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(71) **Applicants**: **LES LABORATOIRES SERVIER** [FR/FR]; 35 rue de Verdun, 92284 Suresnes (FR). **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, 4056 Basel (CH). **GILEAD SCIENCES, INC** [—/US]; 333 Lakeside Drive, Foster City, California 94404 (US).

(72) **Inventors**: **DUMONTET, Charles**; 11, chemin du Laquay, 69200 Vénissieux (FR). **KRAUS-BERTHIER, Laurence**; 20, petite rue des Champarons, 92700 Colombes (FR). **KLOOS, Ioana**; 53, bd Richelieu, 92500 Rueil Malmaison (FR). **MORRIS, Erick**; Novartis Institutes for Biomedical Research, Inc, 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **SCHLAFF, Cody D**; Novartis Institutes for Biomedical Research, Inc, 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **FJAELLSKOG, Helena Marie-Louise**; Novartis Institutes for Biomedical Research, Inc, 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **ADEWOYE, Henry**; Gilead Sciences, Inc, 333, Lakeside Drive, Foster City, California 94404 (US). **TUMAS, Daniel**; Gilead Sciences, Inc, 333, Lakeside Drive, Foster City, California 94404 (US).

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(54) **Title**: COMBINATION OF AN INHIBITOR OF PHOSPHATIDYLINOSITOL 3-KINASE DELTA AND A BCL-2 INHIBITOR, USES AND PHARMACEUTICAL COMPOSITIONS THEREOF

(57) **Abstract**: A combination comprising *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)- 3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1, 3-benzodioxol-5-yl}-*N*-phenyl-5, 6,7,8-tetrahydro-l-indolizine carboxamide, or a pharmaceutically acceptable salt thereof, and idelalisib, or a pharmaceutically acceptable salt thereof, and compositions and uses thereof.

COMBINATION OF AN INHIBITOR OF PHOSPHATIDYLINOSITOL 3-KINASE DELTA AND A BCL-2 INHIBITOR, USES AND PHARMACEUTICAL COMPOSITIONS THEREOF

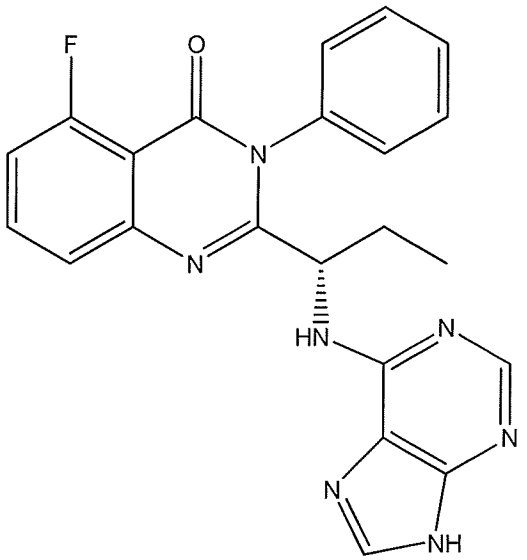
FIELD OF THE INVENTION

The present invention relates to a combination of a Bcl-2 inhibitor and an inhibitor of phosphatidylinositol 3-kinase delta (PI3Kδ), as defined below. The invention also relates to the use of said combination in the treatment of cancer, in particular a non-Hodgkin's lymphoma or leukemia, and more specifically follicular lymphoma or a mantle cell lymphoma. Also provided are pharmaceutical formulations suitable for the administration of such combinations.

BACKGROUND OF THE INVENTION

In the present invention, the Bcl-2 inhibitor is Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or a pharmaceutically acceptable salt thereof. Said Compound 1, its synthesis, its use in the treatment of cancer and pharmaceutical formulations thereof, are described in WO 2013/110890. Compound 1 is a potent and selective Bcl-2 inhibitor which is specifically disclosed in Example 1 of WO 2013/110890, the content of which is incorporated by reference.

Phosphatidylinositol 3-kinase delta (PI3Kδ) is critical for signal transduction downstream of B-cell receptor (BCR), cytokine/chemokine receptors, and adhesion molecules, contributing to the regulation of proliferation, differentiation, migration, and survival of B cells (Fruman et al, *Cancer Discov* 2011, Vol 1(7):562-572). In the present invention, the inhibitor of phosphatidylinositol 3-kinase delta is idelalisib:



(*S*)-2-(1-((9*H*-purin-6-yl)amino)propyl)-5-fluoro-3-phenylquinazolin-4(3*H*)-one

Idelalisib may also be referred to by the following compound name: 5-fluoro-3-phenyl-2-{(1S)-1-[(7*H*-purin-6-yl)amino]propyl}quinazolin-4(3H)-one (WHO Drug Information Vol 27, N°1, 2013).

Idelalisib (also known as GS-1101 or CAL-101) is a drug approved for use in the treatment of chronic lymphocytic leukemia (CLL) in combination with rituximab, and is also approved for use in the treatment of follicular B-cell non-Hodgkin lymphoma and small lymphocytic lymphoma (SLL). Idelalisib selectively inhibits PI3Kδ, thus blocking cell proliferation and inducing apoptosis in B cells (Lannutti et al, *Blood* 2011, Vol 117(2):591-594; Fiorcari et al. *PLoS One* 2013 8(12):e83830). In lymphoid cell lines and primary patient samples, idelalisib blocks PI3K/AKT signaling and promotes apoptosis (Lannutti et al, *Blood* 2011, Vol 117(2):591-594; Herman et al, *Blood* 2011, Vol 117(16):4323-4327). Furthermore, in mantle cell lymphoma (MCL) treatment, idelalisib has demonstrated significant clinical efficacy (Kahl et al, *Blood* 29 May 2014; Vol 123(22):3398-3405). Idelalisib is specifically disclosed in Example 107 of WO2005/113556, the content of which is incorporated by reference, and it can be prepared using the methods described therein. Process for synthesizing idelalisib is also disclosed in WO2015/095601.

Apoptosis is a distinct cell death pathway that is highly regulated and initiated by various stimuli including DNA damage; however evasion of the programmed cell death is a

hallmark of cancer. The efficacy of many chemotherapeutic agents is dependent upon the activation of the intrinsic mitochondrial pathway which is mainly regulated by B-cell like protein-2 (Bcl-2). Bcl-2 has been shown to be up-regulated in many cancers, particularly hematological malignancies such as mantle cell lymphoma (MCL) and follicular lymphoma/diffuse large B-cell lymphoma (FL/D) (Adams and Cory The Bcl-2 apoptotic switch in cancer development and therapy. *Oncogene* 2007 Vol 26:1324–1337). Pharmacological inhibition of anti-apoptotic Bcl-2 family proteins has emerged as a therapeutic strategy to induce apoptosis and cause tumor regression in cancer (Zhang et al, *Drug Resist Updat* 2007 Vol 10(6):207-17). Nevertheless, mechanisms of resistance that develop to Bcl-2 therapy have been observed and investigated (Choudhary GS et al, *Cell Death and Disease* (2015) 6, e1593; doi:10.1038/cddis.2014.525).

There remains a need for new treatments and therapies for the treatment of cancer. The present invention provides a novel combination of the Bcl-2 inhibitor Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or addition salts thereof with a pharmaceutically acceptable acid or base, and the PI3Kδ inhibitor idelalisib, or addition salts thereof with a pharmaceutically acceptable acid or base. It has unexpectedly been found that Compound 1 and idelalisib interact in a synergistic manner to strongly inhibit cell proliferation in certain cell line models.

SUMMARY OF THE INVENTION

According to a first aspect of the invention, there is provided a combination comprising:
(a) Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or a pharmaceutically acceptable salt thereof, and
(b) idelalisib, or a pharmaceutically acceptable salt thereof,
for simultaneous, sequential or separate use.

In another embodiment, the invention provides a combination as described herein, for use in the treatment of cancer.

In another embodiment, the invention provides a combination as described herein, for use in the treatment of cancer, wherein idelalisib is first administered to the patient as a single agent treatment, and thereafter the patient is treated with the pharmaceutical combination of Compound 1 and idelalisib.

In another embodiment, the invention provides the use of a combination as described herein, in the manufacture of a medicament for the treatment of cancer.

In another embodiment, the invention provides a medicament containing, separately or together,
(a) Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or a pharmaceutically acceptable salt thereof, and
(b) idelalisib, or a pharmaceutically acceptable salt thereof,
for simultaneous, sequential or separate administration, and wherein Compound 1 and idelalisib are provided in effective amounts for the treatment of cancer.

In another embodiment, the invention provides a method of treating cancer, comprising administering a jointly therapeutically effective amount of:
(a) Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or a pharmaceutically acceptable salt thereof, and
(b) idelalisib, or a pharmaceutically acceptable salt thereof,
to a subject in need thereof.

In a particular embodiment, Compound 1 is *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Summary of all calculated single agent IC_{50} values and combination index CI values calculated using Chou-Talalay method in NCEB, Granta 519, RL, DOHH2 and TMD8 cells when treated with a range of doses of Compound 1 HCl salt and Idelalisib for 72 hours. Synergistic activity was observed across the cell line panel.

Figure 2. Combination index CI values calculated using Chou-Talalay method in NCEB, Granta 519, RL, DOHH2 and TMD8 cell lines when treated with a range of doses of Compound 1 HCl salt and Idelalisib for 72 hours. Synergistic activity was observed across the cell line panel.

Figure 3: 2D Combination Grid Matrix Plate Set-up Abbreviations: Cmpd: Compound; DMSO: Dimethyl sulfoxide.

Figure 4: Summary of all calculated single agent IC_{50} values, Loewe Synergy Scores and calculated combination indices in a panel of MCL and FL/D cell lines when treated with a range of doses of Compound 1 HCl salt and Idelalisib for 72 hours. A range of synergy from moderately synergistic to highly synergistic was observed across the cell line panel.

Figure 5 illustrates the inhibition and growth inhibition of the MCL line Granta-519 when treated with a range of doses of Compound 1 HCl salt and Idelalisib for 72 hours. Moderate synergy is observed in a full concentration matrix giving a CI of 0.691 and a Loewe Synergy Score of 2.37. Percent inhibition (left matrix heat map), synergy for checkerboard combination of the two agents across a broad concentration matrix (Loewe Excess Matrix, middle heat map) and percent growth inhibition (right matrix heat map) are shown.

Figure 6 illustrates the inhibition and growth inhibition of the MCL line JEKO-1 when treated with a range of doses of Compound 1 HCl salt and Idelalisib for 72 hours. Synergism is observed in a full concentration matrix giving a CI of 0.237 and a Loewe Synergy Score of 9.76. Percent inhibition (left matrix heat map), synergy for checkerboard combination of the two agents across a broad concentration matrix (Loewe Excess Matrix, middle heat map) and percent growth inhibition (right matrix heat map) are shown.

Figure 7 illustrates the inhibition and growth inhibition of the MCL line JVM-2 when treated with a range of doses of Compound 1 HCl salt and Idelalisib for 72 hours. Strong synergy is observed in a full concentration matrix giving a CI of 0.0459 and a Loewe Synergy Score of 7.46. Percent inhibition (left matrix heat map), synergy for checkerboard combination of the two agents across a broad concentration matrix (Loewe Excess Matrix, middle heat map) and percent growth inhibition (right matrix heat map) are shown.

Figure 8 illustrates the inhibition and growth inhibition of the FL/D line Toledo when treated with a range of doses of Compound 1 HCl salt and Idelalisib for 72 hours. Strong synergy is observed in a full concentration matrix giving a CI of 0.0350 and a Loewe Synergy Score of 9.74. Percent inhibition (left matrix heat map), synergy for checkerboard combination of the two agents across a broad concentration matrix (Loewe Excess Matrix, middle heat map) and percent growth inhibition (right matrix heat map) are shown.

Figure 9 illustrates the inhibition and growth inhibition of the FL/D line SU-DHL-6 when treated with a range of doses of Compound 1 HCl salt and Idelalisib for 72 hours. The CI was unable to be calculated here due to the high degree of cell killing observed and inability to obtain a smooth IC50 curve across the dose range tested. A Loewe Synergy Score of 2.05 was calculated. Percent inhibition (left matrix heat map), synergy for checkerboard combination of the two agents across a broad concentration matrix (Loewe Excess Matrix, middle heat map) and percent growth inhibition (right matrix heat map) are shown.

Figure 10 illustrates the inhibition and growth inhibition of the FL/D line DOH-H2 when treated with a range of doses of Compound 1 HCl salt and Idelalisib for 72 hours. Similar to SU-DHL-6 the CI was unable to be calculated due to the high degree of sensitivity to Compound 1 and Idelalisib as a single agent. A Loewe Synergy Score of 6.33 was calculated. Percent inhibition (left matrix heat map), synergy for checkerboard combination of the two agents across a broad concentration matrix (Loewe Excess Matrix, middle heat map) and percent growth inhibition (right matrix heat map) are shown.

Figure 11 illustrates the single Agent IC_{50} determination of Compound 1 in MCL and FL/D Panel. MCL and FL/D lines plus RS4;11 (a reference line) were incubated for 72 hrs with Compound 1 and assessed via CTG to determine the dose at which 50 percent viability is achieved. Sensitivity ranged from extremely potent (< 100 nM) to resistant (> 5.0 μM) across the panel of cell lines.

Figure 12 illustrates the single Agent IC_{50} determination of Idelalisib in MCL and FL/D Panel. MCL and FL/D lines were incubated for 72 hrs with Idelalisib and assessed via CTG to determine the dose at which 50 percent viability is achieved. The majority of cell lines tested were either intermediately sensitive or resistant to single agent Idelalisib.

DETAILED DESCRIPTION OF THE INVENTION

The invention therefore provides in Embodiment E1, a combination comprising,:
(a) Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or addition salts thereof with a pharmaceutically acceptable acid or base, and
(b) idelalisib, or a pharmaceutically acceptable salt thereof,
for simultaneous, sequential or separate use.

Further enumerated embodiments (E) of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.

E2. A combination according to E1, wherein Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide is in the form of the hydrochloride salt.

E3. A combination according to E2, wherein the dose of Compound 1 during the combination treatment is from 50 mg to 1500 mg.

E4. A combination according to any of E1 to E3, wherein the dose of idelalisib during the combination treatment is from 100 mg to 150 mg.

E5. A combination according to E4, wherein the dose of idelalisib during the combination treatment is 100 mg.

E6. A combination according to E4, wherein the dose of idelalisib during the combination treatment is 150 mg.

E7. A combination according to any of E1 to E6, wherein idelalisib is administered during the combination treatment once a day or twice a day.

E8. A combination according to any of E1 to E7, wherein Compound 1 is administered during the combination treatment once a day.

E9. A combination according to any of E1 to E8, wherein the combination treatment of Compound 1 and idelalisib is administered in at least 1 treatment cycle.

E10. A combination according to any of E1 to E9, wherein the combination treatment of Compound 1 and idelalisib is administered in 1, 2, 3 or 4 treatment cycles

E11. A combination according to E10, wherein the combination treatment of Compound 1 and idelalisib is administered in 4 treatment cycles.

E12. A combination according to any of E1 to E11, wherein Compound 1 and idelalisib are administered orally.

E13. A combination according to any of E1 to E12, having an administration schedule that reduces the incidence of tumour lysis syndrome in a cancer patient or patient group.

E14. A combination according to any of E1 to E12, having an administration schedule wherein Compound 1 is administered according to a dose ramp-up schedule.

E15. A combination according to any of E1 to E14, for use in the treatment of cancer.

E16. The combination for use according to E15, wherein Compound 1 and idelalisib are provided in amounts which are jointly therapeutically effective for the treatment of cancer.

E17. The combination for use according to E15, wherein Compound 1 and idelalisib are provided in amounts which are synergistically effective for the treatment of cancer.

E18. The combination for use according to E15, wherein Compound 1 and idelalisib are provided in synergistically effective amounts which enable a reduction of the dose required for each compound in the treatment of cancer, whilst providing an efficacious cancer treatment, with eventually a reduction in side effects.

E19. The combination for use according to any of E15 to E18, wherein the cancer is haematological cancer.

E20. The combination for use according to any of E15 to E18, wherein the cancer is B-cell lymphoma.

E21. The combination for use according to any of E15 to E18, wherein the cancer is a non-Hodgkin's lymphoma.

E22. The combination for use according to E21, wherein the cancer is indolent non-Hodgkin's lymphoma.

E23. The combination for use according to any of E15 to E18, wherein the cancer is follicular lymphoma.

E24. The combination for use according to any of E15 to E18, wherein the cancer is follicular lymphoma/diffuse large B-cell lymphoma (FL/D).

E25. The combination for use according to any of E15 to E18, wherein the cancer is mantle cell lymphoma.

E26. The combination for use according to any of E15 to E18, wherein the cancer is chronic lymphocytic leukemia.

E27. The combination for use according to any of E15 to E26, wherein idelalisib is first administered to the patient as a single agent treatment, and thereafter the patient is treated with the combination of Compound 1 and idelalisib.

E28. The combination for use according to E27, wherein when idelalisib is first administered to the patient as a single agent treatment, the dose of idelalisib is 150 mg.

E29. The combination for use according to E27 or E28, wherein when idelalisib is first administered to the patient as a single agent treatment, idelalisib is administered twice a day.

E30. The combination for use according to E27, E28 or E29, wherein when idelalisib is first administered to the patient as a single agent treatment, it is administered in one treatment cycle.

E31. A combination according to any of E1 to E14, further comprising one or more excipients.

E32. The use of a combination according to any of E1 to E14, in the manufacture of a medicament for the treatment of cancer.

E33. The use according to E32, wherein the cancer is a non-Hodgkin's lymphoma, follicular lymphoma or mantle cell lymphoma.

E34. The use according to E32, wherein the cancer is chronic lymphocytic leukemia.

E35. A medicament containing, separately or together,
(a) Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or addition salts thereof with a pharmaceutically acceptable acid or base, and
(b) idelalisib, or a pharmaceutically acceptable salt thereof,
for simultaneous, sequential or separate administration, and wherein Compound 1 and idelalisib are provided in effective amounts for the treatment of cancer.

E36. A method of treating cancer, comprising administering a jointly therapeutically effective amount of (a) Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or addition salts thereof with a pharmaceutically acceptable acid or base, and
(b) idelalisib, or a pharmaceutically acceptable salt thereof,
to a subject in need thereof.

E37. A method for sensitizing a patient who is (i) refractory to at least one chemotherapy treatment, or (ii) in relapse after treatment with chemotherapy, or both (i) and (ii), wherein the method comprises administering a jointly therapeutically effective amount of (a) Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or addition salts thereof with a pharmaceutically acceptable acid or base, and
(b) idelalisib, or a pharmaceutically acceptable salt thereof,
to said patient.

"Combination" refers to either a fixed dose combination in one unit dosage form (e.g., capsule, tablet, or sachet), non-fixed dose combination, or a kit of parts for the combined

administration where a compound of the present invention and one or more combination partners (e.g. another drug as explained below, also referred to as "therapeutic agent" or "co-agent") may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, e.g. synergistic effect.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (*e.g.* a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

The term "fixed dose combination" means that the active ingredients, e.g. a compound of formula (I) and one or more combination partners, are both administered to a patient simultaneously in the form of a single entity or dosage.

The term "non-fixed dose combination" means that the active ingredients, e.g. a compound of the present invention and one or more combination partners, are both administered to a patient as separate entities either simultaneously or sequentially, with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

"Cancer" means a class of disease in which a group of cells display uncontrolled growth. Cancer types include haematological cancer (lymphoma and leukemia) and solid tumors including carcinoma, sarcoma, or blastoma. In particular "cancer" refers to a non-Hodgkin's lymphoma, and more specifically follicular lymphoma, or a mantle cell lymphoma. Chronic lymphocytic leukemia is also particularly preferred.

The term "jointly therapeutically effective" means that the therapeutic agents may be given separately (in a chronologically staggered manner, especially a sequence-specific manner) in such time intervals that they prefer, in the warm-blooded animal, especially human, to

be treated, still show a (preferably synergistic) interaction (joint therapeutic effect). Whether this is the case can, inter alia, be determined by following the blood levels, showing that both compounds are present in the blood of the human to be treated at least during certain time intervals.

"Synergistically effective" or "synergy" means that the therapeutic effect observed following administration of two or more agents is greater than the sum of the therapeutic effects observed following the administration of each single agent.

"Follicular lymphoma/diffuse large B-cell lymphoma" (FL/D) refers to follicular lymphoma with progression to diffuse large B-cell lymphoma. This corresponds to the evolution of a clinically indolent non-Hodgkin lymphoma to a high-grade, aggressive non-Hodgkin lymphoma (Roulland et al, *Adv. Immunol.* 2011 111:1-46. doi: 10.1016/B978-0-12-385991-4.00001-5; Davies et al, *Br J Haematol.* 2007 January; 136(2):286–293. doi:10.1111/j.1365-2141.2006.06439.x).

"Treatment cycle" means a period of time to receive treatment according to a determined administration schedule after which the efficacy of the treatment is assessed by evaluating the tumour response. The acceptability profile is also evaluated. Preferably, treatment cycle corresponds to 28 day cycle.

Follicular lymphoma includes both relapsed and refractory follicular lymphoma.

Mantle cell lymphoma includes both relapsed and refractory mantle cell lymphoma.

As used herein, the term "treat", "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treat", "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treat", "treating" or "treatment" refers to

modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both.

As used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

In some embodiments, provided herein is a method for treating a patient who exhibits one or more symptoms associated with a B-cell malignancy. In some embodiments, the patient is at an early stage of a B-cell malignancy. In other embodiments, the patient is at an advanced stage of a B-cell malignancy.

In some embodiments, provided herein is a method for treating a patient who is undergoing one or more standard therapies for treating a B-cell malignancy, such as chemotherapy, radiotherapy, immunotherapy, and/or surgery. Thus, in some foregoing embodiments, the combination of a Compound 1 and idelalisib, as described herein, may be administered before, during, or after administration of chemotherapy, radiotherapy, immunotherapy, and/or surgery.

In another aspect, provided herein is a method for treating a patient who is "refractory" to a B-cell malignancy treatment or who is in "relapse" after treatment for a B-cell malignancy. A patient "refractory" to an anti-B-cell malignancy therapy means they do not respond to the particular treatment, also referred to as resistant. The B-cell malignancy may be resistant to treatment from the beginning of treatment, or may become resistant during the course of treatment, for example after the treatment has shown some effect on the B-cell malignancy, but not enough to be considered a remission or partial remission. A patient in "relapse" means that the B-cell malignancy has returned or the signs and symptoms of the B-cell malignancy have returned after a period of improvement, e.g. after a treatment has shown effective reduction in the B-cell malignancy, such as after a subject is in remission or partial remission.

In some variations, the patient is (i) refractory to at least one anti-B-cell malignancy therapy, or (ii) in relapse after treatment with at least one anti-B-cell malignancy therapy, or both (i) and (ii). In some of embodiments, the patient is refractory to at least two, at least

three, or at least four anti-B-cell malignancy therapies (including, for example, standard or experimental chemotherapies).

In another aspect, provided is a method for sensitizing a human who is (i) refractory to at least one chemotherapy treatment, or (ii) in relapse after treatment with chemotherapy, or both (i) and (ii), wherein the method comprises administering Compound 1 in combination with idelalisib, as described herein, to the patient. A patient who is sensitized is a patient who is responsive to the treatment involving administration of Compound 1 in combination with idelalisib, as described herein, or who has not developed resistance to such treatment.

"Having an administration schedule that reduces the incidence of tumour lysis syndrome in a cancer patient or patient group" means an administration schedule wherein the Bcl-2 inhibitor is administered according to a dose ramp-up schedule.

"Dose ramp-up schedule" means an administration schedule wherein the drug starts being administered at lower dose, which dose is then gradually increased up to the maximum tolerated dose (MTD)/ recommended dose.

"Medicament" means a pharmaceutical composition, or a combination of several pharmaceutical compositions, which contains one or more active ingredients in the presence of one or more excipients.

'DLBCL' means diffuse large B-cell lymphoma.

'ALL' means acute lymphoblastic leukemia.

'CLL' means chronic lymphocytic leukemia.

Also provided herein are isotopically labeled forms of compounds detailed herein. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the

disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to ^{2}H (deuterium, D), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl and ^{125}I. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H, ^{13}C and ^{14}C are incorporated, are provided. Such isotopically labeled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of subjects (*e.g.* humans). Also provided for isotopically labeled compounds described herein are any pharmaceutically acceptable salts, or hydrates, as the case may be.

In some variations, the compounds disclosed herein may be varied such that from 1 to n hydrogens attached to a carbon atom is/are replaced by deuterium, in which n is the number of hydrogens in the molecule. Such compounds may exhibit increased resistance to metabolism and are thus useful for increasing the half life of the compound when administered to a mammal. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

Deuterium labeled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to absorption, distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this disclosure can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in the compounds provided herein.

The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

In the pharmaceutical compositions according to the invention, the proportion of active ingredients by weight (weight of active ingredients over the total weight of the composition) is from 5 to 50 %.

Among the pharmaceutical compositions according to the invention there will be more especially used those which are suitable for administration by the oral, parenteral and especially intravenous, per- or trans-cutaneous, nasal, rectal, perlingual, ocular or respiratory route, more specifically tablets, dragées, sublingual tablets, hard gelatin capsules, glossettes, capsules, lozenges, injectable preparations, aerosols, eye or nose drops, suppositories, creams, ointments, dermal gels etc.

The pharmaceutical compositions according to the invention comprise one or more excipients or carriers selected from diluents, lubricants, binders, disintegration agents, stabilisers, preservatives, absorbents, colourants, sweeteners, flavourings etc.

By way of non-limiting example there may be mentioned:

- *as diluents*: lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycerol,
- *as lubricants*: silica, talc, stearic acid and its magnesium and calcium salts, polyethylene glycol,
- *as binders*: magnesium aluminium silicate, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone,
- *as disintegrants*: agar, alginic acid and its sodium salt, effervescent mixtures.

The compounds of the combination may be administered simultaneously or sequentially. The administration route is preferably the oral route, and the corresponding pharmaceutical compositions may allow the instantaneous or delayed release of the active ingredients. The compounds of the combination may moreover be administered in the form of two separate pharmaceutical compositions, each containing one of the active ingredients, or in the form of a single pharmaceutical composition, in which the active ingredients are in admixture.

Preference is given to the pharmaceutical compositions being tablets.

Pharmaceutical composition of Compound 1 HCl salt film-coated tablet containing 50 mg and 100 mg of drug substance

	Amount (mg)		Function
Tablet	**50 mg strength**	**100 mg strength**	
Compound 1 HCl salt	52,58	105,16	Drug Substance
equivalent in base to	50	100	
Lactose monohydrate	178,51	357,02	Diluent
Maize starch	66,6	133,2	Disintegrant
Povidone	23,31	46,62	Binder
Magnesium stearate	3,33	6,66	Lubricant
Silica, colloidal anhydrous	0,67	1,34	Flow agent
Sodium starch glycolate (Type A)	10	20	Disintegrant
For an uncoated tablet with a mass of	335	670	
Film-Coating			
Glycerol	0,507	1,014	Plasticizing agent
hypromellose	8,419	16,838	Film-coating agent
Macrogol 6000	0,538	1,076	Smoothing agent
Magnesium stearate	0,507	1,014	Lubricant
Titanium dioxide	1,621	3,242	Pigment
Intermediary Vehicule			
Water, purified	qs.	qs.	Solvent
For a film-coated tablet with a mass of	346,6	693,2	

EXAMPLE 1: Combination therapy of idelalisib and Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride in lymphoma cell lines

Materials and Methods:

Hematological Non-Hodgkin Lymphoma cell lines (Mantle cell lymphoma: NCEB, GRANTA; Follicular lymphoma : RL, DOHH2 and Diffuse Large B cell Lymphoma: TMD8) were obtained from ATCC or DSMZ. Cells were cultured in RPMI medium supplemented with 10% FBS with increasing doses of *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide hydrochloride alone and idelalisib alone. The IC50 value was determined for each cell line after 72 hours of culture using the MTT assay.

The combined effects of Compound 1 hydrochloride salt and Idelalisib on cell survival were analysed for each cell line using the Compusyn sofware (ComboSyn, Inc., USA) which applies the median-effect equation of Chou and the CI equation of Talalay (Chou TC, *Pharmacol Rev.* 2006 Sep, Vol 58(3):621-81 Erratum in: *Pharmacol Rev.* 2007 Mar, Vol 59(1):124. PubMed PMID: 16968952).
NCEB, Granta 519, RL, DOHH2 and TMD8 cells were exposed in triplicate to a serial dilution of each agent or both in combination using the constant ratio combination design for 72 hours, followed by the MTT assay for cell viability determination. Calculated CIs were used to ascertain the presence of synergism (CI <1), additive effect (CI=1) and antagonism (CI >1) between compound 1 and Idelalisib.

As illustrated in Figures 1-2, strong synergistic activity was demonstrated when combining *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide with idelalisib in Follicular Lymphoma (FL) and Mantle Cell lymphoma

(MCL) cell line models (CI < 0.5). Synergistic activity was also observed in Diffuse Large B-cell Lymphoma (DLBCL) cell line models (CI < 1).

EXAMPLE 2: Combination activity of *N*-(4-hydroxyphenyl)-3-{6-[(3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide (Compound 1) hydrochloride salt in combination with idelalisib (Compound 2) in MCL and FL/D cell lines *in vitro*

Materials and Methods:

Cell lines and Agents:

The MCL cell lines Granta-519, JEKO-1, and JVM-2, as well as the FL/D cell lines SU-DHL6, DOH-H2, and Toledo, were obtained from ATCC or DSMZ. Granta-519, JVM-2, SU-DHL-6 and Toledo cells were grown in Roswell Park Memorial Institute 1640 (RPMI; Gibco Invitrogen Life Science Technologies; Catalog Number: 11875) supplemented with 10% Heat Inactivated Fetal Bovine Serum (HI FBS; Gibco Invitrogen Life Science Technologies; Catalog Number: 10082) and JEKO-1 and DOH-H2 cells were grown in RPMI 1640 supplemented with 20% HI FBS and maintained at 37°C, 5% CO_2. Lyophilized Compound 1 HCl salt and Idelalisib were reconstituted in dimethyl sulfoxide (DMSO; Sigma Aldrich, Catalog Number: D2650) and stored at -20°C at a concentration of 10 mM.

Single Agent IC_{50} determination:

Suspension cultures were seeded at a density of 10,000 cells per well in a tissue culture treated black walled 96-well flat bottom plate (Corning; Catalog Number: 3904) and allowed to equilibrate overnight at 37°C, 5% CO_2. The following day cells were dosed with Compound 1 HCl salt and Idelalisib at a final dose range of 10 µM to 0.013717 µM using a 3-fold dilution series. After 72 hours of treatment, plates were then analyzed for ATP levels using the Cell Titer Glo Assay (CTG; Promega; Catalog Number: G7572) according to the manufacturer's instructions and read on the Envision Plate Reader. All conditions were treated in N=6 with three plates per experiment. Data is represented as the mean ±

standard deviation from 1 to 2 independent experiments and reported as crossing point or the concentration at the 50% viability assessment at the end of the experiment.

2D Combination Dose Matrix:

Suspension cultures were seeded at a density of 10,000 cells per well in a tissue culture treated black walled 96-well flat bottom plate (Corning; Catalog Number: 3904) and allowed to equilibrate overnight at 37°C, 5% CO_2. The following day cells were dosed with Compound 1 HCl salt and Idelalisib according to **Figure 3** using a final dose range from 10 µM to 0.013717 µM using a 3-fold dilution series either as single agents or combined. After 72 hours of treatment, plates were then analyzed for ATP levels using the Cell Titer Glo Assay (CTG; Promega; Catalog Number: G7572) according to the manufacturer's instructions and read on the Envision Plate Reader.

Combination activity was determined according to the Loewe additivity model (Greco WR et al, *Pharmacol Rev.* 1995 Jun, Vol 47(2):331-85 PubMed PMID: 7568331) using a custom-built software (Combination Analysis Module). Briefly, for each combination of two compounds, the combination effect is calculated as the difference between the measured inhibition and the inhibition according to the Loewe additivity model. Combination index (CI) is derived by the following equation (Chou TC, *Pharmacol Rev.* 2006 Sep, Vol 58(3):621-81 Erratum in: *Pharmacol Rev.* 2007 Mar, Vol 59(1):124. PubMed PMID: 16968952) and is freely available through the Combosyn software (www.combosyn.com):

$$CI = \frac{C(A)}{EC_{50}\,(A)} + \frac{C(B)}{EC_{50}\,(B)}$$

Where:

- C(A) and C(B) are the concentration of drug A and B that in combination cause 50% inhibition
- EC_{50}(A) and EC_{50}(B) are the concentration of drug A and B that individually cause 50% inhibition

The CI value quantitatively defines synergism (CI < 1), additivity (CI = 1) and antagonism (CI > 1). Growth Inhibition data is calculated incorporating Day 0 CTG value, such that

values GI < 100 reflect cell growth, GI = 100 reflects stasis, and GI > 100 reflects cell killing. Inhibition data is calculated excluding Day 0 CTG.

Results

The data presented in Figures 1-2 and 4-10 herein show the synergistic combination activity between Compound 1 hydrochloride salt and idelalisib (Compound 2), across a panel of cell lines.

EXAMPLE 3: Clinical Trial Protocol

A phase 1b clinical study was set up to test the safety, tolerability, PK/PD and preliminary anti-tumor activity for *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide (Compound 1) hydrochloride in combination with idelalisib in patients with relapsed or refractory follicular lymphoma (FL), mantle cell lymphoma (MCL) or chronic lymphocytic leukemia (CLL).

The study has two parts (a dose escalation part and a 2-arm dose expansion part). Approximately 65 patients will be enrolled in the study, with approximately 25 patients in the dose escalation, and approximately 20 patients each of FL and MCL in dose expansion. The dose escalation part of the study is designed to characterize the safety and tolerability of Compound 1 hydrochloride salt in combination with idelalisib.

After the maximum tolerated dose (MTD) and the recommended dose expansion (RDE) have been identified, the dose expansion part will further evaluate the safety, tolerability and preliminary antitumor activity in separate treatment arms for FL and MCL. All patients will receive a run-in with single-agent idelalisib at 150 mg twice a day for 28 days. Thereafter, patients at low/intermediate risk for tumor lysis syndrome will receive combination treatment at the MTD/RDE. Patients with MCL at high risk for tumor lysis syndrome will be dosed more cautiously with incremental doses of Compound 1 hydrochloride salt up to MTD/RDE combined with idelalisib at a fixed dose (RDE).

In dose escalation, the treatment period will start on Cycle 1 Day 1 with combination treatment (idelalisib and Compound 1 hydrochloride salt) administered in 28 day cycles.

In dose expansion, the treatment period will start on Cycle 1 Day 1 with idelalisib 150 mg twice a day for 28 days followed by combination treatment (idelalisib and Compound 1 hydrochloride salt) administered in 28 day cycles.

Patients should continue treatment until completion of 4 cycles of study drug(s) after achieving complete release, disease progression, occurrence of unacceptable toxicity that precludes any further treatment, patient's death, and/or treatment is discontinued at the discretion of the investigator or by patient request.

CLAIMS

1. A combination comprising:
(a) Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or a pharmaceutically acceptable salt thereof and
(b) idelalisib, or a pharmaceutically acceptable salt thereof,
for simultaneous, sequential or separate use.

2. A combination according to claim 1, wherein Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide is in the form of the hydrochloride salt.

3. A combination according to claim 2, wherein the dose of Compound 1 during the combination treatment is from 50 mg to 1500 mg.

4. A combination according to any of claims 1 to 3, wherein the dose of idelalisib during the combination treatment is from 100 mg to 150 mg.

5. A combination according to claim 4, wherein the dose of idelalisib during the combination treatment is 100 mg.

6. A combination according to claim 4, wherein the dose of idelalisib during the combination treatment is 150 mg.

7. A combination according to any of claims 1 to 6, wherein idelalisib is administered during the combination treatment once a day or twice a day.

8. A combination according to any of claims 1 to 7, wherein Compound 1 is administered during the combination treatment once a day.

9. A combination according to any of claims 1 to 8, wherein the combination treatment of Compound 1 and idelalisib is administered in at least 1 treatment cycle.

10. A combination according to any of claims 1 to 9, wherein the combination treatment of Compound 1 and idelalisib is administered in 1, 2, 3 or 4 treatment cycles.

11. A combination according to claim 10, wherein the combination treatment of Compound 1 and idelalisib is administered in 4 treatment cycles.

12. A combination according to any of claims 1 to 11, wherein Compound 1 and idelalisib are administered orally.

13. A combination according to any of claims 1 to 12, having an administration schedule that reduces the incidence of tumour lysis syndrome in a cancer patient or patient group.

14. A combination according to any of claims 1 to 12, having an administration schedule wherein Compound 1 is administered according to a dose ramp-up schedule.

15. A combination according to any of claims 1 to 14, for use in the treatment of cancer.

16. The combination for use according to claim 15, wherein Compound 1 and idelalisib are provided in amounts which are jointly therapeutically effective for the treatment of cancer.

17. The combination for use according to claim 15, wherein Compound 1 and idelalisib are provided in amounts which are synergistically effective for the treatment of cancer.

18. The combination for use according to claim 15, wherein Compound 1 and idelalisib are provided in synergistically effective amounts which enable a reduction of the dose required for each compound in the treatment of cancer, whilst providing an efficacious cancer treatment, with eventually a reduction in side effects.

19. The combination for use according to any of claims 15 to 18, wherein the cancer is haematological cancer.

20. The combination for use according to any of claims 15 to 18, wherein the cancer is B-cell lymphoma.

21. The combination for use according to any of claims 15 to 18, wherein the cancer is a non-Hodgkin's lymphoma.

22. The combination for use according to claim 21, wherein the cancer is indolent non-Hodgkin's lymphoma.

23 The combination for use according to any of claims 15 to 18, wherein the cancer is follicular lymphoma.

24. The combination for use according to any of claims 15 to 18, wherein the cancer is follicular lymphoma/diffuse large B-cell lymphoma (FL/D).

25. The combination for use according to any of claims 15 to 18, wherein the cancer is mantle cell lymphoma.

26. The combination for use according to any of claims 15 to 18, wherein the cancer is chronic lymphocytic leukemia.

27. The combination for use according to any of claims 15 to 26, wherein idelalisib is first administered to the patient as a single agent treatment, and thereafter the patient is treated with the combination of Compound 1 and idelalisib.

28. The combination for use according to claim 27, wherein when idelalisib is first administered to the patient as a single agent treatment, the dose of idelalisib is 150 mg.

29. The combination for use according to claims 27 or 28, wherein when idelalisib is first administered to the patient as a single agent treatment, idelalisib is administered twice a day.

30. The combination for use according to claims 27, 28 or 29, wherein when idelalisib is first administered to the patient as a single agent treatment, it is administered in one treatment cycle.

31. A combination according to any of claims 1 to 14, further comprising one or more excipients.

32. The use of a combination according to any of claims 1 to 14, in the manufacture of a medicament for the treatment of cancer.

33. The use according to claim 32, wherein the cancer is a non-Hodgkin's lymphoma, follicular lymphoma or mantle cell lymphoma.

34. The use according to claim 32, wherein the cancer is chronic lymphocytic leukemia.

35. A medicament containing, separately or together,
(a) Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or a pharmaceutically acceptable salt thereof, and
(b) idelalisib, or a pharmaceutically acceptable salt thereof,
for simultaneous, sequential or separate administration, and wherein Compound 1 and idelalisib are provided in effective amounts for the treatment of cancer.

36. A method of treating cancer, comprising administering a jointly therapeutically effective amount of (a) Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or a pharmaceutically acceptable salt thereof, and

(b) idelalisib, or a pharmaceutically acceptable salt thereof,
to a subject in need thereof.

37. A method for sensitizing a patient who is (i) refractory to at least one chemotherapy treatment, or (ii) in relapse after treatment with chemotherapy, or both (i) and (ii), wherein the method comprises administering a jointly therapeutically effective amount of (a) Compound 1: *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide, or addition salts thereof with a pharmaceutically acceptable acid or base, and
(b) idelalisib, or a pharmaceutically acceptable salt thereof,
to said patient.

Figure 1

Summary of Compound 1 HCl salt and Idelalisib Single Agent IC_{50} values and combination index CI values calculated using Chou-Talalay method

Cell line	Single Agent $IC_{50\ (\mu M)}$		Combination synergy score (CI*)
	Compound 1	Idelalisib	Compound 1 x Idelalisib
NCEB (MCL)	0.21	10.62	0.19
GRANTA 519 (MCL)	4.48	15.18	0.48
RL (FL)	1.04	23.48	0.26
DOHH2 (FL)	0.08	0.65	0.16
TMD8 (DLBCL)	5.43	0.15	0.80

*A combination is synergistic when CI < 1

Figure 2. Combination index values calculated using Chou-Talalay method in lymphoma cell lines when treated with *N*-(4-hydroxyphenyl)-3-{6-[((3*S*)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl]-1,3-benzodioxol-5-yl}-*N*-phenyl-5,6,7,8-tetrahydro-1-indolizine carboxamide HCl salt and idelalisib

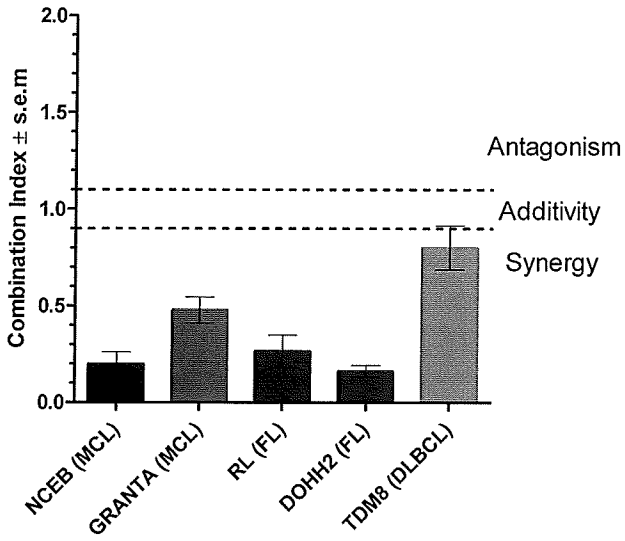


Figure 3

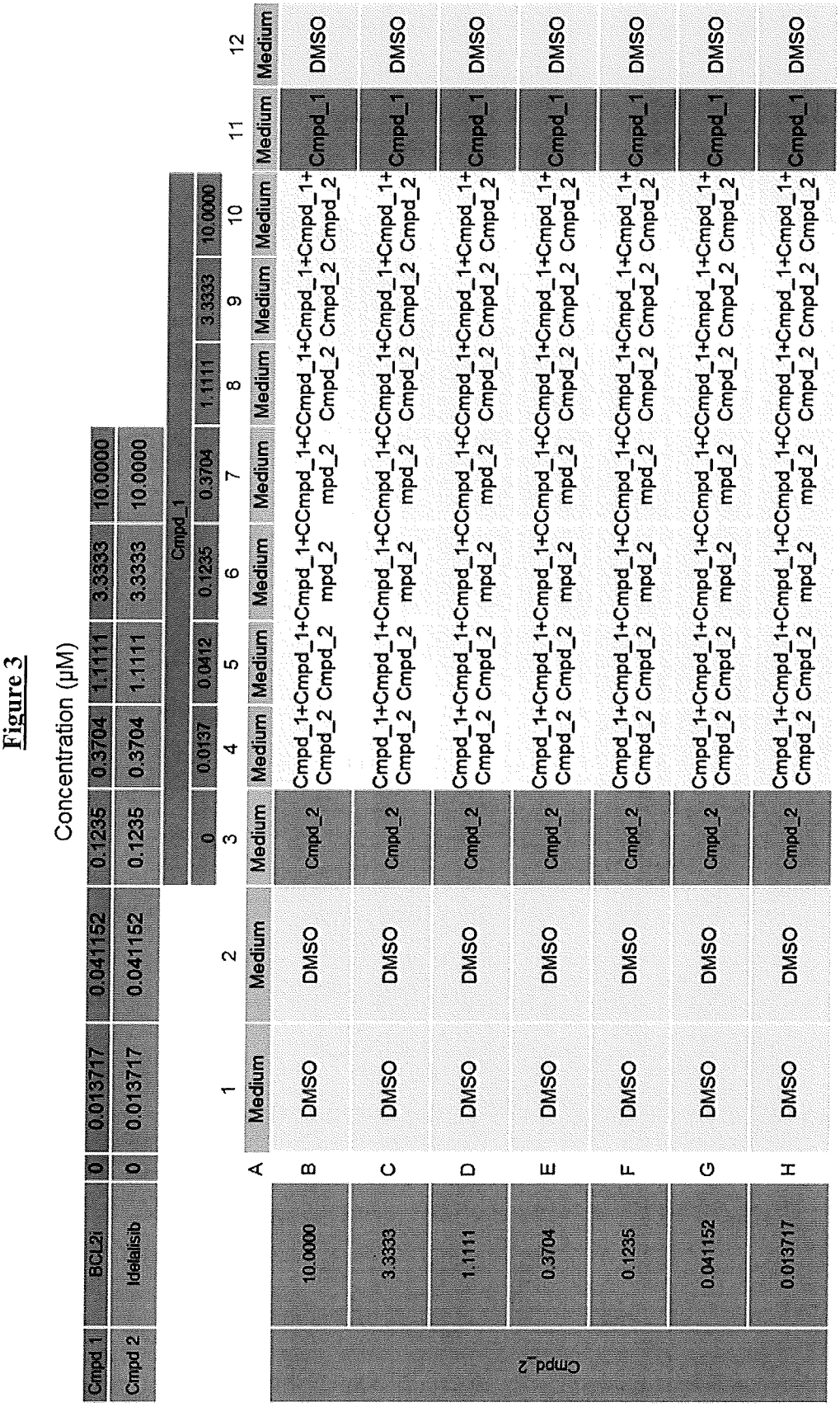

Concentration (µM)
Cmpd 1
BCL2i
0
0.013717
0.041152
0.1235
0.3704
1.1111
3.3333
10.0000
Cmpd 2
Idelalisib
0
0.013717
0.041152
0.1235
0.3704
1.1111
3.3333
10.0000
Cmpd_1
0
0.0137
0.0412
0.1235
0.3704
1.1111
3.3333
10.0000
Cmpd_2
10.0000
3.3333
1.1111
0.3704
0.1235
0.041152
0.013717
1 2 3 4 5 6 7 8 9 10 11 12
A Medium Medium Medium Medium Medium Medium Medium Medium Medium Medium Medium
B DMSO DMSO Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1 DMSO
C DMSO DMSO Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1 DMSO
D DMSO DMSO Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1 DMSO
E DMSO DMSO Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1 DMSO
F DMSO DMSO Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1 DMSO
G DMSO DMSO Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1 DMSO
H DMSO DMSO Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1+Cmpd_2 Cmpd_1 DMSO

Figure 4

Summary of Compound 1 HCl salt and Idelalisib Single Agent IC_{50} values, Loewe Synergy Score and CI calculated using custom Combination Analysis Module

Cell line	Single Agent IC_{50} (μM) all data reported as crossing point		Combinations Loewe Synergy Score (CI†)
	Compound 1	Idelalisib	Compound 1 x Idelalisib
Granta-519 (MCL)	1.04	>10	2.37 (0.691)
JEKO-1 (MCL)	>10	>10	9.76 (0.237)
JVM-2 (MCL)	>10	2.01	7.46 (0.0459)
Toledo (FL/D)	0.58	>10	9.74 (0.0350)
SU-DHL-6 (FL/D)	0.23	0.03	2.05 (0.00)
DOH-H2 (FL/D)	0.21	2.11	6.33 (0.00)

† CI = Loewe Best Combination Index

Figure 5

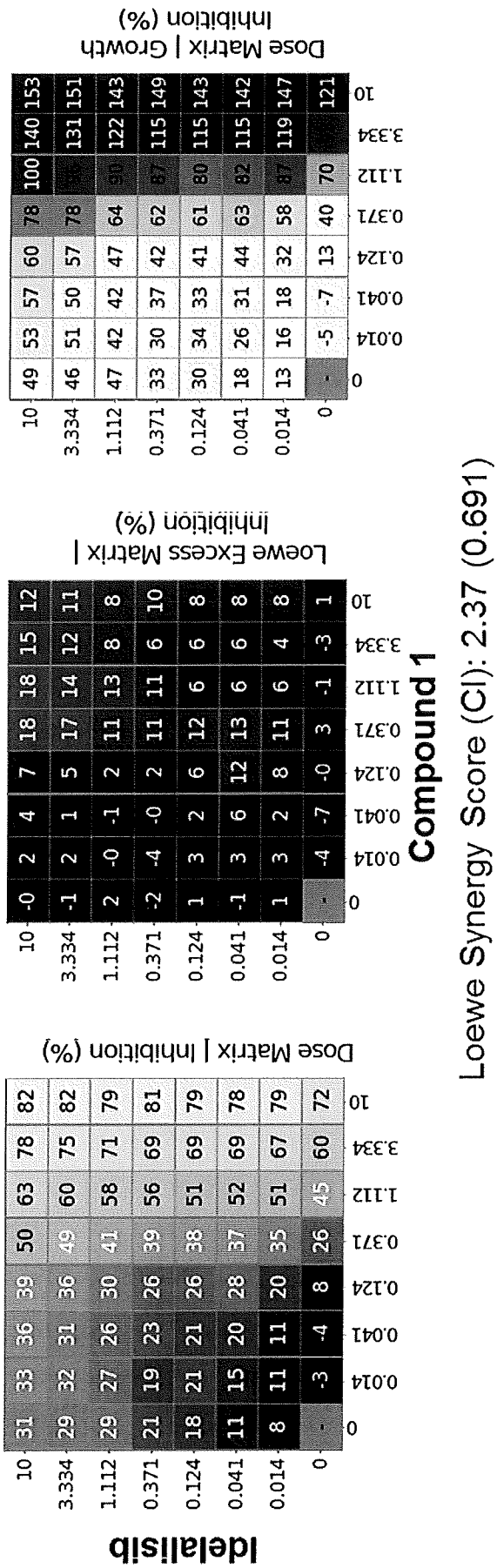

idelalisib
Compound 1
Loewe Synergy Score (CI): 2.37 (0.691)
Dose Matrix | Inhibition (%)
Loewe Excess Matrix | Inhibition (%)
Dose Matrix | Growth Inhibition (%)
10 3.334 1.112 0.371 0.124 0.041 0.014 0
0 0.014 0.041 0.124 0.371 1.112 3.334 10

Figure 6

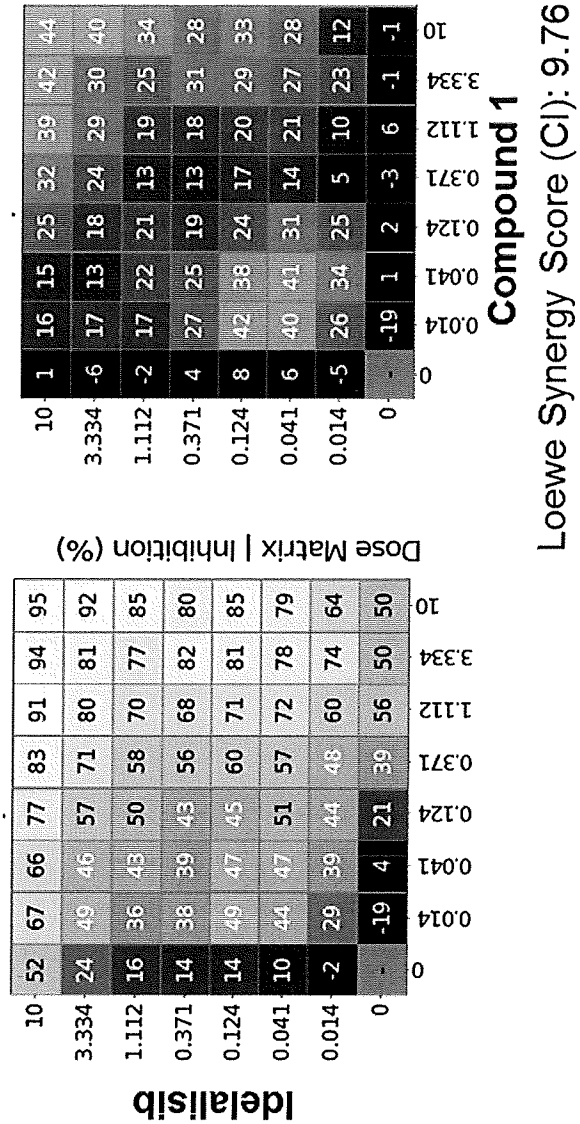

Idelalisib
Dose Matrix | Inhibition (%)
Compound 1
Loewe Excess Matrix | Inhibition (%)
Loewe Synergy Score (CI): 9.76 (0.237)
Dose Matrix | Growth Inhibition (%)

Figure 7

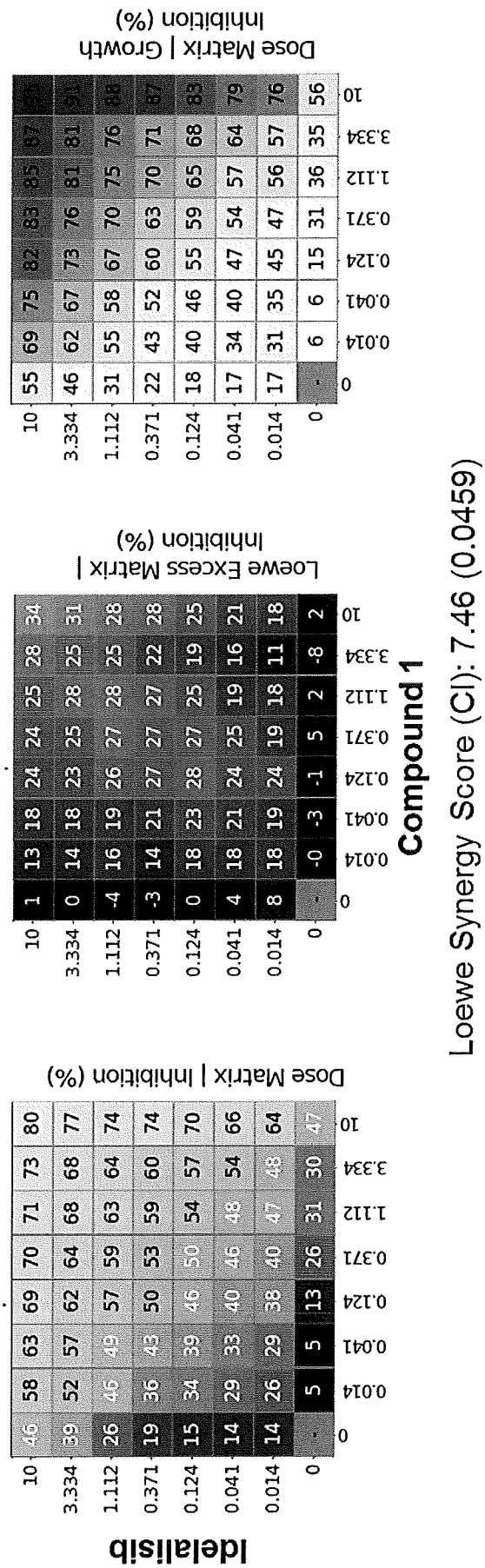

idelalisib
Dose Matrix | Inhibition (%)
Loewe Excess Matrix | Inhibition (%)
Compound 1
Loewe Synergy Score (CI): 7.46 (0.0459)
Dose Matrix | Growth Inhibition (%)
10 3.334 1.112 0.371 0.124 0.041 0.014 0
0.014 0.041 0.124 0.371 1.112 3.334 10

Figure 8

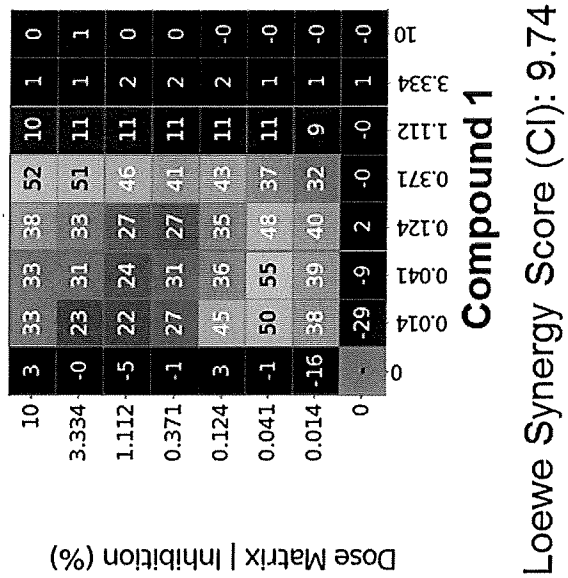

Compound 1
Idelalisib
Dose Matrix | Inhibition (%)
Loewe Excess Matrix | Inhibition (%)
Dose Matrix | Growth Inhibition (%)
Loewe Synergy Score (CI): 9.74 (0.0350)

Figure 9

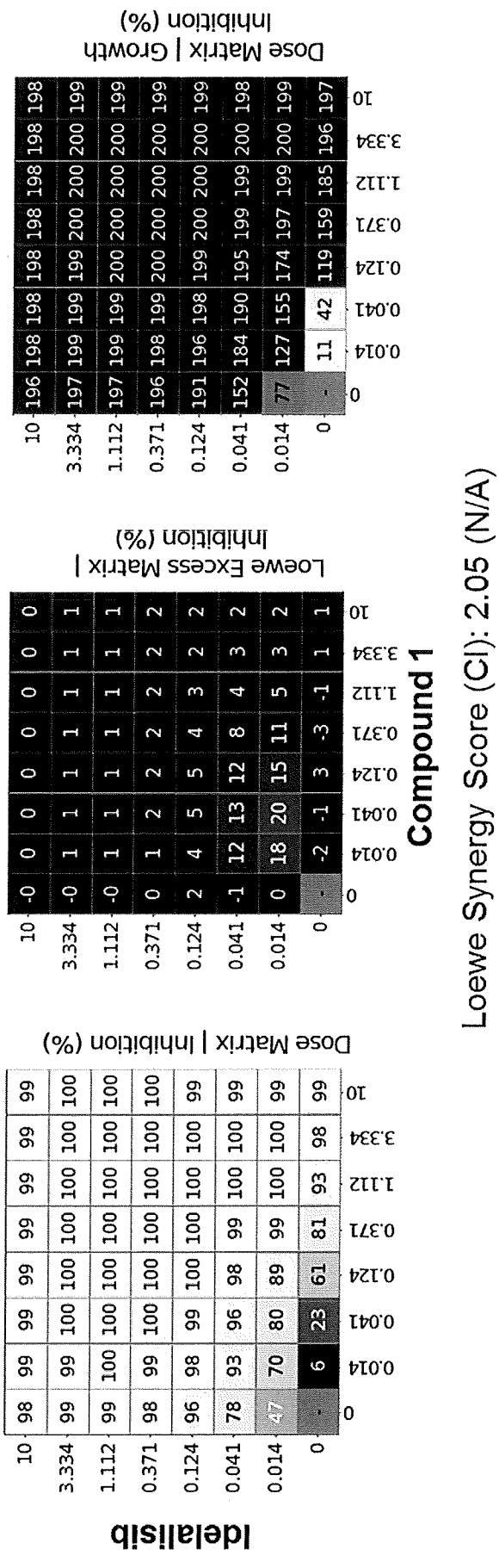

idelalisib
Dose Matrix | Inhibition (%)
Compound 1
Loewe Excess Matrix | Inhibition (%)
Dose Matrix | Growth Inhibition (%)
Loewe Synergy Score (CI): 2.05 (N/A)

Figure 10

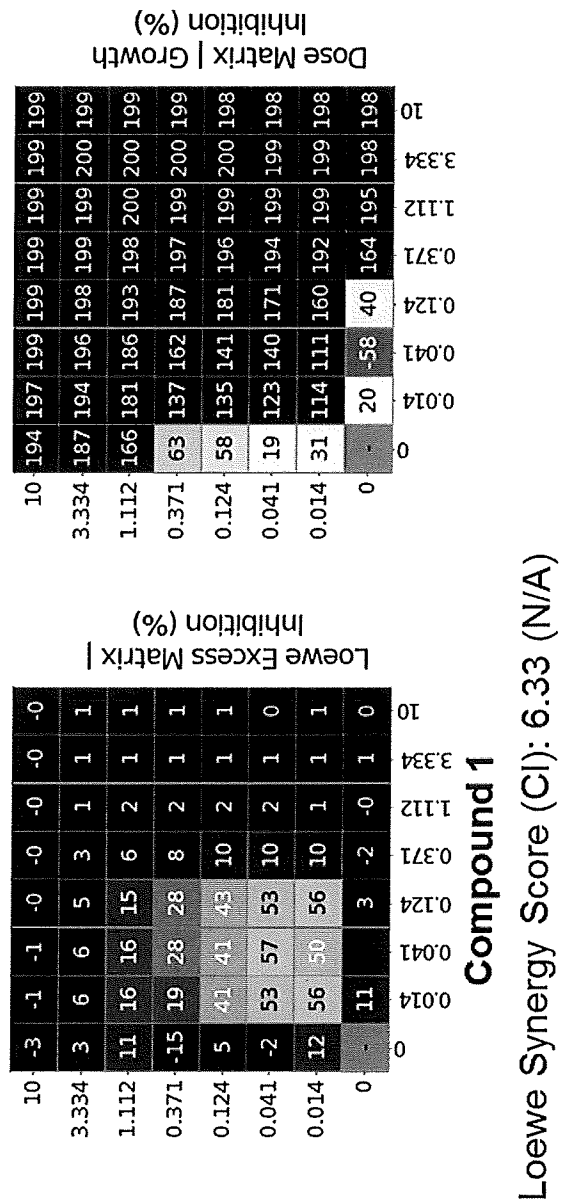
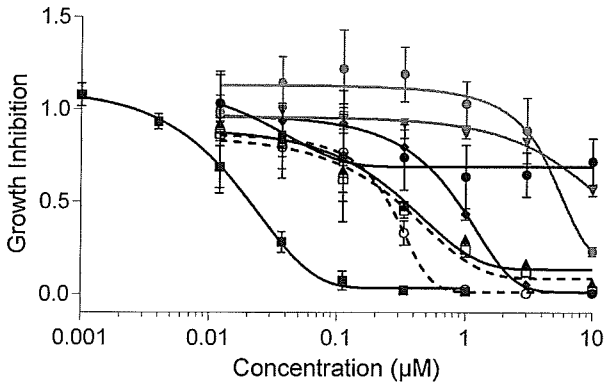

Idelalisib
Dose Matrix | Inhibition (%)
Compound 1
Loewe Synergy Score (CI): 6.33 (N/A)
Loewe Excess Matrix | Inhibition (%)
Dose Matrix | Growth Inhibition (%)

Figure 11.

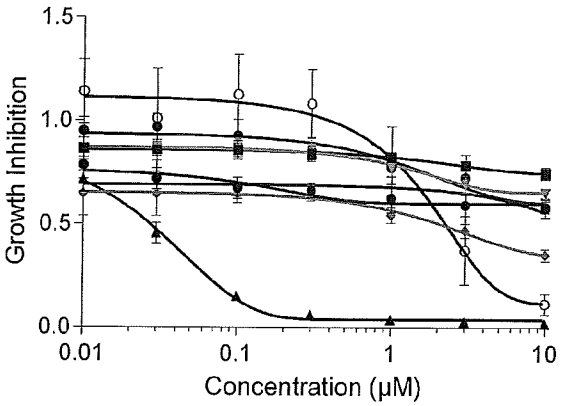
Single Agent IC_{50} determination of Compound 1 in MCL and FL/D panel



Cell Line	Compound 1 IC_{50} (μM)
MINO (MCL)	0.02
RS4;11 (ALL)	0.03
DOH-H2 (FL/D)	0.21
SU-DHL-6 (FL/D)	0.23
Granta-519 (MCL)	0.565
Toledo (FL/D)	0.81
REC-1 (MCL)	6.73
JEKO-1 (MCL)	>10
JVM-2 (MCL)	>10

Figure 12.

Single Agent IC_{50} determination of Idelalisib in MCL and FL/D panel



Cell Line	Idelalisib IC_{50} (μM)
SU-DHL-6 (FL/D)	0.03
JVM-2 (MCL)	2.01
DOH-H2 (FL/D)	2.11
Toledo (FL/D)	>10
Granta-519 (MCL)	>10
JEKO-1 (MCL)	>10
REC-1 (MCL)	>10

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/067699

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/52 A61K31/5355 A61P35/02
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, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHOUDHARY G S ET AL: "MCL-1 and BCL-xL-dependent resistance to the BCL-2 inhibitor ABT-199 can be overcome by preventing PI3K/AKT/mTOR activation in lymphoid malignancies", CELL DEATH & DISEASE, NATURE PUBLISHING GROUP, GB, vol. 6, 15 January 2015 (2015-01-15), pages e1593-1, XP002745557, ISSN: 2041-4889, DOI: 10.1038/CDDIS.2014.525 [retrieved on 2015-01-15] abstract page 6, column 2, last paragraph - page 7, column 2, paragraph 1 figure 6 ----- -/--	1-37

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2016	28/09/2016

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	Rodríguez-Palmero, M

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CAO Y ET AL: "The BCL2 antagonist ABT-199 triggers apoptosis, and augments ibrutinib and idelalisib mediated cytotoxicity in CXCR4 Wild-type and CXCR4 WHIM mutated Waldenstrom macroglobulinaemia cells", BRITISH JOURNAL OF HAEMATOLOGY, WILEY-BLACKWELL PUBLISHING LTD, GB, vol. 170, no. 1, 12 January 2015 (2015-01-12), pages 134-138, XP002745558, ISSN: 0007-1048, DOI: 10.1111/BJH.13278 [retrieved on 2015-01-12] figure 2	1-37
Y	DATABASE BIOSIS, [Online] 19 November 2010 (2010-11-19), JIN LINHUA ET AL: "Efficacy and Mechanisms of Apoptosis Induction by Simultaneous Inhibition of PI3K with GDC-0941 and Blockade of Bcl-2 (ABT-737) or FLT3 (Sorafenib) In AML Cells In the Hypoxic Bone Marrow Microenvironment", XP002678287, retrieved from BIOSIS Database accession no. PREV201100423323 abstract	1-19, 27-37
Y	ZHU S ET AL: "PI3K inhibition potentiates Bcl-2-dependent apoptosis in renal carcinoma cells", JOURNAL OF CELLULAR AND MOLECULAR MEDICINE, UNIVERSITY PRESS CAROL DAVILA, BUCHAREST, RO, vol. 17, no. 3, March 2013 (2013-03), pages 377-385, XP002740727, ISSN: 1582-1838, DOI: 10.1111/JCMM.12019 [retrieved on 2013-02-07] abstract figure 1	1-18, 27-37
Y	WO 2013/110890 A1 (SERVIER LAB [FR]; VERNALIS R & D LTD [GB]) 1 August 2013 (2013-08-01) cited in the application pages 34-37; example 1 page 119; table 1	1-37
A	KUTSCH N ET AL: "Emerging therapies for refractory chronic lymphocytic leukemia", LEUKEMIA AND LYMPHOMA 20150201 INFORMA HEALTHCARE GBR, vol. 56, no. 2, February 2015 (2015-02), pages 285-292, XP009188195, ISSN: 1042-8194 the whole document	1-37

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/067699

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013110890 A1	01-08-2013	AR 089774 A1	17-09-2014
		AU 2013213474 A1	24-07-2014
		CA 2861160 A1	01-08-2013
		CL 2014001829 A1	02-01-2015
		CN 104144930 A	12-11-2014
		CR 20140311 A	07-10-2014
		CU 20140089 A7	27-11-2014
		DO P2014000156 A	15-10-2014
		EA 201400833 A1	30-12-2014
		EP 2807159 A1	03-12-2014
		FR 2986002 A1	26-07-2013
		GT 201400142 A	24-11-2015
		HK 1201527 A1	04-09-2015
		HK 1203507 A1	30-10-2015
		JP 5978317 B2	24-08-2016
		JP 2015506368 A	02-03-2015
		KR 20140129052 A	06-11-2014
		MA 35903 B1	01-12-2014
		MD 20140084 A2	31-12-2014
		NZ 626942 A	29-07-2016
		PE 14052014 A1	20-10-2014
		PH 12014501488 A1	22-09-2014
		RU 2014134388 A	27-03-2016
		SG 11201403748R A	30-10-2014
		TW 201335157 A	01-09-2013
		UA 112215 C2	10-08-2016
		US 2015051189 A1	19-02-2015
		US 2015313911 A1	05-11-2015
		UY 34578 A	02-09-2013
		WO 2013110890 A1	01-08-2013