 20 mg/kg or from about 0.05 to about 15 mg/kg or from about 0.5 to about 12 mg/kg.

Additional combination therapies

Provided herein are also methods of treatment in which the peptidic CXCR4 inhibitor in combination with a phosphatidylinositol-3-kinase (PI3K) inhibitor, is administered to a subject (e.g. a human) in additional combination with one or more additional therapies. Thus, in some embodiments, the method for treating cancer in a subject (e.g. a human), comprises administering to the subject a therapeutically effective amount of a peptidic CXCR4 inhibitor and a phosphatidylinositol-3-kinase (PI3K) inhibitor, together with one or more additional therapies, which can be useful for treating the cancer. The one or more additional therapies may involve the administration of one or more therapeutic agents, preferably therapeutic anti-cancer agents.

Kit of parts

A pharmaceutical combination e.g. a combined preparation (including, for example, formulations and unit dosages) comprising the peptidic CXCR4 inhibitor and the phosphatidylinositol-3-kinase (PI3K) inhibitor, can be prepared and placed in an appropriate container, and labeled for treatment of an indicated condition. Kits of parts also are contemplated. For example, a kit can comprise unit dosage forms of the peptidic CXCR4 inhibitor and the phosphatidylinositol-3-kinase (PI3K) inhibitor, and a package insert containing instructions for use of the composition in treatment of a medical condition. In some embodiments, the kits comprises a unit dosage form of peptidic CXCR4 inhibitor and/or a

phosphatidylinositol-3-kinase (PI3K) inhibitor. The instructions for use in the kit may be for treating a cancer.

Thus, in a fourth aspect the present invention provides a kit of parts comprising a first container, a second container and a package insert, wherein the first container comprises at least one dose of a medicament comprising a peptidic CXCR4 inhibitor; the second container comprises at least one dose of a medicament comprising a phosphatidylinositol-3-kinase (PI3K) inhibitor, and the package insert comprises optionally instructions for treating a subject for cancer using the medicaments. The cancer the instructions relate to are usually the cancers as described supra.

Examples

The present examples are intended to illustrate the present invention without restricting it.

The peptides according to formula (Ia) and formula (I) can be prepared according to WO2008/104090, WO2012/168336 as well as WO2013/182240.

Example 1

Background

Targeting downstream signaling to B-cell receptor (BCR) is one of the promising therapeutic approaches in lymphoma. Inhibition or BCR signaling is being extensively explored as a therapeutic approach for patients with lymphoid neoplasms. Idelalisib was the first-in-class specific PI3Kδ inhibitor to be approved, in combination with rituximab, by the U.S. Food and Drug Administration (FDA) for the treatment of indolent B cell lymphoma (Miller BW, Przepiorka D, de Claro RA, et al.: FDA approval: idelalisib monotherapy for the treatment of patients with follicular lymphoma and small lymphocytic lymphoma, *Clin Cancer Res*. 2015, *21*(7), 1525-1529; Yang Q, Modi P, Newcomb T, Queva C, Gandhi V.: Idelalisib: First-in-Class PI3K Delta Inhibitor for the Treatment of Chronic Lymphocytic Leukemia, Small Lymphocytic Leukemia, and Follicular Lymphoma, *Clin Cancer Res*. 2015, *21*(7), 1537-1542). Promising clinical and preclinical response has been reported in indolent lymphoma, including marginal zone lymphoma (MZL) with second generations PI3Kδ inhibitors, such as copanlisib (pan-class I PI3K inhibitor with predominant activity against PI3Kα/PI3Kδ, Dreyling M, Santoro A, Mollica L, et al.: Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study, *Am J Hematol*. 2020, *95*, 362-371). However, single treatment with BCR signaling inhibitors show limited success in complete response. Moreover, although current treatments are initially effective, they are not curative, and their efficacy decreases upon repeated administrations leading to drug resistance and relapse.

Methods

The VL51 lines derived from splenic marginal zone lymphoma were used in all experiments. VL51 idelalisib-resistant, VL51 copanlisib-resistant and respective parental lines were exposed to increasing doses of the CXCR4 inhibitors POL5551 (cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), and POL6326 (cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:1**), respectively, alone or in combination with increasing doses of idelalisib and copanlisib, respectively. Cell viability was tested by MTT assay upon 72h of treatment, as previously performed (Tarantelli C, Gaudio E, Arribas AJ, et al.: PQR309 Is a Novel Dual PI3K/mTOR Inhibitor with Preclinical Antitumor Activity in Lymphomas as a Single Agent and in Combination Therapy, *Clin Cancer Res*. 2018, *24*(1), 120-129; Boi M, Gaudio E, Bonetti P, et al.: The BET Bromodomain Inhibitor OTX015 Affects Pathogenetic Pathways in Preclinical B-cell Tumor Models and Synergizes with Targeted Drugs, *Clin Cancer Res*. 2015, *21*(7), 1628-1638). The beneficial effect of the combinations versus the single agents will be considered as synergism according to the Chou-Talalay combination index (CI) (Chou TC: Drug combination studies and their synergy quantification using the Chou-Talalay method, *Cancer Res*. 2010, *70*(2), 440-446), as previously performed (Tarantelli C, Gaudio E, Arribas AJ, et al.: PQR309 Is a Novel Dual PI3K/mTOR Inhibitor with Preclinical Antitumor Activity in Lymphomas as a Single Agent and in Combination Therapy, *Clin Cancer Res*. 2018, *24*(1), 120-129; Boi M, Gaudio E, Bonetti P, et al.: The BET Bromodomain Inhibitor OTX015 Affects Pathogenetic Pathways in Preclinical B-cell Tumor Models and Synergizes with Targeted Drugs, *Clin Cancer Res*. 2015, *21*(7), 1628-1638), and as synergistic efficacy according to the multi-dimensional synergy of combinations algorithm (MuSyC) (Meyer CT, Wooten DJ, Paudel BB, et al.: Quantifying Drug Combination Synergy along Potency and Efficacy Axes, *Cell Syst*. 2019, *8*(2), 97-108 e116).

Results

The experiments performed in the VL51 models showed that both CXCR4 inhibitors POL5551

and POL6326 are synergistic with the PI3K inhibitor idelalisib and the PI3K inhibitor copanlisib, respectively. In particular, POL5551 shows synergism in cells resistant to idelalisib and copanlisib, respectively, and similarly in their parental counterpart (**Tables 1** and **2**, **Figures 1** and **2**). Combination of POL6326 with idelalisib or copanlisib is synergistic in either parental or resistant cells (**Tables 1** and **2**, Figures **3** and **4**). Moreover, addition of POL5551 or POL6326 overcomes resistance to PI3K inhibitors in VL51 models (**Figure 5** and **6**).

Table 1. Chou-Talalay index and synergistic efficacy according to MuSyC for the combination of the CXCR4 inhibitors POL5551 and POL6326 with the PI3K inhibitor idelalisib in VL51 parental and resistant models. Anti-tumor activity of POL5551 and POL6326, respectively, was determined in parental and resistant lines to the PI3K inhibitor idelalisib. Parental and resistant lines were derived from the VL51 splenic marginal zone lymphoma model. Cells were exposed (72h) to increasing doses of idelalisib (0.08, 0.4, 2, 10 and 50 μM) in combination with increasing doses of POL5551 (0.08, 0.4, 2, 10 and 50 μM), or to increasing doses of idelalisib (0.05, 0.24, 1.2, 6 and 50 μM) in combination with increasing doses POL6326 (0.08, 0.4, 2, 10 and 50 μM), followed by MTT assay. Displayed in **Table 1** is the median of the 25 values obtained for each combination of doses.

Chou-Talalay index (CI): synergistic: CI<0.9, additive: 0.9<CI<1.1, no benefit: CI>1.1.

Synergistic Efficacy (MuSyC): synergistic: >1, additive: 0<eff<1, no effect: ~0, no benefit: <0.

Cell type	VL51 parental	VL51 idelalisib resistant	VL51 parental	VL51 idelalisib resistant
PI3K inhibitor	idelalisib	idelalisib	idelalisib	idelalisib
CXCR4 inhibitor	POL5551	POL5551	POL6326	POL6326
Median CI	0.01	0.05	0.03	0.02
Median MuSyC	1.672	3.511	0.531	3.271

Table 2. Chou-Talalay index and synergistic efficacy according to MuSyC for the combination of the CXCR4 inhibitors POL5551 and POL6326 with the PI3K inhibitor copanlisib in VL51 parental and resistant models. Anti-tumor activity of POL5551 and POL6326, respectively, was determined in parental and resistant lines to the PI3K inhibitor copanlisib. Parental and resistant lines were derived from the VL51 splenic marginal zone lymphoma model. Cells were exposed (72h) to increasing doses of copanlisib (0.008, 0.04, 0.2, 1 and 5 μM) in combination with increasing doses of POL5551 (0.08, 0.4, 2, 10 and 50 μM) and POL6326 (0.08, 0.4, 2, 10 and 50 μM), respectively, followed by MTT assay. Displayed in **Table 1** is the median of the 25 values obtained for each combination of doses.

Chou-Talalay index (CI): synergistic: CI<0.9, additive: 0.9<CI<1.1, no benefit: CI>1.1.

Synergistic Efficacy (MuSyC): synergistic: >1, additive: 0<eff<1, no effect: ~0, no benefit: <0.

Cell type	VL51 parental	VL51 copanlisib resistant	VL51 parental	VL51 copanlisib resistant
PI3K inhibitor	copanlisib	copanlisib	copanlisib	copanlisib
CXCR4 inhibitor	POL5551	POL5551	POL6326	POL6326
Median CI	0.001	0.00	0.12	0.22
Median MuSyC	1.297	1.669	1.269	1.649

Example 2

Methods

Various cell lines derived from mantle cell lymphoma (MCL) (**Table 3**) were used in the experiments. Cell lines were exposed to increasing doses of the CXCR4 inhibitor POL5551 (cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**), alone or in combination with increasing doses of the PI3K inhibitor copanlisib. Cell viability was tested by MTT assay upon 72h of treatment, as previously performed (Tarantelli C, Gaudio E, Arribas AJ, et al.: PQR309 Is a Novel Dual PI3K/mTOR Inhibitor with Preclinical Antitumor Activity in Lymphomas as a Single Agent and

in Combination Therapy, *Clin Cancer Res*. 2018, *24*(1), 120-129; Boi M, Gaudio E, Bonetti P, et al.: The BET Bromodomain Inhibitor OTX015 Affects Pathogenetic Pathways in Preclinical B-cell Tumor Models and Synergizes with Targeted Drugs, *Clin Cancer Res*. 2015, *21*(7), 1628-1638). The beneficial effect of the combinations versus the single agents was considered as synergism according to the Chou-Talalay combination index (CI) (Chou TC.: Drug combination studies and their synergy quantification using the Chou-Talalay method, *Cancer Res*. 2010, 70(2), 440-446), as previously performed (Tarantelli C, Gaudio E, Arribas AJ, et al.: PQR309 Is a Novel Dual PI3K/mTOR Inhibitor with Preclinical Antitumor Activity in Lymphomas as a Single Agent and in Combination Therapy, *Clin Cancer Res*. 2018, *24*(1), 120-129; Boi M, Gaudio E, Bonetti P, et al.: The BET Bromodomain Inhibitor OTX015 Affects Pathogenetic Pathways in Preclinical B-cell Tumor Models and Synergizes with Targeted Drugs, *Clin Cancer Res*. 2015, *21*(7), 1628-1638).

Table 3. Histology, cell lines and sources

Histology	Cell line	Source
MCL	GRANTA-519	Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ, DE)
	JEKO-1	Eisaku Kondo, (Okayama, JP)
	JVM2	Elias Campo (Barcelona, ES)
	MAVER1	Alberto Zamò (Verona, IT)
	MINO	Robert Kridel (Vancouver, CA)
	REC-1	Finbarr Cotter (London, UK)
	SP49	Robert Kridel (Vancouver, CA)
	SP53	Robert Kridel (Vancouver, CA)
	UPN-1	Robert Kridel (Vancouver, CA)
	Z-138	Robert Kridel (Vancouver, CA)

Results

The experiments performed in various cell lines derived from mantle cell lymphoma (MCL) showed that the CXCR4 inhibitor POL5551 is synergistic with the PI3K inhibitor copanlisib (**Table 4**).

Table 4. Chou-Talalay index for the combination of the CXCR4 inhibitor POL5551 with the PI3K inhibitor copanlisib in various models of MCL. Anti-tumor activity of POL5551 was determined in various cell lines (see **Table 3**) to the PI3K inhibitor copanlisib. Cells were exposed (72h) to increasing doses of copanlisib (0.0016, 0.008, 0.04, 0.2, 1 μM) in combination with increasing doses of POL5551 (0.16, 0.8, 4, 20, 100 μM) followed by MTT assay. Displayed in **Table 4** is the median of the 25 values obtained for each combination of doses.
Chou-Talalay index (CI): synergistic: CI<0.9, additive: 0.9<CI<1.1, no benefit: CI>1.1.

Histology	Cell line	CXCR4 inhibitor	PI3K inhibitor	Median CL
MCL	GRANTA-519	POL5551	Copanlisib	0.48
	JEKO-1	POL5551	Copanlisib	0.62
	JVM2	POL5551	Copanlisib	0.39
	MAVER1	POL5551	Copanlisib	0.26
	MINO	POL5551	Copanlisib	0.32
	REC-1	POL5551	Copanlisib	0.11
	SP49	POL5551	Copanlisib	0.14
	SP53	POL5551	Copanlisib	0.17
	UPN-1	POL5551	Copanlisib	0.65
	Z-138	POL5551	Copanlisib	0.09

CLAIMS

1) A pharmaceutical combination comprising:

(a) a peptidic CXCR4 inhibitor;

(b) a phosphatidylinositol-3-kinase (PI3K) inhibitor; and

(c) optionally one or more pharmaceutically acceptable diluents, excipients or carriers.

2) A pharmaceutical combination according to claim 1, wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^{1}-His^{2}-Xaa^{3}-Cys^{4}-Ser^{5}-Xaa^{6}-Xaa^{7}-Xaa^{8}-Arg^{9}-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-)

(Ia),

in which

Xaa^{3} is Ala; Tyr; or Tyr(Me);

Xaa^{6} is Ala or Acc;

Xaa^{7} is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^{8} is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Acc is 1-aminocyclopropane-1-carboxylic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^{\omega}$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues; and

wherein the compound of formula Ia has a disulfide bond between Cys^{4} and Cys^{11}.

3) A pharmaceutical combination according to claim 1 or 2, wherein said peptidic CXCR4 inhibitor is a backbone cyclized peptidic compound, built up from 16 amino acid residues, or pharmaceutically acceptable salts thereof, of the formula

cyclo(-Tyr^1-His^2-Xaa^3-Cys^4-Ser^5-Ala^6-Xaa^7-Xaa^8-Arg^9-Tyr^{10}-Cys^{11}-Tyr^{12}-Gln^{13}-Xaa^{14}-Xaa^{15}-Pro^{16}-) (I),

in which

Xaa^3 is Ala; Tyr; or Tyr(Me);

Xaa^7 is ^{D}Pro; ^{D}Tyr; or ^{D}Tyr(Me);

Xaa^8 is Dab; or Orn(iPr);

Xaa^{14} is Lys; or Lys(iPr);

Xaa^{15} is ^{D}Pro; or ^{D}Lys(iPr);

wherein

Tyr(Me) is (2*S*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

^{D}Tyr(Me) is (2*R*)-2-amino-3-(4-methoxyphenyl)-propanoic acid;

Dab is (2*S*)-2,4-diaminobutyric acid;

Orn(iPr) is (2*S*)-N$^\omega$-isopropyl-2,5-diaminopentanoic acid;

Lys(iPr) is (2*S*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

^{D}Lys(iPr) is (2*R*)-N$^\omega$-isopropyl-2,6-diaminohexanoic acid;

wherein all of the amino acid residues, which are not explicitly designated as D-amino acid residues, are L-amino acid residues, and

wherein the compound of formula I has a disulfide bond between Cys^4 and Cys^{11}.

4) A pharmaceutical combination according to any one of claims 1 to 3, wherein said peptidic CXCR4 inhibitor is selected from the group consisting of

cyclo(-Tyr-His-Ala-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:1**), and

cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^4 and Cys^{11}, (**SEQ ID NO:2**),

or pharmaceutically acceptable salts thereof.

5) A pharmaceutical combination according to any one of claims 1 to 4, wherein said peptidic CXCR4 inhibitor is
cyclo(-Tyr-His-Tyr-Cys-Ser-Ala-^{D}Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-^{D}Pro-Pro-) having a disulfide bond between Cys^{4} and Cys^{11}, (**SEQ ID NO:2**),
or pharmaceutically acceptable sals thereof.

6) A pharmaceutical combination according to any one of claims 1 to 5, wherein the phosphatidylinositol-3-kinase (PI3K) inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M (SH748), IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, Alpelisib (Piqray™, BYL719), Serabelisib (MLN1117, INK1117, TAK-117), CYH33, GDC-0326, WX-037, GSK2636771, SAR-260301, AZD-8835, AZD-8186, KA2237, VT30, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235, NVP-BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765, SAR245409), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458, GSK458), Panulisib (P7170), VS-5584 (SB2343), BGT-226 (NVP-BGT226), DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302), Fimepinostat (CUDC-907), Rigosertib (ON-01910), BR101801, HEC89736, CHF-6523 and TL117.

7) A pharmaceutical combination according to any one of claims 1 to 5, wherein the phosphatidylinositol-3-kinase (PI3K) inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Pilaralisib (XL-147), ZSTK474, CH5132799 (MEN1611), Pictilisib (GDC-0941), Taselisib (GDC-0032), SN32976, Sonolisib (PX-866), TG100-115, Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib

(GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M (SH748), IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Dactolisib (BEZ235, NVP-BEZ235), Paxalisib (GDC-0084), Voxtalisib (XL765, SAR245409), Samotolisib (LY3023414), Apitolisib (GDC-0980), SF1126, Omipalisib (GSK2126458, GSK458), Panulisib (P7170), VS-5584 (SB2343), BGT-226 (NVP-BGT226), DS-7423, PF-04691502, PKI-179, Puquitinib (XC-302) and Fimepinostat (CUDC-907).

8) A pharmaceutical combination according to any one of claims 1 to 5, wherein the phosphatidylinositol-3-kinase (PI3K) is selected from the group consisting of pan-PI3K inhibitors and isoform-selective PI3K inhibitors.

9) A pharmaceutical combination according to any one of claims 1 to 5, wherein the PI3K inhibitor is selected from the group consisting of Copanlisib (Aliqopa™, BAY 80-6946), Buparlisib (BKM-120), Taselisib (GDC-0032), Idelalisib (Zydelig™, GS-1101, CAL-101), Duvelisib (Copiktra™, IPI-145, INK-1197), Umbralisib (Ukoniq™, RP5264, TGR-1202), Parsaclisib (INCB050465), Zandelisib (ME-401, PWT-143), AMG319 (ACP319), Dezapelisib (INCB040093), HMPL-689, GS9901, Acalisib (GS-9820), Eganelisib (IPI-549), Tenalisib (RP6530), SHC014748M (SH748), IOA244, Nemiralisib (GSK-2269557), GSK2292767, Leniolisib (CDZ173-NX), Seletalisib, RV1729, RV6153, AZD8154, AZD-8835, AZD-8186, Gedatolisib (PF-05212384, PKI-587), Bimiralisib (PQR309), Puquitinib (XC-302 and Fimepinostat (CUDC-907).

10) A pharmaceutical combination according to any one of claims 1 to 5, wherein the phosphatidylinositol-3-kinase (PI3K) inhibitor is Idelalisib (Zydelig™, GS-1101, CAL-101) or Copanlisib (Aliqopa™, BAY 80-6946).

11) A pharmaceutical combination according to any one of claims 1 to 10, for use as a medicament.

12) A pharmaceutical combination according to any one of claims 1 to 10 for use in a method for the prevention, delay of progression or treatment of cancer in a subject.

13) A pharmaceutical combination for use according to claim 12, wherein the cancer is a tumor of the hematopoietic and lymphoid tissues.

14) A pharmaceutical combination for use according to claim 13, wherein the tumor of the hematopoietic and lymphoid tissues is selected from the group consisting of small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia), hairy cell leukaemia, Burkitt lymphoma, marginal zone lymphoma (MZL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL).

15) A pharmaceutical combination for use according to claim 13, wherein the tumor of the hematopoietic and lymphoid tissues is is selected from the group consisting of mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) and splenic marginal zone lymphoma (SMZL).

16) A pharmaceutical combination for use according to claim 13, wherein the tumor of the hematopoietic and lymphoid tissues is mantle cell lymphoma (MCL) or splenic marginal zone lymphoma (SMZL).

17) A pharmaceutical combination for use according to claim 13, wherein the tumor of the hematopoietic and lymphoid tissues is marginal zone lymphoma (MZL) or splenic marginal zone lymphoma (SMZL).

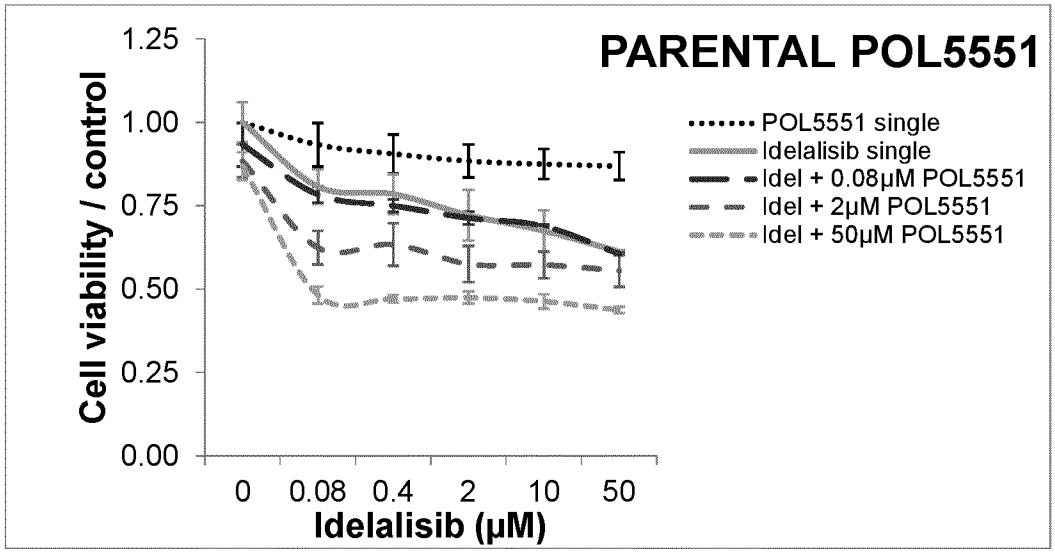
18) A pharmaceutical combination for use according to claim 13, wherein the tumor of the hematopoietic and lymphoid tissues is mantle cell lymphoma (MCL).

19) A pharmaceutical combination for use according to claim 13, wherein the tumor of the hematopoietic and lymphoid tissues is marginal zone lymphoma (MZL).

20) A pharmaceutical combination for use according to claim 13, wherein the tumor of the hematopoietic and lymphoid tissues is splenic marginal zone lymphoma (SMZL).

21) A kit of parts comprising a first container, a second container and a package insert, wherein the first container comprises at least one dose of a medicament comprising a peptidic CXCR4 inhibitor; the second container comprises at least one dose of a medicament comprising a phosphatidylinositol-3-kinase (PI3K) inhibitor, and the package insert comprises optionally instructions for treating a subject for cancer using the medicaments.

Figure 1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Cell viability / control
1.25
1.00
0.75
0.50
0.25
0.00
0
0.08
0.4
2
10
50
Idelalisib (µM)
POL5551 single
Idelalisib single
Idel + 0.08µM POL5551
Idel + 2µM POL5551
Idel + 50µM POL5551

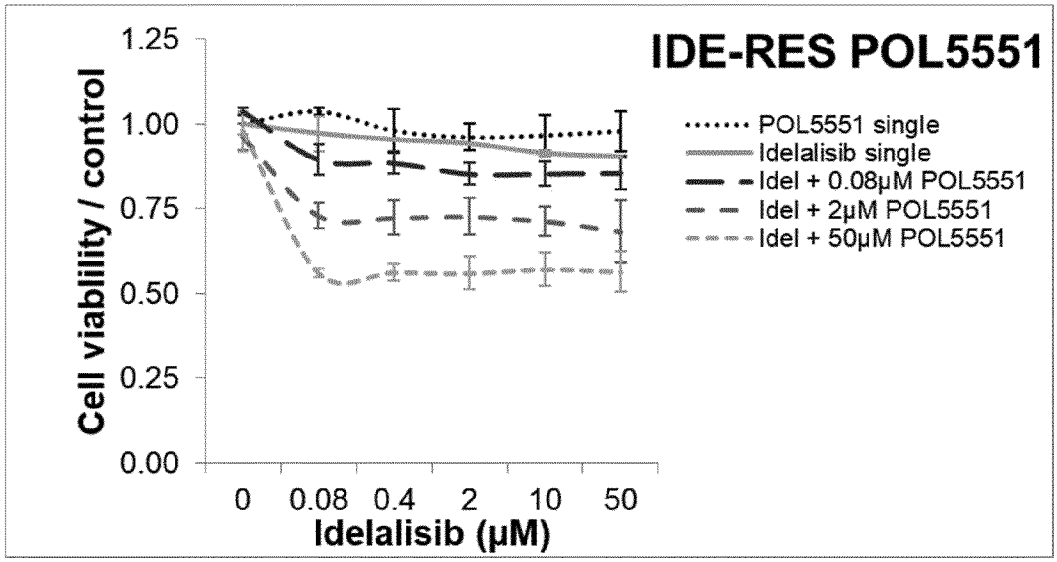
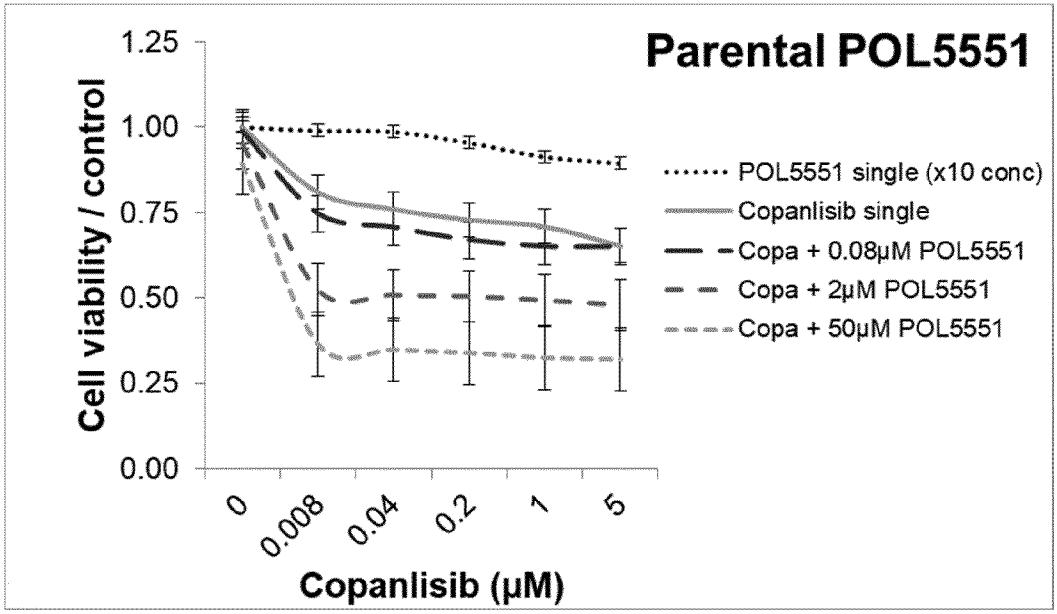

IDE-RES POL5551
Cell viablility / control
1.25
1.00
0.75
0.50
0.25
0.00
0
0.08
0.4
2
10
50
Idelalisib (µM)
POL5551 single
Idelalisib single
Idel + 0.08µM POL5551
Idel + 2µM POL5551
Idel + 50µM POL5551

Figure 2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Cell viability / control
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1.00
0.75
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0.25
0.00
0
0.008
0.04
0.2
1
5
Copanlisib (µM)
POL5551 single (x10 conc)
Copanlisib single
Copa + 0.08µM POL5551
Copa + 2µM POL5551
Copa + 50µM POL5551

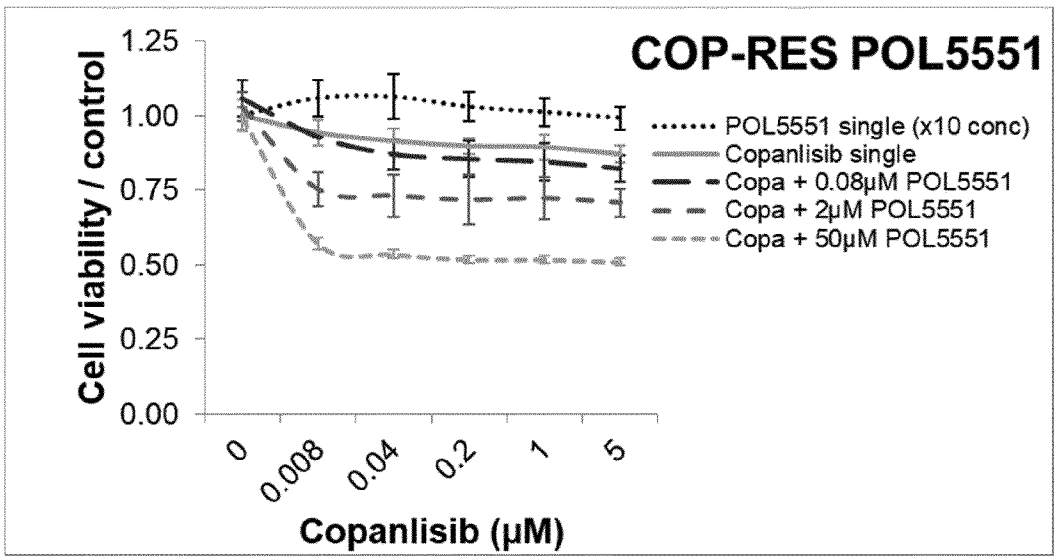
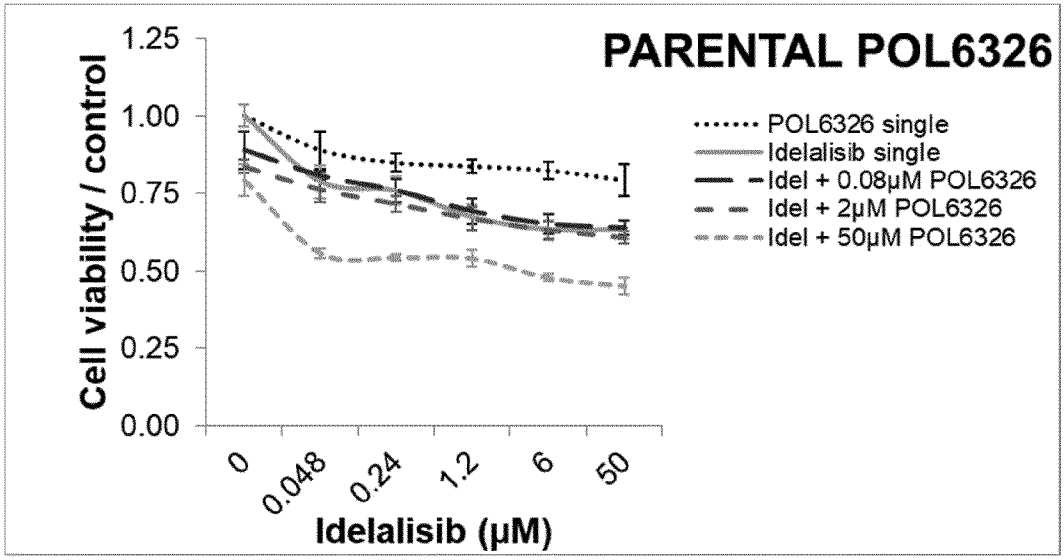

COP-RES POL5551
Cell viability / control
1.25
1.00
0.75
0.50
0.25
0.00
0
0.008
0.04
0.2
1
5
Copanlisib (µM)
POL5551 single (x10 conc)
Copanlisib single
Copa + 0.08µM POL5551
Copa + 2µM POL5551
Copa + 50µM POL5551

Figure 3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Cell viability / control
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0.75
0.50
0.25
0.00
0
0.048
0.24
1.2
6
50
Idelalisib (μM)
POL6326 single
Idelalisib single
Idel + 0.08μM POL6326
Idel + 2μM POL6326
Idel + 50μM POL6326

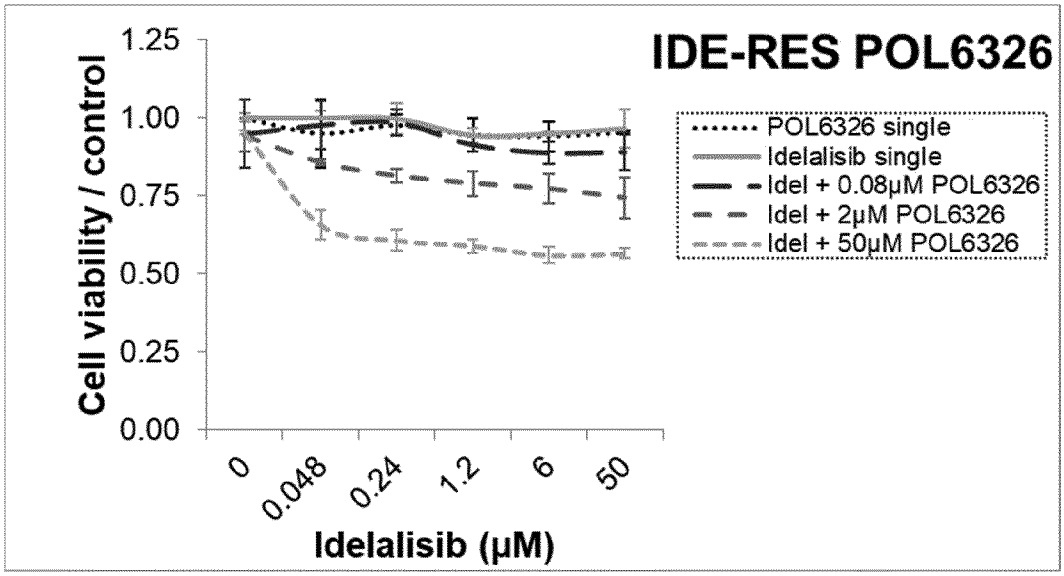
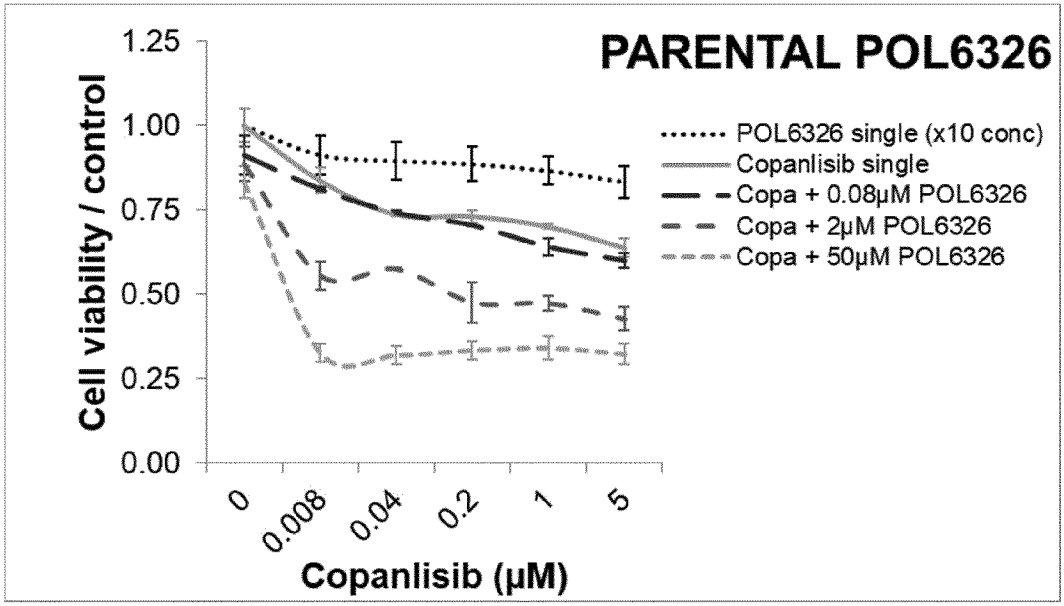

IDE-RES POL6326
Cell viability / control
1.25
1.00
0.75
0.50
0.25
0.00
0
0.048
0.24
1.2
6
50
Idelalisib (μM)
POL6326 single
Idelalisib single
Idel + 0.08μM POL6326
Idel + 2μM POL6326
Idel + 50μM POL6326

Figure 4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Cell viability / control
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0.75
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0.00
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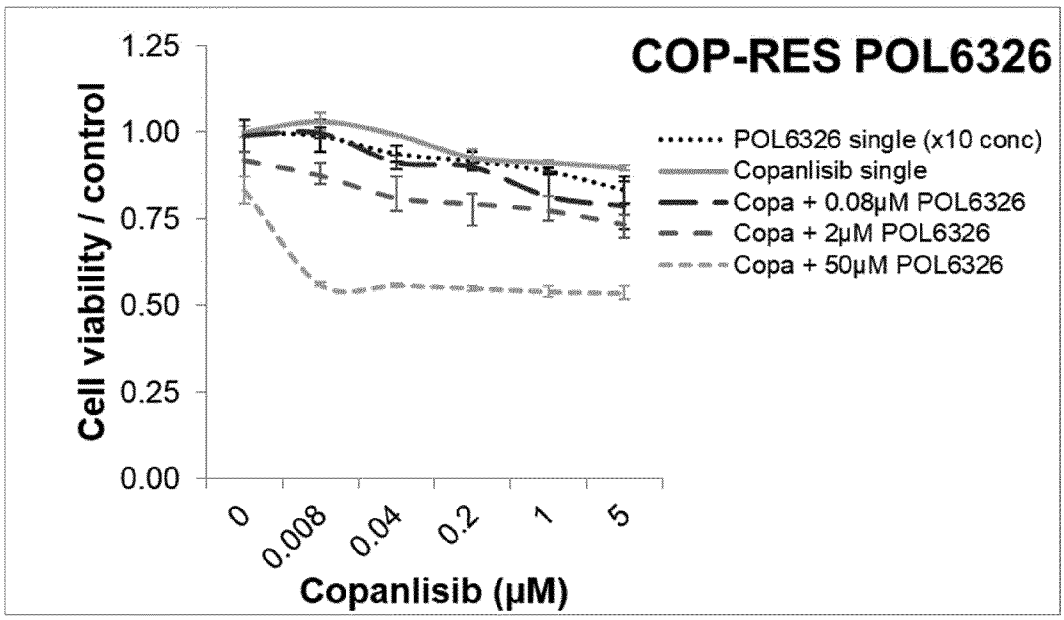
0.008
0.04
0.2
1
5
Copanlisib (µM)
POL6326 single (x10 conc)
Copanlisib single
Copa + 0.08µM POL6326
Copa + 2µM POL6326
Copa + 50µM POL6326


COP-RES POL6326
Cell viability / control
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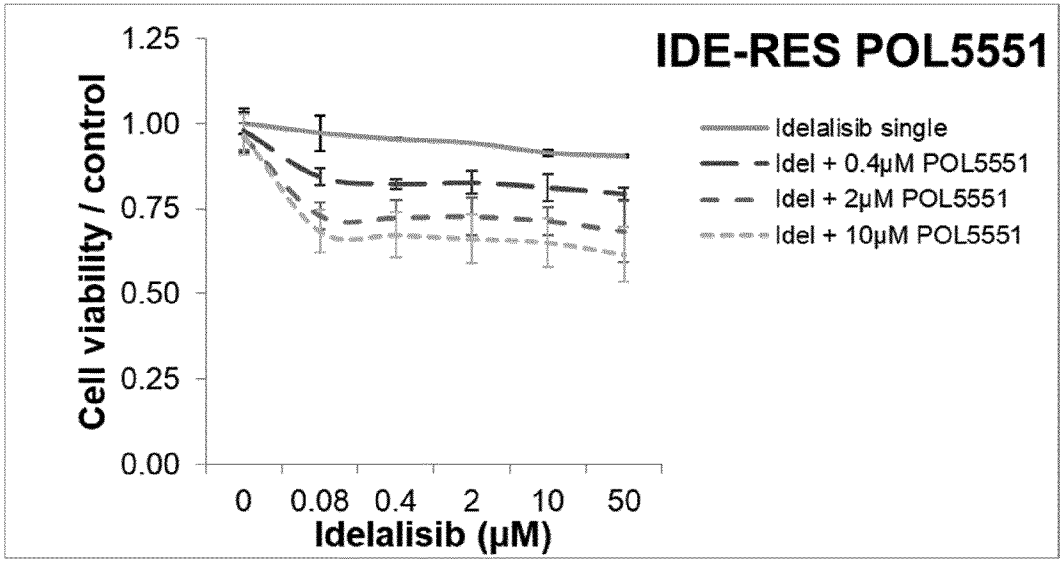
1.00
0.75
0.50
0.25
0.00
0
0.008
0.04
0.2
1
5
Copanlisib (µM)
POL6326 single (x10 conc)
Copanlisib single
Copa + 0.08µM POL6326
Copa + 2µM POL6326
Copa + 50µM POL6326

Figure 5


IDE-RES POL5551
Cell viability / control
1.25
1.00
0.75
0.50
0.25
0.00
0
0.08
0.4
2
10
50
Idelalisib (µM)
Idelalisib single
Idel + 0.4µM POL5551
Idel + 2µM POL5551
Idel + 10µM POL5551

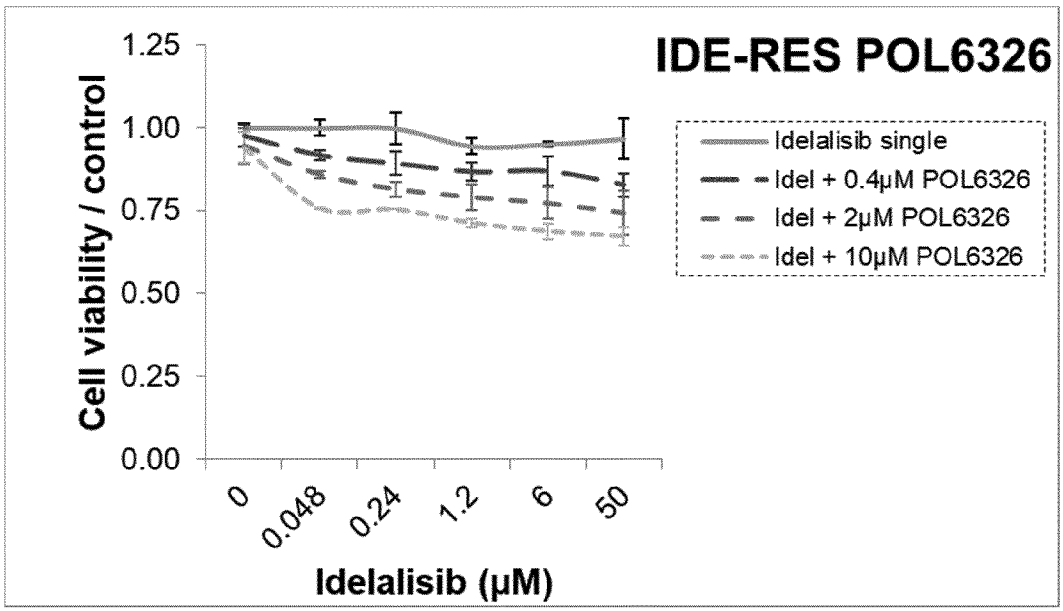
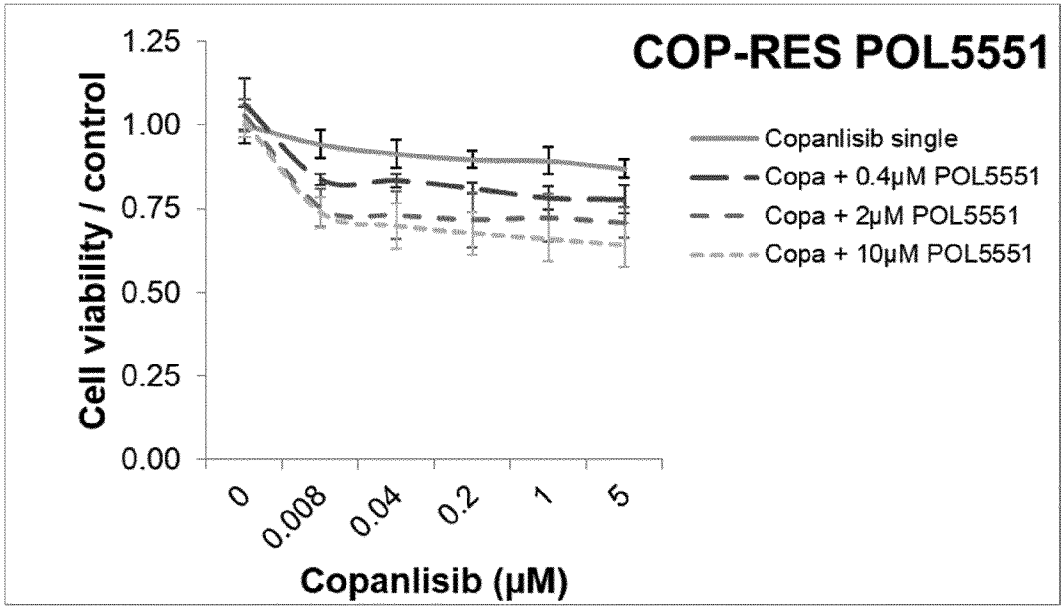
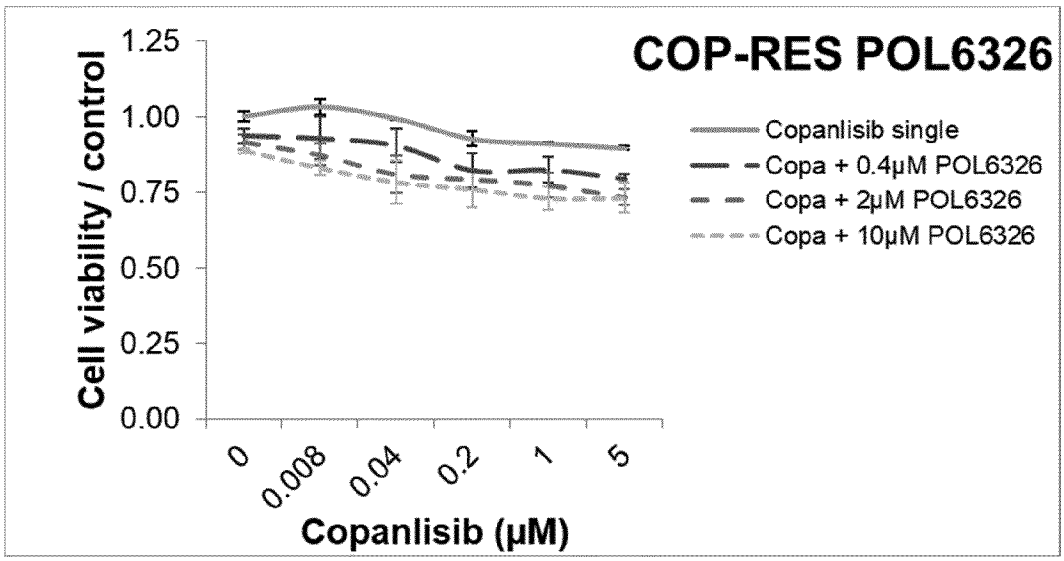

IDE-RES POL6326
Cell viability / control
1.25
1.00
0.75
0.50
0.25
0.00
0
0.048
0.24
1.2
6
50
Idelalisib (µM)
Idelalisib single
Idel + 0.4µM POL6326
Idel + 2µM POL6326
Idel + 10µM POL6326

Figure 6


COP-RES POL5551
Cell viability / control
1.25
1.00
0.75
0.50
0.25
0.00
0
0.008
0.04
0.2
1
5
Copanlisib (µM)
Copanlisib single
Copa + 0.4µM POL5551
Copa + 2µM POL5551
Copa + 10µM POL5551


COP-RES POL6326
Cell viability / control
1.25
1.00
0.75
0.50
0.25
0.00
0
0.008
0.04
0.2
1
5
Copanlisib (µM)
Copanlisib single
Copa + 0.4µM POL6326
Copa + 2µM POL6326
Copa + 10µM POL6326

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/069915

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/04 A61K31/00 A61P35/00
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

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, INSPEC, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEN LINFENG ET AL: "CXCR4 upregulation is an indicator of sensitivity to B-cell receptor/PI3K blockade and a potential resistance mechanism in B-cell receptor-dependent diffuse large B-cell lymphomas", HAEMATOLOGICA, vol. 105, no. 5, 30 August 2019 (2019-08-30), pages 1361-1368, XP55975374, IT ISSN: 0390-6078, DOI: 10.3324/haematol.2019.216218 the whole document compounds AMD3100, R406 ----- -/--	1-21

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 November 2022	23/11/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Orlando, Michele

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2020/138804 A1 (PARASURAMAN SUDHA [US] ET AL) 7 May 2020 (2020-05-07) the whole document claims	1-21
Y	MARTIN MIGUEL ET AL: "At the bedside: Profiling and treating patients with CXCR4?expressing cancers", JOURNAL OF LEUKOCYTE BIOLOGY, 22 October 2020 (2020-10-22), XP055798564, GB ISSN: 0741-5400, DOI: 10.1002/JLB.5BT1219-714R Retrieved from the Internet: URL:https://onlinelibrary.wiley.com/doi/full-xml/10.1002/JLB.5BT1219-714R> the whole document pages 9-12, paragraph 5	1-21
Y	FEDERICA BARBIERI ET AL: "Drug design strategies focusing on the CXCR4/CXCR7/CXCL12 pathway in leukemia and lymphoma", EXPERT OPINION ON DRUG DISCOVERY, vol. 11, no. 11, 20 September 2016 (2016-09-20), pages 1093-1109, XP055558199, London, GB ISSN: 1746-0441, DOI: 10.1080/17460441.2016.1233176 the whole document compounds POL5551, POL6326	1-21
Y	SISON EDWARD ALLAN R ET AL: "POL5551, a Novel and Potent CXCR4 Antagonist, Enhances Sensitivity to Chemotherapy in an in Vivo Model of High-Risk (HR) Pediatric Acute Lymphoblastic Leukemia (ALL)", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 124, no. 21, 14 November 2014 (2014-11-14), page 3707, XP086739324, ISSN: 0006-4971, DOI: 10.1182/BLOOD.V124.21.3707.3707 [retrieved on 2021-06-25] the whole document page 30914, right-hand column, last paragraph; compound POL5551	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2022/069915

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2020138804 A1	07-05-2020	CA 3066778 A1	27-12-2018
		CN 110996952 A	10-04-2020
		EP 3641770 A1	29-04-2020
		JP 2020525427 A	27-08-2020
		US 2020138804 A1	07-05-2020
		WO 2018237158 A1	27-12-2018