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(54) Title: PHARMACEUTICAL COMBINATIONS

(57) Abstract: A pharmaceutical combination comprising (a) a phosphatidylinositol-3-kinase (PI3K) inhibitor compound of formula (I), as defined herein, or a pharmaceutically acceptable salt thereof and (b) lomustine or a pharmaceutically acceptable salt thereof for simultaneous, separate or sequential use, for the treatment of a brain tumor, particularly glioblastoma multiforme; a pharmaceutical composition comprising said combination; the use of said combination for the preparation of a medicament for the treatment of a brain tumor; a method of treating or preventing a brain tumor comprising administering a jointly therapeutically effective amount of such a combination to a subject in need thereof; and a commercial package thereof.



PHARMACEUTICAL COMBINATIONS

Field of the Invention

A pharmaceutical combination comprising (a) a phosphatidylinositol-3-kinase (PI3K) inhibitor compound of formula (I), as defined herein, or a pharmaceutically acceptable salt thereof and (b) lomustine or a pharmaceutically acceptable salt thereof for simultaneous, separate or sequential use for the treatment of a brain tumor, particularly glioblastoma multiforme; a pharmaceutical composition comprising said combination; the use of said combination for the preparation of a medicament for the treatment of a brain tumor; a method of treating or preventing a brain tumor, comprising administering a jointly therapeutically effective amount of such a combination to a subject in need thereof; and a commercial package thereof.

Background of the Invention

Glioblastoma multiforme (or glioblastoma) is the most common malignant primary brain tumor in adults. Classified as a Grade IV astrocytoma, glioblastoma multiforme develop from the lineage of glial cells (i.e., astrocytes) that support nerve cells. The incidence annually is 2 to 3 per 100,000 people in the United States and Europe. Glioblastoma multiforme accounts for 12% to 15% of all intracranial tumors and 50% to 60% of astrocytic tumors. Glioblastoma multiforme is a devastating brain cancer that typically results in death in the first 15 months after diagnosis.

Previously, a randomized Phase III clinical trial conducted in patients with newly diagnosed glioblastoma multiforme, comparing radiotherapy alone to radiotherapy and concomitant daily temozolomide followed by adjuvant temozolomide, demonstrated that the addition of temozolomide to radiotherapy in newly-diagnosed glioblastoma multiforme prolonged the median overall survival (OS) from 12.1 to 14.5 months (HR of 0.63 $p < 0.001$) (Stupp et al, N. Eng. J. Med., 2005, 352:987-96). Nevertheless, almost all patients experience recurrent disease and only a minority of such patients are eligible for second surgery or re-irradiation. Moreover, after tumor relapse, conventional chemotherapy is generally ineffective. Among chemotherapy agents used at time of relapse, temozolomide re-challenge including dose dense or protracted administration regimens reported 6-month progression free survival (PFS-6) ranging from 18% to 36% (Gilbert et al., J. Clin. Oncol., 2012: 112-117).

Bevacizumab single agent has been approved in the United States for treatment of glioblastoma multiforme in patients whose cancer has progressed after prior treatment. Despite the encouraging results obtained with bevacizumab, all patients eventually progress

making the next treatment particularly challenging. Retrospective studies in patients who progress on, or after bevacizumab-containing regimens reported a PFS-6 rate around 2% and a median overall survival of approximately 2 months (Chamberlain et al., J. Neurooncol., 2011, 102(3):427-432).

As shown by the foregoing, there is an unmet medical need for more effective and targeted treatment of brain tumors, particularly glioblastoma multiforme, in patients suffering from said tumor(s). It is believed that the combination of the compound of formula (I) and lomustine will provide improved and effective treatment as compared to each monotherapy for patients suffering from a brain tumor, particularly glioblastoma multiforme.

Summary of the Invention

The present invention relates to a pharmaceutical combination comprising (a) a phosphatidylinositol-3-kinase (PI3K) inhibitor compound of formula (I), as defined herein, or a pharmaceutically acceptable salt thereof and (b) lomustine or a pharmaceutically acceptable salt thereof, for simultaneous, separate or sequential use for the treatment or prevention of a brain tumor.

The present invention also provides a pharmaceutical combination comprising (a) a phosphatidylinositol-3-kinase (PI3K) inhibitor compound of formula (I), as defined herein, or a pharmaceutically acceptable salt thereof and (b) lomustine or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of a brain tumor.

In one embodiment, the present invention further pertains to the use of a COMBINATION OF THE INVENTION for the preparation of a pharmaceutical composition or medicament for the treatment or prevention of a brain tumor.

In one embodiment, the present invention relates to a method of treating or preventing a brain tumor comprising administering a jointly therapeutically effective amount of a COMBINATION OF THE INVENTION to a subject in need thereof.

In one embodiment, the present invention pertains to a pharmaceutical composition comprising a quantity of the COMBINATION OF THE INVENTION, which is jointly therapeutically effective against a brain tumor.

In one embodiment, the present invention further provides a commercial package comprising as therapeutic agents a COMBINATION OF THE INVENTION, together with instructions for simultaneous, separate or sequential administration thereof for use in the treatment or prevention of a brain tumor.

Detailed Description of the Figures

FIGURE 1 shows the percent survival of animals treated with vehicle as compared to the percent survival of animals treated with lomustine alone.

FIGURE 2 shows the percent survival of animals treated with vehicle as compared to the percent survival of animals treated with Compound A alone.

FIGURE 3 shows the percent survival of animals treated with vehicle as compared to the percent survival of animals treated with the combination of Compound A and lomustine.

In the figures herein, the term “percent survival” indicates the percentage of animals that started the experiment that are alive on the specified day of the experiment. The dotted line in Figures 1 and 3 indicates the percent of animals alive at the end of the experiment (Day 123).

Detailed Description of the Invention

The present invention relates to a pharmaceutical combination comprising (a) a phosphatidylinositol-3-kinase (PI3K) inhibitor compound of formula (I), as defined herein, or a pharmaceutically acceptable salt thereof and (b) lomustine or a pharmaceutically acceptable salt thereof, for simultaneous, separate or sequential use for the treatment or prevention of a brain tumor, particularly glioblastoma multiforme.

The present invention also provides a pharmaceutical combination comprising (a) a phosphatidylinositol-3-kinase (PI3K) inhibitor compound of formula (I), as defined herein, or a pharmaceutically acceptable salt thereof and (b) lomustine or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of a brain tumor.

The general terms used herein are defined with the following meanings, unless explicitly stated otherwise:

The terms “comprising” and “including” are used herein in their open-ended and non-limiting sense unless otherwise noted.

The terms “a” and “an” and “the” and similar references in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

The term “combination” or “pharmaceutical combination” as used herein defines either a fixed combination in one dosage unit form or a kit of parts for the combined administration where the compound of formula (I) and lomustine may be administered independently at the same time or separately within time intervals that allow that the therapeutic agents (i.e, the compound of formula (I) and lomustine and pharmaceutically acceptable salts thereof) show a cooperative, e.g., synergistic, effect.

The term “pharmaceutical composition” is defined herein to refer to a mixture or solution containing at least one therapeutic agent to be administered to a subject, e.g., a mammal or human, in order to prevent or treat a particular disease or condition affecting the mammal.

The term “pharmaceutically acceptable” is defined herein to refer to those compounds, materials, compositions and/or dosage forms, which are, within the scope of sound medical judgment, suitable for contact with the tissues a subject, e.g., a mammal or human, without excessive toxicity, irritation allergic response and other problem complications commensurate with a reasonable benefit / risk ratio.

The term “a combined preparation” is defined herein to refer to especially a “kit of parts” in the sense that the therapeutic agents (a) and (b) as defined above can be dosed independently or by use of different fixed combinations with distinguished amounts of the therapeutic agents (a) and (b), i.e., simultaneously or at different time points. The parts of the kit of parts can then e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. The ratio of the total amounts of the therapeutic agent (a) to the therapeutic agent (b) 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 the single patient.

The term “combined administration” as used herein is defined to encompass the administration of the selected therapeutic agents to a single patient, and is 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 “treating” or “treatment” as used herein comprises a treatment relieving, reducing or alleviating at least one symptom in a subject or effecting a delay of progression of a brain tumor. For example, treatment can be the diminishment of one or several symptoms of a brain tumor or complete eradication of a brain tumor. Within the meaning of the present invention, the term “treat” also denotes to arrest, delay the onset (i.e., the period

prior to clinical manifestation of the brain tumor) and/or reduce the risk of developing or worsening the brain tumor. The term "prevention" of a brain tumor refers to the administration of a combination of the invention to a subject before any symptoms of the brain tumor are apparent.

The term "joint therapeutic effect" or "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 or all therapeutic agents are present in the blood of the human to be treated at least during certain time intervals.

An "effective amount" or "therapeutically effective amount" of a combination of therapeutic agents (e.g., a compound of formula (I) or a pharmaceutically acceptable salt thereof and lomustine or a pharmaceutically acceptable salt thereof) is an amount sufficient to provide an observable improvement over the baseline clinically observable signs and symptoms of the glioblastoma multiforme treated with the combination.

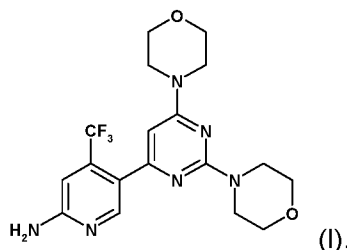
The term "subject" or "patient" as used herein includes animals, which are capable of suffering from or afflicted with a brain tumor or any disorder involving, directly or indirectly, a brain tumor. Examples of subjects include mammals, e.g., humans, dogs, cows, horses, pigs, sheep, goats, cats, mice, rabbits, rats and transgenic non-human animals. In the preferred embodiment, the subject is a human, e.g., a human suffering from, at risk of suffering from, or potentially capable of suffering from a brain tumor.

The term "about" or "approximately" usually means within 20%, more preferably within 10%, and most preferably still within 5% of a given value or range. Alternatively, especially in biological systems, the term "about" means within about a log (*i.e.*, an order of magnitude) preferably within a factor of two of a given value.

The present invention relates to a pharmaceutical combination comprising (a) a phosphatidylinositol-3-kinase (PI3K) inhibitor compound of formula (I), as defined herein, or a pharmaceutically acceptable salt thereof and (b) lomustine or a pharmaceutically acceptable salt thereof, for simultaneous, separate or sequential use for the treatment or prevention of a brain tumor, particularly glioblastoma multiforme.

The present invention also provides a pharmaceutical combination comprising (a) a phosphatidylinositol-3-kinase (PI3K) inhibitor compound of formula (I), as defined herein, or a pharmaceutically acceptable salt thereof and (b) lomustine or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of a brain tumor.

WO07/084786 describes specific pyrimidine derivatives which have been found to inhibit the activity of PI3K. The compound 5-(2,6-di-morpholin-4-yl-pyrimidin-4-yl)-4-trifluoromethyl-pyridin-2-ylamine (hereinafter also referred to as "COMPOUND A" or "Compound of formula (I)") has the chemical structure of formula (I)

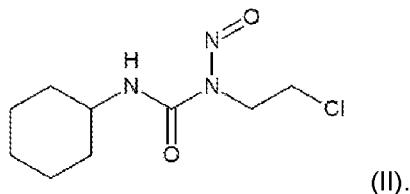


The compound, its salts, its utility as a pan-PI3K inhibitor and synthesis of the compound 5-(2,6-di-morpholin-4-yl-pyrimidin-4-yl)-4-trifluoromethyl-pyridin-2-ylamine are described in WO 2007/084786, which is hereby incorporated by reference in its entirety hereto, for instance as Example 10.

The phosphatidylinositol 3-kinase inhibitor compound of formula (I) may be present in the pharmaceutical combination in the form of the free base or a pharmaceutically acceptable salt thereof. Such salts can be prepared in situ during the final isolation and purification of the compounds, or by separately reacting the base or acid functions with a suitable organic or inorganic acid or base, respectively. Suitable salts of the compound of formula (I) include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemi-sulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2 hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2 naphth-alenesulfonate, oxalate, pamoate, pectinate, persulfate, 3 phenylproionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, p toluenesulfonate, and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl, and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others.

In a preferred embodiment, the compound of formula (I) is in the form of its hydrochloride salt.

Lomustine (also known as CCNU) is an alkylating nitrosourea compound used in chemotherapy. The chemical name for lomustine is 1-(2-chloro-ethyl)-3-cyclohexyl-1-nitrosourea having the chemical formula (II)



It has the empirical formula of $C_9H_{16}ClN_3O_2$ and a molecular weight of 231.71. It was approved in 1977 for the treatment of brain tumors and Hodgkin's disease. Lomustine is commercially available under the tradename CeeNu® (Bristol Meyers Squibb Co., New York, New York).

Also included are the generic forms of lomustine, as well as various dosage forms of lomustine.

Hereinafter, the pharmaceutical combination comprising (a) the compound of formula (I) or a pharmaceutically acceptable salt thereof and (b) lomustine or a pharmaceutically acceptable salt thereof will be referred to as a COMBINATION OF THE INVENTION. The present invention particularly pertains to a COMBINATION OF THE INVENTION useful for separate, simultaneous or sequential administration to a subject in need thereof for treating or preventing a brain tumor.

Unless otherwise specified, or clearly indicated by the text, or not applicable, reference to therapeutic agents useful in the COMBINATION OF THE INVENTION includes both the free base of the therapeutic agents, and all pharmaceutically acceptable salts of the therapeutic agents.

In one embodiment, the present invention further pertains to the use of a COMBINATION OF THE INVENTION for the preparation of a pharmaceutical composition or medicament for the treatment or prevention of a brain tumor.

In one embodiment, the present invention relates to a method of treating or preventing a brain tumor comprising administering a jointly therapeutically effective amount of a COMBINATION OF THE INVENTION to a subject in need thereof.

In one embodiment, the present invention further provides a commercial package comprising as therapeutic agents a COMBINATION OF THE INVENTION, together with

instructions for simultaneous, separate or sequential administration thereof for use in the treatment or prevention of a brain tumor.

In one embodiment, the present invention further provides a commercial package comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof and instructions for simultaneous, separate or sequential administration with lomustine or a pharmaceutically acceptable salt thereof to a subject in need thereof for the treatment or prevention of a brain tumor.

The COMBINATION OF THE INVENTION is particularly useful for treating or preventing a brain tumor in a subject in need thereof. The therapeutic agents of the COMBINATION OF THE INVENTION may be separately, simultaneously, or sequentially administered to a subject in need thereof. Preferably, these therapeutic agents are administered at therapeutically effective dosages which, when combined, provide a joint beneficial effect. Depending on the tumor type and particular combination used, a decrease of the tumor volume or longer time period of overall survival can be obtained. Thus, in one embodiment of the present invention, the COMBINATION OF THE INVENTION is used for the treatment or prevention of glioblastoma multiforme.

Suitable brain tumors that can be treated or prevented with the COMBINATION OF THE INVENTION include, but are not limited to, gliomas (including astrocytomas, glioblastoma multiforme), oligodendroglioma, ependymoma, brain stem gliomas, primary CNS lymphoma, medulloblastoma, craniopharyngioma, and acoustic schwannoma. Preferably, the brain tumor is glioblastoma multiforme.

In one embodiment, the COMBINATION OF THE INVENTION is used for treating or prevention of a brain tumor selected from gliomas (including astrocytomas, glioblastoma multiforme), oligodendroglioma, ependymoma, brain stem gliomas, primary CNS lymphoma, medulloblastoma, craniopharyngioma, acoustic schwannoma, or a combination thereof.

In a preferred embodiment, the COMBINATION OF THE INVENTION is used for treating or prevention of glioblastoma multiforme. Examples of subtypes of glioblastoma multiforme include:

- (a) Classical Glioblastoma Multiforme Tumors
- (b) Proneural Glioblastoma Multiforme Tumors
- (c) Mesenchymal Glioblastoma Multiforme Tumors and
- (d) Neural Glioblastoma Multiforme Tumors.

In a further embodiment, the COMBINATION OF THE INVENTION is used for the treatment or prevention of a glioblastoma multiforme tumor selected from Classical Glioblastoma Multiforme Tumor, Proneural Glioblastoma Multiforme Tumor, Mesenchymal

Glioblastoma Multiforme Tumor, Neural Glioblastoma Multiforme Tumor or a combination thereof.

It is understood that each embodiment herein referring to “treatment or prevention” further includes an embodiment wherein the COMBINATION OF THE INVENTION is used for treatment only and an embodiment wherein the COMBINATION OF THE INVENTION is used for prevention only. In a further embodiment, the COMBINATION OF THE INVENTION is used for the treatment of a brain tumor, particularly glioblastoma multiforme.

The COMBINATION OF THE INVENTION disclosed herein is also suited to prevent the metastatic spread of a brain tumor, particularly glioblastoma multiforme, and the growth or development of micrometastases resulting from a brain tumor, particularly glioblastoma multiforme.

Further, the COMBINATION OF THE INVENTION is suitable for the treatment or prevention of poor prognosis patients, especially such poor prognosis patients having a recurrent brain tumor. The COMBINATION OF THE INVENTION is particularly suited for the treatment or prevention of such poor prognosis patients having a recurrent glioblastoma multiforme after prior treatment with chemotherapy, lomustine, radiotherapy, bevacizumab, or a combination thereof. The phrase “recurrent glioblastoma multiforme after prior treatment with chemotherapy, lomustine, radiotherapy, bevacizumab, or a combination thereof” refers to a glioblastoma multiforme cancer or tumor which has recurred in a patient after receiving treatment with chemotherapy (e.g. temozolomide), lomustine, radiotherapy, bevacizumab, or a combination thereof. The recurrent brain tumor may recur in the same location as a prior brain tumor or arise from a cancer or tumor elsewhere in the body.

The COMBINATION OF THE INVENTION is particularly useful for the treatment or prevention of a brain tumor, particularly glioblastoma multiforme, having a genetic alteration of the phosphatidylinositol-3-kinase pathway such as, for example, amplification of PI3K alpha, somatic mutation of PIK3CA, germline mutations or somatic mutations of PTEN, or mutations and translocation of p85-alpha that serve to up-regulate the p85-p110 complex.

In one embodiment, the present invention relates to a method of treating or preventing a brain tumor, particularly glioblastoma multiforme, comprising administering a jointly therapeutically effectively amount of a COMBINATION OF THE INVENTION to a subject in need thereof. One example of a subject in need of a particular treatment includes, but is not limited to, a subject suffering from or diagnosed with the identified brain tumor.

In a further embodiment, the present invention relates to a method of treating a brain tumor, particularly glioblastoma multiforme, in a patient suffering from said tumor comprising administering to said patient a jointly therapeutically effectively amount of a COMBINATION OF THE INVENTION.

In a further embodiment, the present invention relates to a method of treating or preventing a brain tumor, particularly glioblastoma multiforme, having an amplification of PI3K alpha, somatic mutation of PIK3CA, germline mutations or somatic mutations of PTEN, or mutations and translocation of p85-alpha, comprising administering a jointly therapeutically effectively amount of a COMBINATION OF THE INVENTION to a subject in need thereof.

In a further embodiment, the present invention relates to a method of treating or preventing a recurrent brain tumor comprising administering a jointly therapeutically effectively amount of a COMBINATION OF THE INVENTION to a subject in need thereof. Preferably, the recurrent brain tumor is recurrent glioblastoma multiforme after prior treatment with chemotherapy (e.g, temozolomide), lomustine, radiotherapy, bevacizumab, or a combination thereof.

In each embodiment, it is understood that a subject in need of a particular treatment includes subjects suffering from or diagnosed with the identified brain tumor.

In one embodiment, the present invention pertains to the use of a COMBINATION OF THE INVENTION for the preparation of a medicament for the treatment or prevention of a brain tumor, particularly glioblastoma multiforme.

In one embodiment, the present invention pertains to the use of a COMBINATION OF THE INVENTION for the preparation of a medicament for the treatment of a brain tumor, particularly glioblastoma multiforme.

In a further embodiment, the present invention pertains to the use of a COMBINATION OF THE INVENTION for the preparation of a medicament for the treatment or prevention of a recurrent brain tumor. Preferably, the recurrent brain tumor is recurrent glioblastoma multiforme after prior treatment with chemotherapy (e.g, temozolomide), lomustine, radiotherapy, bevacizumab, or a combination thereof.

In one embodiment, the present invention pertains to the use of a COMBINATION OF THE INVENTION for the treatment or prevention of a brain tumor, particularly glioblastoma multiforme.

In one embodiment, the present invention pertains to the use of a COMBINATION OF THE INVENTION for the treatment of a brain tumor, particularly glioblastoma multiforme.

In a further embodiment, the present invention pertains to the use of a COMBINATION OF THE INVENTION for the treatment or prevention of a recurrent brain tumor. Preferably, the recurrent brain tumor is recurrent glioblastoma multiforme after prior treatment with chemotherapy (e.g, temozolomide), lomustine, radiotherapy, bevacizumab, or a combination thereof.

The nature of a tumor or cancer is multifactorial. Under certain circumstances, drugs with different mechanisms of action may be combined. However, just considering any combination of therapeutic agents having different mode of action does not necessarily lead to combinations with advantageous effects.

The administration of a pharmaceutical combination of the invention may result not only in a beneficial effect, e.g. a synergistic therapeutic effect, e.g. with regard to alleviating, delaying progression of or inhibiting the symptoms, but also in further surprising beneficial effects, e.g. fewer side-effects, more durable response, an improved quality of life, prolonged time period of survival or a decreased morbidity, compared with a monotherapy applying only one of the pharmaceutically therapeutic agents used in the combination of the invention. Preferably, there is at least one beneficial effect, e.g., a mutual enhancing of the effect of the therapeutic agent (a) and (b), in particular a synergism (e.g., a more than additive effect), or additional advantageous effects (e.g., less side effects), or a combined therapeutic effect in a non-effective dosage of one or both of the therapeutic agent (a) and (b), and very preferably a strong synergism of the therapeutic agent (a) and (b).

The term "synergistic effect" or "synergism" as used herein, refers to action of two therapeutic agents such as, for example, a compound of formula (I) and lomustine, producing an effect, for example, slowing the symptomatic progression of a brain tumor or symptoms thereof, which is greater than the simple addition of the effects of each drug administered by themselves. A synergistic effect can be calculated, for example, using suitable methods such as the Sigmoid-Emax equation (Holford, N. H. G. and Scheiner, L. B., Clin. Pharmacokinet. 6: 429-453 (1981)), the equation of Loewe additivity (Loewe, S. and Muischnek, H., Arch. Exp. Pathol Pharmacol. 114: 313-326 (1926)) and the median-effect equation (Chou, T. C. and Talalay, P., Adv. Enzyme Regul. 22: 27-55 (1984)). Each equation referred to above can be applied to experimental data to generate a corresponding graph to aid in assessing the effects of the drug combination. The corresponding graphs associated with the equations referred to above are the concentration-effect curve, isobologram curve and combination index curve, respectively.

It can be shown by established test models that a COMBINATION OF THE INVENTION results in the beneficial effects described herein before. The person skilled in the art is fully enabled to select a relevant test model to prove such beneficial effects. The pharmacological activity of a COMBINATION OF THE INVENTION may, for example, be demonstrated in a clinical study as essentially described hereinafter or in an in vitro model or animal model.

Determining a synergistic interaction between one or more therapeutic agents, the optimum range for the effect and absolute dose ranges of each therapeutic agent for the effect may be definitively measured by administration of the therapeutic agents over different w/w ratio ranges and doses to patients in need of treatment. The observation of synergy in one species can be predictive of the effect in other species and animal models exist, as described herein, to measure a synergistic effect and the results of such studies can also be used to predict effective dose ratio ranges and the absolute doses and plasma concentrations required in other species by the application of pharmacokinetic/pharmacodynamic methods. Established correlations between tumor models and effects seen in man suggest that synergy in animals may be demonstrated, for example, by xenograft models or in appropriate cell lines.

Suitable clinical studies are, for example, multi-center, open label or randomized, dose escalation and efficacy studies in patients having a brain tumor, particularly glioblastoma multiforme. Such studies can prove the additive or synergism of the active ingredients and/or the antitumor activity of the COMBINATIONS OF THE INVENTION. The beneficial effects on proliferative diseases can be determined directly through the results of these studies or by changes in the study design which are known as such to a person skilled in the art. Such studies are, in particular, suitable to compare the effects of a monotherapy and/or existing standard of care treatments to the COMBINATION OF THE INVENTION. Preferably, the therapeutic agent (a) is administered with a fixed dose and the dose of the therapeutic agent (b) is escalated until the Maximum Tolerated Dosage is reached.

The effective dosage of each of the therapeutic agents employed in the COMBINATION OF THE INVENTION may vary depending on the particular therapeutic agent or pharmaceutical composition employed, the mode of administration, the condition being treated, and the severity of the condition being treated. Thus, the dosage regimen of the COMBINATION OF THE INVENTION is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A clinician or physician of ordinary skill can readily determine and prescribe the effective amount of the single therapeutic agents required to alleviate, counter or arrest the progress of the condition.

The compound of formula (I) is preferably administered daily at a dose in the range of from 1.0 to 30 mg/kg body weight. In one preferred embodiment, the dosage of compound of formula (I) is in the range of about 60 mg/day to about 120 mg/day, especially if the warm-blooded animal is an adult human. Preferably, the dosage of compound of formula (I) is in the range of about 60 mg/day to about 100 mg/day for an adult human. The Compound of

formula (I) may be administered orally to an adult human once daily continuously (each day) or intermittently (e.g, 5 out of 7 days) in a suitable dosage.

Lomustine may be administered orally at a dose in the range of about 15 to about 200 mg/m², e.g., about 50 to about 125 mg/ m², or about 70 to about 100 mg/ m² every 6 weeks or 42 days, especially if the warm-blooded animal is an adult human. Preferably, the dosage of lomustine is about 80 mg/ m² to about 100 mg/ m² administered every 6 weeks or 42 days for an adult human.

The optimum ratios, individual and combined dosages, and concentrations of the therapeutic agents (a) and (b) of the COMBINATION OF THE INVENTION that yield efficacy without toxicity are based on the kinetics of the therapeutic agents' availability to target sites, and are determined using methods known to those of skill in the art.

The effective dosage of each of the therapeutic agents may require more frequent administration of one of the therapeutic agent(s) as compared to the other therapeutic agent(s) in the combination. Therefore, to permit appropriate dosing, packaged pharmaceutical products may contain one or more dosage forms that contain the combination of therapeutic agents, and one or more dosage forms that contain one of the combination of therapeutic agents, but not the other therapeutic agent(s) of the combination.

When the therapeutic agents, which are employed in the COMBINATION OF THE INVENTION, are applied in the form as marketed as single drugs, their dosage and mode of administration can be in accordance with the information provided on the package insert of the respective marketed drug, if not mentioned herein otherwise.

The optimal dosage of each therapeutic agents for treatment or prevention of a brain tumor can be determined empirically for each individual using known methods and will depend upon a variety of factors, including, though not limited to, the degree of advancement of the disease; the age, body weight, general health, gender and diet of the individual; the time and route of administration; and other medications the individual is taking. Optimal dosages may be established using routine testing and procedures that are well known in the art.

The amount of each therapeutic agent of the COMBINATION OF THE INVENTION that may be combined with the carrier materials to produce a single dosage form will vary depending upon the individual treated and the particular mode of administration. In some embodiments the unit dosage forms containing the combination of agents as described herein will contain the amounts of each therapeutic agent of the combination that are typically administered when the therapeutic agents are administered alone.

Frequency of dosage may vary depending on the therapeutic agent used and the particular condition to be treated or prevented. Patients may generally be monitored for

therapeutic effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those of ordinary skill in the art.

In one embodiment, the present invention pertains to a pharmaceutical composition or combined preparation comprising a jointly therapeutically effective amount of the COMBINATION OF THE INVENTION and optionally at least one pharmaceutically acceptable carrier, for use in the treatment or prevention of a brain tumor, particularly glioblastoma multiforme. In this composition or combined preparation, the therapeutic agents of the compound of formula (I) or a pharmaceutically acceptable salt thereof and lomustine or a pharmaceutically acceptable salt thereof can be administered together in a single formulation or unit dosage form, administered concurrently but separately, or sequentially by any suitable route.

A therapeutically effective amount of the therapeutic agents of the COMBINATION OF THE INVENTION may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as a fixed combination. For example, the method of treatment or prevention of a brain tumor, particularly glioblastoma multiforme, according to the invention may comprise (i) administration of the first therapeutic agent in free or pharmaceutically acceptable salt form and (ii) administration of the second therapeutic agent in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts. The individual therapeutic agents of the COMBINATION OF THE INVENTION can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The invention is therefore to be understood as embracing all such regimens of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. Preferably, the compound of formula (I) and lomustine are administered separately.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man. Alternatively, when the agents are administered separately, one can be an enteral formulation and the other can be a parenteral formulation.

The novel pharmaceutical composition contain, for example, from about 10 % to about 100 %, preferably from about 20 % to about 60 %, of the active ingredients. Pharmaceutical preparations for the combination therapy for enteral or parenteral administration are, for example, those in unit dosage forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. If not indicated otherwise,

these are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will be appreciated that the unit content of one of the therapeutic agents contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount can be reached by administration of a plurality of dosage units.

In preparing the compositions for oral dosage form, any of the usual pharmaceutically acceptable carriers may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed.

One of ordinary skill in the art may select one or more of the aforementioned carriers with respect to the particular desired properties of the dosage form by routine experimentation and without any undue burden. The amount of each carriers used may vary within ranges conventional in the art. The following references which are all hereby incorporated by reference disclose techniques and excipients used to formulate oral dosage forms. See *The Handbook of Pharmaceutical Excipients*, 4th edition, Rowe et al., Eds., American Pharmaceuticals Association (2003); and *Remington: the Science and Practice of Pharmacy*, 20th edition, Gennaro, Ed., Lippincott Williams & Wilkins (2003).

Examples of pharmaceutically acceptable disintegrants include, but are not limited to, starches; clays; celluloses; alginates; gums; cross-linked polymers, e.g., cross-linked polyvinyl pyrrolidone or crospovidone, e.g., POLYPLASDONE XL from International Specialty Products (Wayne, NJ); cross-linked sodium carboxymethylcellulose or croscarmellose sodium, e.g., AC-DI-SOL from FMC; and cross-linked calcium carboxymethylcellulose; soy polysaccharides; and guar gum. The disintegrant may be present in an amount from about 0% to about 10% by weight of the composition. In one embodiment, the disintegrant is present in an amount from about 0.1% to about 5% by weight of composition.

Examples of pharmaceutically acceptable binders include, but are not limited to, starches; celluloses and derivatives thereof, for example, microcrystalline cellulose, e.g., AVICEL PH from FMC (Philadelphia, PA), hydroxypropyl cellulose hydroxyethyl cellulose and hydroxypropylmethyl cellulose METHOCEL from Dow Chemical Corp. (Midland, MI); sucrose; dextrose; corn syrup; polysaccharides; and gelatin. The binder may be present in an amount from about 0% to about 50%, e.g., 2-20% by weight of the composition.

Examples of pharmaceutically acceptable lubricants and pharmaceutically acceptable glidants include, but are not limited to, colloidal silica, magnesium trisilicate, starches, talc, tribasic calcium phosphate, magnesium stearate, aluminum stearate, calcium stearate, magnesium carbonate, magnesium oxide, polyethylene glycol, powdered cellulose and microcrystalline cellulose. The lubricant may be present in an amount from about 0% to about 10% by weight of the composition. In one embodiment, the lubricant may be present in an amount from about 0.1% to about 1.5% by weight of composition. The glidant may be present in an amount from about 0.1% to about 10% by weight.

Examples of pharmaceutically acceptable fillers and pharmaceutically acceptable diluents include, but are not limited to, confectioner's sugar, compressible sugar, dextrates, dextrin, dextrose, lactose, mannitol, microcrystalline cellulose, powdered cellulose, sorbitol, sucrose and talc. The filler and/or diluent, e.g., may be present in an amount from about 0% to about 80% by weight of the composition.

Moreover, the present invention provides a commercial package comprising as active ingredients of COMBINATION OF THE INVENTION, together with instructions for simultaneous, separate or sequential administration thereof for use in the treatment or prevention of a brain tumor, particularly glioblastoma multiforme.

In a further embodiment, the present invention provides a commercial package comprising as active ingredients of COMBINATION OF THE INVENTION, together with instructions for simultaneous, separate or sequential administration thereof for use in the treatment or prevention of a recurrent brain tumor. Preferably, the recurrent brain tumor is recurrent glioblastoma multiforme after prior treatment with chemotherapy (e.g, temozolomide), lomustine, radiotherapy, bevacizumab, or a combination thereof.

In a further embodiment, the present invention further provides a commercial package comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof and instructions for simultaneous, separate or sequential administration with lomustine or a pharmaceutically acceptable salt thereof to a subject in need thereof for the treatment or prevention of a brain tumor, particularly glioblastoma multiforme.

In further aspects, the present invention provides

- a pharmaceutical combination which comprises a COMBINATION OF THE INVENTION, wherein the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt, and optionally at least one

pharmaceutically acceptable carrier; for simultaneous, separate or sequential use for the treatment or prevention of a brain tumor, particularly glioblastoma multiforme;

- a pharmaceutical combination which comprises a COMBINATION OF THE INVENTION, wherein the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt, and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use for the treatment or prevention of a recurrent brain tumor. Preferably, the recurrent brain tumor is recurrent glioblastoma multiforme after prior treatment with chemotherapy (e.g, temozolomide), lomustine, radiotherapy, bevacizumab, or a combination thereof.
- a pharmaceutical composition comprising a quantity which is jointly therapeutically effective against a brain tumor, particularly glioblastoma multiforme, of a COMBINATION OF THE INVENTION and at least one pharmaceutically acceptable carrier;
- a pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against a recurrent brain tumor, of a COMBINATION OF THE INVENTION and at least one pharmaceutically acceptable carrier; Preferably, the recurrent brain tumor is recurrent glioblastoma multiforme after prior treatment with chemotherapy (e.g, temozolomide), lomustine, radiotherapy, bevacizumab, or a combination thereof.
- a combined preparation comprising (a) one or more unit dosage forms of a therapeutic compound of formula (I) or a pharmaceutically acceptable salt thereof and (b) lomustine or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of a brain tumor, particularly glioblastoma multiforme;
- a combined preparation comprising (a) one or more unit dosage forms of a therapeutic compound of formula (I) or a pharmaceutically acceptable salt thereof and (b) lomustine or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of a recurrent brain tumor. Preferably, the recurrent brain tumor is recurrent glioblastoma multiforme after prior treatment with chemotherapy (e.g, temozolomide), lomustine, radiotherapy, bevacizumab, or a combination thereof.

The following Examples illustrate the invention described above; they are not, however, intended to limit the scope of the invention in any way. The beneficial effects of the COMBINATION OF THE INVENTION can also be determined by other test models known as such to the person skilled in the pertinent art.

Example 1: Clinical Study

A clinical study using (a) a phosphatidylinositol 3-kinase inhibitor COMPOUND A or its hydrochloride salt, in combination with (b) lomustine for treatment of patients with recurrent glioblastoma multiforme (GBM) pre-treated with radiotherapy and temozolomide.

A multi-center Phase Ib/ Phase II clinical trial of the combination comprising (a) COMPOUND A or its hydrochloride salt and (b) lomustine is conducted in patients with recurrent glioblastoma multiforme pre-treated with radiotherapy and temozolomide. In the description below, the dosages provided are for COMPOUND A free base, but either COMPOUND A free base or its hydrochloride salt may be used.

The eligibility of patients is determined during a screening period, which occurs within 1 to 28 days prior to treatment start. Eligible patients must provide a signed study Informed Consent Form prior to any screening procedure and be ≥ 18 years of age on the day of consenting to the study. The following screening inclusion criteria is used:

1. Patient has histologically confirmed diagnosis of glioblastoma multiforme (GBM) with documented recurrence after first line treatment including radiotherapy and temozolomide, not suitable for curative surgery or re-irradiation. (Tumor recurrence is defined as outside previously irradiated area. Patient has documented objective recurrence within the 12 weeks after completion of radiotherapy.)
2. Patient has at least one measurable and/or non-measurable lesion as per Response Assessment in Neuro-Oncology Criteria (RANO) criteria
3. Patient has tumor tissues available (archival or fresh).
4. Patient has recovered (to Grade ≤ 1) from all clinically significant toxicities related to prior antineoplastic therapies with the exception of bone and organs function.
5. Patient has Karnofsky performance status (KPS) $\geq 70\%$.
6. Patient has adequate organ and bone marrow functions as showed by:
 - (a) Absolute Neutrophils Count (ANC) $\geq 1.5 \times 10^9 / L$.
 - (b) Platelets $\geq 100 \times 10^9 / L$ (in case of transfusion stable for ≥ 14 days prior to treatment start)
 - (c) Hemoglobin ≥ 9.0 g/ dL (in case of transfusion stable for ≥ 14 days prior to treatment start)
 - (d) INR ≤ 1.5
 - (e) Serum Creatinine $\leq 1.5 \times$ Upper Limit Normal (ULN), or Creatinine Clearance > 45 mL/ min

- (f) Potassium and calcium (corrected for albumin), sodium and magnesium within institutional normal limits.
 - (g) Serum Bilirubin $\leq$ ULN, Aspartate aminotransferase/ glutamic oxaloacetic transaminase/ GOT (AST) and Alanine aminotransferase/ glutamic oxaloacetic transaminase/ GOT (ALT) $\leq$ ULN
 - (h) Glycosylated hemoglobin (HbA1c) $\leq$ 8%
 - (i) Fasting plasma glucose (FPG) $\leq$ 120 mg/dL or $\leq$ 6.7 mmol/L.
7. Patient is able to swallow and retain oral medication.

Patients must meet all screening inclusion criteria to be eligible. The following screening exclusion criteria is used:

1. Patient has received previous treatment with PI3K pathway inhibitors (e.g. PI3K, AKT, mTOR inhibitor)
2. Patient has received previous treatment with Lomustine or carboplatin for newly diagnosed or recurrent GBM
3. Patient has received previous antineoplastic treatment for recurrent GBM (e.g, VEGF inhibitors, cytotoxic agents).
4. Patient has received more than one line of cytotoxic chemotherapy
5. Patient has known hypersensitivity and/or contraindication to the excipients or of the drug which are be part of the study medications
6. Patient has concurrent use of anti-neoplastic agents including investigational therapy
7. Patient is currently receiving warfarin or other coumarin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin, or fondaparinux is allowed
8. Patient is currently receiving treatment with drugs known to be moderate or strong inhibitors or inducers of isoenzyme CYP3A. The patient must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the treatment is initiated. Switching to a different medication prior to randomization is allowed.
9. Patient is currently receiving an enzyme-inducing anti-epileptic drug (EIAED). The patient must have discontinued EIAED therapy for at least two weeks prior to starting study drug
10. Patient is currently receiving increasing treatment with corticosteroids or another immunosuppressive agent, as chronic administration of corticosteroids (> 5 days) can induce CYP3A4. (Note: Topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airway diseases), eye drops or local injections (e.g.,

intra-articular) are allowed. Patients who are on a stable or decreasing low dose of corticosteroid treatment (e.g., dexamethasone 4 mg/day or other corticosteroids equivalent dose) for at least 14 days before start of study treatment are eligible.)

11. Patient has a concurrent malignancy or malignancy within 3 years of study enrollment (with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer)
12. Patient has received major surgery or wide-field radiotherapy within 4 weeks prior to treatment start or has not recovered from side effects of such therapy
13. Active cardiac disease or history of cardiac dysfunction including any of the following:
 - a. Unstable angina pectoris within 6 months prior to study entry
 - b. Symptomatic pericarditis
 - c. Documented myocardial infarction within 6 months prior to study entry
 - d. History of documented congestive heart failure (New York Heart Association functional classification III-IV)
 - e. Documented cardiomyopathy
14. Patient has a Left Ventricular Ejection Fraction < 50% as determined by Multiple Gated acquisition scan or echocardiogram
15. Patient has any of the following cardiac conduction abnormalities
 - a. Ventricular arrhythmias except for benign premature ventricular contractions
 - b. Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication
 - c. Conduction abnormality requiring a pacemaker
 - d. Other cardiac arrhythmia not controlled with medication
16. Patient has QTc > 480 msec on the screening ECG (using the QTcF formula)
17. Patient is currently receiving treatment with medication that has a known risk to prolong the QT interval or inducing Torsades de Pointes, and the treatment cannot be discontinued or switched to a different medication prior to randomization
18. Patient has impairment of gastrointestinal (GI) function or GI disease that might significantly alter the absorption of COMPOUND A (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
19. Immuno-compromised patients including known history/ sero positivity of HIV infection (testing not mandatory)

20. Other concurrent severe and/or uncontrolled medical conditions that would, in the investigator's judgment, contraindicate participation in this study (e.g. pancreatitis, active hepatitis, chronic obstructive or restrictive pulmonary disease including dyspnea at rest or interstitial lung disease, adrenal insufficiency, uncontrolled hypertension, etc.)
21. Patients with a baseline Forced Vital Capacity <70%.
22. Patient has $\geq$ CTCAE grade 3 anxiety
23. Patient has a score $\geq$ 12 on the Patient Health Questionnaire (PHQ-9) questionnaire
24. Patient selects a response of "1, 2 or 3" to question number 9 on the PHQ-9 questionnaire regarding potential for suicidal thoughts or ideation (independent of the total score of the PHQ-9)
25. Patient has a General Anxiety Disorder Assessment (GAD-7) mood scale score $\geq$ 15
26. Patient has a medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (e.g. risk of doing harm to self or others), or patients with active severe personality disorders (defined according to DSM- IV). For patients with psychotropic treatments ongoing at baseline, the dose and the schedule should not be modified within the previous 6 weeks prior to start of study drug.
27. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).
28. Patient who is unwilling to abide by or use highly effective contraception during the study and through the duration as defined below after the final dose of study treatment
 - Men being treated with paclitaxel and carboplatin are advised to use an effective method of contraception and to not father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment as per paclitaxel and carboplatin label
 - Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and through at least 4 weeks after the final dose of study treatment

Note: contraception timeframe following treatment completion with lomustine or with carboplatin may even be longer than 4 weeks according to the local prescribing information (PI/SmPC).

Patients must not meet any of the screening exclusion criteria to be eligible for the study.

In Phase Ib or II, Patients may voluntarily withdraw from the study treatment or be removed at the investigator's decision. Patients must be withdrawn from the study treatment for reasons of death or pregnancy. Patients may be withdrawn from the study if any of the following occur: adverse event, lost to follow-up, non-compliance with study treatment, physician decision, progressive disease, protocol deviation, study terminated by sponsor, technical problems, or subject/ guardian decision.

In Phase Ib, an open-label dose-escalation study is conducted to determine the maximum tolerated dose (MTD)/ recommended Phase II dose (RP2D) of COMPOUND A when administered orally in combination with carboplatin or in combination with Lomustine in patients with recurrent glioblastoma as measured by dose-limiting toxicities (DLTs) in Cycle 1. Eligible patients are allocated alternatively to receive either: (i) COMPOUND A and carboplatin ("ARM 1") or (ii) COMPOUND A and Lomustine ("ARM 2") in a 1:1 ratio. In each arm, once the MTD / RP2D is been determined, an additional 5-8 evaluable patients are enrolled at that dose level in an expansion cohort to confirm the safety of the dose. Approximately 10-25 eligible patients per treatment arm are enrolled.

In ARM 1, patients are administered (i) the assigned starting dose of oral once daily of COMPOUND A on a continuous dosing schedule starting on Day 1 in combination with (ii) the assigned starting dose of every-3-week carboplatin intravenous at a dose of AUC = 5 (Day 1) on a 21-day cycle. Carboplatin is administered as a 30-minute intravenous infusion of carboplatin AUC 5 on Day 1 of every 21-day cycle and dosed to not exceed 750 mg corresponding to a GFR capped at 125 mL/min. In ARM 2, patients are administered (i) the assigned starting dose of oral once daily of COMPOUND A on a continuous dosing schedule starting on Day 1 in combination with (ii) the assigned starting dose of 100 mg/m² of every-6-week oral Lomustine on a 42 day cycle.

In Phase Ib, the individual doses of COMPOUND A doses will depend on the current dose levels (cohort) at which the patient enters the study. The initial patients assigned to ARM 1 will receive a starting dose of 80 mg of oral once daily of COMPOUND A on a continuous dosing schedule starting on Day 1, and the initial patients assigned to ARM 2 will receive a starting dose of 60 mg of oral once daily of COMPOUND A on a continuous dosing schedule starting on Day 1.

Only COMPOUND A is escalated during Phase Ib of the study. In ARM 1, COMPOUND A is administered at a starting dose of 80 mg orally once daily and may be

evaluated at a reduced dose of 60 mg orally once daily or an increased dose of 100 mg orally once daily. In ARM 2, COMPOUND A is administered at a starting dose of 60 mg orally once daily and may be evaluated at an increased dose of 80 mg orally once daily or 100 mg orally once daily. Dose adjustments are continuing until MTD and/or PR2D is reached.

During the first cycle, carboplatin is given at a fixed dose of AUC=6 every 3 weeks and lomustine at a fixed dose of 100 mg/m² every 6 weeks. Doses subsequent to the initial dose administered at Cycle 1 Day 1 should be adjusted according to local prescribing information for lomustine and carboplatin. Based on local prescribing drug information, there is no dose increase allowed during the study period for carboplatin. For lomustine, the initial dose might be increased at the discretion of the investigator if the patient does not experience hematological toxicity during cycle 1.

For dose escalation decisions, each cohort consists of 3 to 6 newly enrolled patients (at least 3 evaluable patients per cohort) who are treated at the specified dose level. Patients must complete a minimum of 1 cycle of treatment within the minimum safety evaluation and drug exposure for have had a DLT within the first cycle of treatment to be evaluable for dose escalation decisions. Dose escalation decisions occur when the cohort of patients meet this criteria. If only 2 of the 3 patients in a cohort are evaluable and neither experienced a treatment-related toxicity > CTCAE grade 1, dose escalation may be considered.

The recommended dose for the next cohort of subjects is guided by the Bayesian logistic regression model (BLRM) with Escalation with the overdose control (EWOC) principle. In all cases, the dose escalation does not exceed a 100% increase from the previous dose being supplied and the maximum dose level to be evaluated is 100 mg/ day. If the first 2 patients in a cohort experience a DLT, further enrollment to that cohort is stopped and the BLRM is updated with this new information and re-evaluation of available safety data occurs. By this adjustment, additional patients may be enrolled at this dose level or a lower dose level if the BLRM predicts that the risk that this dose exceeds MTD remains below 25% (EWOC). Dose escalation continues until identification of the MTD or a suitable lower dose for expansion cohort. This occurs when the following conditions are met:

- (1) At least 6 patients have been treated at this dose.
- (2) The dose satisfies one of the following conditions: (a) the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or (b) minimum of 9 patients have already been treated on the trial;
- (3) It is the dose recommended for patients, either per the model or by review of all clinical data.

MTD is defined as the highest drug dosage that does not cause medically unacceptable DLTs in more than 35% of the treated patients during the first cycle of treatment. The RP2D is the dose that will be recommended for further use in Phase II. RP2D may be determined the same as MTD. A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occur during Phase Ib cycle I and meets any of the following criteria:

TOXICITY	ANY OF THE FOLLOWING CRITERIA (graded per CTCAE v4.03)
Hematologic	CTCAE grade 4 neutropenia for 7 consecutive days or longer
	CTCAE grade 4 thrombocytopenia
	Febrile neutropenia (ANC $<1.0 \times 10^9/L$, with a single temperature of $\geq 38.3^\circ C$ or a sustained temperature of $\geq 38^\circ C$ for more than one hour) CTCAE grade ≥ 3
	Anemia grade 4
Renal	$\geq$ CTCAE grade 3 serum creatinine for 4 consecutive days or longer
Hepatic	Total bilirubin $\geq 2.0 \times ULN$ to $\leq 3.0 \times ULN$ for > 7 consecutive days.
	AST or ALT CTCAE grade ≥ 3 in conjunction with blood bilirubin CTCAE grade ≥ 2 of any duration
	$\geq$ CTCAE grade 3 total bilirubin
	CTCAE grade 3 AST or ALT for > 7 consecutive days
Endocrine (Hyperglycemia is NOT graded per CTCAE v4.03)	CTCAE Grade 2 hyperglycemia ($> 8.89 - 13.89$ mmol/L or $160 - 250$ mg/dL FPG) (confirmed with a repeat fasting plasma glucose within 24 hours) that does not resolve to normal within 14 consecutive days (after initiation of optimal anti-diabetic treatment)
	CTCAE grade 3 hyperglycemia (> 13.89 mmol/L or 250 mg/dL FPG) (confirmed with a repeat FPG within 24 hours) that does not resolve to grade 1 or less within 7 consecutive days, after the initiation of optimal anti-diabetic treatment
	Grade 4 hyperglycemia (> 27.8 mmol/L, or > 500 mg/dL FPG) confirmed with a repeat FPG within 24 hours
Metabolic/Laboratory	CTCAE grade 3 asymptomatic amylase and/or lipase > 7 consecutive days
	CTCAE grade 4 asymptomatic amylase and/or lipase of any duration
	CTCAE grade ≥ 3 GGT elevation in conjunction with AST/ALT grade ≥ 3
Pancreatitis	$\geq$ CTCAE grade 2 of $>$ than 4 consecutive days
Cardiac	Cardiac toxicity $\geq$ CTCAE grade 3 or cardiac event that is symptomatic or requires medical intervention

	Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Troponin $\geq$ CTCAE grade 3
Neurotoxicity (other than mood alterations)	CTCAE grade ≥ 2
Psychiatric disorders	CTCAE grade 2 mood alteration that does not resolve to $\leq$ grade 1 within 14 days despite medical treatment (for Anxiety only, if worsened from baseline)
	$\geq$ CTCAE grade 3 mood alteration
Dermatologic	$\geq$ CTCAE Grade 2 photosensitivity
	CTCAE Grade 3 rash for > 7 consecutive days despite skin toxicity treatment
	CTCAE Grade 4 rash
Other adverse events	$\geq$ CTCAE grade 3 adverse events (excluding $\geq$ CTCAE grade 3 lymphopenia or $\geq$ CTCAE grade 3 elevations in alkaline phosphatase,
	$\geq$ CTCAE grade 3 vomiting/nausea ≥ 48 hrs, despite the use of anti-emetic therapy
	$\geq$ CTCAE grade 3 diarrhea ≥ 48 hrs, despite the use of anti-diarrheal therapy
	CTCAE grade ≥ 3 fatigue (asthenia) for > 7 consecutive days
	CTCAE grade 4 fatigue (asthenia)
	Any grade ≥ 3 non-hematological AE, despite control by adequate and optimal management

National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 4.03 is used for all grading, except as noted above.

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted to allow the patient to continue the study treatment. All dose modifications must be based on the worst preceding toxicity as graded by the NCI CTCAE version 4.03. Once a dose is reduced during a treatment cycle, re-escalation is not permitted during any subsequent cycle. In Phase Ib, patients treated with COMPOUND A and lomustine at starting dose of 60 mg/day of COMPOUND A are able to have a maximum of only 1 dose reduction to a reduced dose level of 40 mg/day. In Phase Ib, patients treated with COMPOUND A and carboplatin at starting dose of 80 mg/day of COMPOUND A are able to have a maximum of only 2 dose reductions to a reduced dose level of 40 mg/day.

The following table provides potential guidelines for dose modification and dose interruption for COMPOUND A in combination with lomustine:

Worst toxicity (CTCAE Grade)**	Dose Modifications for COMPOUND A/placebo	Dose Modifications for Lomustine
HEMATOLOGICAL		

Worst toxicity (CTCAE Grade)**	Dose Modifications for COMPOUND A/placebo	Dose Modifications for Lomustine
Neutropenia (ANC)		
Grade 1 (ANC < LLN - $1.5 \times 10^9/L$) Grade 2 (ANC < $1.5 - 1.0 \times 10^9/L$)	Maintain dose level	Maintain dose level
Grade 3 (ANC < $1.0 - 0.5 \times 10^9/L$)	Omit dose until resolved to $\leq$ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then $\downarrow 1$ dose level	- Maintain dose level - If day 1 of next cycle is delayed for ≥ 14 days, then $\downarrow 1$ dose level
Grade 4 (ANC < $0.5 \times 10^9/L$)	Omit dose until resolved to $\leq$ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then $\downarrow 1$ dose level	- If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then $\downarrow 1$ dose level - If Day 1 of next cycle is delayed for ≥ 14 days, then $\downarrow 1$ dose level - If Day 1 of next cycle delayed ≥ 21 days, then discontinue lomustine
Febrile neutropenia (ANC < $1.0 \times 10^9/L$, with a single temperature of $\geq 38.3^\circ C$ or a sustained temperature of $\geq 38^\circ C$ for more than one hour)	Omit dose until resolved, then $\downarrow 1$ dose level	If resolved $\downarrow 1$ dose level
Thrombocytopenia		
Grade 1 (PLT < LLN - $75 \times 10^9/L$) Grade 2 (PLT <	Maintain dose level	Maintain dose level

Worst toxicity (CTCAE Grade)**	Dose Modifications for COMPOUND A/placebo	Dose Modifications for Lomustine
75 - 50 x 10 ⁹ /L)		
Grade 3 (PLT < 50-25 x 10 ⁹ /L)	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level	- If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level - If Day 1 of next cycle is delayed for ≥14 days, then ↓ 1 dose level - If Day 1 of next cycle delayed ≥ 21 days, then discontinue lomustine
Grade 4 (PLT < 25 x 10 ⁹ /L)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	- If resolved in ≤ 7 days, then maintain dose - If resolved in > 7 days, then ↓ 1 dose level - If Day 1 of next cycle is delayed for ≥14 days, then ↓ 1 dose level - If Day 1 of next cycle delayed ≥ 21 days, then discontinue lomustine
RENAL		
Serum creatinine		
Grade 1 (>1.5 x ULN) Grade 2 (> 1.5 - 3.0 x ULN)	Maintain dose level	Maintain dose level
Grade 3 (> 3.0 -	Omit dose until resolved to ≤ grade 1, then:	If resolved in

Worst toxicity (CTCAE Grade)**	Dose Modifications for COMPOUND A/placebo	Dose Modifications for Lomustine
6.0 x ULN)	If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then $\downarrow$ 1 dose level	≤ 7 days, then maintain dose level - If resolved in > 7 days, then $\downarrow$ 1 dose level - If Day 1 of next cycle is delayed for ≥ 14 days, then $\downarrow$ 1 dose level - If Day 1 of next cycle delayed ≥ 21 days, then discontinue lomustine
Grade 4 ($> 6.0 \times$ ULN)	Permanently discontinue patient from COMPOUND A/placebo	Permanently discontinue patient from lomustine
HEPATIC		
Bilirubin (*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only) will be fractionated if elevated		
Grade 1 ($> \text{ULN} - 1.5 \times \text{ULN}$)	Maintain dose level with LFTs* monitored as per protocol	Maintain dose level with LFTs* monitored as per protocol
Grade 2 ($> 1.5 - 3.0 \times \text{ULN}$) with ALT or AST $\leq 3.0 \times \text{ULN}$	Omit dose until resolved to $\leq$ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then $\downarrow$ 1 dose level	- If resolved ≤ 7 days maintain dose level If resolved in > 7 days then $\downarrow$ 1 dose level - If Day 1 of next cycle is delayed for ≥ 14 days, then $\downarrow$ 1 dose level - If Day 1 of next cycle delayed ≥ 21

Worst toxicity (CTCAE Grade) 4.03**	Dose Modifications for COMPOUND A/placebo	Dose Modifications for Lomustine
		days, then discontinue lomustine
Grade 3 (> 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days discontinue patient from COMPOUND A/placebo	- If resolved in ≤ 7 days, ↓ 1 dose level - If resolved in > 7 days discontinue patient from lomustine - If Day 1 of next cycle is delayed for ≥ 14 days, then ↓ 1 dose level - If Day 1 of next cycle delayed ≥ 21 days, then discontinue lomustine
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from COMPOUND A/placebo	Permanently discontinue patient from lomustine
AST or ALT		
Grade 1 (> ULN – 3.0 x ULN)	Maintain dose level with LFTs* monitored per protocol	Maintain dose level with LFTs* monitored per protocol
Grade 2 (> 3.0 - 5.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level	- If resolved in ≤ 7 days, then maintain dose level - If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 5.0 - 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level	- If resolved in ≤ 7 days, then maintain dose level - If resolved in > 7 days, then ↓ 1 dose

Worst toxicity (CTCAE Grade)**	Dose Modifications for COMPOUND A/placebo	Dose Modifications for Lomustine
		level - If Day 1 of next cycle is delayed for ≥ 14 days, then $\downarrow$ 1 dose level - If Day 1 of next cycle delayed ≥ 21 days, then discontinue lomustine
Grade 4 ($> 20.0 \times$ ULN) without bilirubin elevation to $> 2.0 \times$ ULN	Omit dose until resolved to $\leq$ grade 1, then $\downarrow$ 1 dose level	- If resolved in < 21 days, then $\downarrow$ 1 dose level - If resolved in ≥ 21 days, then discontinue from lomustine
AST or ALT and concurrent Bilirubin		
AST or ALT $> 3.0 \times$ ULN and total bilirubin $> 2.0 \times$ ULN	Permanently discontinue COMPOUND A/placebo	Permanently discontinue lomustine
*(LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin $> 2.0 \times$ ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT) Hepatic toxicity monitoring (*for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin $> 2.0 \times$ ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT): Cycle 1 and 2: every other week (if visit schedule allows a more frequent monitoring this should be considered) or more frequently if clinically indicated especially for patients with borderline acceptable AST/ALT/bilirubin* values Cycle 3 and onward: monthly or more frequently if clinically indicated In case of any occurrence of ALT/AST/ bilirubin* increase $\geq$ grade 2 the liver function tests must be monitored weekly or more frequently if clinically indicated until resolved to $\leq$ grade 1 In case of any occurrence of ALT/ AST/ bilirubin* increase $\geq$ grade 3 the liver function tests must be monitored weekly or more frequently if clinically indicated until resolved to $\leq$ grade 1; hereafter the monitoring should be continued every other week or more frequently if clinically indicated until the end of treatment with study medication Patients who discontinued study treatment should be monitored weekly, including LFTs* or more frequently if clinically indicated until resolved to $\leq$ grade 1 or stabilization (no CTCAE grade change over 4 weeks).		

Worst toxicity (CTCAE Grade) 4.03**	Dose Modifications for COMPOUND A/placebo	Dose Modifications for Lomustine
ENDOCRINE/METABOLIC		
Fasting Plasma Glucose (FPG)		
Grade 1 (> ULN - 160 mg/dL) (> ULN - 8.9 mmol/L)	• Maintain dose level, check FPG every week • initiate or intensify medication with appropriate anti-diabetic treatment as per investigator's discretion • instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study • consider use of oral anti-hyperglycemic therapy such as metformin (or intensify existing medications), • check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks	• Maintain dose level
Grade 2 (>160 - 250 mg/dL) (> 8.9 - 13.9 mmol/L)	• If signs or symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), manage as for grade 3 hyperglycemia (see below) • If asymptomatic, maintain dose and re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at grade 2: • maintain dose level and monitor FPG at least weekly until FPG resolves to ≤ grade 1 • initiate or intensify medication with appropriate anti-diabetic treatment such as metformin; consider adding a second oral agent if not improvement after several days. • instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study • if FPG does not resolve to ≤ grade 1 within 14 days after institution of appropriate anti-diabetic treatment reduce COMPOUND A/placebo by 1 dose level • Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks	• Maintain dose level
Grade 3 (> 250 - 500 mg/dL) (> 13.9 - 27.8 mmol/L)	• Omit COMPOUND A /placebo initiate or intensify medication with appropriate anti-diabetic treatment, re-check FPG within	• Maintain dose level

Worst toxicity (CTCAE Grade)**	Dose Modifications for COMPOUND A/placebo	Dose Modifications for Lomustine
mmol/L)	24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at grade 3: • administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate • continue to omit COMPOUND A /placebo • monitor FPG at least twice weekly until FPG resolves to $\leq$ grade 1 • if FPG resolves to $\leq$ grade 1 in 7 days or less, then re-start COMPOUND A and $\downarrow$ 1 dose level • if FPG remains greater than grade 1 severity for more than 7 days, then discontinue patient from COMPOUND A/placebo • initiate or continue anti-diabetic treatment as appropriate: • instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study • consider use of oral anti-hyperglycemic therapy such as metformin • check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks For non-fasting plasma glucose >250-500 mg/dL (> 13.9 - 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, omit COMPOUND A/placebo and following guidance for management of grade 3 fasting plasma glucose (FPG)	
Grade 4 (> 500 mg/dL) (≥ 27.8 mmol/L)	• Immediately omit COMPOUND A/placebo, initiate or intensify medication with appropriate anti-diabetic treatment, re-check within 24 hours. If grade improves then follow specific grade recommendations. If FPG is confirmed at grade 4: • administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate • discontinue patient from COMPOUND	• Maintain dose level

Worst toxicity (CTCAE Grade)** 4.03	Dose Modifications for COMPOUND A/placebo	Dose Modifications for Lomustine
	A/placebo • instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study • consider use of oral anti-hyperglycemic therapy such as metformin • check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks if clinically indicated For non-fasting plasma glucose >500 mg/dL (> 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, discontinue COMPOUND A/placebo and following guidance for management of grade 4 fasting plasma glucose (FPG).	
CARDIAC		
Cardiac - Left Ventricular systolic dysfunction		
Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	• Maintain dose level, and continue COMPOUND A/placebo with caution - Repeat LVEF within 4 weeks or as clinically appropriate	• Maintain dose level
Symptomatic, responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	• Omit COMPOUND A/placebo until resolved* (as defined below), then ↓ 1 dose level - LVEF measurement to be repeated, if not resolved* within 28 days, permanently discontinue patient from COMPOUND A/placebo / treatment	• Maintain dose level
Refractory or poorly controlled, ejection fraction < 20%	• Permanently discontinue patient from COMPOUND A/placebo	• Maintain dose level
*the event is considered resolved when the patient is asymptomatic, has a resting ejection fraction ≥ 40% and ≤20% decrease from baseline.		
Cardiac – QTc prolongation		
QTcF > 500 ms (≥ grade 3) or > 60 ms change from baseline on at least two	First Occurrence: • Omit COMPOUND A/placebo • Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal	• Maintain dose level

Worst toxicity (CTCAE Grade)**	Dose Modifications for COMPOUND A/placebo	Dose Modifications for Lomustine
separate ECGs	limits. Concomitant medication usage must be reviewed. • Perform a repeat ECG within one hour of the first QTcF of > 500 ms or >60ms from baseline • If QTcF remains > 500 ms or >60ms from baseline, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms. Seek cardiologist input. • Once QTcF prolongation has resolved, COMPOUND A/placebo may be restarted at a one lower dose level • Second Occurrence: • Permanently discontinue patient from COMPOUND A/placebo	
Other Cardiac Events		
Grade 1 or 2	• Maintain dose level	• Maintain dose level
Grade 3	• Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	• Maintain dose level
Grade 4	• Permanently discontinue patient from COMPOUND A/placebo	• Maintain dose level
OTHER		
Mood alteration		
* Note: For all grades, if question 9 on the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), omit study drug and refer patient for psychiatric consult regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued.		• Maintain dose level
Grade 1*	• Maintain dose level • Consider psychiatric consultation at the investigator's discretion and introduce optimal management (e.g. as per local guidelines and/or psychiatric/expert consultation)	• Maintain dose level
Grade 2*	• Omit dose until resolved to ≤ grade 1 or baseline status • Consider psychiatric consultation at the investigator's discretion and introduce optimal management (e.g. as per local guidelines and/or psychiatric/expert consultation) • First event: if the condition resolved to grade ≤ 1 or to baseline status, continue to co-medicate and then maintain the dose level • Second and further events: if the condition resolved to grade ≤ 1 or to baseline status,	• Maintain dose level

Worst toxicity (CTCAE Grade)**	Dose Modifications for COMPOUND A/placebo	Dose Modifications for Lomustine
	continue to co-medicate and then ↓ 1 dose level	
Grade 3*	• Omit dose until resolved to ≤ grade 1 or baseline status • Psychiatric consultation is required and introduce optimal management • if the condition resolved to grade ≤1 or to baseline status, continue to co-medicate and then ↓ 1 dose level	• Maintain dose level
Grade 4*	• Permanently discontinue patient from COMPOUND A/placebo • Psychiatric consultation should be performed • Introduce optimal management (e.g. as per local guidelines and/or psychiatric/expert consultation)	• Maintain dose level
Rash		
Grade 1	• Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)	• Maintain dose level.
Grade 2	• First occurrence: Omit dose until resolved to grade ≤ 1 then: • If resolved in ≤ 2 weeks, maintain dose level. • If resolved in more than 2 weeks, ↓ 1 dose level. • Second occurrence: ↓ 1 dose level. Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)	• Maintain dose level
Grade 3	• First occurrence: omit dose until resolved to CTCAE grade ≤ 1; then ↓ 1 dose level. • Second occurrence: permanently discontinue patient from COMPOUND A/placebo. If skin rash is readily manageable, re-introduction at a reduced dose level might be considered at the discretion of the investigator According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.	• Maintain dose level
Grade 4	• Permanently discontinue patient from COMPOUND A/placebo According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for	• Permanently discontinue patient from lomustine

Worst toxicity (CTCAE Grade)**	Dose Modifications for COMPOUND A/placebo	Dose Modifications for Lomustine
	local histopathology assessment) if clinical appropriate.	
Fatigue (asthenia)		
Grade 1 or 2	Maintain dose level	Maintain dose level
Grade 3	- Omit dose until resolved to $\leq$ grade 1, then: - If resolved in $\leq$ 7 days, maintain dose level - If resolved in $>$ 7 days, $\downarrow$ 1 dose level	- If resolved in $\leq$ 7 days, maintain dose level - If resolved in $>$ 7 days, $\downarrow$ 1 dose level
Pneumonitis		
Other non- hematological adverse events		
Grade 1 or 2	Maintain dose level	Maintain dose level
Grade 3	Omit dose until resolved to $\leq$ grade 1, then $\downarrow$ 1 dose level	Resolved to $\leq$ grade 1, then $\downarrow$ 1 dose level
Grade 4	Permanently discontinue patient from COMPOUND A/placebo Note: Omit dose for $\geq$ grade 3 vomiting or grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic	Permanently discontinue patient from lomustine
Stomatitis/Oral mucositis		
Grade 1 / Tolerable Grade 2	Maintain dose level. Non-alcoholic or salt water mouth wash	Maintain dose level
Intolerable Grade 2 or Grade 3	- First occurrence: hold until resolved to grade $\leq$ grade 1 and $\downarrow$ 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator). - Second occurrence: hold until resolved to grade $\leq$ grade 1 and $\downarrow$ 1 dose level.	Maintain dose level
Grade 4	Permanently discontinue patient from COMPOUND A/placebo.	Maintain dose level
** Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. These changes must be recorded on the Dosage Administration Record eCRF.		

Two dose reductions for lomustine are allowed, the lowest dose permitted is 80 mg every 42 days.

The following table provides guidelines for dose modification and dose interruption for COMPOUND A in combination with carboplatin:

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for COMPOUND A	Dose Modifications for carboplatin
HEMATOLOGICAL		
Neutropenia (ANC)		
Grade 1 (ANC < LLN - $1.5 \times 10^9/L$) Grade 2 (ANC < $1.5 - 1.0 \times 10^9/L$)	Maintain dose level	Maintain dose level
Grade 3 (ANC < $1.0 - 0.5 \times 10^9/L$) Grade 4 (ANC < $0.5 \times 10^9/L$)	Omit dose until resolved to $\leq$ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then $\downarrow 1$ dose level	Dose reduce by 20% to AUC 4
Febrile neutropenia (ANC < $1.0 \times 10^9/L$, with a single temperature of $\geq 38.3^\circ C$ or a sustained temperature of $\geq 38^\circ C$ for more than one hour)	Omit dose until resolved, then $\downarrow 1$ dose level	Dose reduce by 20% to AUC 4
Thrombocytopenia		
Grade 1 (PLT < LLN - $75 \times 10^9/L$) Grade 2 (PLT < $75 - 50 \times 10^9/L$)	Maintain dose level	Maintain dose level
Grade 3 (PLT < $50 - 25 \times 10^9/L$)	Omit dose until resolved to $\leq$ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then $\downarrow 1$ dose level	Dose reduce by 20% to AUC 4
Grade 4 (PLT < $25 \times 10^9/L$)	Omit dose until resolved to $\leq$ grade 1, then $\downarrow 1$ dose level	Dose reduce by 20% to AUC 4
RENAL		
Serum creatinine		
Grade 1 (< $2 \times$ ULN)	Maintain dose level	Delay cycle until patient returns to $\leq$ ULN
Grade 2 ($2 - 3 \times$ ULN)	Omit dose until resolved to $\leq$ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then $\downarrow 1$ dose level	- Delay cycle until patient returns to $\leq$ ULN - If resolved in ≤ 7 days, then maintain dose

Worst toxicity (CTCAE Grade)**	Dose Modifications for COMPOUND A	Dose Modifications for carboplatin
		level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 – 6.0 x ULN)	Permanently discontinue patient from COMPOUND A	- Delay cycle until patient returns to ≤ ULN - If resolved in < 21 days, then ↓ 1 dose level % to AUC 4 - If resolved in ≥ 21 days, then discontinue from carboplatin
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from COMPOUND A	- Delay cycle until patient returns to ≤ ULN - If resolved in < 21 days, then ↓ 1 dose level % to AUC 4 - If resolved in ≥ 21 days, then discontinue from carboplatin
HEPATIC		
Bilirubin (*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only) will be fractionated if elevated		
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level with LFTs* monitored as per protocol	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level	Maintain dose level.
Grade 3 (> 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days discontinue patient from COMPOUND A	Maintain dose level.
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from COMPOUND A	Maintain dose level.
AST or ALT		
Grade 1 (> ULN – 3.0 x ULN)	Maintain dose level with LFTs* monitored per protocol	Maintain dose level.

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for COMPOUND A	Dose Modifications for carboplatin
Grade 2 (> 3.0 - 5.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	- Omit dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, then maintain dose level - If resolved in > 7 days, then ↓ 1 dose level	Maintain dose level.
Grade 3 (> 5.0 - 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	- Omit dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, then maintain dose level - If resolved in > 7 days, then ↓ 1 dose level	Maintain dose level
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	Maintain dose level.
AST or ALT and concurrent Bilirubin		
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Permanently discontinue COMPOUND A	Maintain dose level
*(LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT) Hepatic toxicity monitoring (*for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT): Cycle 1 and 2: every other week (if visit schedule allows a more frequent monitoring this should be considered) or more frequently if clinically indicated especially for patients with borderline acceptable AST/ ALT/ bilirubin* values Cycle 3 and onward: monthly or more frequently if clinically indicated In case of any occurrence of ALT/AST/ bilirubin* increase ≥ grade 2 the liver function tests must be monitored weekly or more frequently if clinically indicated until resolved to ≤ grade 1 In case of any occurrence of ALT/ AST/ bilirubin* increase ≥ grade 3 the liver function tests must be monitored weekly or more frequently if clinically indicated until resolved to ≤ grade 1; hereafter the monitoring should be continued every other week or more frequently if clinically indicated until the end of treatment with study medication Patients who discontinued study treatment should be monitored weekly, including LFTs* or more frequently if clinically indicated until resolved to ≤ grade 1 or stabilization (no CTCAE grade change over 4 weeks).		
ENDOCRINE/METABOLIC		
Fasting Plasma Glucose (FPG)		
Grade 1 (> ULN - 160 mg/dL) (> ULN - 8.9 mmol/L)	- Maintain dose level, check FPG every week - initiate or intensify medication with appropriate anti-diabetic treatment as per investigator's discretion - instruct patient to follow dietary guidelines according to local and/or institutional	Maintain dose level

Worst toxicity (CTCAE Grade) 4.03**	Dose Modifications for COMPOUND A	Dose Modifications for carboplatin
	standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study • consider use of oral anti-hyperglycemic therapy such as metformin (or intensify existing medications), • check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks	
Grade 2 (>160 - 250 mg/dL) (> 8.9 - 13.9 mmol/L)	• If signs or symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), manage as for grade 3 hyperglycemia (see below) • If asymptomatic, maintain dose and re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at grade 2: • maintain dose level and monitor FPG at least weekly until FPG resolves to $\leq$ grade 1 • initiate or intensify medication with appropriate anti-diabetic treatment such as metformin; consider adding a second oral agent if not improvement after several days. • instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study • if FPG does not resolve to $\leq$ grade 1 within 14 days after institution of appropriate anti-diabetic treatment reduce COMPOUND A by 1 dose level • Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks	• Maintain dose level
Grade 3 (> 250 - 500 mg/dL) (> 13.9 - 27.8 mmol/L)	• Omit COMPOUND A, initiate or intensify medication with appropriate anti-diabetic treatment, re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at grade 3: • administer intravenous hydration and intervention for	• Maintain dose level

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for COMPOUND A	Dose Modifications for carboplatin
	electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate • continue to omit COMPOUND A • monitor FPG at least twice weekly until FPG resolves to $\leq$ grade 1 • If FPG resolves to $\leq$ grade 1 in 7 days or less, then re-start COMPOUND A and $\downarrow$ 1 dose level • If FPG remains greater than grade 1 severity for more than 7 days, then discontinue patient from COMPOUND A • initiate or continue anti-diabetic treatment as appropriate • instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study • consider use of oral anti-hyperglycemic therapy such as metformin • check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks For non-fasting plasma glucose >250-500 mg/dL (> 13.9 - 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, omit COMPOUND A and following guidance for management of grade 3 fasting plasma glucose (FPG)	
Grade 4 (> 500 mg/dL) (≥ 27.8 mmol/L)	• Immediately omit COMPOUND A, initiate or intensify medication with appropriate anti-diabetic treatment, re-check within 24 hours. If grade improves then follow specific grade recommendations. If FPG is confirmed at grade 4: • administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate • discontinue patient from COMPOUND A • instruct patient to follow dietary guidelines	• Maintain dose level

Worst toxicity (CTCAE Grade)**	Dose Modifications for COMPOUND A	Dose Modifications for carboplatin
	according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study - consider use of oral anti-hyperglycemic therapy such as metformin - check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks if clinically indicated For non-fasting plasma glucose >500 mg/dL (> 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, discontinue COMPOUND A and following guidance for management of grade 4 fasting plasma glucose (FPG).	
CARDIAC		
Cardiac - Left Ventricular systolic dysfunction		
Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	Maintain dose level, and continue COMPOUND A with caution Repeat LVEF within 4 weeks or as clinically appropriate	Maintain dose level
Symptomatic, responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	- Omit COMPOUND A until resolved* (as defined below), then ↓ 1 dose level - LVEF measurement to be repeated, if not resolved* within 28 days, permanently discontinue patient from COMPOUND A treatment	Maintain dose level
Refractory or poorly controlled, ejection fraction < 20%	Permanently discontinue patient from COMPOUND A	Maintain dose level
*the event is considered resolved when the patient is asymptomatic, has a resting ejection fraction ≥ 40% and ≤20% decrease from baseline.		
Cardiac – QTc prolongation		
QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two	- First Occurrence: - omit COMPOUND A - Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant	- Prior to Administration of Cycle Therapy: 1. Do not start carboplatin administration

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for COMPOUND A	Dose Modifications for carboplatin
separate ECGs	medication usage must be reviewed. • Perform a repeat ECG within one hour of the first QTcF of > 500 ms or >60ms from baseline • If QTcF remains > 500 ms or >60ms from baseline, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms. Seek cardiologist input. • Once QTcF prolongation has resolved, COMPOUND A may be restarted at a one lower dose level • Second Occurrence: • Permanently discontinue patient from COMPOUND A	when an ECG with QTc > 450 msec for males and > 470 for females by automated reading is identified at the site. • 2. Perform a repeat ECG within 1 hour. COMPOUND A may not be administered if QT prolongation is still present • 3. For any QTc prolongation the concomitant medications should be reviewed to determine the possible cause. If QTc prolongation persists at the repeat ECG the patient will be rescheduled to return for treatment the following day. During or Immediately After Administration of Cycle Therapy: • 1. Patients exhibiting QTc prolongation following study treatment will undergo repeat ECG(s) every hour until returning to baseline or grade ≤1.

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for COMPOUND A	Dose Modifications for carboplatin
		2. The investigator may choose to closely monitor or hospitalize the patient (report as SAE) if the patient continues to exhibit QT prolongation 6 hours post infusion.
Other Cardiac Events		
Grade 1 or 2	Maintain dose level	Maintain all dose levels
Grade 3	Omit dose until resolved to $\leq$ grade 1, then $\downarrow$ 1 dose level	Delay cycle until patient returns to grade 1, then administer reduced dose by 20% (AUC 4)
Grade 4	Permanently discontinue patient from COMPOUND A	Permanently discontinue carboplatin
OTHER		
Mood alteration		
* Note: For all grades, if question 9 on the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), omit study drug and refer patient for psychiatric consult regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued.		
Grade 1*	- Maintain dose level - Consider psychiatric consultation at the investigator's discretion and introduce optimal management (e.g. as per local guidelines and/or psychiatric/expert consultation)	Maintain dose level
Grade 2*	- Omit dose until resolved to $\leq$ grade 1 or baseline status - Consider psychiatric consultation at the investigator's discretion and introduce optimal management (e.g. as per local guidelines and/or psychiatric/expert consultation) - First event: if the condition resolved to grade $\leq$ 1 or to baseline status, continue to co-	Maintain dose level

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for COMPOUND A	Dose Modifications for carboplatin
	medicate and then maintain the dose level Second and further events: if the condition resolved to grade ≤ 1 or to baseline status, continue to co-medicate and then $\downarrow$ 1 dose level	
Grade 3*	- Omit dose until resolved to $\leq$ grade 1 or baseline status - Psychiatric consultation is required and introduce optimal management - if the condition resolved to grade ≤ 1 or to baseline status, continue to co-medicate and then $\downarrow$ 1 dose level	Maintain dose level
Grade 4*	- Permanently discontinue patient from COMPOUND A - Psychiatric consultation should be performed - Introduce optimal management (e.g. as per local guidelines and/or psychiatric/expert consultation)	Maintain dose level
Rash		
Grade 1	Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)	Maintain dose level
Grade 2	- First occurrence: Omit dose until resolved to grade ≤ 1 then: - If resolved in ≤ 2 weeks, maintain dose level. - If resolved in more than 2 weeks, $\downarrow$ 1 dose level. - Second occurrence: $\downarrow$ 1 dose level. Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)	Maintain dose level
Grade 3	First occurrence: omit dose until resolved to CTCAE grade ≤ 1; then $\downarrow$ 1 dose level. Second occurrence: permanently discontinue patient from COMPOUND A. If skin rash is readily manageable, re-introduction at a reduced dose level might be considered at the discretion of the investigator According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.	Maintain dose level

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for COMPOUND A	Dose Modifications for carboplatin
Grade 4	Permanently discontinue patient from COMPOUND A According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.	Maintain dose level
Fatigue (asthenia)		
Grade 1 or 2	Maintain dose level	Maintain dose level
Grade 3	- Omit dose until resolved to $\leq$ grade 1, then: - If resolved in $\leq$ 7 days, maintain dose level - If resolved in $>$ 7 days, $\downarrow$ 1 dose level	- If resolved in $\leq$ 7 days, maintain dose level - If resolved in $>$ 7 days, reduce dose by 20% to AUC 4
Pneumonitis		
Other non- hematological adverse events		
Grade 1 or 2	Maintain dose level	Maintain dose level
Grade 3	Omit dose until resolved to $\leq$ grade 1, then $\downarrow$ 1 dose level	- If Day 1 of next cycle is delayed for $\geq$14 days, then $\downarrow$ 1 dose level - If Day 1 of next cycle delayed $\geq$ 21 days, then discontinue lomustine
Grade 4	Permanently discontinue patient from COMPOUND A Note: Omit dose for $\geq$ grade 3 vomiting or grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic	Permanently discontinue carboplatin
Stomatitis/Oral mucositis		
Grade 1 / Tolerable Grade 2	Maintain dose level. Non-alcoholic or salt water mouth wash	Maintain dose level
Intolerable Grade 2 or Grade 3	First occurrence: hold until resolved to grade $\leq$ G1 and $\downarrow$ 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator).	Maintain dose level

Worst toxicity (CTCAE Grade)**	Dose Modifications for COMPOUND A	Dose Modifications for carboplatin
	Second occurrence: hold until resolved to grade $\leq$ G1 and $\downarrow$ 1 dose level.	
Grade 4	Permanently discontinue patient from COMPOUND A.	Permanently discontinue carboplatin
** Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. These changes must be recorded on the Dosage Administration Record eCRF.		

One dose reduction for carboplatin is allowed, the lowest dose is AUC=4 every 21 days.

If Grade 2 Pneumonitis develops, COMPOUND A should be reduced 1 dose level until recovery to < grade 1 and patients are discontinued if this does not occur within 3 weeks, and lomustine should be reduced if patients recover within 3 weeks. If Grade 3 Pneumonitis develops, COMPOUND A treat is held until recovery to < grade 1 and may restart at 1 reduced dose level if clinical benefit, and lomustine should be reduced if patients recover within 3 weeks. If Grade 4 Pneumonitis develops, COMPOUND A and lomustine are discontinued.

If administration of the drugs or placebo is interrupted for reasons other than toxicity, treatment may be resumed at the same dose. If the patient experienced an unacceptable toxicity not specifically identified in Table 1 or Table 2, treatment may be resumed at the same dose provided that this toxicity resolved to $\leq$ CTCAE grade 1. Any patients requiring a treatment delay of > 21 consecutive days must be permanently discontinued.

Patients are evaluated for overall response rate (i.e., the proportion of the patients with the best overall response of complete response (CR) or partial response) and progression-free survival (i.e., the time from start date of study treatment until objective tumor progression).

Patients continue on study treatment until disease progression, unacceptable toxicity, death or discontinuation from the study due to any other reason. All patients are followed for safety for 30 days after the end of treatment. Patients discontinuing for reasons other than progression or death continue to be followed every 6 weeks for efficacy until progression or start of a new antineoplastic therapy. After progression, all patients are continuing to be followed for survival.

Phase Ib is ending when all patients have discontinued treatment and completed the 30 days safety follow-up. If Phase II is not initiated (e.g, failure to declare an MTD or substantial safety concern) or all patients discontinue prior to Phase II start, then Phase Ib end is occurring when all patients complete 24-week progression free survival follow-up.

In Phase II, an efficacy study is conducted to assess the anti-tumor activity of COMPOUND A in combination with Lomustine versus lomustine with placebo on PFS in patients with recurrent glioblastoma who have progressed after prior treatment with radiotherapy and temozolomide, as measured by PFS from date of randomization to date of progression event or death. After the MTD/ PR2D is determined in each of the Phase Ib arms, the corresponding Phase II will start. Once the MTD/ RP2D is determined in one arm, the enrollment will start in the corresponding Phase II arm regardless of the status of the other arm. Eligible patients are allocated alternatively to either (i.) the group treated with COMPOUND A and carboplatin ("ARM A") or (ii.) the group treated with COMPOUND A in combination with Lomustine or lomustine with placebo ("ARM B") by interactive response technology in a ratio of 1:2 respectively. Within ARM B, patients are randomized by interactive response technology using a blinded 1:1 ratio. Approximately 140 patients are enrolled in Phase II as follows: (a) 40 patients are allocated to the carboplatin with COMPOUND A group (open-label), and (b) 100 patients are randomized 1:1 to lomustine with placebo versus lomustine with COMPOUND A. No patients from Phase Ib are permitted to transfer to Phase II. No patients are permitted to cross-over between treatment groups.

In ARM A, patients treated with the combination of COMPOUND A and carboplatin are administered (i) the MTD/ RP2D dosage of orally once daily of COMPOUND A on a continuous dosing schedule starting on Day 1 in combination with (ii) the assigned starting dose of AUC = 5 (Day 1) of every-3-week carboplatin intravenous on a 21-day cycle. In ARM B, patients treated with the combination of COMPOUND A and Lomustine are administered (i) the MTD/ RP2D dosage of orally once daily of COMPOUND A on a continuous dosing schedule starting on Day 1 in combination with (ii) the assigned starting dose of 100 mg/m² of every-6-week oral Lomustine on a 42 day cycle. The patients treated with Lomustine alone are administered the assigned starting dose of 100 mg/m² of every-6-week oral Lomustine on a 42 day cycle.

Only one COMPOUND A dose reduction is permitted in Phase II.

Patients are evaluated for overall survival (ie., the time from date of randomization for COMPOUND A + Lomustine combination or from the first study drug intake for COMPOUND A + Carboplatin) to the date of death. In addition to regular assessments of safety and efficacy and antitumor activity, MRI is performed every 6 weeks (+/- 7 days) from start study treatment until disease progression, withdrawal consent, lost to follow-up, start of another anti-neoplastic therapy, or death, whichever occurs first. Efficacy assessments further include evaluations including measurable enhancing lesions, non-enhancing lesions, steroid usage, and clinical status for KPS.

Patients continue on study treatment until disease progression or until pre-defined discontinuation criteria is met. Treatment with COMPOUND A or placebo in combination with lomustine will not exceed 6 cycles. All patients are followed for safety for 30 days after the end of treatment. Patients discontinuing for reasons other than progression or death are followed every 6 weeks for efficacy until progression or start of a new antineoplastic therapy. After progression, all patients are followed every 12 weeks for survival.

Phase II is ending when data collection ends and the final analysis of the study occurs. Phase II end of study is declared at the latest occurrence of: (a) at least 9 months elapse since the data cut-off dates for the primary analysis in each of the Carboplatin and Lomustine arms and all patients have completed the safety follow-up period (30 days after treatment discontinuation), or (ii) at least 75% of patients have died in each of the Carboplatin and Lomustine. If the primary objectives are not met, then data collection will terminate and Phase II end is declared after all patients have completed the safety follow-up period (30 days after treatment discontinuation).

Example 2: In Vivo Experiment in Orthotopic Human Glioblastoma Xenograft Tumor in Nude Mice

6-8 weeks old BALB/c nude female mice weighing approximately 18-22 grams are used for this experiment. An acclimation period of approximately one week is allowed between animal receipt and tumor inoculation in order to accustom the animals to the laboratory environment. Animals are kept in a room environment of 20~26°C and 40~70 % humidity with a light cycle of 12 hours light and 12 hours dark. All animals have free access to standard certified laboratory diet.

All surgical procedures are performed under anesthesia. Mice are anesthetized by intraperitoneal injection of pentobarbital sodium (50 mg/kg intraperitoneal) before tumor inoculation. The mouse scalp is sterilized and 1-cm midline cut is made to expose the skull. Each mouse is intracranially injected with 1×10^5 BN2276 human glioblastoma tumor cells suspended in 2 μ l phosphate-buffered saline (PBS) over 5 minutes, 2.5 mm intraparenchymally, 2 mm lateral from and 0.5 mm anterior to the bregma. After inoculation, the mice are checked daily for bleeding, morbidity and mortality.

Before commencement of treatment, the mice are randomized into the treatment groups (10 mice per group) according to their body weight. The treatments started 7 days post-tumor cell inoculation. The treatment groups are shown as following table:

Grps	n	Treatment	Dose	Dosing	Dosing	Schedule
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			(mg/kg)	Volume (ul/g)	Route	
1	10	Vehicle (1% MC and 1% Tween 80)	--	10 ul/g	p.o.	once daily (QD) x 28 days
2	10	Lomustine (or CCNU)	20	10 ul/g	p.o.	once weekly (QW) x 4 weeks
3	10	Compound A	30	10 ul/g	p.o.	once daily (QD) (x 5days; 2 days off- repeat) x 4 weeks
4	10	Compound A + Lomustine (or CCNU)	30+20	10 ul/g+10 ul/g	p.o.+ p.o	once daily (QD) (x 5days; 2 days off- repeat) + once weekly x 4 weeks

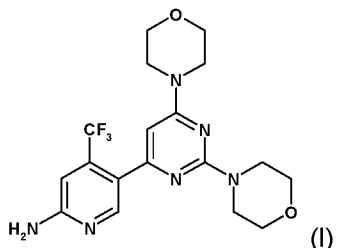
Note: n: animal number; Dosing volume: 10 ul/g

For this experiment, the major endpoint is to determine if the animal survival can be increased. Animals are checked daily and animals having deteriorating and moribund condition are euthanized with CO₂. The survival of all animals is followed and a median survival time (MST) is calculated for each group. The increased in life-span (ILS) is calculated by dividing the MST of treatment group by the MST of the control group and is expressed as the percent increase over the life-span of the control animals. Termination of the study can be considered when the survival percentage of the non-vehicle treatment groups are below 50% after vehicle control group is terminated.

Following this procedure, the results are provided in Figures 1, 2 and 3 of this patent application.

What is claimed is:

1. A pharmaceutical combination comprising (a) a compound of formula (I)



or a pharmaceutically acceptable salt thereof, and (b) lomustine or a pharmaceutically acceptable salt thereof, for simultaneous, separate or sequential use for the treatment or prevention of a brain tumor.

2. The pharmaceutical combination according to claim 1 wherein compound of formula (I) about 60 mg/day to about 120 mg/day in an adult human.

3. The pharmaceutical combination according to any of the preceding claims wherein the lomustine is administered in a dose amount ranging from approximately about 15 to 200 mg/m² every 6 weeks in an adult human.

4. The pharmaceutical combination according to any of the preceding claims wherein the brain tumor is glioblastoma multiforme.

5. The pharmaceutical combination according to any of the preceding claims wherein the brain tumor is a glioblastoma multiforme selected from Classical Glioblastoma Multiforme Tumors, Proneural Glioblastoma Multiforme Tumors, Mesenchymal Glioblastoma Multiforme Tumors, Neural Glioblastoma Multiforme Tumors or a combination thereof.

6. The pharmaceutical combination according to any one of claims 1 to 3 wherein the brain tumor is recurrent glioblastoma multiforme after prior treatment with chemotherapy (e.g, temozolomide), lomustine, radiotherapy, bevacizumab, or a combination thereof.

7. A pharmaceutical composition comprising a jointly therapeutically effective amount of a pharmaceutical combination according to claim 1 and optionally at least one pharmaceutically acceptable carrier for use in the treatment or prevention of a brain tumor.

8. A combined preparation, which comprises (a) one or more unit dosage forms of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof and (b) one or more unit dosage forms of lomustine or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of a brain tumor.

9. Use of the pharmaceutical combination according to any one of claims 1 to 3 for the preparation of a medicament for use in the treatment or prevention of a brain tumor.

10. The use according to claim 9, wherein the brain tumor is glioblastoma multiforme.

11. The use according to claim 9, wherein the brain tumor is recurrent glioblastoma multiforme after prior treatment with chemotherapy, lomustine, radiotherapy, bevacizumab, or a combination thereof.

12. A method of treating or preventing a brain tumor comprising administering a jointly therapeutically effective amount of the pharmaceutical combination according any one of claims 1 to 3 to a subject in need thereof.

13. The method according to claim 12, wherein the brain tumor is glioblastoma multiforme.

14. The method according to claim 12, wherein the brain tumor is recurrent glioblastoma multiforme after prior treatment with chemotherapy, lomustine, radiotherapy, bevacizumab, or a combination thereof.

15. A commercial package comprising the pharmaceutical combination according to claim 1, together with instructions for simultaneous, separate or sequential administration thereof for use in the treatment or prevention of a brain tumor.

FIGURE 1

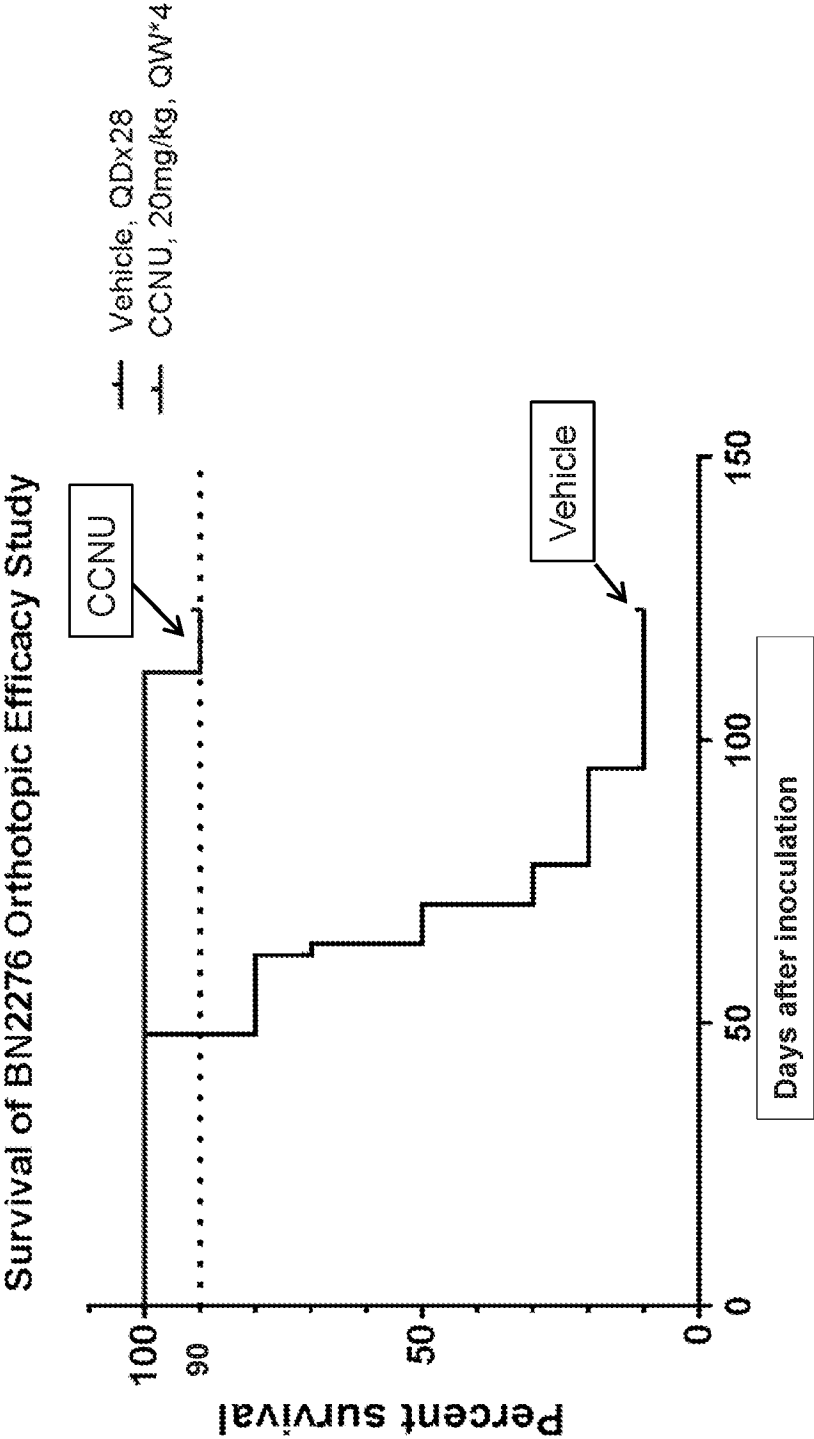


FIGURE 2

Survival of BN2276 Orthotopic Efficacy Study

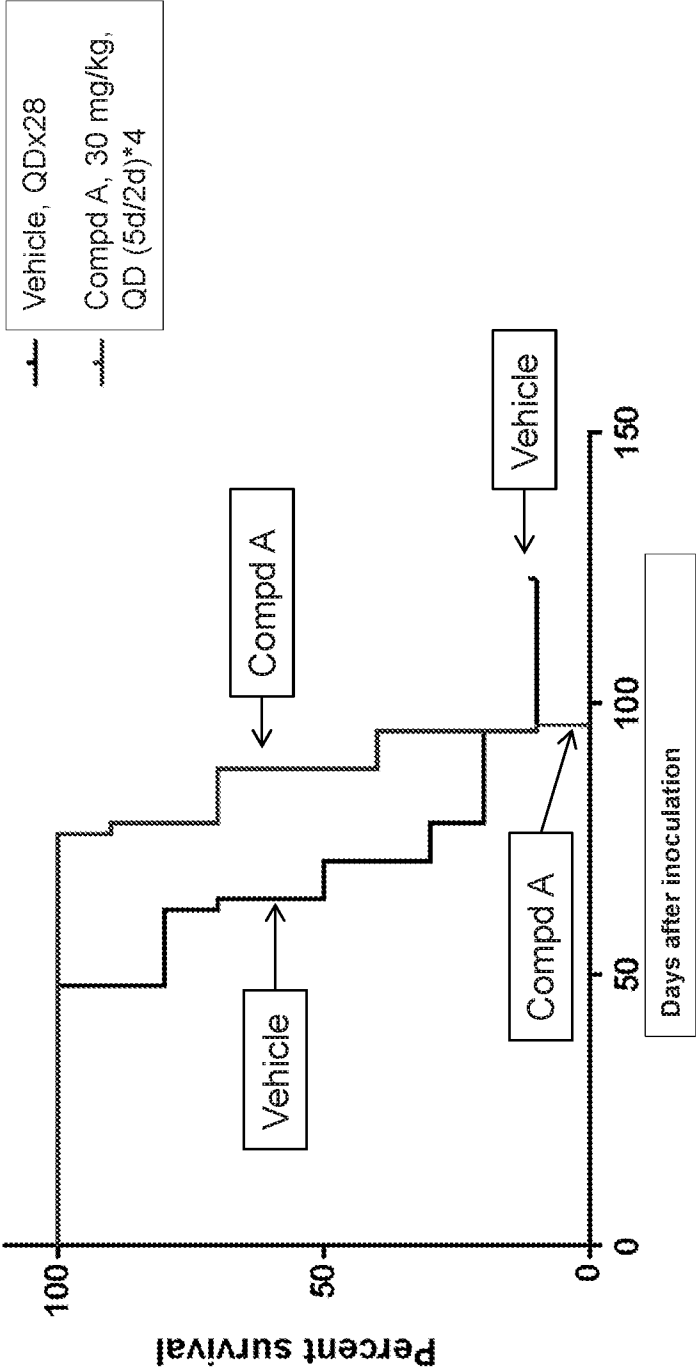
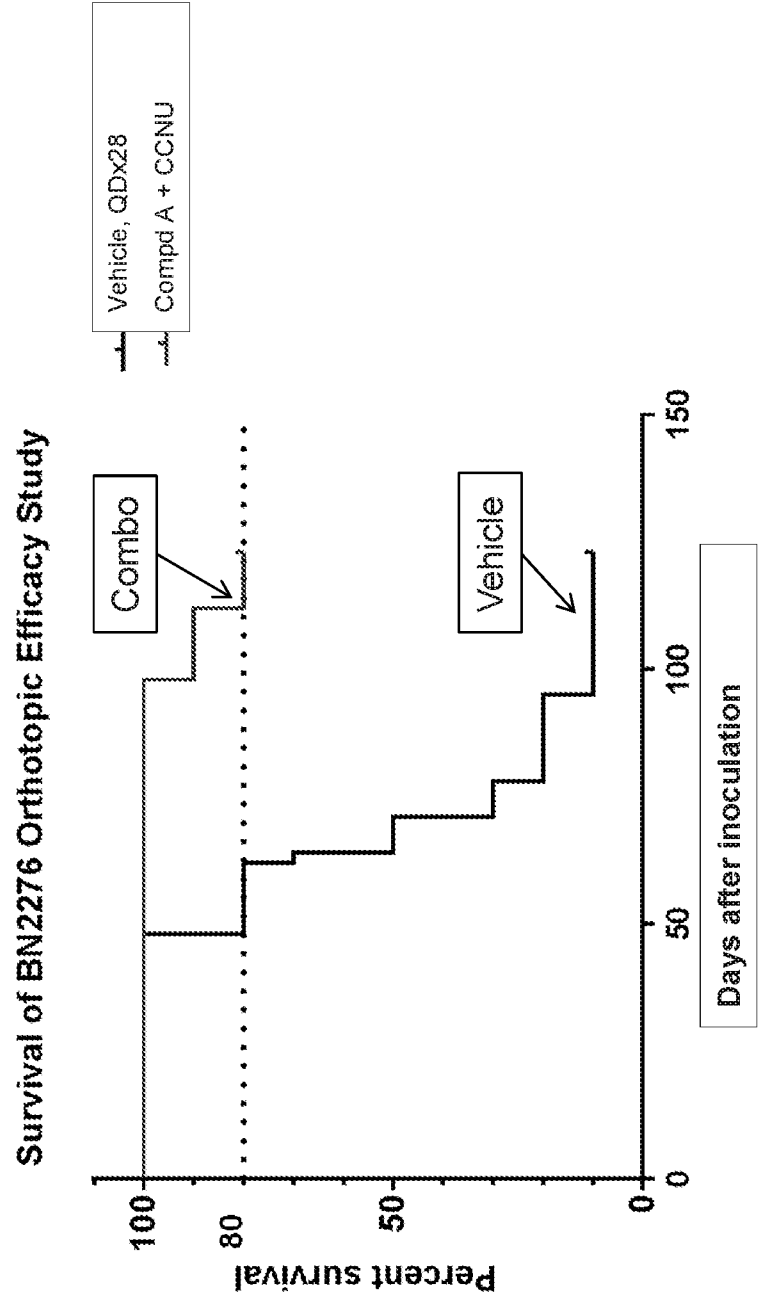


FIGURE 3



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/063903

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61P35/00 A61K31/175 A61K31/506 A61K31/5377
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

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)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CRISTIAN MASSACESI ET AL: "Challenges in the clinical development of PI3K inhibitors", ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 1280, no. 1, 1 March 2013 (2013-03-01), pages 19-23, XP055089169, ISSN: 0077-8923, DOI: 10.1111/nyas.12060 page 21 ----- -/-	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

29 September 2014

Date of mailing of the international search report

07/10/2014

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Haider, Ursula

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/063903

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	W. WICK ET AL: "Phase III Study of Enzastaurin Compared With Lomustine in the Treatment of Recurrent Intracranial Glioblastoma", JOURNAL OF CLINICAL ONCOLOGY, vol. 28, no. 7, 1 February 2010 (2010-02-01), pages 1168-1174, XP055089310, ISSN: 0732-183X, DOI: 10.1200/JCO.2009.23.2595 page 1169, left-hand column, paragraph 3 page 1172 -----	1-15