COMBINATION THERAPY FOR TREATING GLIOBLASTOMAS

RELATED APPLICATION DATA

The present application claims priority from Australian Patent Application No. 2024900813 entitled "Combination Therapy" filed on 26 March 2024, the entire contents of which is hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates generally to a method of treating a glioblastoma. The method comprises administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy, and optionally Temozolomide chemotherapy, to a patient in need thereof.

BACKGROUND OF THE INVENTION

Malignant gliomas, including glioblastomas, astrocytomas, oligodendrogliomas, and ependymomas, are a family of cancerous tumours that originate in the glial cells of the brain or the spine. Malignant gliomas account for more than 60% of all primary brain tumours, with an annual incidence of 3 to 4 per 100,000 population.

In particular, glioblastoma, also known as glioblastoma multiforme, is the most aggressive type of cancer known to originate in the brain. Initially, the symptoms of glioblastoma are non-specific, though they often can progress to include headaches, nausea, personality changes, and even unconsciousness. While the cause of glioblastoma remains largely unknown, known risk factors include genetic disorders (e.g., Li-Fraumeni syndrome, neurofibromatosis) and previous radiation therapy. Glioblastoma are typically diagnosed through a combinatorial approach of computed tomography (CT) scan, magnetic resonance imagine (MRI) scan, and tissue biopsy.

First line treatment of glioblastoma involves surgery, in which maximal tumour resection is undertaken. Surgery is typically followed by a combined treatment regimen of chemotherapy and radiotherapy. To this extent, Temozolomide, sold under the trade names Temodar®, Temodal®, and Temcad® amongst others, is a first-line therapeutic agent in the chemotherapy of glioblastoma. Temozolomide exerts its chemotherapeutic effect by alkylating/methylating DNA of cancerous cells, thereby triggering their death. However, some cancerous cells are able to repair the damaged DNA, and are therefore able to overcome Temozolomide treatment, rendering Temozolomide only limitedly effective. As a consequence,

vigorous radiotherapy (e.g., external beam radiation) is used in combination with Temozolomide chemotherapy for maximal therapeutic effect.

However, even with a combined treatment approach of Temozolomide chemotherapy and external beam radiotherapy, the prognosis of a patient having been diagnosed with glioblastoma remains poor. The typical length of survival following diagnosis is 12 to 15 months, with fewer than 3% to 7% of people surviving for longer than five years.

Accordingly, there remains a need for improved therapies and/or treatment regimens for the treatment of glioblastoma.

SUMMARY OF THE INVENTION

The present inventors have surprisingly discovered an improved therapy and/or treatment regimen for the treatment of glioblastoma.

In some embodiments, there is provided a method of treating a glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and optionally Temozolomide chemotherapy, to a patient in need thereof.

In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of at least about 1 GBq, optionally between about 2 GBq and about 18 GBq. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of between about 1 GBq and about 12 GBq, between about 2 GBq and about 12 GBq, between about 2 GBq and about 10 GBq, between about 2 GBq and about 8 GBq, or between about 2 GBq and about 6 GBq. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in parallel with external beam radiotherapy. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of and/or after completion of external beam radiotherapy. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose of about 1 GBq per dose, about 2 GBq per dose, about 3 GBq per dose, about 4 GBq per dose, about 5 GBq per dose, about 6 GBq per dose, about 7 GBq per dose, about 8 GBq per dose, about 9 GBq per dose, about 10 GBq per dose, about 11 GBq per dose, or about 12 GBq per dose. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in more than one dose, optionally wherein each of the more than one dose administers a substantially equal dose of 4-*L*-[^{131}I]iodo-phenylalanine. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses; optionally wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses of about 3 GBq per

dose, about 4 GBq per dose, about 5 GBq per dose, or about 6 GBq per dose. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three, substantially equal doses; optionally wherein the 4-L-[131I]iodo-phenylalanine is administered as three, substantially equal doses of about 2 GBq per dose, about 3 GBq per dose, or about 4 GBq per dose. In some embodiments, the external beam radiation is administered in an amount of about 20 Gray to about 60 Gray, optionally wherein the external beam radiation is administered in one or more fractions, optionally about 10, about 20, or about 30 fractions. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is formulated for intravenous administration, optionally wherein the 4-*L*-[^{131}I]iodo-phenylalanine is formulated in an amount of about 8 mg to about 12 mg of 4-*L*-[^{131}I]iodo-phenylalanine per about 25 mL of buffered solution. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in combination with external beam radiotherapy and Temozolomide chemotherapy. In some embodiments, the Temozolomide is administered in an amount of between about 75 mg/m^2 and about 200 mg/m^2, per day. In some embodiments, the Temozolomide is administered in an amount of about 75 mg/m^2, per day. In some embodiments, the method further includes the step of administering Temozolomide as a maintenance dose during a period in which the patient is not receiving the combined 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy treatment; optionally wherein the Temozolomide is administered as a maintenance dose in an amount of about 150 mg/m^2 to about 200 mg/m^2. In some embodiments, a reduction in one or more adverse events is observed in comparison to administration of Temozolomide chemotherapy and external beam radiotherapy alone; optionally wherein the one or more adverse events is selected from the group consisting of haematological toxicity, inflammation-induced intracranial hypertension, fatigue, thrombocytopenia, weight loss, diarrhea, and headache. In some embodiments, the patient has previously undergone maximal surgical resection of the glioblastoma, optionally wherein treatment with 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolomide chemotherapy and external beam radiotherapy commences within about 14 days to about 42 days following maximal surgical resection of the glioblastoma. In some embodiments, the method provides for an increase in the progression free survival of the patient in comparison to administration of Temozolomide chemotherapy and external beam radiotherapy alone. In some embodiments, the progression free survival is increased by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, in comparison to administration of Temozolomide chemotherapy and external beam radiotherapy alone. In some embodiments, the glioblastoma is a recurrent glioblastoma. In some embodiments, the glioblastoma is a high-grade glioma (HGG), optionally a recurrent high-grade glioma (HGG).

In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of a glioblastoma, wherein the medicament is formulated for administration in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.

Any embodiment herein shall be taken to apply *mutatis mutandis* to any other embodiment unless specifically stated otherwise. For instance, as the skilled person would understand, details of the amounts of 4-*L*-[^{131}I]iodo-phenylalanine to be administered in the course of the methods described herein may be applicable to all aspects and embodiments of the present disclosure. Equally, any particulars of the administration of external beam radiotherapy, such as the associated timing and doses, may be applicable to all aspects and embodiments described herein. Similarly, all comments on the patient population, types of glioblastoma to be treated, and/or relative amounts of the disclosed chemotherapy agents to be administered in combination with 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy, are to be taken as applicable to all aspects and embodiments described herein.

The present disclosure is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally-equivalent products, compositions and methods are clearly within the scope of the invention, as described herein.

Throughout this specification, unless specifically stated otherwise or the context requires otherwise, reference to a single step, composition of matter, group of steps or group of compositions of matter shall be taken to encompass one and a plurality (i.e. one or more) of those steps, compositions of matter, groups of steps or group of compositions of matter.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagram depicting the [3+3] dose escalation study scheme for the clinical trial described in Example 4: Phase I Trial of 4-*L*-[131I]Iodo-phenylalanine in Combination with Temozolomide Chemotherapy and External Beam Radiotherapy in Patients with Newly Diagnosed Glioblastoma.

DETAILED DESCRIPTION OF THE INVENTION

General Techniques and Definitions

Unless specifically defined otherwise, all technical and scientific terms used herein shall be taken to have the same meaning as commonly understood by one of ordinary skill in the art (e.g., chemistry, medicinal chemistry and the like). As used herein, the term “and/or”, e.g., “X

and/or Y" shall be understood to mean either "X and Y" or "X or Y" and shall be taken to provide explicit support for both meanings or for either meaning.

As used herein, the term about, unless stated to the contrary, refers to +/- 20%, more preferably +/- 10%, of the designated value.

As used herein, singular forms "a", "an" and "the" include plural aspects, unless the context clearly indicates otherwise.

Throughout this specification, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

As used herein, the terms "patient" or "subject" refer to any organism susceptible to a cancer, particularly a glioblastoma. For example, the subject can be a mammal, primate, livestock (e.g., sheep, cow, horse, pig), companion animal (e.g., dog, cat), or laboratory animal (e.g., mouse, rabbit, rat, guinea pig, hamster). In one example, the subject is a mammal. In one embodiment, the subject is a human. In one embodiment, the disease or condition is a glioblastoma.

As used herein, the term "treating" includes alleviation of the symptoms associated with a specific disorder or condition and reducing and/or eliminating said symptoms. For example, as used herein, the term "treating a cancer" refers to alleviating the symptoms associated with a cancer and reducing and/or eliminating the symptoms associated with a cancer. In one example, the term "treating" includes alleviation of the symptoms associated with a glioblastoma. For example, as used herein, the term "treating a glioblastoma" refers to alleviating the symptoms associated with a glioblastoma and reducing and/or eliminating the symptoms associated with a glioblastoma. In one example, the term "treating cancer" refers to an increase in progression-free survival. As used herein, the term "progression-free survival" refers to the length of time during and after the treatment of a cancer that a patient lives with the disease, i.e., glioblastoma, but does not have a recurrence or increase in symptoms of the disease. In one embodiment, the term "preventing glioblastoma" refers to slowing or halting the progression of the glioblastoma. In one example, "preventing glioblastoma" refers to slowing or halting the glioblastoma increasing in size/volume. In one example, "preventing glioblastoma" refers to slowing or preventing metastasis.

As used herein, the term "therapeutically effective amount" refers to a therapeutic agent and/or treatment approach, or a combination of therapeutic agents and/or treatment approaches, being administered in an amount sufficient to alleviate or prevent to some extent one or more of the symptoms of the disorder or condition being treated. The result can be the reduction and/or

alleviation of the signs, symptoms, or causes of a disease or condition, or any other desired alteration of a biological system. In one embodiment, the term "therapeutically effective amount" refers to a therapeutic agent being administered in an amount sufficient to result in a reduction of one or more symptoms associated with a cancer (e.g., glioblastoma). In the example of a cancerous tumour, the result may be a reduction in tumour size. In one example, the term "therapeutically effective amount" refers to a therapeutic agent being administered in an amount sufficient to result in an increase in progression-free survival. The term, "effective amount", as used herein, refers to an amount of a therapeutic agent effective to achieve a desired pharmacologic effect or therapeutic improvement without undue adverse side effects or to achieve a desired pharmacologic effect or therapeutic improvement with a reduced side effect profile. It is understood that "an effective amount" or "a therapeutically effective amount" can vary from subject to subject, due to variation in metabolism of the compound and any of age, weight, general condition of the subject, the condition being treated, the severity of the condition being treated, and the judgment of the prescribing physician. Thus, it is not always possible to specify an exact "effective amount". However, an appropriate "effective amount" in any individual case may be determined by one of ordinary skill in the art using routine experimentation. Where more than one therapeutic agent is used in combination, a "therapeutically effective amount" of each therapeutic agent or treatment approach can refer to an amount of the therapeutic agent that would be therapeutically effective when used on its own, or may refer to an adjusted (e.g., reduced) amount that is therapeutically effective by virtue of its combination with one or more additional therapeutic agents or treatment approaches.

Therapeutic Methods and Uses

Provided herein are methods of treating a glioblastoma.

As discussed above, glioblastoma is the most common form of malignant primary brain tumour and is associated with substantial morbidity and mortality. Recent advances have aided the understanding of the molecular pathogenesis and biology of these tumours, but this has not translated into significantly improved outcomes. In contrast, the present inventors have determined that an advantageous combination of 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy, which may be further combined with a chemotherapy comprising Temozolomide, may provide a safe, tolerable, effective and/or reliable treatment for patients with glioblastoma, including newly diagnosed glioblastoma, recurrent glioblastoma, and/or high-grade glioma.

Without being bound by theory, it was realised that a combination of 4-*L*-[^{131}I]iodo-phenylalanine with external beam radiotherapy may provide molecularly targeted radiation that may have a therapeutic effect in glioblastoma patients.

Accordingly, there is provided a method of treating glioblastoma comprising the administration of a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy. There is also provided a method of treating glioblastoma comprising the administration of a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.

In embodiments, the methods described herein comprise the administration of a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy, to a patient in need thereof. Where the method comprises the administration of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy, the therapy may be referred to as a "di-combination therapy".

In some embodiments, the methods described herein comprise the administration of a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolomide chemotherapy and external beam radiotherapy, to a patient in need thereof. In the instance where the method comprises the administration of 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolomide chemotherapy and external beam radiotherapy, the therapy may be referred to as a "tri-combination therapy".

It has been surprisingly found that 4-L-[131I]iodo-phenylalanine, administered in combination with external beam radiotherapy, provides an improved method of treating glioblastoma. Similarly, it has been surprisingly found that 4-L-[131I]iodo-phenylalanine, administered in combination with Temozolomide chemotherapy and external beam radiotherapy, provides an improved method of treating glioblastoma. Those of ordinary skill in the art will appreciate that, as with most cancer therapies, the therapeutic methods described herein are not to be interpreted as, restricted to, or otherwise limited to a "cure" for cancer; rather the methods of treatment are directed to the use of the described compositions to "treat" a cancer, i.e., to effect a desirable or beneficial change in the health of an individual who has cancer. Such benefits are recognized by skilled healthcare providers in the field of oncology and include, but are not limited to, a stabilization of patient condition, a decrease in tumour size (tumour regression), an improvement in vital functions (e.g., improved function of cancerous tissues or organs), a decrease or inhibition of further metastasis, a decrease in opportunistic infections, an increased survival, a decrease in pain, improved motor function, improved cognitive function, improved feeling of energy (vitality, decreased malaise), improved feeling of well-being, restoration of normal appetite, restoration of healthy weight gain, and combinations thereof. For example, the methods described herein may provide an increase in the overall survival of the patients, which can be monitored by survival follow-up phone calls at any suitable time interval(s), such as a 6-

month, one-year or two-year survival. In one instance, the survival is a Progression Free Survival (PFS) from the date of the commencement of treatment to the date of progression or death for any cause, whichever comes first, assessed at a suitable time period, such as a period of 52 weeks. In addition, a beneficial change in the health of a patient administered the method described herein may be assessed by an Objective Response Rate (ORR) at any suitable time interval(s) as defined by modified Response in Neuro-Oncology (mRANO) criteria. Further, the therapeutic methods described herein may result in an improvement of a Quality of Life (QoL), for example a QoL as determined using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire and/or Quality of Life Questionnaire – Brain Neoplasm questionnaires, or any number of neurocognitive tests, such as, for example, Controlled Oral Word Association Test (COWA test), Hopkins Verbal Learning Test-Revised (HVLT-R test), or Trail Making Test (TMT). In addition, a decrease in tumour size in an individual (e.g., as the result of treatments described herein) may be assessed by imaging methods known to a person skilled in the art before, during and/or after treatment administration. In addition, an effect of the methods described herein may present as any morphological and metabolic changes indicative of tumour response using T1 gadolinium-enhanced Magnetic Resonance Imaging (MRI), and/or O-2-^{18}F-fluoroethyl-l-tyrosine ([^{18}F]-FET) Positron Emission Tomography (PET). For example, any tumour regression or normalisation induced by employing the methods of this disclosure may be indicated by Sum of the Product of the Perpendicular Diameters (SPPD) as determined, for example, by contrast enhanced T1 MRI, and/or changes in parameters within the metabolic tumour volume (MTV), and/or tumour-to-brain ratios as determined by, for example, [^{18}F]-FET-PET.

Glioblastoma (glioblastoma multiforme, GBM; World Health Organization (WHO) grade IV astrocytoma) accounts for 60% to 70% of malignant gliomas and remains the most aggressive subtype of glioma. Glioblastomas for which the methods described herein may be applicable may include, for example, newly diagnosed, diagnosed, or recurrent glioblastomas, as well as high-grade glioma (HGGs). Unexpectedly, it has been found that 4-L-[131I]iodo-phenylalanine, administered in combination with external beam radiotherapy, provides an improved method of treating a glioblastoma. Similarly, it has been surprisingly found that 4-L-[131I]iodo-phenylalanine, administered in combination with Temozolomide chemotherapy and external beam radiotherapy, provides an improved method of treating a glioblastoma.

In one example, the glioblastoma is recurrent glioblastoma. It will be understood that "recurrent glioblastoma" refers to glioblastoma that has returned to the patient following a period of remission. Recurrent glioblastoma may be diagnosed by, for example, the appearance of residual tumour growth on imaging studies or the manifestation of associated clinical symptoms.

Accordingly, it has been found that 4-*L*-[^{131}I]iodo-phenylalanine, administered in combination with external beam radiotherapy, provides an improved method of treating recurrent glioblastoma. Similarly, it has been surprisingly found that 4-*L*-[^{131}I]iodo-phenylalanine, administered in combination with Temozolomide chemotherapy and external beam radiotherapy, provides an improved method of treating recurrent glioblastoma.

In one example, the glioblastoma is high-grade glioma (HGG), e.g. a recurrent high-grade glioma (HGG). It will be understood that "high-grade glioma" refers to gliomas of Grade 3 or Grade 4, based on how rapidly and/or aggressively the cancer cells duplicate. Generally, glioblastoma are considered high-grade gliomas, with glioblastomas typically designated as a Grade 4 glioma. Accordingly, it has been found that 4-*L*-[^{131}I]iodo-phenylalanine, administered in combination with external beam radiotherapy, provides an improved method of treating high-grade glioma (HGG), e.g. a recurrent high-grade glioma (HGG). Similarly, it has been surprisingly found that 4-*L*-[^{131}I]iodo-phenylalanine, administered in combination with Temozolomide chemotherapy and external beam radiotherapy, provides an improved method of treating high-grade glioma (HGG), e.g. a recurrent high-grade glioma (HGG).

Accordingly, there is provided a method of treating a glioblastoma (e.g., recurrent glioblastoma) comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy, to a patient in need thereof. There is also provided a method of treating a glioblastoma (e.g., recurrent glioblastoma) comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolamide chemotherapy and external beam radiotherapy, to a patient in need thereof.

There is also provided a use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of glioblastoma, recurrent glioblastoma, and/or high-grade glioma (HGG), e.g. a recurrent high-grade glioma (HGG), wherein the medicament is administered in combination with and external beam radiotherapy. There is also provided 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy, for use in the treatment of glioblastoma, recurrent glioblastoma, and/or high-grade glioma (HGG), e.g. a recurrent high-grade glioma (HGG). There is also provided 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy, when used in the treatment of glioblastoma, recurrent glioblastoma, and/or high-grade glioma (HGG), e.g. a recurrent high-grade glioma (HGG).

There is also provided a use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of glioblastoma, recurrent glioblastoma, and/or high-grade glioma (HGG), e.g. a recurrent high-grade glioma (HGG), wherein the medicament is administered in combination with Temozolomide chemotherapy and external beam radiotherapy.

There is also provided 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolomide chemotherapy and external beam radiotherapy, for use in the treatment of glioblastoma, recurrent glioblastoma, and/or high-grade glioma (HGG), e.g. a recurrent high-grade glioma (HGG).

There is also provided 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolomide chemotherapy and external beam radiotherapy, when used in the treatment of glioblastoma, recurrent glioblastoma, and/or high-grade glioma (HGG), e.g. a recurrent high-grade glioma (HGG).

In some embodiments, the high-grade glioma (HGG) is a recurrent high-grade glioma (HGG). For example, the methods described herein may be effective in the treatment of a recurrent IDH1/2 wildtype high-grade glioma (HGG).

In some embodiments, there is provided 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy for use in a method of treating glioblastoma. In some embodiments, there is provided 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and optionally Temozolomide chemotherapy for use in a method of treating glioblastoma.

In some embodiments, there is provided a method of treating a newly diagnosed glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and optionally Temozolomide chemotherapy, to a patient in need thereof.

In some embodiments, there is provided a method of treating a newly diagnosed glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and Temozolomide chemotherapy, to a patient in need thereof.

In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of newly diagnosed glioblastoma, wherein the medicament is formulated for administration in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.

It will be appreciated that the term “newly diagnosed” refers to a newly identified glioblastoma. Accordingly, a “newly diagnosed” glioblastoma is not a recurrent glioblastoma. Therefore, any treatment that targets a “newly diagnosed” glioblastoma is considered a first-line therapy.

In some embodiments, there is provided a method of treating a recurrent glioma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy.

In some embodiments, there is provided a method of treating a recurrent glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy.

In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of recurrent glioblastoma, wherein the medicament is formulated for administration in combination with external beam radiotherapy.

In some embodiments, there is provided a method of treating a recurrent high-grade glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy.

In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of recurrent high-grade glioblastoma, wherein the medicament is formulated for administration in combination with external beam radiotherapy.

In some embodiments, there is provided a method of treating a glioblastoma multiforme comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy.

In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of glioblastoma multiforme, wherein the medicament is formulated for administration in combination with external beam radiotherapy.

In some embodiments, there is provided a method of treating a recurrent glioma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.

In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of recurrent glioma, wherein the medicament is formulated for administration in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.

In some embodiments, there is provided a method of treating a recurrent glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.

In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of recurrent glioblastoma, wherein the medicament is formulated for administration in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.

In some embodiments, there is provided a method of treating a recurrent high-grade glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-

phenylalanine in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.

In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of recurrent high-grade glioblastoma, wherein the medicament is formulated for administration in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.

In some embodiments, there is provided a method of treating a glioblastoma multiforme comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.

In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of glioblastoma multiforme, wherein the medicament is formulated for administration in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.

In some embodiments, there is provided a method of treating a recurrent glioma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and Temozolomide chemotherapy.

In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of recurrent glioma, wherein the medicament is formulated for administration in combination with external beam radiotherapy and Temozolomide chemotherapy.

In some embodiments, there is provided a method of treating a recurrent glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and Temozolomide chemotherapy.

In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of recurrent glioblastoma, wherein the medicament is formulated for administration in combination with external beam radiotherapy and Temozolomide chemotherapy.

In some embodiments, there is provided a method of treating a recurrent high-grade glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and Temozolomide chemotherapy.

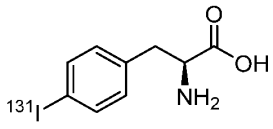
In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of recurrent high-grade glioblastoma, wherein the medicament is formulated for administration in combination with external beam radiotherapy and Temozolomide chemotherapy.

In some embodiments, there is provided a method of treating a glioblastoma multiforme comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and Temozolomide chemotherapy.

In some embodiments, there is provided the use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of a glioblastoma multiforme, wherein the medicament is formulated for administration in combination with external beam radiotherapy and Temozolomide chemotherapy.

4-L-[^{131}I]iodo-phenylalanine

4-*L*-[^{131}I]iodo-phenylalanine, also referred to as ^{131}I-IPA and TLX101, is a radiolabelled synthetic amino acid having the structure:



Structure of 4-*L*-[^{131}I]iodo-phenylalanine.

4-*L*-[^{131}I]iodo-phenylalanine inhibits the L-type/large neutral amino acid transporter 1, LAT1 (SLC7A5), which has repeatedly been found to be overexpressed in a vast array of cancers including breast cancer, prostate cancer, lung cancer, bladder cancer, and bone cancer, amongst others. LAT1 is also known to be expressed in brain tumours, including glioblastoma.

LAT1 serves as an important route for essential amino acid entry into cells, a critical component for tumerous cell proliferation. It has been postulated that inhibitors, or blockers, of LAT1 may lead to decreased uptake of essential amino acids by tumorous cells, and therefore decreased tumerous cell proliferation. In this way, it is understood that inhibitors of LAT1, such as 4-*L*-[^{131}I]iodo-phenylalanine, may exert a chemotherapeutic effect.

4-*L*-[^{131}I]iodo-phenylalanine is known to be able to rapidly cross the blood-brain barrier (BBB). As a result, 4-*L*-[^{131}I]iodo-phenylalanine is able to access glioblastoma tumour cells where it can exert its chemotherapeutic effect. As a result of its high uptake across the BBB, chemotherapy with 4-*L*-[^{131}I]iodo-phenylalanine advantageously results in very little peripheral dosimetry. 4-*L*-[^{131}I]iodo-phenylalanine is therefore a highly useful chemotherapy tool in the treatment of glioblastoma.

In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount sufficient to treat the glioblastoma when administered in combination with external beam radiotherapy and optionally Temozolamide chemotherapy.

That is, in some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount sufficient to treat the glioblastoma when administered in combination with external beam radiotherapy (i.e., "di-combination therapy").

Similarly, in some other embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount sufficient to treat the glioblastoma when administered in combination with Temozolamide chemotherapy and external beam radiotherapy (i.e., "tri-combination therapy").

The amount of 4-*L*-[^{131}I]iodo-phenylalanine administered is quantified by its radiation dose (i.e., radioactive dose level), as measured in Becquerel (Bq). As would be understood by the skilled person, one Becquerel is defined as the activity of a quantity of radioactive material in which one nucleus decays per second.

In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of at least about 0.5 GBq, at least about 1.0 GBq, at least about 1.5 GBq, at least about 2.0 GBq, at least about 4.0 GBq, at least about 6.0 GBq, at least about 8.0 GBq, at least about 10 GBq, at least about 12 GBq, at least about 14 GBq, at least about 16 GBq, at least about 18 GBq, or at least about 20 GBq. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered is an amount of less than about 0.5 GBq, less than about 1.0 GBq, less than about 1.5 GBq, less than about 2.0 GBq, less than about 4.0 GBq, less than about 6.0 GBq, less than about 8.0 GBq, less than about 10 GBq, less than about 12 GBq, less than about 14 GBq, less than about 16 GBq, less than about 18 GBq, or less than about 20 GBq.

In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered is an amount of between about 0.5 GBq and about 20 GBq, between about 1.0 GBq and about 18 GBq, between about 2.0 GBq and about 16 GBq, between about 2.0 GBq and about 12 GBq, between about 2.0 GBq and about 10 GBq, between about 2.0 GBq and about 6.0 GBq, between about 4.0 GBq and about 14 GBq, or between about 8.0 GBq and about 12 GBq. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of between about 2.0 GBq and about 18 GBq. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of between about 2.0 GBq and about 8.0 GBq. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of between about 2.0 GBq and about 12 GBq, between about 2.0 GBq and about 10 GBq, between about 2.0 GBq and about 8.0 GBq, or between about 2.0 GBq and about 6.0 GBq.

The methods of treatment described herein may provide for the administration of the 4-*L*-[^{131}I]iodo-phenylalanine in any number of doses (or fractions) and at any suitable time so as to maximise the therapeutic efficacy of the treatment, including a combination treatment. That is, the 4-*L*-[^{131}I]iodo-phenylalanine may be administered in any number of doses (or fractions) at any number of timepoints (e.g., days from commencement of treatment) so as to provide maximal therapeutic efficacy of the treatment. That is, selecting the number of doses (or fractions) of 4-*L*-

[^{131}I]iodo-phenylalanine administered, and the particular timepoints of administration of each dose (or fraction) throughout the duration of treatment, may further maximise the therapeutic efficacy of the combination treatment (both "di-combination therapy" and "tri-combination therapy").

Accordingly, the methods of treatment described herein may involve the administration of 4-*L*-[^{131}I]iodo-phenylalanine as a single dose, or alternatively as more than one dose. As will be appreciated by a person skilled in the art, the stated doses of administered 4-*L*-[^{131}I]iodo-phenylalanine may be a sum or a cumulative dose, also referred to as a total dose, of two or more fractions or doses. For example, a dose of 6 GBq 4-*L*-[^{131}I]iodo-phenylalanine may be a sum of three equal doses of 2 GBq, a dose of 9 GBq 4-*L*-[^{131}I]iodo-phenylalanine may be a sum of three equal doses of 3 GBq, and a dose of 12 GBq 4-*L*-[^{131}I]iodo-phenylalanine may be a sum of three equal doses of 4 GBq. In other examples, a dose of 6 GBq 4-*L*-[^{131}I]iodo-phenylalanine may be a sum of a dose of 4 GBq and a dose of 2 GBq, a dose of 9 GBq 4-*L*-[^{131}I]iodo-phenylalanine may be a sum of a dose of 6 GBq and a dose of 3 GBq, and a dose of 12 GBq 4-*L*-[^{131}I]iodo-phenylalanine may be a sum of a dose of 8 GBq and a dose of 4 GBq. In other examples, a dose of 6 GBq 4-*L*-[^{131}I]iodo-phenylalanine may be a sum of two equal doses of 3 GBq, a dose of 8 GBq 4-*L*-[^{131}I]iodo-phenylalanine may be a sum of two equal doses of 4 GBq, a dose of 10 GBq 4-*L*-[^{131}I]iodo-phenylalanine may be a sum of two equal doses of 5 GBq, and a dose of 12 GBq 4-*L*-[^{131}I]iodo-phenylalanine may be a sum of two equal doses of 6 GBq.

In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose of between about 2.0 GBq and about 18 GBq. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose of between about 2.0 GBq and about 12 GBq. In another example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose of between about 2.0 GBq and about 8.0 GBq.

In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, three, four, five, six, seven, eight, or more doses (or fractions). Each dose may administer a substantially equal dose of 4-*L*-[^{131}I]iodo-phenylalanine, or may administer a substantially unequal dose of 4-*L*-[^{131}I]iodo-phenylalanine. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, three, four, five, six, seven, eight, or more substantially equal doses. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two substantially equal doses. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as four substantially equal doses. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as five substantially equal doses. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as six substantially equal doses. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as seven substantially equal doses.

In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as eight substantially equal doses. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as 10 substantially equal doses.

In some preferred embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of at least about 2.0 GBq, 3.0 GBq, 4.0 GBq, 5.0 GBq, 6.0 GBq, 8.0 GBq, 10 GBq, 12 GBq, 16 GBq, or 18 GBq. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of at least about 2.0 GBq. This amount may be as an individual dose or a cumulative dose (i.e., the summation of doses provided over two or more administrations). In some preferred embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an individual dose amount of at least about 2.0 GBq, 3.0 GBq, 4.0 GBq, 5.0 GBq, 6.0 GBq, 7.0 GBq, 8.0 GBq, 9.0 GBq, 10 GBq, 11 GBq, 12 GBq, 13 GBq, 14 GBq, 15 GBq, 16 GBq, or 18 GBq. In some preferred embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in a cumulative dose amount of at least about 2.0 GBq, 3.0 GBq, 4.0 GBq, 5.0 GBq, 6.0 GBq, 7.0 GBq, 8.0 GBq, 9.0 GBq, 10 GBq, 11 GBq, 12 GBq, 13 GBq, 14 GBq, 15 GBq, 16 GBq, or 18 GBq. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered in a cumulative dose amount of about 6.0 GBq.

In some preferred embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two substantially equal doses. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two substantially equal doses of about 3.0 GBq (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 6.0 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two substantially equal doses of about 4.0 GBq (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 8.0 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two substantially equal doses of about 5.0 GBq (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 10 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two substantially equal doses of about 6.0 GBq (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 12 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two substantially equal doses of 3.0 GBq to 6.0 GBq, the first dose being administered at least a week prior to commencement of external beam radiotherapy, and the second dose being administered after completion (e.g., cessation) of external beam radiotherapy.

In some preferred embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses of about 0.67 GBq (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 2.0 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses of about 2.0 GBq (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 6.0 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses of about 2.67 GBq (i.e., a total dose of 4-*L*-

[^{131}I]iodo-phenylalanine of about 8.0 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses of about 3.33 GBq (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 10 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses of 4.0 GBq (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 12 GBq).

In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses of about 2 GBq (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 6 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses of about 3 GBq (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 9 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses of about 4 GBq (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 12 GBq).

In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered prior to commencement of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[131I]iodo-phenylalanine is administered several minutes, hours, days or weeks (e.g., 0-10 days) prior to commencement of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered in parallel or sequentially with external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered several minutes, hours, days or weeks (e.g., 0-10 days) prior to commencement of external beam radiotherapy, and a further one or more doses are administered in parallel or sequentially with external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered in parallel or sequentially with external beam radiotherapy within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered several minutes, hours, days or weeks (e.g., 0-10 days) prior to commencement of external beam radiotherapy, and a further one or more doses are administered in parallel or sequentially with external beam radiotherapy within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose.

In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered in parallel with external beam radiotherapy. That is, the one or more doses of 4-*L*-

[^{131}I]iodo-phenylalanine and external beam radiotherapy may be administered, for example, on the same day or within the same suitable time interval during the treatment period. For example, the one or more doses of 4-*L*-[^{131}I]iodo-phenylalanine may be administered within some hours after administration of external beam radiotherapy. In such parallel administration, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy may be administered at any suitable time intervals, such as e.g. every 1-10 days, throughout the treatment period. In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy are administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine. In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy are administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the commencement of the methods of treatment described herein.

In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered prior to commencement of and/or after completion (e.g., cessation) of external beam radiotherapy. In other words, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine may be administered sequentially with external beam radiotherapy. For example, in some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered after completion (e.g., cessation) of external beam radiotherapy. For example, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine may be administered within several minutes, hours, days or weeks (e.g., 0-10 days) after the completion (e.g., cessation) of external beam radiotherapy. In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered within one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks after the completion (e.g., cessation) of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered after completion (e.g., cessation) of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered within several minutes, hours, days or weeks (e.g., 0-10 days) after the completion (e.g., cessation) of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered several minutes, hours, days or weeks (e.g., 0-10 days) prior to commencement of external beam radiotherapy, and a further one or more doses are administered within several minutes, hours, days or weeks (e.g., 0-10 days) after the completion (e.g., cessation) of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is

administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks after the completion (e.g., cessation) of external beam radiotherapy.

The methods of treatment described herein may involve the administration of a single dose of 4-*L*-[^{131}I]iodo-phenylalanine being administered at any time point (e.g., days from commencement of treatment) throughout the duration of treatment. In the instance where administration of 4-*L*-[^{131}I]iodo-phenylalanine does not commence on day one, it will be understood that administration of external beam radiotherapy (in the instance of the "di-combination therapy"), or the administration of Temozolomide chemotherapy or external beam radiotherapy (in the instance of the "tri-combination therapy"), will signify the commencement of the methods of treatment described herein (i.e., day one). In one example, a single dose of 4-*L*-[^{131}I]iodo-phenylalanine is administered between day one and day 42, between day one and day 35, day one and day 28, day one and day 21, day one and day 14, or day one and day seven, from the commencement of the methods of treatment described herein. Further, as will be appreciated by the person skilled in the art, administration of 4-*L*-[^{131}I]iodo-phenylalanine on the day of commencement of the methods of treatment described herein will be taken as administration on "day zero". Accordingly, in one example, a single dose of 4-*L*-[^{131}I]iodo-phenylalanine is administered between day zero and day 42, between day zero and day 35, day zero and day 28, day zero and day 21, day zero and day 14, or day zero and day seven, from the commencement of the methods of treatment described herein.

In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose on day zero, one, two, three, four, five, six, seven, or more, from commencement of the methods of treatment described herein. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose on day zero from commencement of the methods of treatment described herein. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose on day one from commencement of the methods of treatment described herein. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose on day two from commencement of the methods of treatment described herein. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose on day three from commencement of the methods of treatment described herein. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose on day four from commencement of the methods of treatment described herein. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose on day five from commencement of the methods of treatment described herein. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose on day six from commencement of the methods of treatment described herein. In one example,

4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose on day seven (i.e., one week) from commencement of the methods of treatment described herein.

In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as more than one dose at any two or more timepoints (e.g., days from commencement of treatment) throughout the duration of treatment. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as more than one dose, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a further dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as more than one dose, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as four substantially equal doses, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as five substantially equal doses, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as six substantially equal doses, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as multiple substantially equal doses, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as multiple substantially equal doses, and the first dose is administered on day one from commencement of the methods

of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose, with each dose administered at regular intervals over the treatment period.

In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as more than one dose, and the first dose is administered on day one from commencement of the methods of treatment described herein. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as more than one dose, and the first dose is administered on day zero from commencement of the methods of treatment described herein. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two doses on days zero and 46, from commencement of treatment. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two substantially equal doses on days zero and 46, from commencement of treatment. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two doses on days one and seven, from commencement of treatment. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two substantially equal doses on days one and seven, from commencement of treatment. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three doses on days one, seven, and 14, from commencement of treatment.

In some preferred embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses on days one, seven, and 14, from commencement of treatment. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three, substantially equal doses of about 0.67 GBq per dose on days one, seven, and 14, from commencement of treatment (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 2.0 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three, substantially equal doses of about 2.0 GBq per dose on days one, seven, and 14, from commencement of treatment (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 6.0 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three, substantially equal doses of about 2.67 GBq per dose on days one, seven, and 14, from commencement of treatment (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 8.0 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three, substantially equal doses of about 3.33 GBq per dose on days one, seven, and 14, from commencement of treatment (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 10 GBq). In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three, substantially equal doses of about 4.0 GBq per dose on days one, seven, and 14, from commencement of treatment (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 12 GBq). In yet another example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three, substantially equal doses of about 2 GBq per dose on days one, 43, and 85, or on days one, 29 and 57, from commencement of treatment (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 6 GBq). In yet another example, the 4-

L-[^{131}I]iodo-phenylalanine is administered as three, substantially equal doses of about 3 GBq per dose on days one, 43, and 85, or on days one, 29 and 57, from commencement of treatment (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 9 GBq). In yet another example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three, substantially equal doses of about 4 GBq per dose on days one, 43, and 85, or on days one, 29 and 57, from commencement of treatment (i.e., a total dose of 4-*L*-[^{131}I]iodo-phenylalanine of about 12 GBq).

In any of the embodiments described above, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine may be administered prior to commencement of external beam radiotherapy, in parallel with external beam radiotherapy, or prior to commencement of and/or after completion (e.g., cessation) of external beam radiotherapy. In other words, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine may be administered sequentially with external beam radiotherapy.

Accordingly, in some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered prior to commencement of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered in parallel or sequentially with external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered several minutes, hours, days or weeks (e.g., 0-10 days) prior to commencement of external beam radiotherapy, and a further one or more doses are administered in parallel or sequentially with external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered in parallel or sequentially with external beam radiotherapy within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered several minutes, hours, days or weeks (e.g., 0-10 days) prior to commencement of external beam radiotherapy, and a further one or more doses are administered in parallel or sequentially with external beam radiotherapy within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose.

In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered in parallel with external beam radiotherapy. That is, the one or more doses of 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy may be administered, for example, on the same day or within the same suitable time interval during the treatment period. For example, the one or more doses of 4-*L*-[^{131}I]iodo-phenylalanine may be administered within some hours after administration of external beam radiotherapy. In such parallel administration, the one or

more doses of the 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy may be administered at any suitable time intervals, such as e.g. every 1-10 days, throughout the treatment period. In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy are administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine. In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy are administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the commencement of the methods of treatment described herein.

In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered prior to commencement of and/or after completion (e.g., cessation) of external beam radiotherapy. In other words, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine may be administered sequentially with external beam radiotherapy. For example, in some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered after completion (e.g., cessation) of external beam radiotherapy. For example, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine may be administered several minutes, hours, days or weeks (e.g., 0-10 days) after the completion (e.g., cessation) of external beam radiotherapy. In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered within one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks after the completion (e.g., cessation) of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered after completion (e.g., cessation) of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered within several minutes, hours, days or weeks (e.g., 0-10 days) after the completion (e.g., cessation) of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered several minutes, hours, days or weeks (e.g., 0-10 days) prior to commencement of external beam radiotherapy, and a further one or more doses are administered within several minutes, hours, days or weeks (e.g., 0-10 days) after the completion (e.g., cessation) of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks after the completion (e.g., cessation) of external beam radiotherapy.

External beam radiotherapy

External beam radiotherapy, also referred to as external radiation therapy (XRT), is a method for delivering a beam, or several beams, of high-energy x-rays targeted to a tumour site.

In some embodiments, the external beam radiotherapy is administered in an amount sufficient to treat the glioblastoma when administered in combination with 4-*L*-[^{131}I]iodo-phenylalanine (i.e., "di-combination therapy").

In some other embodiments, the external beam radiotherapy is administered in an amount sufficient to treat the glioblastoma when administered in combination with 4-*L*-[^{131}I]iodo-phenylalanine and Temozolamide chemotherapy (i.e., "tri-combination therapy").

The amount of external beam radiotherapy administered is quantified by its ionizing radiation dose, as measured in Gray (Gy). As would be understood by the skilled person, one Gray is defined as the absorption of one joule of radiation energy per kilogram of matter and so represents an absorbed dose of radiation.

In some embodiments, the external beam radiotherapy is administered in an amount of at least about 5 Gy, at least about 10 Gy, at least about 20 Gy, at least about 30 Gy, at least about 40 Gy, at least about 50 Gy, at least about 60 Gy, at least about 70 Gy, at least about 80 Gy, at least about 90 Gy, or at least about 100 Gy, in total (e.g., in total throughout the duration of the methods of treatment described herein). In some embodiments, the external beam radiotherapy is administered in an amount of less than about 100 Gy, less than about 90 Gy, less than about 80 Gy, less than about 70 Gy, less than about 60 Gy, less than about 50 Gy, less than about 40 Gy, less than about 30 Gy, less than about 20 Gy, or less than about 10 Gy, in total (e.g., in total throughout the duration of the methods of treatment described herein). In some embodiments, the external beam radiotherapy is administered in an amount of about 5 Gy, about 10 Gy, about 20 Gy, about 30 Gy, about 40 Gy, about 50 Gy, about 60 Gy, about 70 Gy, about 80 Gy, about 90 Gy, or about 100 Gy, in total (e.g., in total throughout the duration of the methods of treatment described herein). In one example, the external beam radiotherapy is administered in an amount of about 60 Gy, in total (e.g., in total throughout the duration of the methods of treatment described herein). In some embodiments, the external beam radiotherapy is administered in an amount of between about 5 Gy and about 100 Gy, between about 10 Gy and about 90 Gy, between about 20 Gy and about 80 Gy, between about 30 Gy and about 70 Gy, or between about 40 Gy and about 60 Gy, in total (e.g., in total throughout the duration of the methods of treatment described herein). In one example, the external beam radiotherapy is administered in an amount of between about 40 Gy and about 70 Gy, in total (e.g., in total throughout the duration of the methods of treatment described herein). In one example, the external beam radiotherapy is

administered in an amount of between about 20 Gy and about 60 Gy, in total (e.g., in total throughout the duration of the methods of treatment described herein). In one example, the external beam radiotherapy is administered in an amount of between about 20 Gy and about 40 Gy, in total (e.g., in total throughout the duration of the methods of treatment described herein). In one example, the external beam radiotherapy is administered in an amount of between about 30 Gy and about 36 Gy, in total (e.g., in total throughout the duration of the methods of treatment described herein).

The methods of treatment described herein may provide for the administration of the external beam radiotherapy in any number of doses (or fractions) and at any suitable time so as to maximise the therapeutic efficacy of the combination treatment. That is, the external beam radiotherapy may be administered in any number of doses (or fractions) at any number of timepoints (e.g., days from commencement of treatment) so as to provide maximal therapeutic efficacy of the treatment. That is, selecting the number of doses (or fractions) of external beam radiotherapy administered, and the particular timepoints of administration of each dose (or fraction) throughout the duration of treatment, may further maximise the therapeutic efficacy of the combination treatment.

Accordingly, the methods of treatment described herein may involve the administration of the external beam radiotherapy as a single dose, or alternatively as more than one dose. In one example, the external beam radiotherapy is administered as a single dose. In one example, the external beam radiotherapy is administered as a single dose of between about 40 Gy and about 70 Gy. In one example, the external beam radiotherapy is administered as a single dose of about 60 Gy. In one example, the external beam radiotherapy is administered as a single dose of about 30 to 40 Gy.

In one example, the external beam radiotherapy is administered as five, 10, 15, 20, 25, 30, or more, doses (or fractions). Each dose may administer a substantially equal dose of radiation, or may administer a substantially unequal dose of radiation. In one example, the external beam radiotherapy is administered as five, 10, 15, 20, 25, 30, or more, substantially equal doses.

In some preferred embodiments, the external beam radiotherapy is administered as 30 substantially equal doses. In one example, the external beam radiotherapy is administered as 30 substantially equal doses of about 2.0 Gy (i.e., a total dose of external beam radiotherapy of 60 Gy). In one example, the external beam radiotherapy is administered as 20 substantially equal doses of about 3.0 Gy (i.e., a total dose of external beam radiotherapy of 60 Gy). In one example, the external beam radiotherapy is administered as 10 substantially equal doses of about 6.0 Gy (i.e., a total dose of external beam radiotherapy of 60 Gy). In one example, the external beam radiotherapy is administered as 5 substantially equal doses (fractions) of about 6.0 Gy (i.e., a total

dose of external beam radiotherapy of 30 Gy). In one example, the external beam radiotherapy is administered as 18 substantially equal doses (fractions) of about 2.0 Gy (i.e., a total dose of external beam radiotherapy of 36 Gy).

The methods of treatment described herein may involve the administration of a single dose of external beam radiotherapy being administered at any time point (e.g., days from commencement of treatment) throughout the duration of treatment. In the instance where administration of external beam radiotherapy does not commence on day one, it will be understood that administration of 4-*L*-[^{131}I]iodo-phenylalanine (in the instance of "di-combination therapy"), and 4-*L*-[^{131}I]iodo-phenylalanine or Temozolomide chemotherapy (in the instance of "tri-combination therapy"), will signify the commencement of the methods of treatment described herein (i.e., day one). In one example, a single dose of external beam radiotherapy is administered between day one and day 42, between day one and day 35, day one and day 28, day one and day 21, day one and day 14, or day one and day seven, from the commencement of the methods of treatment described herein.

In one example, a single dose (or fraction) of external beam radiotherapy is administered each day for the duration of the methods of treatment described herein. In instances where more than one dose (or fraction) of external beam radiation is administered, each dose of external beam radiation may be administered at any suitable timepoint throughout the duration of treatment. For example, these multiple doses of external beam radiation may be spaced substantially evenly (i.e., at regular time intervals) throughout the duration of treatment.

In one example, the external beam radiation is administered as 10 substantially equal doses spaced substantially evenly throughout the duration of treatment. In one example, the external beam radiation is administered as 20 substantially equal doses spaced substantially evenly throughout the duration of treatment. In one example, the external beam radiation is administered as 30 substantially equal doses spaced substantially evenly throughout the duration of treatment. In one example, the external beam radiation is administered as 30 substantially equal doses of about 2.0 Gy spaced substantially evenly throughout the duration of treatment.

In some preferred embodiments, the methods of treatment described herein include the administration of external beam radiation for a duration of 42 days (e.g., six weeks) from the commencement of treatment. In one example, the external beam radiation is administered in an amount of about 60 Gy for a duration of about 42 days (e.g., six weeks) from commencement of treatment. In one example, the external beam radiation is administered in an amount of about 60 Gy as 30 substantially equal doses spaced substantially evenly throughout a duration of 42 days (e.g., six weeks) from the commencement of treatment. In one example, the external beam radiation is administered in an amount of about 60 Gy as 30 substantially equal doses of about

2.0 Gy spaced substantially evenly throughout a duration of 42 days (e.g., six weeks) from the commencement of treatment.

In some preferred embodiments, the methods of treatment described herein include the administration of 4-*L*-[^{131}I]iodo-phenylalanine as a first dose prior to commencement of external beam radiotherapy, and at least one subsequent dose after completion (e.g., cessation) of external beam radiotherapy. In one example, the first dose of 4-*L*-[^{131}I]iodo-phenylalanine is about 4.0 GBq. In one example, the at least one subsequent dose of 4-*L*-[^{131}I]iodo-phenylalanine is about 2.0 GBq.

In some embodiments, the methods of treatment described herein include the administration of the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine prior to commencement of external beam radiotherapy. In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered in parallel with external beam radiotherapy. In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered prior to commencement of and after completion (e.g., cessation) of external beam radiotherapy. In other words, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine may be administered sequentially with external beam radiotherapy. In some embodiments, the total dose of 4-*L*-[^{131}I]iodo-phenylalanine is at least about 1 GBq, at least about 2 GBq, at least about 3 GBq, at least about 4 GBq, at least about 5 GBq, at least about 6 GBq, at least about 7 GBq, at least about 8 GBq, at least about 9 GBq, at least about 10 GBq, at least about 11 GBq, at least about 12 GBq, at least about 13 GBq, at least about 14 GBq, at least about 15 GBq, at least about 15 GBq, at least about 16 GBq, at least about 17 GBq, at least about 18 GBq, at least about 19 GBq, or at least about 20 GBq. In some embodiments, the total dose of 4-*L*-[^{131}I]iodo-phenylalanine is between about 0.5 GBq and about 20 GBq, between about 1.0 GBq and about 18 GBq, between about 2.0 GBq and about 16 GBq, between about 2.0 GBq and about 12 GBq, between about 2.0 GBq and about 10 GBq, between about 2.0 GBq and about 6.0 GBq, between about 4.0 GBq and about 14 GBq, or between about 8.0 GBq and about 12 GBq. In one example, the total dose of 4-*L*-[^{131}I]iodo-phenylalanine is between about 2.0 GBq and about 18 GBq. In one example, the total dose of 4-*L*-[^{131}I]iodo-phenylalanine is between about 2.0 GBq and about 8.0 GBq. In some examples of the methods described herein, the total dose of 4-*L*-[^{131}I]iodo-phenylalanine is between about 2.0 GBq and about 12 GBq, between about 2.0 GBq and about 10 GBq, between about 2.0 GBq and about 8.0 GBq, or between about 2.0 GBq and about 6.0 GBq.

In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered prior to commencement of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered several minutes, hours, days or weeks (e.g., 0-10 days) prior to commencement of external beam radiotherapy. In some

embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered in parallel or sequentially with external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered several minutes, hours, days or weeks (e.g., 0-10 days) prior to commencement of external beam radiotherapy, and a further one or more doses are administered in parallel or sequentially with external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered in parallel or sequentially with external beam radiotherapy within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered several minutes, hours, days or weeks (e.g., 0-10 days) prior to commencement of external beam radiotherapy, and a further one or more doses are administered in parallel or sequentially with external beam radiotherapy within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose.

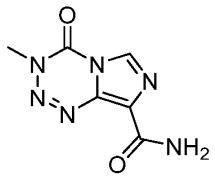
In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered in parallel with external beam radiotherapy. That is, the one or more doses of 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy may be administered, for example, on the same day or within the same suitable time interval during the treatment period. For example, the one or more doses of 4-*L*-[^{131}I]iodo-phenylalanine may be administered within some hours after administration of external beam radiotherapy. In such parallel administration, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy may be administered at any suitable time intervals, such as e.g. every 1-10 days, throughout the treatment period. In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy are administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine. In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy are administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the commencement of the methods of treatment described herein.

In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered prior to commencement of and/or after completion (e.g., cessation) of external beam radiotherapy. In other words, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine may be administered sequentially with external beam radiotherapy. For example, in some embodiments,

the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered after completion (e.g., cessation) of external beam radiotherapy. For example, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine may be administered several minutes, hours, days or weeks (e.g., 0-10 days) after the completion (e.g., cessation) of external beam radiotherapy. In some embodiments, the one or more doses of the 4-*L*-[^{131}I]iodo-phenylalanine are administered within one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks after the completion (e.g., cessation) of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered after completion (e.g., cessation) of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered within several minutes, hours, days or weeks (e.g., 0-10 days) after the completion (e.g., cessation) of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered several minutes, hours, days or weeks (e.g., 0-10 days) prior to commencement of external beam radiotherapy, and a further one or more doses are administered within several minutes, hours, days or weeks (e.g., 0-10 days) after the completion (e.g., cessation) of external beam radiotherapy. In some embodiments, a first dose of the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy, and a further one or more doses are administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks after the completion (e.g., cessation) of external beam radiotherapy.

Temozolomide

Temozolomide, sold under the trade names Temodar®, Temodal®, Temcad®, and others, is a front-line therapy for the treatment of glioblastoma, having the structure:



Temozolomide.

In some embodiments, the Temozolomide is administered in an amount sufficient to treat the glioblastoma when administered in combination with 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy (i.e., “tri-combination therapy”).

The methods of treatment described herein may provide for the administration of the Temozolomide in any number of doses and at any suitable time so as to maximise the therapeutic efficacy of the combination treatment. Typically, the Temozolomide is administered daily throughout the duration of the methods of treatment described herein. In one example, the Temozolomide is administered daily.

The Temozolomide may be administered daily for a duration of one day, seven days, 14 days, 21 days, 28 days, 35 days, 42 days, or more, from the commencement of treatment. In one example, the Temozolomide is administered daily for a duration of about 42 days (e.g., six weeks) from the commencement of treatment.

In some embodiments, the Temozolomide is administered in an amount of at least about 10 mg/m^2, at least about 25 mg/m^2, at least about 50 mg/m^2, at least about 75 mg/m^2, at least about 100 mg/m^2, at least about 125 mg/m^2, at least about 150 mg/m^2, at least about 175 mg/m^2, at least about 200 mg/m^2, at least about 250 mg/m^2, or at least about 300 mg/m^2, per day. In some embodiments, the Temozolomide is administered in an amount of less than about 300 mg/m^2, less than about 250 mg/m^2, less than about 200 mg/m^2, less than about 150 mg/m^2, less than about 100 mg/m^2, less than about 75 mg/m^2, less than about 50 mg/m^2, or less than about 25 mg/m^2, per day. In some embodiments, the Temozolomide is administered in an amount of about 50 mg/m^2, about 75 mg/m^2, about 100 mg/m^2, about 125 mg/m^2, about 150 mg/m^2, about 175 mg/m^2, about 200 mg/m^2, about 250 mg/m^2, or about 300 mg/m^2, per day. In some embodiments, the Temozolomide is administered in an amount of between about 25 mg/m^2 and about 300 mg/m^2, between about 50 mg/m^2 and about 250 mg/m^2, or between about 50 mg/m^2 and about 200 mg/m^2, per day. In one example, the Temozolomide is administered in an amount of between about 50 mg/m^2 and about 200 mg/m^2, per day.

In some preferred embodiments, the methods of treatment described herein include the administration of Temozolomide daily for a duration of 42 days (e.g., six weeks) from the commencement of treatment. In one example, the Temozolomide is administered in an amount of between about 75 mg/m^2 and about 200 mg/m^2, per day, for a duration of about 42 days (e.g., six weeks) from commencement of treatment. In one example, the Temozolomide is administered in an amount of about 75 mg/m^2, per day, for a duration of about 42 days (e.g., six weeks) from commencement of treatment.

In the methods of treatment described herein, Temozolomide administration may cease after a certain period of time. Typically, completion (e.g., cessation) of Temozolomide administration coincides with the completion (e.g., cessation) of 4-*L*-[^{131}I]iodo-phenylalanine administration and/or external beam radiotherapy treatment.

In one example, Temozolomide administration is ceased after 42 days (e.g., six weeks) from commencement of treatment. In this instance, the 42 days from commencement of treatment may be referred to as the "initial phase" of treatment. Following completion (e.g., cessation) of Temozolomide administration, an assessment may be made as to whether to provide the patient with a maintenance dose of Temozolomide, and at what particular dose and suitable time (e.g., interval). In one example, the methods of treatment described herein further include the step of administering Temozolamide as a maintenance dose during a period in which the patient is not receiving the combined 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy treatment.

In one example, the maintenance dose of Temozolamide includes the administration of a single dose of Temozolomide. In one example, the maintenance dose of Temozolamide includes the administration of a two or more doses of Temozolomide. In some embodiments, the maintenance dose of Temozolomide includes the administration of two, three, four, five, six, seven, eight, or more doses of Temozolomide. In one example, the maintenance dose of Temozolomide includes the administration of six doses of Temozolomide.

The amount of Temozolomide administered as part of the maintenance dose may be the same as the dosage administered during the initial phase of the methods of treatment described herein (i.e., "tri-combination therapy"). Alternatively, the amount of Temozolomide administered as part of the maintenance dose may differ to the dosage administered during the initial phase of the methods of treatment described herein (i.e., "tri-combination therapy"). In one example, the amount of Temozolomide administered as the maintenance dose is about 50 mg/m^2, about 75 mg/m^2, about 100 mg/m^2, about 125 mg/m^2, about 150 mg/m^2, about 175 mg/m^2, about 200 mg/m^2, about 225 mg/m^2, or about 250 mg/m^2, per day. In one example, the amount of Temozolomide administered as the maintenance dose is about 150 mg/m^2, per day. In one example, the amount of Temozolomide administered as the maintenance dose is about 175 mg/m^2, per day. In one example, the amount of Temozolomide administered as the maintenance dose is about 200 mg/m^2, per day. In one example, the amount of Temozolomide administered as the maintenance dose is between about 50 mg/m^2 and about 300 mg/m^2, per day. In one example, the amount of Temozolomide administered as the maintenance dose is between about 150 mg/m^2 and about 200 mg/m^2, per day.

In one example, the maintenance dose of Temozolomide is administered from about 42 days (e.g., six weeks), from the commencement of treatment (i.e., immediately following the initial phase of treatment). In some embodiments, the maintenance dose of Temozolomide is administered for a period of about one, about two, about three, about four, about six, about eight, about 10, about 12, or more, weeks. In some embodiments, the maintenance dose of Temozolomide is administered for a period of between about one and about 12 weeks, between

about two and about 12 weeks, between about four and about 12 weeks, or between about six and about 12 weeks. In one example, the maintenance dose of Temozolomide is administered for a period of about one week. In one example, the maintenance dose of Temozolomide is administered for a period of about two weeks. In one example, the maintenance dose of Temozolomide is administered for a period of about three weeks. In one example, the maintenance dose of Temozolomide is administered for a period of about four weeks. In one example, the maintenance dose of Temozolomide is administered for a period of about 12 weeks. In one example, the maintenance dose of Temozolomide is administered for a period of between about one and about 12 weeks.

In embodiments where the Temozolomide is administered in combination with 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy (i.e., "tri-combination therapy"), the methods described herein comprise administering the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and Temozolomide chemotherapy throughout the same treatment period. That is, the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optional Temozolomide chemotherapy may each be administered at any suitable time (e.g., interval) throughout the same treatment period, which will be considered to qualify as being administered in combination.

In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered, in combination with external beam radiotherapy and Temozolomide chemotherapy, as a single dose, on day zero, one, two, three, four, five, six, seven, or more, from commencement of the methods of treatment described herein.

In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered, in combination with external beam radiotherapy and Temozolomide chemotherapy, as more than one dose at any two or more timepoints (e.g, days from commencement of treatment) throughout the duration of treatment. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as more than one dose, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a further dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as more than one dose, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as three substantially equal doses, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks,

nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as four substantially equal doses, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as five substantially equal doses, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as six substantially equal doses, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as multiple substantially equal doses, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered as multiple substantially equal doses, and the first dose is administered on day one from commencement of the methods of treatment described herein, and a final dose is administered within about one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, or ten weeks of the first dose, with each dose administered at regular intervals over the treatment period.

In some embodiments, the total dose of 4-*L*-[^{131}I]iodo-phenylalanine, administered in combination with external beam radiotherapy and Temozolomide chemotherapy, is at least about 1 GBq, at least about 2 GBq, at least about 3 GBq, at least about 4 GBq, at least about 5 GBq, at least about 6 GBq, at least about 7 GBq, at least about 8 GBq, at least about 9 GBq, at least about 10 GBq, at least about 11 GBq, at least about 12 GBq, at least about 13 GBq, at least about 14 GBq, at least about 15 GBq, at least about 15 GBq, at least about 16 GBq, at least about 17 GBq, at least about 18 GBq, at least about 19 GBq, or at least about 20 GBq. In some embodiments, the total dose of 4-*L*-[^{131}I]iodo-phenylalanine is between about 0.5 GBq and about 20 GBq, between about 1.0 GBq and about 18 GBq, between about 2.0 GBq and about 16 GBq, between about 2.0 GBq and about 12 GBq, between about 2.0 GBq and about 10 GBq, between about 2.0 GBq and about 6.0 GBq, between about 4.0 GBq and about 14 GBq, or between about 8.0 GBq and about 12 GBq. In one example, the total dose of 4-*L*-[^{131}I]iodo-phenylalanine is between about 2.0 GBq and about 18 GBq. In one example, the total dose of 4-*L*-[^{131}I]iodo-phenylalanine

is between about 2.0 GBq and about 8.0 GBq. In some examples of the methods described herein, the total dose of 4-*L*-[^{131}I]iodo-phenylalanine is between about 2.0 GBq and about 12 GBq, between about 2.0 GBq and about 10 GBq, between about 2.0 GBq and about 8.0 GBq, or between about 2.0 GBq and about 6.0 GBq.

Treatment Regimen

The methods of treatment described herein comprise administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and optionally Temozolomide. That is, in some embodiments, the methods of treatment described herein comprise administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy (i.e., "di-combination therapy"). In some other embodiments, the methods of treatment described herein comprise administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolomide chemotherapy and external beam radiotherapy (i.e., "tri-combination therapy").

The phrase "in combination with" will be taken to mean that the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide chemotherapy are administered to the patient throughout the same treatment period.

As discussed above, when the methods of treatment described herein comprise the administration of the "di-combination therapy", "in combination with" will be taken to mean that the 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy are administered to the patient throughout the same treatment period. Also as discussed above, when the methods of treatment described herein comprise the administration of the "tri-combination therapy", "in combination with" will be taken to mean that the 4-*L*-[^{131}I]iodo-phenylalanine, Temozolomide chemotherapy, and external beam radiotherapy are administered to the patient throughout the same treatment period.

Throughout administration of either of the "di-combination therapy" or the "tri-combination therapy", it is not necessary for each of the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide chemotherapy to be co-administered or simultaneously administered, at the same point in time (e.g., within the same day/hour/minute), to the patient. Accordingly, in one example, the method described herein comprises administering the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide chemotherapy throughout the same treatment period. That is, the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optional Temozolomide chemotherapy may each be administered at any suitable time (e.g., interval) throughout the same treatment period, which will be considered to qualify as being administered in combination.

The treatment period will be considered to commence upon the administration of any one of the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optional Temozolomide chemotherapy. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is administered on day one of treatment, and may signify the commencement of the treatment period (for either of the "di-combination therapy" or "tri-combination therapy"). In one example, Temozolomide chemotherapy is administered on day one of treatment, and may signify the commencement of the treatment period (for the "tri-combination therapy"). In one example, external beam radiotherapy is administered on day one of treatment, and may signify the commencement of the treatment period (for the "di-combination therapy" or the "tri-combination therapy").

The treatment period may be any suitable duration, as determined by the person skilled in the art, so as to treat the glioblastoma. In some embodiments, the treatment period is between about one and about 52 weeks, between about one and about 36 weeks, between about one and about 24 weeks, between about one and about 24 weeks, between about one and about 12 weeks, or between about one and about six weeks in duration. In some embodiments, the treatment period is at least about one week, at least about two weeks, at least about four weeks, at least about six weeks, at least about 12 weeks, at least about 24 weeks, at least about 36 weeks, or at least about 48 weeks in duration. In some embodiments, the treatment period is less than about 52 weeks, less than about 48 weeks, less than about 36 weeks, less than about 24 weeks, less than about 12 weeks, or less than about six weeks in duration. In one example, the treatment period is about six weeks in duration.

In one example, the treatment period further comprises a maintenance period. The maintenance period may be any suitable duration, as determined by the person skilled in the art, so as to maintain treatment of the glioblastoma. In some embodiments, the maintenance period is between about one and about 52 weeks, between about one and about 36 weeks, between about one and about 24 weeks, between about one and about 24 weeks, between about one and about 12 weeks, or between about one and about six weeks in duration. In some embodiments, the maintenance period is at least about one week, at least about two weeks, at least about four weeks, at least about six weeks, at least about 12 weeks, at least about 24 weeks, at least about 36 weeks, or at least about 48 weeks in duration. In some embodiments, the maintenance period is less than about 52 weeks, less than about 48 weeks, less than about 36 weeks, less than about 24 weeks, less than about 12 weeks, or less than about six weeks in duration. In one example, the maintenance period is about 12 weeks in duration.

In one example, the maintenance period commences immediately after the completion (e.g., cessation) of the treatment period. In one example, the methods of treatment described

herein comprise an initial treatment period of about six weeks in duration, followed immediately by a maintenance period of about 12 weeks in duration.

In some embodiments, any one of the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide chemotherapy is commenced on day one of the treatment period. In one example, 4-*L*-[^{131}I]iodo-phenylalanine is commenced on day one of the treatment period. In one example, external beam radiotherapy is commenced on day one of the treatment period. In one example, Temozolomide chemotherapy is commenced on day one of the treatment period. In some embodiments, any combination of the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide chemotherapy is commenced on day one of the treatment period. In one example, 4-*L*-[^{131}I]iodo-phenylalanine and Temozolomide chemotherapy are each commenced on day one of the treatment period (for "tri-combination therapy"). In one example, 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy are each commenced on day one of the treatment period (for "di-combination therapy" or "tri-combination therapy"). In one example, Temozolomide chemotherapy and external beam radiotherapy are commenced on day one of the treatment period (for "tri-combination therapy"). In one example, 4-*L*-[^{131}I]iodo-phenylalanine, Temozolomide chemotherapy, and external beam radiotherapy are each commenced on day one of the treatment period (for "tri-combination therapy").

Following commencement of the treatment period, each of the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide chemotherapy may be administered to the patient at any suitable time (e.g., interval) for the duration of the treatment period as determined by the person skilled in the art. In one example, each of the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide chemotherapy are administered to the patient on the same day(s) of the treatment period. In one example, each of the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide chemotherapy are administered to the patient on different (e.g., staggered) day(s) of the treatment period. Purely by way of example, the 4-*L*-[^{131}I]iodo-phenylalanine may be administered on day one, and external beam radiotherapy may be administered on day two of the treatment period (for "di-combination therapy"). Similarly, and purely by way of example, the 4-*L*-[^{131}I]iodo-phenylalanine may be administered on day one, the Temozolomide chemotherapy may be administered on day two, and external beam radiotherapy may be administered on day three of the treatment period (for "tri-combination therapy").

The pattern of administration of each of the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide chemotherapy, being the interval dosing regimen, may remain consistent throughout the treatment period. For example, administration of each of the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide

chemotherapy may occur every one, two, three, four, five, six, seven, or more days throughout the treatment period for the duration of treatment. Alternatively, the pattern of administration of each of the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide chemotherapy, being the interval dosing regimen, may be varied throughout the treatment period (e.g., irregular dosing intervals).

Just as it is not necessary for the administration of each of the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide chemotherapy to commence on the same day of the treatment period, it is not necessary for the administration of each of the 4-*L*-[^{131}I]iodo-phenylalanine, external beam radiotherapy and optionally Temozolomide chemotherapy to conclude on the same day of the treatment period. Purely by way of example, administration of the 4-*L*-[^{131}I]iodo-phenylalanine may conclude during week 4 of the treatment period, and administration of the external beam radiotherapy may conclude during week 5 of the treatment period (for "di-combination therapy"). Similarly, and purely by way of example, administration of the 4-*L*-[^{131}I]iodo-phenylalanine may conclude during week 4 of the treatment period, administration of the Temozolomide chemotherapy may conclude during week 5 of the treatment period, and administration of the external beam radiotherapy may conclude during week 6 of the treatment period (for "tri-combination therapy"). Regardless, such treatment will be considered as being in combination throughout the treatment period.

Patient Population

The methods of treatment described herein may be administered to a patient that has been diagnosed with glioblastoma through any conventional means as would be understood by the person skilled in the art. For example, the patient may have been diagnosed with glioblastoma through any one or more of a computed tomography (CT) scan, a magnetic resonance imaging (MRI) scan, or tissue biopsy. In one example, the patient has been diagnosed with glioblastoma through a CT scan. In one example, the patient has been diagnosed with glioblastoma through an MRI scan. In one example, the patient has been diagnosed with glioblastoma through a tissue biopsy.

The methods of treatment described herein may be administered to a patient suffering from any form of glioblastoma (e.g., primary or secondary). Primary glioblastoma is the most common form of glioblastoma, and is also acknowledged as the most aggressive form. In one example, the method of treatment described herein is administered to a patient suffering from primary glioblastoma. Secondary glioblastoma is a less common form of glioblastoma, and is less aggressive due to its understood origination from lower-grade, less aggressive astrocytoma.

In one example, the method of treatment described herein is administered to a patient suffering from secondary glioblastoma.

The glioblastoma may be diagnosed as being located in any area of the patient's brain. That is, a glioblastoma may form in any lobe of the brain, most commonly the frontal lobe and temporal lobe, though even the brain stem and cerebellum. Similarly, the glioblastoma may not be localized to one particular area of the brain, and may instead be observed throughout two or more areas of the brain. In one example, the method of treatment described herein is administered to a patient diagnosed with glioblastoma primarily in the frontal lobe of the brain. In one example, the method of treatment described herein is administered to a patient diagnosed with glioblastoma primarily in the temporal lobe of the brain. In one example, the method of treatment described herein is administered to a patient diagnosed with glioblastoma primarily in the brain stem. In one example, the method of treatment described herein is administered to a patient diagnosed with glioblastoma primarily in the cerebellum. In one example, the method of treatment described herein is administered to a patient diagnosed with glioblastoma that is not primarily localized in the infratentorial compartment.

The diagnosed glioblastoma may be one tumour, or may instead be more than one tumour located within the brain and/or body. Where the glioblastoma is more than one tumour, it is understood that the distant tumour lesions are likely to have originated from the primary glioblastoma tumour. Such distant tumour lesions may be referred to as multifocal distant recurrence tumour lesions. In one example, the method of treatment described herein is administered to a patient that does not have multifocal distant recurrence tumour lesions.

The methods of treatment described herein may be administered to a patient of any particular age. In one example, the method of treatment described herein is administered to an adult patient (i.e., a patient of at least ($\geq$) 18 years of age). For example, the patient may be at least 18, at least 30, at least 40, at least 50, at least 60, at least 70, or at least 80 years of age. In one example, the patient is at least 18 years of age. In one example, the method of treatment described herein is administered to a non-adult patient (i.e., a patient less than ($<$) 18 years of age). In one example, the patient is less than 18 years of age. In one example, the method of treatment described herein is administered to a paediatric patient (i.e., a patient of less than ($<$) 12 years of age). In one example, the patient is less than 12 years of age.

The methods of treatment described herein may be administered to a male or female patient. In one example, the method of treatment described herein is administered to a male patient. In one example, the method of treatment described herein is administered to a female patient.

In embodiments, the methods of treatment described herein are intended to be administered to patients that have undergone prior surgical resection of the glioblastoma tumour. As would be understood by the person skilled in the art, surgical resection of the glioblastoma is a front-line treatment that involves the surgical removal (decompression) of the tumour. In one example, the method of treatment described herein is administered to a patient that has undergone surgical resection of the glioblastoma tumor. In one example, the method of treatment described herein is administered to a patient that has undergone maximal surgical resection of the glioblastoma tumor.

However, even maximal surgical resection is often unable to completely remove the glioblastoma tumour with any suitable margins from the brain tissue, meaning glioblastoma tumour cells will remain in the patient's brain. Due to this, following maximal surgical resection of the glioblastoma tumour, subsequent chemotherapy and/or radiotherapy is additionally required.

Accordingly, the methods of treatment described herein may be commenced at any desirable time following maximal surgical resection of the glioblastoma. In one example, the methods of treatment described herein are commenced immediately following maximal surgical resection of the glioblastoma. Alternatively, there may be a period of delay following maximal surgical resection prior to the methods of treatment described herein being commenced. This may allow, for example, for a patient to recover from the surgery. This period of delay may be, for example, one day, seven days, 10 days, 14 days (i.e., two weeks), 21 days (i.e., three weeks), 28 days (i.e., four week), 35 days (i.e., five weeks), 42 days (i.e., six weeks), 49 days (i.e., seven weeks), 56 days (i.e., eight weeks), 63 days (i.e., nine weeks), 70 days (i.e., 10 weeks), or more. In one example, the methods of treatment described herein are commenced within about 42 days following maximal surgical resection of the glioblastoma. In one example, the methods of treatment described herein are commenced within about 35 days following maximal surgical resection of the glioblastoma. In one example, the methods of treatment described herein are commenced within about 28 days following maximal surgical resection of the glioblastoma. In one example, the methods of treatment described herein are commenced within about 21 days following maximal surgical resection of the glioblastoma. In one example, the methods of treatment described herein are commenced within about 14 days following maximal surgical resection of the glioblastoma. Similarly, the period of delay may be, for example, between about one day and about 70 days, between about seven days and about 56 days, or between about 14 days and about 42 days. In one example, the methods of treatment described herein commence within about 14 days to about 42 days following maximal surgical resection of the glioblastoma.

The methods of treatment described herein may be administered to a patient that has not received prior chemotherapy for the diagnosed glioblastoma. In this instance, the patient may have previously received chemotherapy for another medical reason, including the treatment of a cancerous tumour, but not for the currently specifically diagnosed glioblastoma. That is, the patient has not previously received chemotherapeutics for the treatment of the currently specifically diagnosed glioblastoma. In one example, the method of treatment described herein is administered to a patient that has not received prior chemotherapy for the currently specifically diagnosed glioblastoma. Such prior chemotherapeutic treatment may include any chemotherapeutic indicated in the treatment of glioblastoma such as, for example, Temozolomide, Carmustine, Bevacizumab, and Lomustine. In one example, the patient has not previously received prior chemotherapy being Temozolomide. In one example, the patient has not previously received prior chemotherapy being Carmustine. In one example, the patient has not previously received prior chemotherapy being Bevacizumab. In one example, the patient has not previously received prior chemotherapy being Lomustine.

Similarly, the methods of treatment described herein may be administered to a patient that has not received prior radiotherapy for the currently specifically diagnosed glioblastoma. In this instance, the patient may have previously received radiotherapy for another medical reason, including the treatment of a cancerous tumour, but not for this currently specifically diagnosed glioblastoma. That is, the patient has not previously received radiotherapy for the treatment of the currently specifically diagnosed glioblastoma. In one example, the method of treatment described herein is administered to a patient that has not received prior radiotherapy for the currently specifically diagnosed glioblastoma.

Efficacy

As would be understood by the person skilled in the art, numerous adverse events, or side effects, may be observed during treatment of various cancers with chemotherapy and/or radiotherapy. These side effects are typically due to systemic toxicity such as hematologic toxicity, neurological toxicity, cardiotoxicity, hepatotoxicity, nephrotoxicity, ototoxicity, and gastrointestinal toxicity. Such side effects include, but are not limited to, diarrhoea, myelosuppression, neutropenia, neutropenic fever, neutropenic infection, leukopenia, thrombocytopenia, lymphopenia, hypersensitivity, renal impairment, renal failure, pulmonary toxicity (dyspnea, cough, pneumonia, interstitial lung disease), teratogenicity, nausea, vomiting, dehydration, abdominal pain, septic shock, constipation, anorexia, mucositis, anemia, asthenia, pain, fever, infection, dizziness, somnolence, confusion, vasodilatation, hypotension, thromboembolic events, abnormal bilirubin, rash, alopecia, and decreasing body weight.

The methods of treatment described herein may provide for a reduction in one or more adverse events in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy alone.

The toxicity of a drug refers to the degree to which damage is caused to the organism and is measured by its effect off-target. In oncology, one such measurement of toxicity in animal models is weight loss, which can determine the maximum tolerated dose (MTD). In humans, toxicity is commonly determined by specified adverse events (AE), which typically identify the dose limiting toxicity. It will be appreciated that usually in oncology, there is a narrow therapeutic window and off-target toxicities are considered a normal side effect of killing tumour cells. In some embodiments, the methods of treatment described herein provide for a reduction in toxicity in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy. In some embodiments, the methods of treatment described herein provide for a reduction in toxicity, as measured by the number of patients in which a specific adverse event is observed, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy.

In some embodiments, the methods of treatment described herein provide for a reduction in an observed adverse event of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts. In some embodiments, the methods of treatment described herein provide for a reduction in the severity of an observed adverse event in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, of the patient population, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts.

In one example, the methods of treatment described herein provide for a reduction in an observed adverse event of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, wherein the adverse event is selected from the group consisting of diarrhoea, myelosuppression, neutropenia, neutropenic fever, neutropenic infection, leukopenia, thrombocytopenia, lymphopenia, hypersensitivity, renal impairment, renal failure, pulmonary toxicity (dyspnea, cough, pneumonia, interstitial lung disease), teratogenicity, nausea, vomiting, dehydration, abdominal pain, septic shock, constipation, anorexia, mucositis, anemia, asthenia, pain, fever, infection, dizziness, somnolence, confusion, vasodilatation, hypotension, thromboembolic events, abnormal bilirubin, rash, alopecia, and decreasing body weight.

In one example, the methods of treatment described herein provide for a reduction in the severity of an observed adverse event in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, of the patient population, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, wherein the adverse event is selected from the group consisting of diarrhea, myelosuppression, neutropenia, neutropenic fever, neutropenic infection, leukopenia, thrombocytopenia, lymphopenia, hypersensitivity, renal impairment, renal failure, pulmonary toxicity (dyspnea, cough, pneumonia, interstitial lung disease), teratogenicity, nausea, vomiting, dehydration, abdominal pain, septic shock, constipation, anorexia, mucositis, anemia, asthenia, pain, fever, infection, dizziness, somnolence, confusion, vasodilatation, hypotension, thromboembolic events, abnormal bilirubin, rash, alopecia, and decreasing body weight.

In one example, the methods of treatment described herein provide for a reduction in an observed adverse event of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, wherein the adverse event is selected from the group consisting of haematological toxicity, inflammation-induced intracranial hypertension, fatigue, thrombocytopenia, weight loss, diarrhea, and headache.

In one example, the methods of treatment described herein provide for a reduction in the severity of an observed adverse event in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, of the patient population, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, wherein the adverse event is selected from the group consisting of haematological toxicity, inflammation-induced intracranial hypertension, fatigue, thrombocytopenia, weight loss, diarrhea, and headache.

In one example, the methods of treatment described herein provide for a reduction in haematological toxicity in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, of the patient population, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, or in comparison to the administration of external beam radiotherapy and, in substantially equivalent amounts. In one example, the methods of treatment described herein provide for a reduction in haematological toxicity of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts.

In one example, the methods of treatment described herein provide for a reduction in inflammation-induced intracranial hypertension in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, of the patient population, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts. In one example, the methods of treatment described herein provide for a reduction in inflammation-induced intracranial hypertension of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts.

In one example, the methods of treatment described herein provide for a reduction in fatigue in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, of the patient population, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts. In one example, the methods of treatment described herein provide for a reduction in fatigue of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts.

In one example, the methods of treatment described herein provide for a reduction in thrombocytopenia in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, of the patient population, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts. In one example, the methods of treatment described herein provide for a reduction in thrombocytopenia of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts.

In one example, the methods of treatment described herein provide for a reduction in weight loss in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, of the patient population, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts. In one example, the methods of treatment described herein provide for a reduction in weight loss of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts.

In one example, the methods of treatment described herein provide for a reduction in diarrhea in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, of the patient population, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts. In one example, the methods of treatment described herein provide for a reduction in diarrhea of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts.

In one example, the methods of treatment described herein provide for a reduction in headache severity and/or incidence in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, of the patient population, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts. In one example, the methods of treatment described herein provide for a reduction in headache of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, in comparison to the administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts.

In some embodiments, the methods of treatment described herein provide enhanced clinical efficacy in comparison to administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts. In some embodiments, the methods of treatment described herein provide an improved efficacy property selected from the group consisting of progression free survival, time to progression, objective response rate (PR + CR), overall response rate, overall survival, and duration of response, in comparison to administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts.

As would be understood by the person skilled in the art, both progression free survival and overall survival may be measured at any suitable end-point. In some embodiments, progression free survival is measured at 10 months, 12 months, 18 months, 24 months, 36 months, 48 months, or 60 months, following commencement of the methods of treatment described herein. Similarly, in some embodiments, overall survival is measured at 10 months, 12 months, 18 months, 24 months, 36 months, 48 months, or 60 months, following commencement of the methods of treatment described herein.

In some embodiments, the methods of treatment described herein provide for an increase in progression free survival of the patient in comparison to administration of external beam

radiotherapy and/or Temozolomide chemotherapy alone. In some embodiments, the methods of treatment described herein provide for an increase in progression free survival of the patient by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, in comparison to administration of external beam radiotherapy and/or Temozolomide chemotherapy alone. In some embodiments, the methods of treatment described herein provide for an increase in progression free survival of the patient in comparison to administration of external beam radiotherapy and/or Temozolomide chemotherapy when measured at 12 months following commencement of the methods of treatment described herein. In some embodiments, the methods of treatment described herein provide for an increase in progression free survival of the patient by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, in comparison to administration of external beam radiotherapy and/or Temozolomide chemotherapy, in substantially equivalent amounts, when measured at 12 months following commencement of the methods of treatment described herein.

In some embodiments, the methods of treatment described herein provide for an increase in overall survival of the patient in comparison to administration of external beam radiotherapy and/or Temozolomide chemotherapy alone, in substantially equivalent amounts, when measured at 12 months following commencement of the methods of treatment described herein. In some embodiments, the methods of treatment described herein provide for an increase in overall survival of the patient by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, in comparison to administration of external beam radiotherapy and/or Temozolomide chemotherapy alone, in substantially equivalent amounts, when measured at 12 months following commencement of the methods of treatment described herein.

In some embodiments, the methods of treatment described herein provide for an increase in overall survival of the patient in comparison to administration of external beam radiotherapy and/or Temozolomide chemotherapy alone, in substantially equivalent amounts, when measured at 24 months following commencement of the methods of treatment described herein. In some embodiments, the methods of treatment described herein provide for an increase in overall survival of the patient by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, in comparison to administration of external beam radiotherapy and/or Temozolomide chemotherapy alone, in substantially equivalent amounts, when measured at 24 months following commencement of the methods of treatment described herein.

Compositions

The methods of treatment described herein involve the administration of 4-*L*-[^{131}I]iodo-phenylalanine in any suitable formulation or composition. That is, the 4-*L*-[^{131}I]iodo-

phenylalanine is administered to a subject in the form of a suitable formulation or composition. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a composition. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a pharmaceutical composition.

Accordingly, the present disclosure also provides pharmaceutical formulations or compositions comprising 4-*L*-[^{131}I]iodo-phenylalanine or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, and optionally any other therapeutic ingredients, stabilisers, or the like. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not unduly deleterious to the recipient thereof. Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the present disclosure are listed in "Remington: The Science & Practice of Pharmacy", 19.sup.th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52.sup.nd ed., Medical Economics, Montvale, N.J. (1998), and in "Handbook of Pharmaceutical Excipients", Third Ed., Ed. A. H. Kibbe, Pharmaceutical Press, 2000.

The 4-*L*-[^{131}I]iodo-phenylalanine of the present disclosure may be formulated in compositions including those suitable for intranasal delivery, inhalation to the lung, by aerosol, or parenteral (including intraperitoneal, intravenous, subcutaneous, or intramuscular injection) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the 4-*L*-[^{131}I]iodo-phenylalanine into association with a carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by bringing the 4-*L*-[^{131}I]iodo-phenylalanine into association with a liquid carrier to form a solution or a suspension, or alternatively, bring the 4-*L*-[^{131}I]iodo-phenylalanine into association with formulation components suitable for forming a solid, optionally a particulate product, and then, if warranted, shaping the product into a desired delivery form.

In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine composition is formulated for parenteral delivery. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine composition is formulated for intravenous administration. For example, in one embodiment, the formulation may be a sterile, lyophilized composition that is suitable for reconstitution in an aqueous vehicle prior to injection (e.g., intravenous administration).

In some embodiments, a formulation suitable for parenteral administration conveniently comprises a sterile aqueous preparation of the 4-*L*-[^{131}I]iodo-phenylalanine, which may for example be formulated to be isotonic with the blood of the recipient. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine composition is formulated in a buffered solution. As would be understood by the person skilled in the art, a buffered solution is employed to maintain pH at a

largely consistent value such that it resists changes to pH upon exposure to strongly acidic and/or strongly basic environments.

In one example, the 4-*L*-[^{131}I]iodo-phenylalanine formulation comprises any one or more of ascorbic acid, sodium ascorbate, and ethanol. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine formulation comprises ascorbic acid. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine formulation comprises sodium ascorbate. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine formulation comprises ethanol. The formulation may be provided as a lyophilized powdered form for reconstitution in sterile water for injection. Alternatively, the formulation may be provided already reconstituted in sterile water for injection. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine formulation comprises sterile water for injection. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine formulation comprises any one or more of ascorbic acid, sodium ascorbate, ethanol, and water for injection.

In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine composition is provided as a 25 mL solution. In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine composition comprises at least about 2 mg, at least about 4 mg, at least about 6 mg, at least about 7 mg, at least about 8 mg, at least about 9 mg, at least about 10 mg, at least about 11 mg, at least about 12 mg, at least about 14 mg, at least about 16 mg, at least about 18 mg, or at last about 20 mg of 4-*L*-[^{131}I]iodo-phenylalanine composition per 25 mL solution. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine composition comprises an amount of between about 4 mg and about 16 mg 4-*L*-[^{131}I]iodo-phenylalanine per 25 mL solution. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine composition comprises an amount of between about 8 mg and about 12 mg 4-*L*-[^{131}I]iodo-phenylalanine per 25 mL solution.

In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is provided as a solution for injection, wherein each 25 mL of solution comprises between about 8 mg and about 12 mg 4-*L*-[^{131}I]iodo-phenylalanine, ascorbic acid, sodium ascorbate, ethanol, and water for injection. In one example, the 4-*L*-[^{131}I]iodo-phenylalanine is provided as a solution for injection, wherein each 25 mL of solution comprises between about 8 mg and about 12 mg 4-*L*-[^{131}I]iodo-phenylalanine, 272.5 mg ascorbic acid, 817.5 mg sodium ascorbate, about 2.8 mL ethanol, and water for injection.

In some embodiments, the 4-*L*-[^{131}I]iodo-phenylalanine composition is formulated for co-administration with Temozolomide. In this instance, the 4-*L*-[^{131}I]iodo-phenylalanine composition may be formulated for sequential co-administration with Temozolomide or may alternatively be formulated for simultaneous co-administration with Temozolomide (i.e., 4-*L*-[^{131}I]iodo-phenylalanine and Temozolomide are formulated in the same composition for single administration).

The present disclosure will now be described with reference to the following examples which illustrate some particular aspects of the present disclosure. However, it is to be understood that the particularity of the following description of the present disclosure is not to supersede the generality of the preceding description of the present disclosure.

EXAMPLES

Example 1: Safety and Efficacy Phase I/II Trial of 4-*L*-[^{131}I]iodo-phenylalanine in Combination with External Beam Radiotherapy in Patients with Recurrent Glioblastoma

Study Title

A Multi-centre, Open-label, Single-arm, Dose-finding Phase I/II Study to Evaluate Safety, Tolerability, Dosing Schedule, and Preliminary Efficacy of Carrier-added 4-L-[131I]Iodo-phenylalanine (131I-IPA), Administered as Single or Repetitive Injections in Patients With Recurrent Glioblastoma Multiforme (GBM), Concomitantly to Second Line External Radiation Therapy (XRT) ('IPAX-1').

Primary Objectives

The primary objectives of the trial were to evaluate the safety, tolerability, dosing schedule, and preliminary efficacy of 4-*L*-[^{131}I]iodo-phenylalanine in combination with second-line external beam radiotherapy in patients with recurrent glioblastoma.

Methodology

The study was conducted on 10 patients. A total of 10 patients have been dosed, and 8 have completed the protocol mandated end of study visit. The study was a multicenter, open-label, single-arm, dose-finding study.

In the study, patients received intravenous 4-*L*-[^{131}I]iodo-phenylalanine (also referred to as ^{131}I-IPA or [^{131}I]IPA) at a starting dose of 2 GBq, followed by dose escalation, concomitantly to second-line external beam radiotherapy, also referred to as external radiation therapy (XRT). The 4-*L*-[^{131}I]iodo-phenylalanine starting dose of 2 GBq was administered in one of three different dosing regimens:

1) single dose (one fraction, 1f; ^{131}I-IPA 2 GBq before XRT);

2) fractionated parallel dose (three fractions in parallel, 3Fp; three ^{131}I-IPA 670 MBq fractions in parallel with second-line XRT); and

3) fractionated sequential dose (three fractions in sequence, 3Fs; three ^{131}I-IPA 670 MBq fractions before and after XRT).

External beam radiotherapy was administered in 18 fractions of 2 Gy each. The optimal dosing regimen from the 2 GBq dose level was implemented during dose escalation. Dose escalation was performed in 2 GBq increments until maximum tolerated dose was achieved. Preliminary efficiacy was assessed via FET imaging: Metabolic tumor responses were determined using O-(2-[^{18}F]fluoroethyl)-l-tyrosine positron emission tomography, while single-photon emission computed tomography was used to guide [^{131}I]IPA tumor dosimetry.

Inclusion Criteria

Patients who met all of the following criteria at Screening were eligible to participate in the study:

1. Age ≥ 18 years.
2. Previously confirmed histological diagnosis of glioblastoma, with evidence of first occurrence.
3. History of glioblastoma standard therapy.
4. At least six months since termination of first-line external beam radiotherapy.
5. Pathologically increased amino acid tumour update shown by molecular imaging.
6. Current indication for repeat radiation.
7. Glioblastoma tumour volume of up to 4.8 cm diameter.

Dosage and Mode of Administration

The study determined the most suitable dose of 36 Gy is administered in 18 fractions of 2 Gy, concomitantly to second-line external beam radiotherapy.

All patients evaluated in the preliminary results received a similar total activity dose of about 2 GBq of 4-*L*-[^{131}I]iodo-phenylalanine, and the total injected activity doses were comparable for all groups. The mean total body effective doses were 150.67 ± 59.01 µSv/MBq in the 1f group, 165.00±49.12µSv/MBq in the 3Fp group, and 215.00 µSv/MBq in the one patient in the 3Fs group. The overall mean (±SD) was 166.00 ± 49.83µSv/MBq (see below Table).

Injected Activity (MBq) (mean±SD)	**Single dose 1f (n=4)**	**Fractionated dose 3f-parallel (n=3)**	**Fractionated dose 3f-sequential (n=1)**	**Total (N=8)**
Dose 1	1915.00 ± 63.41	661.00 ± 82.02	688.00 ±.NA	–
Dose 2	–	682.00 ± 81.07	688.00 ± NA	–
Dose 3	–	643.67 ± 63.09	696.00 ± NA	–

Overall Total	1915.00 ± 63.41	1986.67 ± 223.74	2072.00 ± NA	1968.14 ± 146.31

Results

The most frequent treatment-related adverse side effect that was observed in the study was fatigue, which occurred in three patients (37.5%), followed by diarrhea, decreased lymphocyte count, headache, and cerebral oedema, which all occurred in two patients each (25%). With the exception of cerebral oedema, all the adverse events had an intensity of grade 1 or grade 2.

It was found that injections of single or fractionated doses of 4-*L*-[^{131}I]iodo-phenylalanine containing a total activity of 2 GBq in combination with external beam radiotherapy in patients with recurrent glioblastoma were safe and well tolerated.

Further, it was found that overall survival of 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy combination treatment was 15.97 months, with three patients exhibiting stable disease at day 135, and two patients with stable disease at 6 months.

Conclusions

The results of the IPAX-1 study demonstrated a favourable safety profile and encouraging preliminary therapeutic effect of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy for the treatment of recurrent glioma. One of the major adverse events reported in this trial population was cerebral oedema. This adverse event is commonly associated with the use of radiation therapy and is normally managed by prophylactic administration of steroids, which should be considered prophylactically.

Example 2: Phase II Trial of 4-*L*-[^{131}I]iodo-phenylalanine in Combination with External Beam Radiotherapy in Patients with Recurrent High-Grade Gliomas, Including Glioblastoma Multiforme

Study Title

An open label, single arm monocentric phase II study to evaluate safety, tolerability, and preliminary efficacy of carrier-added 4-*L*-[131I]iodo-phenylalanine (131I-IPA), administered as sequential injections in patients with recurrent IDH1/2 high grade glioma (HGG) concomitantly to second line external beam radiation therapy ('IPAX-Linz')

Study Objectives

The primary objective of the study is to assess the safety and tolerability of intravenous 4-*L*-[^{131}I]iodo-phenylalanine administered concomitantly to external beam radiation therapy in recurrent high-grade gliomas (HGG), including glioblastoma multiforme (GBM).

The secondary objectives of the study are to measure the quality of life of patients before and after therapy; to assess response to the therapy using mRANO criteria; to determine Time to Progression and Progression free Survival; and to determine overall survival.

Inclusion Criteria

To participate in the study, patients must meet all of the following criteria:

1. Previously confirmed histological diagnosis of HGG IDH1/2 wildtype, with current clinical or imaging evidence for first or second recurrence according to modified RANO criteria (2017). History of standard therapy (debulking surgery, followed by radio-chemotherapy (50–60 Gy in 2 Gy fractions, temozolomide). Patients treated with radiotherapy alone in first line according to the elderly GBM protocol could also be included.
2. Interval since the end of first line external beam radiation therapy ≥6 months.
3. Amino acid based molecular imaging (preferably 18F-FET-PET) indicating pathologically increased amino acid uptake inside or in the vicinity of the tumour, clearly discernible from background activity. Surgery for relapsed tumour is allowed, if postoperative MRI and/or PET shows residual tumour in contrast enhanced MRI and/or 18 F-FET-PET. In recurrent tumours with no preceded surgery, MRI lesion with contrast enhancement is the target. The target in re-operated tumours is residual tumour in CE-MRI or 18F-FET PET with metabolic tumour residuum (TBR ≥ 2). Screening 18F-FET-PET is planned -14 to -1 days before start of therapy.
4. Current indication for repeat radiation therapy as discussed at the multidisciplinary neuro-oncological tumour board meeting.
5. Gross tumour volume (GTV) of up to 5 cm diameter, clinical target volume (CTV) 0.5 cm margin and planning target volume (PTV) ≤ 0.5 cm margin.
6. Male or female ≥18 years of age.
7. Karnofsky performance status (KPS) ≥70. Life expectancy of at least 16 weeks.
8. Haematological, liver and renal function test results as follows:
   - WBC: >3*109/L
   - Haemoglobin >80 g/L
   - PLT >100*109/L

- ALT, ALP, AST: ≤5 times upper international limit of normal (UILN)
- Bilirubin ≤3 times UILN
- Serum creatinine: within normal limits or <120 μmol/L for patients aged 60 years or older
- Urine protein dipstick: no protein.

9. Female patients surgically sterile or postmenopausal for at least 2 years. Participants of generative potential agreeing to use effective contraception during the period of therapy and 6 months after the end of study.
10. Written informed consent

Exclusion Criteria

A patient will be excluded from participation in the trial if one or more of the following criteria are met:

1. Primary external beam radiation therapy dose > 60 Gy.
2. Doses to organs at risk defined by Yasar and Tugrul (2005) exceeded or reached by prior radiation therapy; e.g. cumulative total dose on the optical chiasm >54 Gy for 2 Gy/fraction, $\alpha/\beta=2$
3. Multifocal distant recurrence, defined as tumour lesion outside the primary external beam radiation therapy field, as evidenced by amino acid based PET imaging or CE-MRI.
4. Prior treatment with brachytherapy or bevacizumab.
5. History or evidence of delayed-type hypersensitivity (DTH)-dependent chronic infection (e.g. tuberculosis, systemic fungal or parasitic infection), potentially exacerbating under systemic corticoid therapy.
6. Localisation of tumour related to brain stem or axis, unless sufficient reserve capacity (e.g. remnant resection cavity, marked atrophy) to accommodate possible post–procedural tissue reactions, or pre- therapeutic consent for emergency trepanation.
7. Haemostaseologic conditions, precluding catheterisation or invasive procedures.
8. Clinically significant illness or clinically relevant trauma within 2 weeks before the administration of the investigational product.
9. Known impairment of liver or kidney function or known liver or kidney disease, such as hepatitis, cirrhosis, renal failure.
10. Known human immunodeficiency virus positive serology or chronically active hepatitis B or C.

11. Ongoing toxicity > grade 2 NCI-CTC (version 4.03) from previous standard or investigational therapies.
12. Administration of another investigational medicinal product within 90 days prior to screening.
13. Expected non-compliance with longer-term admission at isolated nuclear medicine ward.
14. In pre-menopausal women: Pregnant as evidenced by a positive pregnancy test, or breast-feeding.
15. Patients with known phenylketonuria.

Methodology

Approximately 10 patients will be enrolled in the study, in accordance with the above inclusion/exclusion criteria. It is anticipated to recruit approximately 10 male or female patients ≥18 years old with previously diagnosed IDH1/2 wt HGG, who are scheduled for second line external beam radiation therapy, due to diagnosis of recurrence or progression of their disease.

Gross tumour volume (GTV) delineation will be made based on contrast-enhanced MRI and/or amino acid-based PET imaging (18F-FET). Clinical target volume (CTV) for external beam radiation therapy will be defined by adding a margin of 0.5 cm to the GTV.

4-*L*-[^{131}I]iodo-phenylalanine will be administered by intravenous injection(s). Dosage of intravenous 4-*L*-[^{131}I]iodo-phenylalanine for all patients is specified as sequential administration of a dose with 4 GBq before and 2 GBq after second line external beam radiation therapy, providing the cumulative dose of 6 GBq of 4-*L*-[^{131}I]iodo-phenylalanine.

Patients will be treated with fractionated external beam radiation therapy with distinct dosages and fraction sizes dependent on tumour volume. For tumours with low volume, defined as tumour diameter of up to 3 cm, application of a dosage of 30 Gy in 5 fractions is planned. For tumours with a diameter from > 3 to ≤ 5 cm FSRT will be performed with 36 Gy in 18 fractions.

The study flow chart is shown in the table below.

Examination/Evaluation	**Screening**	**Treatment**								**Follow Up**			
Time point	**BL**												
Day	**-14 to -1**	**0**	**1**						**End of RTX**	**Week 4 After RTX**	**3 monthly FU**	**Early withdrawal**	**EOS visit**
h*		pre dose	dose	post dose	24	48	72	96 (A)					
Informed Consent	X												
Review Inclusion/Exclusion criteria	X												
General													

Medical History/interim history	X								X	X	X	X
MGMT promoter methylation status	X											
Physical Exam	X								X	X	X	X
Vital Signs	X								X	X	X	X
Neurological exam (NANO status)	X								X	X	X	X
Haematology	X	X						X		X		
Serum Chemistry	X	X						X		X		
Urine analysis	X	X						X		X		
Pregnancy Test	X											
12-Lead ECG	X									X		
EORTC QLQ-C30/BN20	X									X	X	X
Concomitant Medications	X	X						X		X	X	X
Baseline findings/Adverse Events	X	X						X		X	X	X
Outcome imaging												
[^{18}F]-FET PET	X									X	X	X
MRI with contrast	X									X	X	X
Treatment & dosimetry imaging												
XRT, 2nd line								X				
^{131}I-IPA infusion sequential			X						X			
^{131}I-IPA Brain SPECT/SPECT-CT (B)					X				X			
^{131}I-IPA whole body planar imaging (C)				X	X	X	X	X				
Hospitalisation (D)		X	X	X	X	X	X	X	X			

(A) or earlier as possible due to local radiation safety regulations

(B) SPECT imaging at 24 hours p. inf. as far as feasible

(C) Whole body planar imaging at 0.5 (±0.25), 24, 48 (±8) & once 96 hours as far as feasible in line with local radiation safety regulations,

(D) as long as necessary dependent on local radiation safety regulations.

Safety and tolerability will be assessed by standard safety parameters (clinical monitoring, lab, ECG), and HRQOL questionnaires: EORTC QLQ-C30 & BN20 (brain tumour).

4-*L*-[^{131}I]iodo-phenylalanine tumour targeting and therapeutic dosimetry will be assessed by analysing tumour targeting and retention of 4-*L*-[^{131}I]iodo-phenylalanine using 3D SPECT/CT imaging, acquired at 24 hours post injection as far as feasible.

Efficacy will be assessed by:

- Morphological/functional imaging: Brain MRI contrast enhanced and 18F-FET-PET: baseline (BL), 4 weeks after end of radiotherapy (as reference imaging for RANO outcome assessment), thereafter 3-monthly f/u until progression or end of study (EOS), classified according to current mRANO criteria (2017).

- Survival, as determined by patient report, clinical and radiological observations.
- Functional performance, as determined by physical status, including vital signs and KPS; and standardised neurological status (NANO status).

The statistical analyses in this study will primarily be descriptive. Descriptive analyses will include:

- Mean, standard deviation, median and range for continuous variables,
- Median, range and frequency distribution for discrete (ordinal) variables,
- Frequency distribution for nominal variables.

Duration of Treatment and Study

Patients will participate in the study for 12 months.

Dosage and Mode of Administration of 4-L-[^{131}I]iodo-phenylalanine

4-*L*-[^{131}I]iodo-phenylalanine will be prepared by iodine exchange (carrier added; c.a.). 44-*L*-[^{131}I]iodo-phenylalanine will be formulated as a solution for injection in glass vials for single intravenous use. The 4-*L*-[^{131}I]iodo-phenylalanine therapeutic drug product will be manufactured as a "ready-to-use medicine". The composition of 4-*L*-[^{131}I]iodo-phenylalanine solution for injection will include the active pharmaceutical ingredient in a buffered solution without other excipients.

The composition of 4-*L*-[^{131}I]iodo-phenylalanine per 25 mL "ready for administration":

- 8-12 mg 4-*L*-[^{131}I]iodo-phenylalanine (excipient);
- 272.5 mg ascorbic acid (excipient);
- 817.5 mg sodium ascorbate (excipient);
- up to 2.8 mL ethanol (excipient but not part of diluent solution);
- made up to 25 mL with water for injection (excipient).

The final product will contain 667–6875 MBq 4-*L*-[^{131}I]iodo-phenylalanine (active substance) at the end of synthesis.

4-*L*-[^{131}I]iodo-phenylalanine will be provided in 25 mL solution (in one single vial) per batch ready for administration as and when needed.

Dose level of 4.0 GBq 4-*L*-[^{131}I]iodo-phenylalanine will be administered sequentially before and 2 GBq at the end of radiotherapy (cumulative dose 6 GBq). Unit doses of 4-*L*-[^{131}I]iodo-phenylalanine will be centrally provided for each scheduled administration sufficiently in advance (typically the day before planned administration). 4-*L*-[^{131}I]iodo-phenylalanine will

be administered as an intravenous short infusion using an intravenous cannula, placed into the cubital vein of the non-dominant arm.

Radiotherapy

Re-irradiation will be performed according to institutional standards with a fractionated scheme of 30 Gy in 5 fractions for low volumes (tumor diameter up to 3 cm). For tumours > 3 to ≤ 5 cm the radiation dose will be 36 Gy in 18 fractions. Target definition for re-irradiation will be performed using contrast-enhanced MRI scans that are co-registered with the planning CT scan and 18F-FET-PET scans. The gross tumour volume (GTV) will consist of the contrast-enhancing regions on T1 sequences of the MRI, in addition to high-uptake areas on the FET-PET scans. The planning target volume (PTV) will be derived from the GTV after the addition of 0.5 cm 3D margin around the GTV. As abnormalities on T2 sequences may be due to the previous treatment, these will not be included specifically in the target volume. Re-irradiation to the PTV will be delivered using the most conformal radiation technique to date, i.e. volumetric modulated arc therapy (VMAT, RapidArc, Varian Medical Systems).

Treatment planning will ensure the dose delivered to the PTV to be within the 95%–107% dose range, unless surrounding critical organs at risk such as optic apparatus or brainstem necessitate a local under-dosage. This will be reported specifically.

Example 3: Safety and Efficacy Trial of 4-*L*-[^{131}I]iodo-phenylalanine in Combination with Temozolomide Chemotherapy and External Beam Radiotherapy in Patients with Newly Diagnosed Glioblastoma

Primary Objectives

The primary objectives of the primary trial will be to i) determine the Maximum Tolerated Dose (MTD) of 4-*L*-[^{131}I]iodo-phenylalanine (also referred to as '^{131}I-TLX-101') in combination with standard of care treatment chemoradiation consisting of External Beam Radiation (XRT) and temozolomide (TMZ), and ii) determine the incidence of Treatment-emergent Adverse Events.

The primary objective of the secondary trial will be to i) determine the one-year overall survival rate of patients treated with ^{131}I-TLX-101 plus chemoradiation compared to chemoradiation only.

Methodology

An estimated 12-18 patients will be enrolled in the primary trial. It will be an open label, single-arm, randomized, parallel-group, multicenter dose finding study to evaluate ascending

radioactive dose levels of 4-*L*-[^{131}I] iodo-phenylalanine administered intravenously in combination with standard chemoradiation in newly diagnosed GBM patients.

Patients will be treated in cohorts according to a 3+3 study design with standard treatment consisting of external beam radiotherapy of 60 Gy/30 fractions for 6 weeks plus 75 mg/m^2 Temozolomide daily (chemoradiotherapy), followed by 4 weeks of treatment break. Patients will receive a maintenance treatment with 6 maintenance cycles of Temozolomide 150 mg/m^2 to 200 mg/m^2 on Days 1 to 5 q28, which can be continued up to 12 weeks at the discretion of the investigator. 4-*L*-[^{131}I] iodo-phenylalanine will be administered in 3 fractions corresponding to ⅓ full dose activity on Days 1, 7 and 14. Patients at the entry dose level of 6 GBq will undergo 4-*L*-[^{131}I] iodo-phenylalanine brain SPECT for tumour dosimetry, whole body planar imaging for determination of biodistribution and whole-body safety dosimetry.

Gross tumor volume (GTV) delineation will be made based on contrast-enhanced MRI and amino acid-based PET imaging (^{18}F-FET, using a uniform tumour segmentation algorithm across all sites) PET imaging may be performed using either PET/CT or PET/MRI systems. For external beam radiation, Clinical Target Volume (CTV) will be defined by adding a margin of 0.5 cm to the GTV.

Dose escalation will be made in steps of 2.0 GBq, i.e., 6.0 (3x2 GBq), 8.0 GBq (3x2.67 GBq), 10.0 GBq (3x3.33 GBq) and up to 12.0 GBq (3x4 GBq) until the maximum tolerated dose (MTD) is reached, using cohorts of N=3 patients. If maximum tolerated dose (MTD) has not been reached at 12.0 GBq, dose escalation may proceed, increasing the dose fractions to a total dose 4-*L*-[^{131}I] iodo-phenylalanine >12 GBq using cohorts of N=3 until MTD is reached or until a satisfactory antineoplastic efficacy is observed.

In the secondary trial, 32 patients will be treated with standard treatment consisting of radiotherapy of 60 Gy/30 fractions for 6 weeks plus 75 mg/m^2 Temozolomide daily (chemoradiotherapy), followed by 4 weeks of treatment break. Patients will receive a maintenance treatment with 6 maintenance cycles of Temozolomide 150 mg/m^2 to 200 mg/m^2 on Days 1 to 5 q28 which can be continued up to 12 weeks at the discretion of the investigator. 4-*L*-[^{131}I] iodo-phenylalanine will be administered in 3 fractions at the recommended dosage determined in the primary trial of this study on Days 7, 14 and 21 after the commencement of chemoradiation therapy.

In the secondary trial, a further approximately 200-250 patients will be randomized 1:1 and treated with standard treatment consisting of radiotherapy of 60 Gy/30 fractions for 6 weeks plus 75 mg/m^2 Temozolomide daily (chemoradiotherapy), followed by 4 weeks of treatment break. Patients will receive a maintenance treatment with 6 maintenance cycles of Temozolomide

150 mg/m^2 to 200 mg/m^2 on Days 1 to 5 q28 which can be continued up to 12 weeks at the discretion of the investigator. 4-*L*-[^{131}I] iodo-phenylalanine will be administered in 3 fractions at the recommended dosage determined in this study on Days 1, 7 and 14 or chemoradiation alone.

Inclusion Criteria

Patients who meet all of the following criteria at Screening will be eligible to participate in the study:

1. Participants must have histologically confirmed intracranial glioblastoma following maximum surgical resection. Tumors primarily localized in the infratentorial compartment will be excluded.
2. Amino acid-based molecular imaging (by ^{18}F-FET- PET) indicating pathologically increased amino acid uptake inside or in the vicinity of the tumour, clearly discernible from background activity.
3. Participants may have had prior surgery for glioblastoma but no systemic or radiation therapy.
4. Age ≥ 18 years.
5. Karnofsky performance status ≥60.
6. Life expectancy of greater than 6 months.
7. Participants must plan to begin radiation therapy 14-42 days after surgical resection.
8. Have adequate organ function at Screening:
    a) Bone marrow:
        1. Leukocytes ≥3,000/mL
        2. Absolute neutrophil count ≥1500/mL
        3. Platelets ≥100,000/mL
        4. Hemoglobin ≥9g/dL
    b) Liver function:
        1. Total bilirubin ≤1.5×the upper limit of normal (ULN). For patients with known Gilbert's Syndrome ≤3×ULN is permitted
        2. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤2.5×ULN
    c) Renal function:
        1. Serum/plasma creatinine ≤1.5×ULN or creatinine clearance ≥50 mL/min

9. Patients must have at least 15 slides without staining or a tissue block (frozen or paraffin-embedded) available from a previous biopsy or surgery (tumour sample previously archived).

Dosage and Mode of Administration

4-*L*-[^{131}I] iodo-phenylalanine will be prepared by iodine exchange (carrier added; c.a.). 4-*L*-[^{131}I] iodo-phenylalanine will be formulated as a solution for injection in glass vials for single intravenous use. The 4-*L*-[^{131}I] iodo-phenylalanine therapeutic drug product will be manufactured as a "ready-to-use medicine". The composition of 4-*L*-[^{131}I] iodo-phenylalanine solution for injection will include the active pharmaceutical ingredient in a buffered solution without other excipients. The composition per 25 mL will be:

- 8-12 mg 4-*L*-[^{131}I] iodo-phenylalanine
- 272.5 mg ascorbic acid
- 817.5 mg sodium ascorbate
- up to 2.8 mL ethanol
- made up to 25 mL with water for injection.

The formulation will be provided as a clear and colorless solution for IV administration, free of particulates. The volume for each single dose of 4-*L*-[^{131}I] iodo-phenylalanine will be provided in 25 mL solution (in one single vial) per batch ready for administration as, and when, needed.

Duration of Treatment and Study

Patients will participate in the study for up to 58 weeks.

Concomitant Therapy

The concomitant standard of care consists of radiotherapy of 60 Gy/30 fractions for 6 weeks plus 75 mg/m^2 Temozolomide daily (chemoradiotherapy), followed by 4 weeks of treatment break, followed by maintenance treatment with 6 maintenance cycles of Temozolomide 150 mg/m^2 to 200 mg/m^2 on Days 1 to 5 q28.

Criteria for Evaluation

The primary trial primary endpoints will include a determination of the Maximum Tolerated Dose (MTD) of 4-*L*-[^{131}I] iodo-phenylalanine in combination with standard of care treatment chemoradiation consisting of External Beam Radiation and Temozolomide. Tolerability will be assessed by Health-Related Quality of Life (HRQOL) total scores on

European Organisation for Research and Treatment of Cancer – EORTC QLQ-C30 and EORTC-BN20 questionnaires.

A further primary endpoint of the primary trial will be the determination of Treatment emergent adverse events (TEAE), including their type according to MedDRA (Medical Dictionary for Regulatory Activities), frequency, severity according to NCI CTCAE V5.0, seriousness, and relationship to study treatment. Laboratory abnormalities will be assessed according to the NCI CTCAE v.5.0Events.

Secondary endpoints of the primary trial that may also be observed include whole body biodistribution and dosimetry (safety dosimetry), residence times for discernible organs (MBq*h), organ and whole body absorbed radiation doses (μGy/MBq), tumour dosimetry of 4-*L*-[^{131}I] iodo-phenylalanine following systemic administration (therapeutic dosimetry), Cmax (maximum activity concentration in tumour Bq/cm^3), tmax (time point of maximum activity concentration in tumour), TAC (time activity curve) for metabolic tumour volume (MTV) defined by BL 18F-FET PET and 4-*L*-[^{131}I] iodo-phenylalanine SPECT, tumour absorbed radiation dose (μGy/MBq), and absorbed radiation doses (expressed as Gy/MBq of administered 4-*L*-[^{131}I] iodo-phenylalanine) to kidneys, liver, lungs, spleen, bone/red marrow, gastrointestinal tract and below acceptable safe limits as defined by ARPANSA (see Radiation Risk Assessment).

The secondary trial primary endpoints will include a determination of one-year overall survival rate of patients treated with 4-*L*-[^{131}I] iodo-phenylalanine plus chemoradiation compared to chemoradiation only.

The secondary trial primary endpoints will also include a determination of Progression free survival (from the date of enrolment to the date of progression or death for any cause, whichever came first, assessed up to 58 weeks), Objective Response Rate (ORR) in patients with complete response at weeks 10, 22, 34, 46 and 58 as defined by iRANO criteria, Objective Response Rate (ORR) in patients with partial response at weeks 10, 22, 34, 46 and 58 as defined by iRANO criteria, Disease Control Rate (DCR) in patients with complete response at weeks 10, 22, 34, 46 and 58 as defined by iRANO criteria, Disease Control Rate (DCR) in patients with partial response at weeks 10, 22, 34, 46 and 58 as defined by iRANO criteria, Disease Control Rate (DCR) in patients with stable disease at weeks 10, 22, 34, 46 and 58 as defined by iRANO criteria, Best Overall Response Rate (BORR) is defined as the rate of complete response from date of enrolment to week 58 as defined according to iRANO criteria, Best Overall Response Rate (BORR) is defined as the rate of partial response from date of enrolment to week 58 as defined according to iRANO criteria, Best Overall Response Rate (BORR) is defined as the rate of stable disease from date of enrolment to week 58 as defined according to iRANO criteria,

Safety throughout study completion for each patient, a minimum of 58 weeks for each patient, and Quality of life as determined using the EORTC QLQ-C30 and QLQ-BN20 questionnaires.

Analysis

All primary and secondary outcome data will be collected for all patients. Baseline factors across groups will be compared using mean (standard deviation) and median (25th and 75th percentiles) summary measures. Bland-Altman plots and Wilcoxon tests for paired data will be performed using GraphPad Prism v. 8. Due to clinical interest in departures from both sides of the null hypothesis, all test statistics will be two-sided.

Example 4: Phase I Trial of 4-*L*-[^{131}I]iodo-phenylalanine in Combination with Temozolomide Chemotherapy and External Beam Radiotherapy in Patients with Newly Diagnosed Glioblastoma

Study Title

A Phase I safety and dose finding study of 4-*L*-[^{131}I]iodo-phenylalanine plus standard of care in patients with newly diagnosed glioblastoma ('IPAX-2').

Background

The current standard of care for patients with newly diagnosed GBM is maximum safe surgical resection followed by concurrent Temozolomide (75 mg/m2/day for 6 weeks) and radiotherapy (60 Gy in 30 fractions) and then six maintenance cycles of Temozolomide (150–200 mg/m^2/day for the first 5 days of a 28-day cycle), according to the results of the phase III European Organisation for the Research and Treatment of Cancer (EORTC 26981).

The purpose of this study is to assess the safety and tolerability of intravenous 4-*L*-[^{131}I]iodo-phenylalanine administered concomitantly and sequentially with post-surgical standard of care treatment comprised of external beam radiotherapy and Temozolomide in newly diagnosed (first line) glioblastoma (GBM) patients.

Study Objectives and Endpoints

Objectives	**Endpoints**
Primary	
• To determine the safety and tolerability of 4-*L*-[^{131}I]iodo-phenylalanine in combination with standard of care treatment in newly diagnosed Glioblastoma (GBM) patients, by determining the Dose Limiting Toxicities (DLT), Maximum Tolerated Dose (MTD), and Recommended Phase 2 Dose (RP2D).	• Assessing TEAEs type according to MedDRA (Medical Disctionaly for Regulatory Activities), frequence, severity according to to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0, seriousness, and relationship of study treatment

• To determine the incidence of Treatment-Emergent Adverse Events (TEAE).	will be assessed. Laboratory abnormalities will be assessed according to the NCI CTCAE V5.0. • Incidence rate and the grade (severity) of DLTs based on the occurrence of Adverse Events (AEs) reported according to the NCI CTCAE v5.0. DLTs include any grade ≥ 3 events considered possibly related to the study drug, but excludes cerebral oedema, and haematological toxicity.
Secondary	
• 1-year overall survival rate of patients treated with 4-*L*-[^{131}I]iodo-phenylalanine plus standard of care treatment. • 2-year overall survival rate of patients treated with 4-*L*-[^{131}I]iodo-phenylalanine plus standard of care treatment. • To determine Progression Free Survival (PFS) from the date of enrolment to the date of progression or death for any cause, whichever comes first, assessed up to 52 weeks. • To determine best Objective Response Rate (ORR) in patients with partial response at weeks 7-8, 15, 23, 31, 43±1, and 51±1 as defined by modified Response in Neuro-Oncology (mRANO)* criteria. • To determine ORR in patients with stable disease at weeks 7-8, 15, 23, 31, 43±1, and 51±1 as defined by mRANO criteria. • To determine safety throughout study completion for each participant, for a minimum of 51±1 weeks. • To determine Quality of Life (QoL) as determined using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and Quality of Life Questionnaire – Brain Neoplasm (QLQBN20) questionnaires, and neurocognitive tests: Controlled Oral Word Association Test (COWA test), Hopkins Verbal Learning Test-Revised (HVLT-R test), and Trail Making Test (TMT). * Modified RANO Criteria Specification	
Exploratory	
• To examine the morphological and metabolic changes indicative of tumor response with 4-*L*-[^{131}I]iodo-phenylalanine in combination with standard of care using T1 gadolinium-enhanced MRI and [^{18}F]-FET PET respectively. • To determine the association between treatment induced changes in PFS and OS and changes in [^{18}F]-FET-PET parameters post treatment. • To quantitatively determine the extent of tumor targeting of 4-*L*-[^{131}I]iodo-phenylalanine with SPECT imaging.	• Sum of the Product of the Perpendicular. • Diameters (SPPD) on contrast enhanced T1w MRI. • SUV_{max}, SUV_{mean}, and SUV_{peak} within the metabolic tumor volume (MTV), and tumour-to-brain ratios (TBRmax and TBRmean) for [^{18}F]-FET-PET. • Quantitative 4-*L*-[^{131}I]iodo-phenylalanine uptake for SPECT imaging.

• To determine if there is an association between OS at 12 months and MGMT (O^6-methylguanine-DNA methyltransferase) status. • To determine if there is an association between PFS and MGMT methylation status. • To determine if there is an association between OS and LAT-1 (L-type Amino Acid Transporter 1) expression. • To determine if there is an association between PFS and LAT-1 expression.	

Inclusion Criteria

Participants who meet all the following criteria at Screening are eligible to participate in the study, if they:

1. Understand and voluntarily sign the informed consent form prior to any study related procedure and/or assessments being conducted.
2. Are Male or Female, and aged 18-65 years of age inclusive, at the time of signing the informed consent.
3. Have histologically confirmed intracranial glioblastoma (per WHO 2021 definition) following surgical resection. Tumours primarily localised in the infratentorial compartment will be excluded.
4. Have had prior surgery for glioblastoma, but no systemic therapy or radiation therapy for GBM.
5. Have a Karnofsky Performance Status ≥70.
6. Plan to begin chemoradiation therapy 3-6 weeks after surgical resection with Stupp regimen.
7. Have adequate organ function at Screening:
    a) Bone marrow:
        1. Leukocytes ≥3,000/mL
        2. Absolute neutrophil count ≥1500/mL
        3. Platelets ≥100,000/mL
        4. Hemoglobin ≥9g/dL
    b) Liver function:
        1. Total bilirubin ≤1.5×the upper limit of normal (ULN). For patients with known Gilbert's Syndrome ≤3×ULN is permitted
        2. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤2.5×ULN
    c) Renal function:

1. Serum/plasma creatinine ≤1.5×ULN or creatinine clearance ≥50 mL/min

8. Have at least 6 slides without staining or a tissue block (frozen or paraffin-embedded) available from a previous biopsy or surgery (tumour sample previously archived).

9. Have the capacity to understand the study and be able and willing to comply with all protocol requirements, including compliance with the radiation protection guidelines (including hospital admissions and isolation) that are applied by the treating institution to protect their contacts and the public.

10. Agree to practice adequate precautions to prevent pregnancy to avoid potential problems associated with radiation exposure to the unborn child.

11. Females must have a negative pregnancy test at screening and on dosing day, must not be lactating.

Exclusion Criteria

Patients who meet any of the following criteria are not eligible to participate in the study, if they:

1. Are unable to provide signed informed consent
2. Have had prior treatment for glioma, excluding surgery.
3. Are unable to undergo contrast-enhanced MRI.
4. Intend to be treated with tumor-treating fields prior to progression.
5. Have a history or evidence of delayed-type hypersensitivity (DTH)-dependent chronic infection (e.g., tuberculosis, systemic fungal or parasitic infection), potentially exacerbating under systemic corticoid therapy.
6. Have a known history of allergy to Temozolomide, any excipient in the study medication or any other intravenously administered human proteins/peptides/antibodies.
7. Have haemostaseologic conditions, precluding catheterisation or invasive procedures; or phenylketonuria.
9. Have any medical condition that in the opinion of the Investigator may interfere with the participant's ability to adhere to the study or may impose a risk to the participant's health.
10. Major trauma including major surgery (such as abdominal/cardiac/thoracic surgery) within 3 weeks of administration of study treatment except surgery on primary tumour.
11. Pregnant, breastfeeding or planning to get pregnant during the duration of the study.
12. Requirement of chronic administration of high dose corticosteroids or other immunosuppressant drugs. Limited or occasional use of corticosteroids to treat or prevent acute adverse reactions is not considered an exclusion criterion.

13. Have presence of active and uncontrolled infections or other severe concurrent disease, which, in the opinion of the investigator, would place the participant at undue risk or unable to comply with study requirements. HIV-positive participants may be included in the study if they are on a stable dose of anti-retroviral therapy.

14. Have concurrent malignancies (except: basal cell carcinoma, in situ breast cancer) unless the patient has been disease-free without intervention for at least 2 years.

15. Have taken growth factors or immunomodulatory agents within 7 days prior to the administration of study treatment.

16. Have serious, non-healing wound, ulcer, or bone fracture.

17. Have a requirement of concurrent use of other anti-cancer treatments or agents other than study medication.

18. Have received any other IMP within 90 days prior to the planned administration of study drug.

19. Have uncontrolled Hashimoto's or Grave's disease

20. Have on-going and unresolved Grade ≥ 1 AEs following surgical resection

Methodology

This is an open label, single-arm, randomized, parallel-group, multicenter, dose finding study to evaluate the safety of ascending dose levels of intravenously administered 4-*L*-[^{131}I]iodo-phenylalanine (which may also be referred to as ^{131}I-IPA or ^{131}I-TLX101) in combination with standard chemoradiation in newly diagnosed GBM patients.

An estimated 12 participants will be treated in cohorts according to 3+3 study design with Standard of Care (SoC) consisting of external beam radiotherapy of 60 Gy/30 fractions for 6 weeks plus 75 mg/m^2 Temozolomide daily (chemoradiotherapy), followed by 4 weeks of treatment break.

Participants will receive a maintenance treatment consisting of 6 maintenance cycles of Temozolomide 150-200 mg/m^2 on Days 1 to 5 q28. 4-*L*-[^{131}I]iodo-phenylalanine will be administered in 2 fractions corresponding to 1/2 full dose activity, via intravenous (IV) infusion on Day 0 (one week prior to commencement of chemoradiation therapy) and at Day 46 at the end of chemoradiation therapy, with the starting dose of 6.0 GBq. Summary of dose excalation per cohort is shown in the below Table.

Cohort Number	Number of participants	IP Total Dose/Fractionated Dose
1	3	6.0 GBq (2*3.0 GBq)
2	3	8.0 GBq (2*4.0 GBq)
3	3	10.0 GBq (2*5.0 GBq)

4	3	12.0 GBq (2*6.0 GBq)

*IP = Investigational Product

Participants will be admitted to the hospital or research facility at Day 0 and receive their first dose of 4-*L*-[^{131}I]iodo-phenylalanine prior to the commencement of chemoradiation therapy and admitted again on Day 46, after completion of chemoradiation therapy, to receive the second dose of 4-*L*-[^{131}I]iodo-phenylalanine, and discharged at Day 50±3. The first dose of 4-*L*-[^{131}I]iodo-phenylalanine must be given at least a week prior to commencement of chemoradiotherapy, and the second dose of 4-*L*-[^{131}I]iodo-phenylalanine must be given after and on the same day of completion of chemoradiotherapy.

A classic "3+3" study design will be followed to establish DLT, MTD and RP2D (see below Scheme). Initially, 3 participants will be enrolled to a cohort, the occurrence of a single drug related, grade ≥3 DLT in one of these 3 participants will prompt the enrolment of an additional 3 participants to that same cohort. If more than one grade ≥3 DLT occurs in ≤6 participants in a dosing cohort, dose escalation will be stopped, and this dose level will be identified as the non-tolerated dose. A schematic of the study design is shown in FIG. 1.

Doses between the non-tolerated dose and the preceding lower dose, where ≤ 1 grade ≥3 DLT occurred, may be explored to more precisely define the MTD. If the MTD has not been reached at 12.0 GBq, dose escalation may proceed, increasing the dose fractions to a total dose 4-*L*-[^{131}I]iodo-phenylalanine >12 GBq using cohorts of N=3 until MTD is reached. In summary:

a) if no grade ≥3 DLT events occur, dose escalation should proceed;

b) if 1 grade ≥3 DLT event occurs at that dose level, then another 3 participants will be enrolled at the same dose level, then if 2 out 6 participants suffer a grade ≥3 DLT, the preceding dose will be defined as the MTD. If 1 out 6 participants suffers a grade ≥3 DLT, dose escalation should proceed;

c) if 2 out of 6 participants suffer a grade ≥3 DLT, the MTD will be defined as the preceding dose level.

The MTD is defined as the highest dose cohort at which <33% of participants experience 131I- TLX101 related DLTs in the first 53 days of treatment.

The DLT is defined using the NCI CTCAE V5.0 in the first 53 days of treatment. All toxicities will be considered related to 4-*L*-[^{131}I]iodo-phenylalanine if they cannot be explained (with certainty) by underlying disease, intercurrent illness or concomitant medications. Any TEAEs Grade 3 or Grade 4 toxicity, unless clearly and incontrovertibly unrelated to 4-*L*-[^{131}I]iodo-phenylalanine. Exceptions are Grade 3 or Grade 4 nausea or vomiting that is controlled

by anti-emetics or other therapy appropriate therapy, cerebral oedema, and haematological toxicity.

The RP2D may be as high as the MTD and will be determined in discussion with the Safety Review Committee. Observations related to any cumulative toxicity observed after multiple dose escalations may be included in the rationale supporting the RP2D.

The study is composed of four phases:

- Screening phase: 6 weeks of screening (Day -42 to Day -1);
- Treatment Period including Concomitant Therapy: 7-8 weeks (Day 0 to Day 50±3);
- Temozolomide maintenance therapy: 6 months (Day 74±2 to Day 214); and
- Follow Up Period: approximately 60 weeks (Day 298±7 to Day 712±7) (two on-site visits over 8 weeks, and one phone call later).

Overall, a classical Phase I dose escalation design, using cohorts of 3+3 participants/dose level, as appropriate for oncological compounds, was chosen to establish MTD of 4-*L*-[^{131}I]iodo-phenylalanine in combination with chemoradiation (consisting of radiotherapy of 60 Gy/30 fractions for 6 weeks plus 75 mg/m^2 Temozolomide daily) followed by 4 weeks of treatment break. Escalation to the next higher dose will only occur if the previous dose level was deemed to be safe and well tolerated following review of the safety and tolerability data. 4-*L*-[^{131}I]iodo-phenylalanine will be administered in 2 fractions corresponding to 1/2 full dose (3.0 GBq) activity on Days 0 and 46. Dose escalation will be by radioactive dose only (in GBq), while keeping the 4-*L*-iodo-phenylalanine mass dose per injection constant. The first dose of 3.0 GBq corresponds to ½ of well tolerated doses reported in the literature in combination with external beam radiation therapy. In addition to MRI, amino acid-based molecular imaging (^{18}[F]FET-PET) will be used for assessment of possible antineoplastic effects during dose escalation, and for assessment of treatment-induced changes based on a single post-therapeutic imaging study.

Imaging

MRI Imaging: Contrast enhanced MRI imaging will be performed at screening (if the existing images were collected more than 4 weeks prior to the screening visit), (post-surgery), at Week 7-8, (depending on the day of the week, the study week begins on a Monday) upon completion of EBRT + TMZ treatment (baseline MRI for mRANO); then every 8 weeks until the end of TMZ maintenance therapy (Week 31) study visit. Additional MRIs will be performed at Week 43±1 and at Week 51±1.). If a participant develops symptoms and an MRI is performed outside of these timepoints, treatment response shall be assessed, and the visit

must be entered in the eCRF as an unscheduled visit. MRI image acquisition should be performed per local protocol.

[^{18}F]FET-PET: Cerebral [^{18}F]FET-PET will be performed at baseline (post-surgery but prior to commencement of chemoradiation therapy), Weeks 15, 31, 43±1, and 51±1at , and if possible, at the early withdrawal visit. [^{18}F]FET-PET imaging prior to starting chemoradiotherapy must be done no sooner than 2 weeks after surgery due to potentially increased amino acid uptake (mediated by wound-healing). If a participant develops symptoms and an MRI is performed outside of these timepoints, a [^{18}F]FET-PET should also be performed to confirm progression/pseudoprogression, and the visit must be entered in the eCRF as an unscheduled visit. [^{18}F]FET-PET image acquisition, review and assessment will in accordance with the Image Acquisition Manual and reviewed centrally. Briefly, a static [^{18}F]FET-PET scans will be acquired according to standard protocols after intravenous administration of approximately 125 – 200MBq ±10% [^{18}F]FET. Static scans will be performed approximately between 20 and 40min post injection with approximately 10min acquisition. The outcome parameters will be SUVmax, SUVmean and SUVpeak within the MTV and tumour-to-brain ratios (TBR_{max} and TBR_{mean}).

SPECT - Single-Photon Emission Computed Tomography: of 4-*L*-[^{131}I]iodo-phenylalanine uptake will be quantified by cerebral SPECT after the participant completes the post of 4-*L*-[^{131}I]iodo-phenylalanine dose isolation period, prior to the participant's discharge from the hospital or research unit.

Study Intervention(s)

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Intervention Label	^{131}I-TLX101	TMZ	EBRT	^{18}F-FET
Intervention Name	4-*L*-[^{131}I]iodo-phenylalanine (also known as ^{131}I-TLX101 or ^{131}I-IPA)	Temozolomide	External Beam Radiation Therapy	O-(2-[F-18]fluoroethyl)-L- tyrosine
Type	Radiopharmaceutical drug	Drug	Radiation Therapy	Radiopharmaceutical tracer/drug
Dose Formulation	Intravenous (IV) solution	Capsule	N/A	Intravenous (IV)
Unit Dose Strength(s)/Dosage Levels	Starting dose will be 2 * 3.0 GBq, (a total dose of 6 GBq). Subsequent doses will be decided by the	75 mg/m^2 for 6 weeks 150-200mg/m^2 for 5 days for up	60 Gy/30 fractions, daily for 6 weeks.	125 - 200MBq ± 10%

	Safety Monitoring Committee, but also given in 2 fractions (i.e., 2 * 4.0 GBq, 2 * 5.0 GBq, and so on).	to 12 weeks		
Route of Administration	IV	Oral	External Beam	IV
Mode of Administration	^{131}I-TLX101 will be administered as an intravenous infusion (10 minutes) using an intravenous cannula, placed into the cubital vein of the non-dominant arm. Where possible, administration should be made with an automated infusion system for radiation protection reasons.	Oral	N/A	^{18}F-FET will be administered as an intravenous cannula, placed into the cubital vein of the non-dominant arm. Where possible, administration should be made with an automated infusion for radiation reasons.
Use	Experimental	Standard of Care	Standard of Care	Experimental
Supplier	Telix International Pty Ltd	Sourced at the study centre	Sourced at the study centre	Cyclotek (Aus) Pty Limited or sourced locally
Packaging and Labelling	All clinical study material will be packaged and labelled to comply with local regulations. Separate documentation regarding the expiry date will be made available.	All clinical study material will be packaged and labelled to comply with local regulations. Separate documentation regarding the expiry date will be made available.	N/A	All clinical study will be packaged labelled to comply with local regulations. documentation the expiry date will be made available.
Dose Preparation	^{131}I-TLX101 is formulated as a solution for injection in glass vials for single intravenous use and manufactured as a “ready-to-use medicine". The composition of ^{131}I-TLX101 solution for injection includes the	Ready to dispense.	N/A	10mL ^{18}F-FET will be shipped in a Type A package with the IMP contained in a vial, then need to be into the final syringe by site, prior to administration. If sourced locally, the

	active pharmaceutical ingredient in a buffered solution without other excipients. ^{131}I-TLX101 will be provided in 25 mL solution (in one single vial) per batch ready for administration as and when needed.			will be prepared, and shipped per standard procedures.

Statistical Considerations

Inferential statistical analysis is not planned for this study. The study is designed to identify safe, tolerated doses of 4-*L*-[^{131}I]iodo-phenylalanine administered as an IV infusion to newly diagnosed GBM patients in addition to standard of care. The data will be used to select doses for further investigation of the safety, tolerability and efficacy of 4-*L*-[^{131}I]iodo-phenylalanine administered to patients in a later phase clinical trial.

The sample size is not based on statistical considerations but is typical for studies of this nature and is consider adequate to characterise the distribution of the planned endpoints. Any statistical testing will be considered exploratory and descriptive.

The Statistical Analysis Plan (SAP) will be developed and finalised before database lock and will describe the participant analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

For purposes of analysis, the analysis sets in below Table are defined.

Analysis Set	**Description**
Entered Analysis Set	All participants who sign the ICF.
Enrolled Analysis Set	All participants who have met all eligibility criteria.
Safety Analysis Set	All participants who take at least 1 dose of 4-*L*-[^{131}I]iodo-phenylalanine. Participants will be analysed according to the treatment they actually received.
Efficacy Analysis Set	All participants from the Safety Analysis Set who have received 4-*L*-[^{131}I]iodo-phenylalanine and also have sufficient follow-up data (imaging: at least one post baseline scan at D50±3; and clinical) to assess either response (morphological or metabolic) or survival

ITEMISED LIST OF EMBODIMENTS

Disclosed herein are the following numbered embodiments.

Embodiment 1. A method of treating a glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolomide chemotherapy and external beam radiotherapy, to a patient in need thereof.

Embodiment 2. The method of embodiment 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of at least about 2 GBq.

Embodiment 3. The method of embodiment 1 or embodiment 2, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of between about 2 GBq and about 18 GBq.

Embodiment 4. The method of any one of embodiments 1 to 3, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of between about 2 GBq and about 12 GBq, between about 2 GBq and about 10 GBq, between about 2 GBq and about 8 GBq, or between about 2 GBq and about 6 GBq.

Embodiment 5. The method of any one of embodiments 1 to 4, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose.

Embodiment 6. The method of any one of embodiments 1 to 4, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in more than one dose.

Embodiment 7. The method of any one of embodiments 1 to 4 and 6, wherein each of the more than one dose administers a substantially equal dose of 4-*L*-[^{131}I]iodo-phenylalanine.

Embodiment 8. The method of embodiment 6 or embodiment 7, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses.

Embodiment 9. The method of embodiment 8, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses on days zero and 46, from commencement of treatment.

Embodiment 10. The method of any one of embodiments 6 to 9, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses of 3.0 GBq per dose on days zero and 46, from commencement of treatment.

Embodiment 11. The method of any one of embodiments 6 to 9, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses of 4.0 GBq per dose on days zero and 46, from commencement of treatment.

Embodiment 12. The method of any one of embodiments 6 to 9, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses of 5.0 GBq per dose on days zero and 46, from commencement of treatment.

Embodiment 13. The method of any one of embodiments 6 to 9, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses of 6.0 GBq per dose on days zero and 46, from commencement of treatment.

Embodiment 14. The method of any one of embodiments 6 to 9, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses of 3.0 GBq to 6.0 GBq per dose, the first dose being administered at least a week prior to commencement of external beam radiotherapy, and the second dose being administered after completion of external beam radiotherapy.

Embodiment 15. The method of any one of embodiments 1 to 14, wherein the Temozolomide is administered in an amount of between about 75 mg/m^2 and about 200 mg/m^2, per day.

Embodiment 16. The method of embodiment 15, wherein the Temozolomide is administered in an amount of about 75 mg/m^2, per day.

Embodiment 17. The method of embodiment 16, wherein the Temozolomide is administered in an amount of about 75 mg/m^2 daily for a duration of about 6 weeks from commencement of treatment.

Embodiment 18. The method of any one of embodiments 1 to 17, wherein the method further includes the step of administering Temozolomide as a maintenance dose during a period in which the patient is not receiving the combined 4-*L*-[^{131}I]iodo-phenylalanine, Temozolomide chemotherapy and external beam radiotherapy treatment.

Embodiment 19. The method of embodiment 18, wherein the Temozolomide is administered as a maintenance dose in an amount of about 150 mg/m^2 to about 200 mg/m^2.

Embodiment 20. The method of embodiment 19, wherein the Temozolomide is administered as a maintenance dose for a duration of about one, about two, about three, about four, about five, about six, or about seven days.

Embodiment 21. The method of any one of embodiments 18 to 20, wherein administration of the maintenance dosage is administered from about six to about 11 weeks from commencement of treatment.

Embodiment 22. The method of any one of embodiments 1 to 21, wherein the external beam radiation is administered in an amount of about 20 Gray to about 60 Gray.

Embodiment 23. The method of any one of embodiments 1 to 22, wherein the external beam radiation is administered in an amount of about 20 Gray to about 60 Gray in one or more fractions.

Embodiment 24. The method of any one of embodiments 1 to 23, wherein the external beam radiation is administered in about 10, about 20, or about 30 fractions.

Embodiment 25. The method of any one of embodiments 1 to 24, wherein the external beam radiation is administered in an amount of about 20 Gray to about 60 Gray in about 10, about 20, or about 30 fractions.

Embodiment 26. The method of any one of embodiments 1 to 25, wherein the external beam radiation is administered for a duration of about six weeks from commencement of treatment.

Embodiment 27. The method of any one of embodiments 1 to 26, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is formulated for intravenous administration.

Embodiment 28. The method of embodiment 27, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is formulated in a buffered solution.

Embodiment 29. The method of embodiment 27 or embodiment 28, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is formulated in an amount of about 8 mg to about 12 mg of 4-*L*-[^{131}I]iodo-phenylalanine per about 25 mL of buffered solution.

Embodiment 30. The method of any one of embodiments 27 to 29, wherein the 4-*L*-[^{131}I]iodo-phenylalanine formulation further comprises any one or more of ascorbic acid, sodium ascorbate, and ethanol.

Embodiment 31. The method of any one of embodiments 1 to 30, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered intravenously.

Embodiment 32. The method of any one of embodiments 1 to 31, wherein a reduction in one or more adverse events is observed in comparison to administration of Temozolomide chemotherapy and external beam radiotherapy alone.

Embodiment 33. The method of embodiment 32, wherein the one or more adverse events is selected from the group consisting of haematological toxicity, inflammation-induced intracranial hypertension, fatigue, thrombocytopenia, weight loss, diarrhea, and headache.

Embodiment 34. The method of any one of embodiments 1 to 33, wherein the patient has previously undergone maximal surgical resection of the glioblastoma.

Embodiment 35. The method of embodiment 34, wherein treatment with 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolomide chemotherapy and external beam radiotherapy commences within about 14 days to about 42 days following maximal surgical resection of the glioblastoma.

Embodiment 36. The method of any one of embodiments 1 to 35, wherein the glioblastoma is not primarily localized in the infratentorial compartment.

Embodiment 37. The method of any one of embodiments 1 to 36, wherein the patient does not have multifocal distant recurrence tumor lesions.

Embodiment 38. The method of any one of embodiments 1 to 37, wherein the patient has not received prior chemotherapy or radiation therapy.

Embodiment 39. The method of any one of embodiments 1 to 38, wherein the method provides for an increase in the progression free survival of the patient in comparison to administration of Temozolomide chemotherapy and external beam radiotherapy alone.

Embodiment 40. The method of embodiment 39, wherein the progression free survival is increased by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, in comparison to administration of Temozolomide chemotherapy and external beam radiotherapy alone.

Embodiment 41. The method of any one of embodiments 1 to 38, wherein the method provides for an increase in overall survival of the patient in comparison to administration of Temozolomide chemotherapy and external beam radiotherapy alone.

Embodiment 42. The method of embodiment 41, wherein the overall survival is increased by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, in comparison to administration of Temozolomide chemotherapy and external beam radiotherapy alone.

Embodiment 43. The method of any one of embodiments 1 to 42, wherein the glioblastoma is recurrent glioblastoma.

Embodiment 44. The method of any one of embodiments 1 to 43, wherein the glioblastoma is high-grade glioma (HGG).

Embodiment 45. Use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of a glioblastoma, wherein the medicament is formulated for administration in combination with Temozolomide chemotherapy and external beam radiotherapy.

Embodiment 46. Use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of a glioblastoma, wherein the medicament is administered in combination with Temozolomide chemotherapy and external beam radiotherapy.

Embodiment 47. 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolomide chemotherapy and external beam radiotherapy, for use in the treatment of a glioblastoma.

Embodiment 48. 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolomide chemotherapy and external beam radiotherapy, when used in the treatment of a glioblastoma.

Embodiment 49. A method of treating a glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and optionally Temozolomide chemotherapy, to a patient in need thereof.

Embodiment 50. A method of treating a glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy, to a patient in need thereof.

Embodiment 51. Use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of a glioblastoma, wherein the medicament is formulated for administration in combination with external beam radiotherapy.

Embodiment 52. Use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of a glioblastoma, wherein the medicament is administered in combination with external beam radiotherapy.

Embodiment 53. 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy, for use in the treatment of a glioblastoma.

Embodiment 54. 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy, when used in the treatment of a glioblastoma.

FURTHER ITEMIZED LIST OF EMBODIMENTS

Also disclosed herein are the following numbered embodiments.

Embodiment 1. A method of treating a glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and optionally Temozolomide chemotherapy, to a patient in need thereof.

Embodiment 2. The method of embodiment 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of at least about 1 GBq, optionally between about 2 GBq and about 18 GBq.

Embodiment 3. The method of embodiments 1 and 2, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of between about 1 GBq and about 12 GBq, between about 2 GBq and about 12 GBq, between about 2 GBq and about 10 GBq, between about 2 GBq and about 8 GBq, or between about 2 GBq and about 6 GBq.

Embodiment 4. The method of any one of embodiments 1 to 3, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy.

Embodiment 5. The method of any one of embodiments 1 to 4, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in parallel with external beam radiotherapy.

Embodiment 6. The method of any one of embodiments 1 to 5, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of and/or after completion of external beam radiotherapy.

Embodiment 7. The method of any one of embodiments 1 to 6, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose.

Embodiment 8. The method of any one of embodiments 1 to 7, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose of about 1 GBq per dose, about 2 GBq per dose, about 3 GBq per dose, about 4 GBq per dose, about 5 GBq per dose, about 6 GBq per dose, about 7 GBq per dose, about 8 GBq per dose, about 9 GBq per dose, about 10 GBq per dose, about 11 GBq per dose, or about 12 GBq per dose.

Embodiment 9. The method of any one of embodiments 1 to 8, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in more than one dose, optionally wherein each of the more than one dose administers a substantially equal dose of 4-*L*-[^{131}I]iodo-phenylalanine.

Embodiment 10. The method of any one of embodiments 1 to 9, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses; optionally wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses of about 3 GBq per dose, about 4 GBq per dose, about 5 GBq per dose, or about 6 GBq per dose.

Embodiment 11. The method of any one of embodiments 1 to 9, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three, substantially equal doses; optionally wherein the 4-L-[131I]iodo-phenylalanine is administered as three, substantially equal doses of about 2 GBq per dose, about 3 GBq per dose, or about 4 GBq per dose.

Embodiment 12. The method of any one of embodiments 1 to 11, wherein the external beam radiation is administered in an amount of about 20 Gray to about 60 Gray, optionally wherein the external beam radiation is administered in one or more fractions, optionally about 10, about 20, or about 30 fractions.

Embodiment 13. The method of any one of embodiments 1 to 12, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is formulated for intravenous administration, optionally wherein the 4-*L*-[^{131}I]iodo-phenylalanine is formulated in an amount of about 8 mg to about 12 mg of 4-*L*-[^{131}I]iodo-phenylalanine per about 25 mL of buffered solution.

Embodiment 14. The method of any one of embodiments 1 to 13, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in combination with external beam radiotherapy and Temozolomide chemotherapy.

Embodiment 15. The method of embodiment 14, wherein the Temozolomide is administered in an amount of between about 75 mg/m^2 and about 200 mg/m^2, per day.

Embodiment 16. The method of embodiments 14 and 15, wherein the Temozolomide is administered in an amount of about 75 mg/m^2, per day.

Embodiment 17. The method of any one of embodiments 1 to 16, wherein the method further includes the step of administering Temozolomide as a maintenance dose during a period in which the patient is not receiving the combined 4-*L*-[^{131}I]iodo-phenylalanine and external

beam radiotherapy treatment; optionally wherein the Temozolomide is administered as a maintenance dose in an amount of about 150 mg/m^2 to about 200 mg/m^2.

Embodiment 18. The method of any one of embodiments 14 to 17, wherein a reduction in one or more adverse events is observed in comparison to administration of each of Temozolomide chemotherapy and external beam radiotherapy alone; optionally wherein the one or more adverse events is selected from the group consisting of haematological toxicity, inflammation-induced intracranial hypertension, fatigue, thrombocytopenia, weight loss, diarrhea, and headache.

Embodiment 19. The method of any one of embodiments 14 to 18, wherein the patient has previously undergone maximal surgical resection of the glioblastoma, optionally wherein treatment with 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolomide chemotherapy and external beam radiotherapy commences within about 14 days to about 42 days following maximal surgical resection of the glioblastoma.

Embodiment 20. The method of any one of embodiments 1 to 19, wherein the method provides for an increase in the progression free survival of the patient in comparison to administration of Temozolomide chemotherapy and external beam radiotherapy alone.

Embodiment 21. The method of embodiment 20, wherein the progression free survival is increased by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, in comparison to administration of Temozolomide chemotherapy and external beam radiotherapy alone.

Embodiment 22. The method of any one of embodiments 1 to 21, wherein the glioblastoma is a recurrent glioblastoma.

Embodiment 23. The method of any one of embodiments 1 to 21, wherein the glioblastoma is a high-grade glioma (HGG), optionally a recurrent high-grade glioma (HGG).

Embodiment 24. Use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of a glioblastoma, wherein the medicament is formulated for administration in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.

CLAIMS

1. A method of treating a glioblastoma comprising administering a therapeutically effective amount of 4-*L*-[^{131}I]iodo-phenylalanine in combination with external beam radiotherapy and optionally Temozolomide chemotherapy, to a patient in need thereof.

2. The method of claim 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of at least about 1 GBq, optionally between about 2 GBq and about 18 GBq.

3. The method of claim 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in an amount of between about 1 GBq and about 12 GBq, between about 2 GBq and about 12 GBq, between about 2 GBq and about 10 GBq, between about 2 GBq and about 8 GBq, or between about 2 GBq and about 6 GBq.

4. The method of claim 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of external beam radiotherapy.

5. The method of claim 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in parallel with external beam radiotherapy.

6. The method of claim 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered prior to commencement of and/or after completion of external beam radiotherapy.

7. The method of claim 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose.

8. The method of claim 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as a single dose of about 1 GBq per dose, about 2 GBq per dose, about 3 GBq per dose, about 4 GBq per dose, about 5 GBq per dose, about 6 GBq per dose, about 7 GBq per dose, about 8 GBq per dose, about 9 GBq per dose, about 10 GBq per dose, about 11 GBq per dose, or about 12 GBq per dose.

9. The method of claim 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in more than one dose, optionally wherein each of the more than one dose administers a substantially equal dose of 4-*L*-[^{131}I]iodo-phenylalanine.

10. The method of claim 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses; optionally wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as two, substantially equal doses of about 3 GBq per dose, about 4 GBq per dose, about 5 GBq per dose, or about 6 GBq per dose.

11. The method of claim 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered as three, substantially equal doses; optionally wherein the 4-L-[131I]iodo-phenylalanine is administered as three, substantially equal doses of about 2 GBq per dose, about 3 GBq per dose, or about 4 GBq per dose.

12. The method of claim 1, wherein the external beam radiation is administered in an amount of about 20 Gray to about 60 Gray, optionally wherein the external beam radiation is administered in one or more fractions, optionally about 10, about 20, or about 30 fractions.

13. The method of claim 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is formulated for intravenous administration, optionally wherein the 4-*L*-[^{131}I]iodo-phenylalanine is formulated in an amount of about 8 mg to about 12 mg of 4-*L*-[^{131}I]iodo-phenylalanine per about 25 mL of buffered solution.

14. The method of claim 1, wherein the 4-*L*-[^{131}I]iodo-phenylalanine is administered in combination with external beam radiotherapy and Temozolomide chemotherapy.

15. The method of claim 14, wherein the Temozolomide is administered in an amount of between about 75 mg/m^2 and about 200 mg/m^2, per day.

16. The method of claim 14, wherein the Temozolomide is administered in an amount of about 75 mg/m^2, per day.

17. The method of claim 1, wherein the method further includes the step of administering Temozolomide as a maintenance dose during a period in which the patient is not receiving the combined 4-*L*-[^{131}I]iodo-phenylalanine and external beam radiotherapy treatment; optionally wherein the Temozolomide is administered as a maintenance dose in an amount of about 150 mg/m^2 to about 200 mg/m^2.

18. The method of claim 14, wherein a reduction in one or more adverse events is observed in comparison to administration of each of Temozolomide chemotherapy and external beam radiotherapy alone; optionally wherein the one or more adverse events is selected from the group consisting of haematological toxicity, inflammation-induced intracranial hypertension, fatigue, thrombocytopenia, weight loss, diarrhea, and headache.

19. The method of claim 14, wherein the patient has previously undergone maximal surgical resection of the glioblastoma, optionally wherein treatment with 4-*L*-[^{131}I]iodo-phenylalanine in combination with Temozolomide chemotherapy and external beam radiotherapy commences within about 14 days to about 42 days following maximal surgical resection of the glioblastoma.

20. The method of claim 1, wherein the method provides for an increase in the progression free survival of the patient in comparison to administration of Temozolomide chemotherapy and external beam radiotherapy alone.

21. The method of claim 20, wherein the progression free survival is increased by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, in comparison to administration of Temozolomide chemotherapy and external beam radiotherapy alone.

22. The method of claim 1, wherein the glioblastoma is a recurrent glioblastoma.

23. The method of claim 1, wherein the glioblastoma is a high-grade glioma (HGG), optionally a recurrent high-grade glioma (HGG).

24. Use of 4-*L*-[^{131}I]iodo-phenylalanine in the manufacture of a medicament for the treatment of a glioblastoma, wherein the medicament is formulated for administration in combination with external beam radiotherapy and optionally Temozolomide chemotherapy.