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(54) Title: METHODS OF TREATMENT

(57) Abstract: The present invention is directed to methods of treating or preventing multiple myeloma in a patient in need thereof by administering 4-²¹¹At]Astato-L-phenylalanine (4-²¹¹At]APA) or a pharmaceutical derivative thereof to said patient.



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Methods of treatment

Field of the invention

The present invention is directed to methods of treating or preventing multiple myeloma in a patient in need thereof by administering 4-[²¹¹At]Astatato-L-phenylalanine (4-
5 [²¹¹At]APA) or a pharmaceutical derivative thereof to said patient.

Related application

This application claims priority from Australian provisional application AU 2020902585, the contents of which are hereby incorporated by reference in their entirety.

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Background of the Invention

Multiple myeloma (MM) is a heterogeneous hematologic malignancy arising from plasma cells, the white blood cells responsible for antibody production. The disease begins in multiple sites in the bone-marrow compartment and morbidity and mortality from MM is the result of end organ damage from hypercalcemia, renal dysfunction, anemia
15 and lytic bone lesions [Palumbo & Anderson, 2011]. MM occurs mainly in the elderly population with a median age at diagnosis of 66 years [Rajkumar, 2016]; and accounts for up to 10% of hematological malignancies. The estimated prevalence of MM in the US in 2020 is 128,894 cases, with 32,270 new cases and 12,830 deaths [Siegel, 2020]. MM is twice as common in black populations [Landgren 2014], and the overall population has
20 a 0.8% chance of developing MM at some point in their lifetime [SEER, 2017 statistics]. The overall 5-year survival for MM is 53.9% and for localized, distant (metastasized), and unknown (un-staged) stages of myeloma 74.8%, 52.9%, and 76.8%, respectively [SEER, 2017 statistics].

Although classified as a distinct disease, MM exhibits considerable heterogeneity
25 in several of its features including clinical course, responsiveness to treatment and underlying genetic alterations [Wajs & Sawicki, 2013], resulting in highly variable treatment regimens and difficulty in treating relapsed, refractory disease. MM progresses through several asymptomatic stages before metastasis and the vast majority (95%) of patients present with metastatic disease [SEER, 2017 statistics]. Symptomatic MM is
30 characterized by lytic bone disease, anemia, hypercalcemia, renal failure and

susceptibility to bacterial infections [Corre, Munshi et al 2015]. Treatments can extend overall survival but are not curative. Upon relapse, treatment options for refractory MM are limited to palliative care or inclusion into a clinical trial.

There is no clearly established cause for MM but environmental factors including certain chemicals, radiation and viruses (such as HIV) have been linked to an increased risk of MM [<https://www.cancer.org.au/about-cancer/types-of-cancer/myeloma.html>]; for example, the risk of MM is increased in radiologists with long-term exposure [Lewis, 1963]. These factors are thought to lead to multistep genetic changes in plasma cells that ultimately lead to malignant transformation [Tricot, 2000; Palumbo & Anderson, 2011].

MM arises from the proliferation of monoclonal plasma cells from B cell populations in germinal centres, which migrate to the bone marrow. The rearrangement of immunoglobulin genes and their strong promoter sequences initiates the overexpression of oncogenes [Palumbo and Anderson, 2011]. Promoter elements for immunoglobulin genes may be inserted before an oncogene, commonly MAF, MMSET or FGFR3; this initial deregulation progresses to other sites, activating classical oncogenes such as MYC, NRAS and KRAS.

Oncogene activation leads to expression of adhesion molecules, growth factors and cytokines [Palumbo & Anderson, 2011, Fonseca, 2004], disruption of programmed cell death, increased cell proliferation and changes in the tumor microenvironment [Kuehl and Bergsagel, 2002]. The adhesion of MM cells to extracellular matrix proteins (e.g., collagen, fibronectin, laminin, and vitronectin) triggers up-regulation of cell-cycle regulatory proteins and anti-apoptotic proteins. Interactions between MM cells and normal cells in the bone marrow compartment leads to tumor growth, survival, migration and drug resistance.

In asymptomatic patients, MM is most likely to be identified through laboratory abnormalities. Symptomatic patients generally present late in the course of disease with symptoms related to end-organ damage that may be nonspecific, such as nausea, vomiting, malaise, weakness, recurrent infections, or weight loss.

The classic definition of MM required detection of a clonal proliferation of plasma cells with evidence of end-organ damage defined by the CRAB criteria: increased calcium level, renal dysfunction, anemia, and destructive bone lesions

[<https://www.myeloma.org/international-myeloma-working-group-imwg-criteria-diagnosis-multiple-myeloma>]. In 2014 the International Myeloma Working Group (IMWG) presented updated diagnostic criteria [Rajkumar et al, 2014] that included three validated biomarkers to enable earlier detection of disease – clonal bone marrow plasma cells >10%, biopsy-proven bony plasmacytoma or biopsy-proven extramedullary plasmacytoma. The presence of at least one of these markers is considered sufficient for a diagnosis of MM, regardless of the presence or absence of symptoms or CRAB features. Each of these markers has been shown in two or more independent studies to be associated with an approximately 80% or higher risk of developing MM-related organ damage within two years.

Laboratory testing and imaging of symptomatic areas with MRI or PET/CT are required for the differential diagnosis from other plasma cell proliferative disorders including monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM) or plasma cell leukemia, amyloidosis, Waldenström macroglobulinemia or POEMS syndrome [Michels, 2017].

In addition to non-specific symptoms such as nausea, vomiting, malaise, weakness, recurrent infections, or weight loss patients with MM are more likely to experience symptoms of renal impairment, bone disease, thromboembolic events, infection and anemia as the disease progresses patients. Symptoms of bone disease (e.g., pain from fracture or plasmacytoma, spinal cord compression), peripheral neuropathy, or hyperviscosity (e.g., dyspnea, transient ischemic attack, retinal hemorrhage, deep venous thrombosis) can occur and anemia occurs nearly always at some point in the disease [Michels, 2017].

There are two conventional staging systems for MM (Table 1). The Revised-International Staging System (R-ISS) provides objective grading of disease based on typical alterations in Beta-2-Microglobulin (M protein) overexpression by malignant B cells and underlying genetic changes [Palumbo et al, 2015]. The Durie-Salmon system incorporates similar measures of associated serum proteins with subjective testing such as cell mass and extent of bone lesions [Rajkumar et al, 2016]. The majority of patients will present with an intermediate R-ISS score, which leads to a median overall survival (OS) of 44 months.

Table 1. Multiple Myeloma Staging

Stage	R-ISS	Frequency	Median OS	Durie Salmon
I	Serum albumin > 3.5g/dL Serum Beta-2- microglobulin <3.5mg/L No high-risk cytogenetics Normal lactate dehydrogenase (LDH)	28%	62 months	Low cell mass AND All of: Hemoglobin (Hb) > 10g/dl Serum IgG <5 g/dL Serum IgA <3 g/dl Normal serum calcium Urine monoclonal protein excretion <4 g/day No general lytic bone lesions
II	Neither stage I or III	62%	44 months	Intermediate cell mass
III	Serum Beta-2- microglobulin >5.5 mg/L High-risk cytogenetics OR Elevated LDH	10%	29 months	High cell mass AND One or more of: Hb < 8.5g/dl Serum IgG >7 g/dL Serum IgA >5 g/dl Serum calcium >12 mg/dl Urine monoclonal protein excretion >12 g/day Advanced lytic bone lesions

For newly diagnosed MM, the treatment paradigm follows the course of primary therapy, autologous stem cell transplant (ASCT, if eligible), consolidation/maintenance therapy and treatment of relapse [NCCN guidelines, 2020]. The choice of primary therapy depends on the patient's risk stratification upon diagnosis, with patients considered at standard and intermediate risk recommended to receive a 4-cycle course of bortezomib, lenalidomide and dexamethasone (VRD); and patients considered high risk a 4-cycle course of carfilzomib, lenalidomide and dexamethasone (KRD).

Following induction therapy, patients undergo ASCT if they are determined eligible based on their age, performance status and comorbidities. ASCT extends median OS by 12 months by re-establishing immune cell populations. For patients who are ineligible for ASCT, the initial triplet regimen (VRD or KRD) is continued for a further 8-12 cycles.

5 Allogeneic stem cell transplants are not usually recommended for patients with MM due to the high morbidity related to graft-vs-host disease [Rajkumar et al, 2016].

Maintenance therapy after ASCT is evolving with more treatment options and combinations now available but often consists of a therapeutic combination containing bortezomib [Rajkumar et al, 2016]. Treatment of relapsed MM is more variable and
10 complex, depending upon product availability, response to previous therapy, aggressiveness of the relapse, eligibility for ASCT, and whether the relapse occurred while the patient was receiving or not receiving therapy. Various combinations of bortezomib, or dexamethasone-based triplet therapy with ixazomib, carfilzomib, elotuzumab and daratumumab have all shown efficacy with manageable toxicities
15 [Minnema & Gavriatopoulou, 2018].

There have been promising advances in the treatment of MM through the optimization of regimens using the proteasome inhibitors bortezomib, carfilzomib or ixazomib in combination with immunomodulators such as thalidomide or its analogues pomalidomide or lenalidomide; also often used with dexamethasone and the CD38-
20 targeting antibody daratumumab. Nevertheless, current treatments for MM have limited efficacy – none are curative – and often have severe side effects including gastrointestinal toxicity, transient cytopenias, fatigue, peripheral neuropathy, rash, thrombocytopenia, and neutropenia [<https://www.myeloma.org/multiple-myeloma-drugs>].

The prognosis of patients diagnosed with MM is poor. It varies by subtype, stage,
25 and grade with a poorer prognosis for patients with metastases [SEER, Palombo & Anderson, 2011]. The overall 5-year survival for MM is 53.9% and for localized, distant (metastasized), and unknown (un-staged) stages of myeloma 74.8%, 52.9%, and 76.8%, respectively [SEER, 2017 statistics].

New experimental therapies including antibodies, small molecules with novel
30 mechanisms of action (e.g. venetoclax), BiTE therapy and CAR-T cells all show some promise but the prognosis remains poor and there remains an unmet need for new

treatment options to improve patients' quality of life and achieve durable responses to prolong survival [Minnema & Gavriatopoulou, 2018].

The prognosis for MM remains poor despite recent advances in treatment and there remains a need for effective treatments.

5 Summary of the invention

The present inventors have found that ^{211}At [APA] shows surprising efficacy in the treatment and prevention of MM in models of the disease.

4-[²¹¹At]Astato-L-phenylalanine (4-[²¹¹At]APA) is an astatinated derivative of phenylalanine in which the phenyl ring is labelled at the 4-position with astatine-211, an alpha particle-emitting isotope of astatine.

In the prior art, radio-halogenated phenylalanine derivatives have been considered in the treatment of malignant neoplasias. However, the focus has been on the treatment of gliomas with radio-iodinated phenylalanines which emit beta particles (and not alpha particles). The use of radio-astatinated phenylalanines in the models of multiple myeloma or in the treatment or prevention of multiple myeloma has not previously been carried out and its surprising efficacy has not been contemplated.

Accordingly, in a first embodiment, there is provided a method of treating or preventing multiple myeloma in a patient in need thereof comprising administering 4-[²¹¹At]Astat-L-phenylalanine (4-[²¹¹At]APA) or a pharmaceutically acceptable derivative thereof to the patient, thereby treating or preventing multiple myeloma in the patient..

In a second embodiment, there is provided 4-[²¹¹At]Astato-L-phenylalanine (4-[²¹¹At]APA) or a pharmaceutically acceptable derivative thereof, for use in the treatment of multiple myeloma in a patient in need thereof.

In a third embodiment, there is provided the use of 4-[²¹¹At]Astato-L-phenylalanine
25 (4-[²¹¹At]APA) or a pharmaceutically acceptable derivative thereof in the manufacture of
a medicament for treating or preventing multiple myeloma in a patient in need thereof.

In each embodiment of the invention, 4-iodo-L-phenylalanine may be co-administered with the 4-[²¹¹At]APA.

As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additives, components, integers or steps.

Further aspects of the present invention and further embodiments of the aspects described in the preceding paragraphs will become apparent from the following description, given by way of example and with reference to the accompanying drawings.

Brief description of the drawings

- Figure 1. Chemical structure of 4-[²¹¹At]Astat-L-phenylalanine, 4-[²¹¹At]APA.
- Figure 2. Kaplan-Meier survival curve of 4-[²¹¹At]APA treatment in syngeneic orthotopic MOPC315.BM mouse of MM model.
- Figure 3. 4-[²¹¹At]APA treatment efficacy in mice dosed with 1 MBq 4-[²¹¹At]APA (n=10, *p* = 0.0463), 1.5 MBq 4-[²¹¹At]APA (n=10, *p* = 0.0001) and 2 MBq 4-[²¹¹At]APA (n=10, *p* = 0.008) as compared to mice treated with 1.5 µg cold 4-IPA (4-IPA, n=10) in syngeneic orthotopic MOPC315.BM mouse MM model. * indicates significant differences.
- Figure 4. 4-[²¹¹At]APA treatment efficacy in mice treated with 2 MBq 4-[²¹¹At]APA (n=10, *p* = 0.0039), 3 MBq 4-[²¹¹At]APA (n=10, *p* = 0.0014), 4 MBq 4-[²¹¹At]APA (n=10, *p* = 0.0005) and 5 MBq 4-[²¹¹At]APA (n=10, *p* = 0.0005) as compared to mice treated with 1.5 µg cold 4-IPA (4-IPA, n=10) in syngeneic orthotopic MOPC315.BM mouse MM model.
- Figure 5. 4-[²¹¹At]APA dose response on MOPC315.BM multiple myeloma cells. (A) Results table of 4-[²¹¹At]APA activities and % MOPC315.BM survival. (B) MOPC315.BM dose response curve to 4-[²¹¹At]APA.

Detailed description of the embodiments

4-[²¹¹At]APA is a small molecule radiopharmaceutical that belongs to the class of Molecularly Targeted Radiation (MTR) drugs. MTR drugs are designed to deliver a radiation payload to tumor cells *via* a selective uptake mechanism, thereby targeting radiation to tumor cells whilst maintaining the radiation dose to healthy tissues at acceptable levels. Such treatments have the potential to be combined with the current array of chemotherapeutics, antibodies and other novel targeted agents.

The active pharmaceutical ingredient (API) of 4-[²¹¹At]APA is 4-[²¹¹At]astato-L-phenylalanine with the chemical structure shown in Figure 1. The API is prepared by the chemical transformation of a suitable precursor compound such as 4-iodo-L-phenylalanine or 4-borono-L-phenylalanine, followed by purification using reverse phase chromatography (e.g. HPLC or cartridge).

The drug product may be formulated for intravenous injection in a simple, buffered solution containing excipients L-ascorbic acid, sodium hydrogen carbonate and water for injection (WFI).

The radionuclide astatine-211 (²¹¹At) is produced by cyclotron irradiation of ²⁰⁹Bi with α -particles, has a well-defined decay profile, and can be obtained in high radionuclidic purity after isolation from the target. ²¹¹At has tractable halide-like chemistry, enabling synthetic incorporation into biomolecules such as phenylalanine.

The compound has been shown to be effective in models of multiple myeloma.

Accordingly, in a first embodiment, there is provided a method of treating or preventing multiple myeloma in a patient in need thereof by administering 4-[²¹¹At]Astato-L-phenylalanine (4-[²¹¹At]APA) or a pharmaceutically acceptable derivative thereof to said patient.

In a second embodiment, there is provided 4-[²¹¹At]Astato-L-phenylalanine (4-[²¹¹At]APA) or a pharmaceutically acceptable derivative thereof for use in the treatment of multiple myeloma in a patient in need thereof.

In a third embodiment, there is provided the use of 4-[²¹¹At]Astatato-L-phenylalanine (4-[²¹¹At]APA) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for treating or preventing multiple myeloma in a patient in need thereof.

Reference will now be made in detail to certain embodiments of the invention.

5 While the invention will be described in conjunction with the embodiments, it will be understood that the intention is not to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

10 One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described.

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned
15 or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

Reference to any prior art in the specification is not an acknowledgment or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be understood, regarded
20 as relevant, and/or combined with other pieces of prior art by a skilled person in the art.

4-[²¹¹At]APA for use in accordance with the embodiments of the present invention may be obtained using any method known to the skilled person, including the methods described herein in the Examples.

The term “pharmaceutically acceptable derivative” may include any
25 pharmaceutically acceptable salt, solvate (including a hydrate), tautomer or prodrug, or any other compound which upon administration to a subject, is capable of providing (directly or indirectly) a compound of 4-[²¹¹At]APA or an active metabolite or residue thereof.

Suitable pharmaceutically acceptable salts include, but are not limited to, salts of
30 pharmaceutically acceptable inorganic acids such as hydrochloric, sulphuric, phosphoric,

nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, malic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, toluenesulphonic, benzenesulphonic, salicylic, sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

Base salts include, but are not limited to: those formed with pharmaceutically acceptable cations, such as: sodium, potassium, lithium, calcium, magnesium, zinc, ammonium and alkylammonium; salts formed from triethylamine; alkoxyammonium salts such as those formed with ethanolamine; and salts formed from ethylenediamine, choline or amino acids such as arginine, lysine or histidine

General information on types of pharmaceutically acceptable salts and their formation is known to those skilled in the art and is as described in general texts such as "Handbook of Pharmaceutical salts" P. H. Stahl, C. G. Wermuth, 1st edition, 2002, Wiley-VCH.

Basic nitrogen-containing groups may be quarternised with such agents as lower alkyl halide, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others.

4-[²¹¹At]APA or salts, or prodrugs thereof may be provided in the form of solvates.

Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, alcohols such as methanol, ethanol or isopropyl alcohol, DMSO, acetonitrile, dimethyl formamide (DMF) and the like with the solvate forming part of the crystal lattice by either non-covalent binding or by occupying a hole in the crystal lattice.

Hydrates are formed when the solvent is water, alcoholates are formed when the solvent is alcohol. Solvates of the compounds of the present invention can be conveniently prepared or formed during the processes described herein. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues, is covalently joined to

free amino, hydroxy or carboxylic acid groups of compounds of 4-[²¹¹At]APA. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include: 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, 5 citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters, which may be covalently bonded to the above substituents of 4-[²¹¹At]APA through the carbonyl carbon prodrug side chain. Prodrugs also include phosphate derivatives of compounds of 4-[²¹¹At]APA (such as acids, salts of acids, or esters) joined through a phosphorus 10 oxygen bond to a free hydroxyl of compounds of 4-[²¹¹At]APA.

The pharmaceutically acceptable derivatives of 4-[²¹¹At]APA may demonstrate tautomerism. Tautomers are two interchangeable forms of a molecule that typically exist within an equilibrium. Any tautomers of the compounds of 4-[²¹¹At]APA may be used in the methods of the invention.

15 Any nitrogen atom in a compound of 4-[²¹¹At]APA may exist as an N-oxide. Accordingly, the present invention also contemplates pharmaceutically acceptable derivatives of 4-[²¹¹At]APA that are N-oxides of ²¹¹At]APA.

The term "treatment", as used herein in the context of treating multiple myeloma, pertains generally to treatment and therapy, whether of a human or an animal (e.g. in 20 veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment, as used herein, also covers the treatment of multiple myeloma *in vivo*, including in animals other than humans, *ex vivo*, and *in vitro*, e.g., in spheroids.

25 The term "prevention" means use of 4-[²¹¹At]APA as a prophylactic measure (i.e. prophylaxis) in a patient susceptible to or considered to be at risk of developing MM.

The phrases "administration of" and or "administering" 4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof should be understood to mean providing 4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof, to a subject in need 30 thereof.

4-[²¹¹At]APA or pharmaceutical composition comprising 4-[²¹¹At]APA may be administered to a subject by any convenient route of administration, whether systemically/peripherally or at the site of desired action, including but not limited to, oral (e.g. by ingestion); topical (including e.g. transdermal, intranasal, ocular, buccal, and sublingual);
5 pulmonary (e.g. by inhalation or insufflation therapy using, e.g. an aerosol, e.g. through mouth or nose); rectal; vaginal; parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a
10 depot, for example, subcutaneously or intramuscularly.

The recipients of the compounds and compositions are referred herein with the interchangeable terms "patient", "recipient", "individual", and "subject". These four terms are used interchangeably and refer to any human or animal (unless indicated otherwise), as defined herein.

15 In preferred embodiments, 4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof, or pharmaceutical compositions comprising the same, are administered intravenously.

While it is possible for 4-[²¹¹At]APA to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation) comprising at least 4-
20 [²¹¹At]APA, as defined above, together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions
25 comprising 4-[²¹¹At]APA, for use or when used in accordance with the methods described herein.

The term "pharmaceutically acceptable" as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of a subject (e.g. human)
30 without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also

be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Suitable carriers, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing
5 Company, Easton, Pa., 1990.

The formulations may be prepared by any methods well known in the art of pharmacy.

Formulations suitable for parenteral administration (e.g. by injection, including cutaneous, subcutaneous, intramuscular, intravenous and intradermal), include aqueous
10 and non-aqueous isotonic, pyrogen-free, sterile injection solutions which may contain anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the
15 compound to blood components or one or more organs. Examples of suitable isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection.

It will be appreciated that appropriate dosages (typically assessed in radiation units such as MBq) can vary from patient to patient. Determining the optimal dosage will
20 generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the treatments of the present invention. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or
25 materials used in combination, and the age, sex, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

30 Administration *in vivo* can be effected in one dose, continuously or intermittently (e.g. in divided doses at appropriate intervals) throughout the course of treatment.

Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being

5 selected by the treating physician.

4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof, may be provided in an "effective amount", for example when added to a pharmaceutical composition for administration to a subject. "Effective amount" is taken to mean an amount of 4-[²¹¹At]APA that will elicit a desired biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician administering 4-[²¹¹At]APA or a composition including 4-[²¹¹At]APA.

10

An "effective amount" (including a therapeutically effective or prophylactically effective amount) is an amount of 4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof, that is effective for treating or preventing MM.

15 "Therapeutically effective amount" or "therapeutic amount" refers to an amount of 4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof, that when administered to a patient suffering from MM, will have the intended therapeutic effect, e.g., alleviation, amelioration, palliation or elimination of one or more symptoms or manifestations of MM in the patient. For example, and without limitation, the relevant symptoms or manifestations of MM include, proliferation of a single clone of plasma cells engaged in the production of a specific immunoglobulin; a bone marrow with > 10% plasma cells or plasmacytoma and one of the following: monoclonal protein in serum (usually > 3g/dL), monoclonal protein in urine, lytic bone lesions; bone pain; anemia; fatigue; hypercalcemia; and renal insufficiency. The therapeutically effective amount will vary depending upon the subject and the condition being treated, the weight and age of the subject, the severity of the condition, the particular composition or excipient chosen, the dosing regimen to be followed, timing of administration, the manner of administration and the like, all of which can be determined readily by one of ordinary skill in the art.

20

25

The full therapeutic effect may not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations. For example, and

30

without limitation, a therapeutically effective amount of 4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof, in the context of treating multiple myeloma, refers to an amount of 4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof that alleviates, ameliorates, palliates, or eliminates one or more manifestations of the MM in the patient.

A prophylactically effective amount is an amount of 4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof, that when administered to a patient at risk of or suspected of having or developing MM, will have the intended preventative/prophylactic effect (including delaying the onset of disease in the subject).

An individual requiring treatment for MM in accordance with the methods described herein, may be an individual having any type of MM including smoldering or indolent multiple myeloma, active multiple myeloma, multiple solitary plasmacytomas, extramedullary plasmacytoma, secretory, non-secretory, IgG lambda or kappa light chain (LC) types. The most common immunoglobulins (Ig) made by myeloma cells in multiple myeloma are IgG, IgA and IgM, less commonly, IgD or IgE is involved. By "multiple myeloma" it is meant any type of B-cell malignancy characterised by the accumulation of terminally differentiated B -cells (plasma cells) in the bone marrow, including multiple myeloma cancers which produce light chains of kappa-type and/or light chains of lambda-type; drug resistant multiple myeloma, relapsed and/or refractory multiple myeloma, primary or secondary refractory multiple myeloma or aggressive multiple myeloma, including primary plasma cell leukemia (PCL); and/or optionally including any precursor forms of the disease, including but not limited to benign plasma cell disorders such as MGUS (monoclonal gammopathy of undetermined significance) and/or Waldenstrom's macroglobulinemia (WM, also known as lymphoplasmacytic lymphoma) which may proceed to multiple myeloma; and/or smoldering multiple myeloma (SMM), and/or indolent multiple myeloma, premalignant forms of multiple myeloma which may also proceed to multiple myeloma. With regard to premalignant or benign forms of the disease, optionally the compositions and methods thereof may be applied for prevention, in addition to or in place of treatment, for example optionally to halt the progression of the disease to a malignant form of multiple myeloma.

As used herein, "primary refractory multiple myeloma" refers to multiple myeloma, which does not respond to induction or first line therapy. "Relapsed and/or refractory

multiple myeloma" refers to a multiple myeloma unresponsive to a drug or a therapy administered prior to treatment with 4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof. For example and without limitation, relapsed and/or refractory multiple myeloma includes multiple myeloma in patients whose first progression occurs in the
5 absence of any treatment following successful treatment with a drug or a therapy; multiple myeloma in patients who progress on a treatment, or within 60 days of the treatment; and multiple myeloma in patients who progress while receiving treatment. Examples of relapsed and/or refractory multiple myeloma include, without limitation, bortezomib refractory relapse or lenalidomide refractory relapse multiple myeloma.

10 Although the invention finds application in humans, the invention is also useful for therapeutic veterinary purposes. The invention is useful for domestic or farm animals such as cattle, sheep, horses and poultry; for companion animals such as cats and dogs; and for zoo animals.

It will be appreciated that treatment MM according to the present invention may be
15 combined with other treatment methods known in the art (i.e., combination therapy).

As used herein the term "combination therapy" refers to the simultaneous or consecutive administration of two or more medications or types of therapy to treat a single disease. In particular, the term refers to the use of 4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof in combination with at least one additional medication or
20 therapy. Thus, treatment of MM using 4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof may be combined with therapies well known in the art that include, but are not limited to, radiation therapy, antibody therapy, chemotherapy or surgery or in combination therapy with other biological agents, conventional drugs, anti-cancer agents, immunosuppressants, cytotoxic drugs for cancer, chemotherapeutic agents. According to
25 at least some embodiments, treatment of MM using 4-[²¹¹At]APA or a pharmaceutically acceptable derivative thereof may be combined with an agent including but not limited to Melphalan, thalidomide (MPT), or combination Bortezomib (Velcade), melphalan, prednisone (VMP) or a combination of Lenalidomide plus low-dose dexamethasone; and/or bisphosphonates; chemotherapy (e.g., alkylating agents, vincristine, doxorubicin);
30 autologous stem cell transplantation; and corticosteroids (e.g., prednisone and dexamethasone).

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

5 **Examples**

The invention will now be described by reference to the following non-limiting examples.

Nonclinical Data

Preclinical *in vitro* and *in vivo* studies using 4-[²¹¹At]APA are reported below.

10 Summary of Nonclinical Studies

Nonclinical laboratory studies of labeled 4-[²¹¹At]APA have demonstrated that 4-[²¹¹At]APA therapy exhibited a clear dose response in tumor reduction and increased in overall survival in a validated syngeneic orthotopic mouse model of multiple myeloma (MM, MOPC315BM). Dose limiting toxicity was observed at 5 MBq in this model.

15 Furthermore, a clonogenicity assay using MOPC315.BM multiple myeloma cell line showed an increase in 4-[²¹¹At]APA uptake in response to increase in 4-[²¹¹At]APA exposure.

In vivo studies

20 A mouse model of MM was used to evaluate the efficacy of 4-[²¹¹At]APA in a model that is indicative of the human disease [Chérel, 2013]. The model developed at Nantes University is a syngeneic model, consisting in i.v. injection of MOPC 315.BM cell line in Balb/c mice, and similar to other syngeneic models reported in the literature [Manning, 1992]. In this model, tumor cells migrate after injection to the bones, thus resulting in the establishment of an orthotopic MM model. This mimics several features of the human
25 disease, including bone resorption. Between 25 to 30 days after i.v. injection, tumor growth induces mice paraplegia, starting with paralysis of one rear limb and quickly evolving into paralysis in both rear limbs. As a consequence, access to food is more difficult and mice lose weight fast. When the first signs of paralysis appear, animals

usually have to be sacrificed within 48h. 4-[²¹¹At]APA was evaluated in two separate studies, using different dose ranges.

Efficacy Study 1

MM tumor cells (MOPC 315.BM) were injected intravenously and allowed 10 days for the tumor establishment as characterized in a previous study [Manning, 1992]. The control group in the current study demonstrated high consistency and reliability of tumor development such that 100% animals developed a tumor and died between between 24 and 31 days. At 11 days after MM tumor cell injection, mice (n=10 per group) were treated with i.v. injection of 4-[²¹¹At]APA with a range of activities from 0.375 to 2 MBq. As there is no existence of cold astatine, the cold iodine analogue, 4-IPA, was added into the injection solution to achieve a constant mass of phenylalanine “carrier”, being 1.5 µg in all treatment groups. Two control groups were included in the experiment with one non-treatment group receiving PBS injection and one group injected with 1.5 µg cold 4-IPA. Animals were monitored daily during the first week after treatment, then 3 times a week until day 23 after tumor graft to reveal any treatment related adverse effects. When the first mouse was sacrificed due to humane end-point of MM symptoms, daily monitoring was conducted for the rest of animals until all animal reached end-points. Animal weight was measured at each monitoring time, 3 blood samples (at day 0, 19 and end-point) were taken for blood cell count and serum was separated and stored for further toxicity analysis. A summary of the dose groups is presented in Table 2.

Table 2. Groups used in first efficacy study.

Group	Treatment	Radiation Dose	n
Dose Group 1	4-[²¹¹ At]APA + IPA q.s. for 1.5 µg	0.375	10
Dose Group 1	4-[²¹¹ At]APA + IPA q.s. for 1.5 µg	0.75	10
Dose Group 1	4-[²¹¹ At]APA + IPA q.s. for 1.5 µg	1.0	10
Dose Group 1	4-[²¹¹ At]APA + IPA q.s. for 1.5 µg	1.5	10

Dose Group 1	4-[²¹¹ At]APA + IPA q.s. for 1.5 µg	2.0	10
Control Group 1	1.5 µg IPA	0	10
Control Group 2	PBS	0	10

Figure 2 shows the survival curve of 4-[²¹¹At]APA treatment between 0.375 and 2 MBq. The data showed moderate improvement in treatment efficacy compared to the controls (4-IPA and PBS), with median survival correlated with radiation dose. These treatments also showed no adverse effects of 4-[²¹¹At]APA, with animal loss being only due to MM cancer progression.

An analysis of the results of animals treated with 0.375 or 0.75 MBq ²¹¹At[APA] shows an effect as compared to the cold 4-IPA group (**Figure 2**). A significant increase in MM was, however, observed in mice treated with 1, 1.5 and 2 MBq 4-[²¹¹At]APA compared to the 4-IPA group (**Figure 3**), with p-values of p = 0.0463, p = 0.0001, and p = 0.008 respectively. These data demonstrate that 4-[²¹¹At]APA can efficiently delay MM cancer progression at dosing levels above 1 MBq. Since no animal showed any symptoms or loss due to ²¹¹At-APA, the radiation-related dose limiting toxicity (DLT) was not reached in this study. Higher radiation doses were used in efficacy study 2.

Efficacy Study 2

Study number 2 was designed to increase the radiation doses from 2 MBq up to 10 MBq to examine the treatment efficacy, together with some safety assessment. The study method was the same as Study 1, using the MOPC315.BM mouse MM model and dosing 4-[²¹¹At]APA at 2, 3, 4, 5, 7.5 and 10 MBq. 4-[²¹¹At]APA was dosed 11 days after MM tumor grafting with 3 animals per group (Table 3**Table 3**). Animals were monitored daily during the first week after treatment, then 3 times a week until humane end point. Animal weight was measured at each monitoring time.

Table 3. Groups used in Efficacy Study 2.

Group	Treatment	Radiation Dose	n
Dose Group 1	4-[²¹¹ At]APA + IPA q.s. 1.5 µg	2.0	10
Dose Group 2	4-[²¹¹ At]APA + IPA q.s. 1.5 µg	3.0	10
Dose Group 3	4-[²¹¹ At]APA + IPA q.s. 1.5 µg	4.0	10
Dose Group 4	4-[²¹¹ At]APA + IPA q.s. 1.5 µg	5.0	10
Dose Group 5	4-[²¹¹ At]APA + IPA q.s. 1.5 µg	7.5	10
Dose Group 6	4-[²¹¹ At]APA + IPA q.s. 1.5 µg	10	10
Control Group 1	1.5 µg IPA	0	10
Control Group 2	PBS	0	10

5 **Figure 4** shows animal survival curves in all groups of animals. 4-[²¹¹At]APA dose levels at 7.5 and 10 MBq were toxic to animals, all mice died at day 5 after dosing. Other dosing levels, 2 to 5 MBq were tolerated by animals and didn't show any radiation related toxicity. The median survival (MS) of 2 and 3 MBq were the same being 38 days; while 4 MBq had MS 43 days and longest being 5 MBq at 45 days. The 5 MBq MS was 19 days longer than the 4-IPA treated controls (MS 26 days), that demonstrated significant efficacy in treating animals with MM tumor. Body weight showed that animals tolerated up to 5 MBq well. Although up to 15% weight reduction was observed in the 5 MBq group within first 10 days of dosing, they recovered to the baseline level over the following 20 days.

15 In conclusion, two efficacy studies were conducted to examine the efficacy of 4-[²¹¹At]APA in an orthotopic MM tumor model. These studies identified the maximum tolerability of 4-[²¹¹At]APA at 5 MBq per mouse injection. This level did not result in animal

loss due to radiation-related effects and all animals recovered with normal body weight at the end of experiment. 4-[²¹¹At]APA dosed at 5 MBq showed significant increase in animal median survival up to 19 days longer than the control animals and demonstrated the potential of 4-[²¹¹At]APA as a treatment for MM.

5 In vitro studies

Clonogenicity assay

A clonogenic assay was developed to evaluate *in vitro* efficacy of 4-[²¹¹At]APA using a limiting dilution assay format in 96-well plates. MOPC315.BM cell line showed good sensitivity and cell number dependent growth, seeded at 5 cells per well or below.

10 Using optimized conditions, the assay was validated and a dose response experiment performed using the MOPC315.BM cell line at 5 cells/well, and 4-[²¹¹At]APA at activities ranging from 3.9 kBq/ml to 1 MBq/ml. Analysis was performed 21 days after exposure to 4-[²¹¹At]APA (**Figure 4**).

MOPC315.BM exhibited high sensitivity to 4-[²¹¹At]APA exposure with an EC₅₀ = 31.3
15 kBq/ml and 100% growth inhibition with activities ranging from 1 MBq/ml to 125 kBq/ml. The high *in vitro* sensitivity of MOPC315.BM to 4-[²¹¹At]APA demonstrates the potential of this agent in MM and the use of this MM cell line in *in vivo* experiments.

SYNTHESIS OF 4-[²¹¹At]APA

Material & Methods

20 All purchased chemicals as well as analytical grade solvents were of the highest commercially available purity and used without further purification unless specified. Reactions were monitored by analytical TLC on Kieselgel 60 F254 (Merck) on plastic support under UV light (254 nm) or with a Cyclone Storage Phosphor Imager (Perkin Elmer) using Packard Optiquant software. HPLC analyses were carried out on a Waters
25 Alliance e2695 HPLC system, equipped with a diode-array detector and a Flow-Star LB 513 radioactivity detector (BERTHOLD Technologies). A HPLC method was developed for compounds analyses:

Method 1: RP-HPLC (Symmetry Shield RP₈ 5 µm 4.6 mm x 150 mm, Waters) with 0.05% TFA (A) / ACN 0.05% TFA (B) as eluent. *Gradient:* 0-2 min 10-30% B ; 2-8 min

30-50% B ; 8-10 min 50-100% B ; 10-12 min 100% B ; 12-15 min 100-10% B at a flow rate of 1.5 mL.min⁻¹. UV-Vis detection was achieved with a HPLC PDA detector at 254 nm. For this method, retention time of 4-[²¹¹At]-PA is around 3.3-3.4 min.

General radiolabeling procedure: 0.5 mg of Na₂S₂O₅ (and/or 0.5 mg of SnSO₄ for radioiodination) were added to the dry astatine-211 before to be transferred to a sealed vial containing 0.2 mg of CuSO₄, 2.5 mg of citric acid, 1.25 mg of gentisic acid and 200 µL of a 4-IPA solution at 0.25 mg/mL in 0.1 N H₃PO₄. After 20 min at 100°C, the labeling efficiency was determined by TLC (1-butanol / H₂O/ CH₃COOH – 4:1:1) and HPLC (Method 1). These two methods usually indicated the formation of 4-[²¹¹At]-PA with 81-95% radiochemical yield (RCY) and 5-19% of free [²¹¹At]⁻. The reaction mixture was then dropped off on a Sep-Pak C₁₈ Plus Short cartridge (Waters), washed with 20 mL of H₂O and 2 mL of EtOH to recover the expected product. After evaporation under a stream of nitrogen and a slight heating (50°C), the dry labeled compound was dissolved in about 1 mL of PBS for a potential use in biological experiments.

Stability with respect to human serum: Fresh 4-[²¹¹At]-PA (1000 µL) prepared as described above was incubated with human serum (1000 µL) at 37°C. Aliquots of the solution were taken at different time points, and then, serum proteins were precipitated by adding 500 µL of organic solvents mixture (ACN/DCM 100:1). Supernatant was separated by centrifugation at 4000 rpm and controlled by TLC (1-butanol / H₂O/ CH₃COOH – 4:1:1) and/or HPLC (**Method 1**).

Results

Application of the procedure developed

Overall, radiolabeling was engaged in a starting activity from 76 up to 527 MBq and resulted in radiochemical yields (RCYs) always between 58 and 70%. **Table 4** summarizes the main data of all the trials carried out with an average percentage of loss for each step.

Table 4: Table summarizing data of all radiolabeling (n=7) carried out for biological investigations of 4-[²¹¹At]-PA. Range of activities measured for each step of the process are reported as well as average percentage of loss for the transfer step or purification phase.

			Average percentage of loss
Radiolabeling step	Volume of 4-IPA solution 0.25 mg/mL	200 µL	-
	Dry astatine	76.2-527 MBq	-
	Evaporation vial	4.7-16 MBq	5.8%
	Starting activity	66.8-510 MBq	-
	Labeling yield HPLC	At: 5-15% 4-[²¹¹ At]PA : 85-95%	-
	Labeling yield TLC	At: 7-19% 4-[²¹¹ At]-PA : 81-93%	-
Purification step *measured with activimeter; **final tube measured with the γ-counter	Reaction vial	0.3-3.1 MBq	0.7%
	Sep-Pak	1.0-16.7 MBq	3.3%
	V ₀	1.7-23.4 MBq	6.1%
	20 mL H ₂ O	7.4-59.2 MBq	12.3%
	2 mL EtOH	47.8-290.5 MBq*	-
	4 mL V-vial remain	2.1-14.9 MBq	2.8%

	Final tube	49-251.5 MBq**	-
RCY	-	58-70%	-

In order to illustrate these results, it is interesting to give details of the experiment performed with the highest activity. Indeed, an astatine-211 production was dedicated to this part of the project and allowed us to work with high activity. HPLC and TLC analysis of the reaction mixture clearly showed a radiolabeling yield in the expected range (88-95%). Reasonable loss was observed in the purification step and around 251 MBq of 4-[²¹¹At]-PA with high radiochemical purity (RCP) (94-95%) were obtained at the end of the process. The global RCY of 65% expresses the fact that an increase of the starting activity seems to not have any effect on the radiolabeling efficiency.

10 **References**

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CLAIMS

1. A method of treating or preventing multiple myeloma in a patient in need thereof
by administering 4-[²¹¹At]Astato-L-phenylalanine (4-[²¹¹At]APA) or a
pharmaceutically acceptable derivative thereof to said patient.
2. 4-[²¹¹At]Astato-L-phenylalanine (4-[²¹¹At]APA) or a pharmaceutically acceptable
derivative thereof for use in the treatment of multiple myeloma in a patient in need
thereof.
3. Use of 4-[²¹¹At]Astato-L-phenylalanine (4-[²¹¹At]APA) or a pharmaceutically
acceptable derivative thereof in the manufacture of a medicament for treating or
preventing multiple myeloma in a patient in need thereof.
4. A method, 4-[²¹¹At]Astato-L-phenylalanine for use, or a use according to any one
of claims 1 to 3, wherein 4-iodo-L-phenylalanine is not co-administered with the 4-
[²¹¹At]APA.

Figure 1.

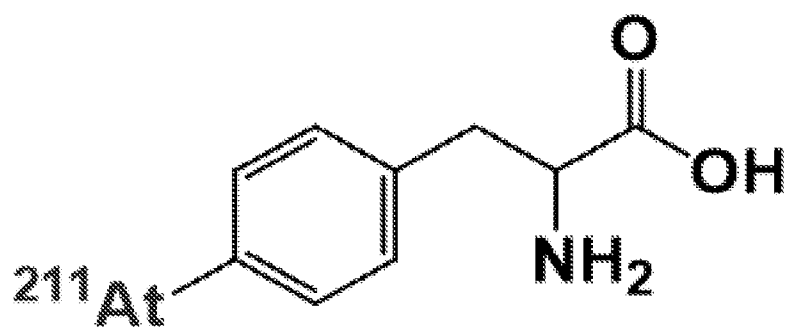


Figure 2.

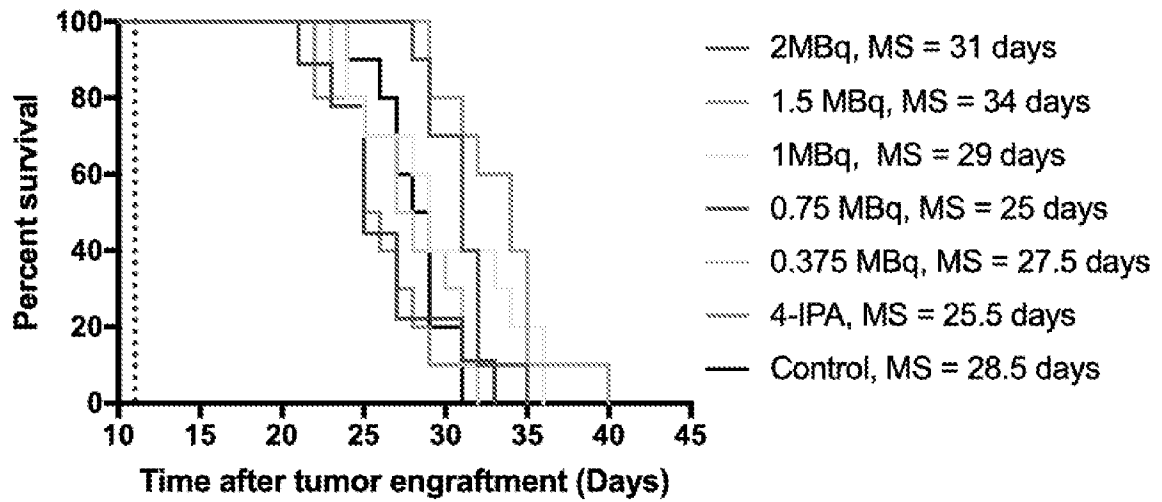


Figure 3.

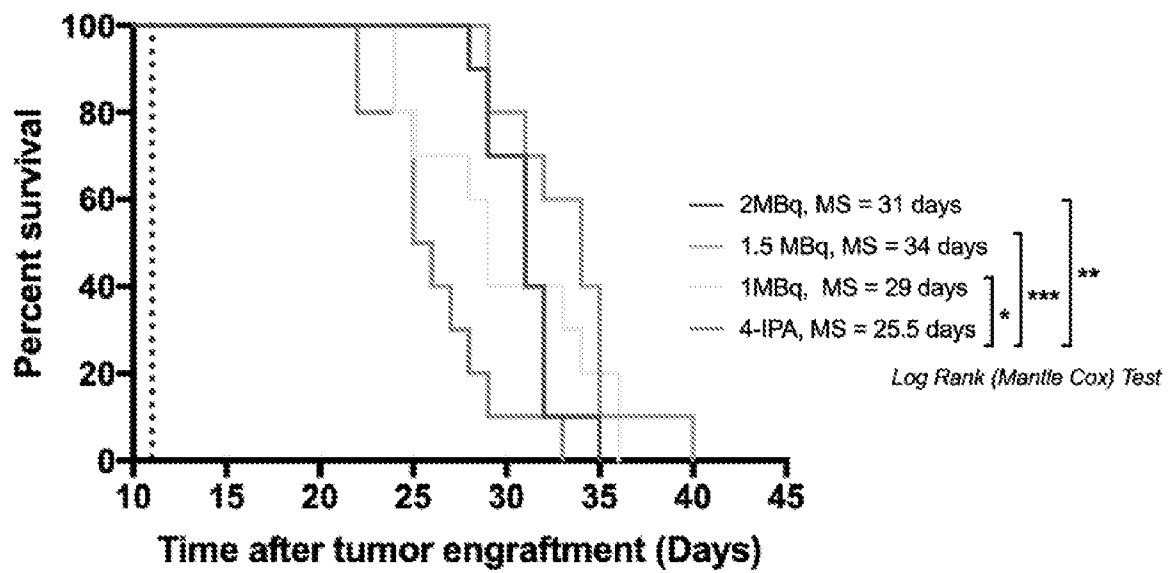


Figure 4.

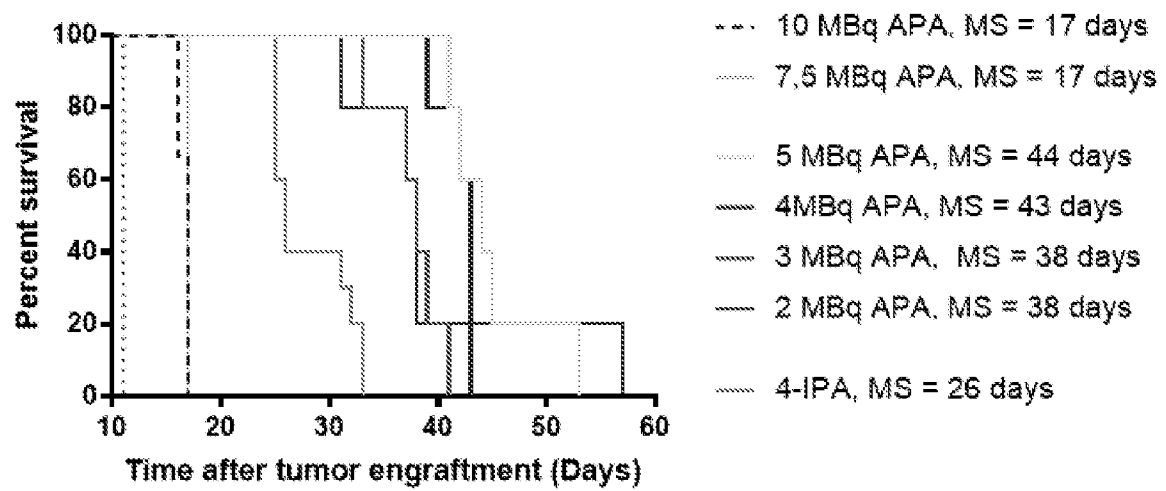
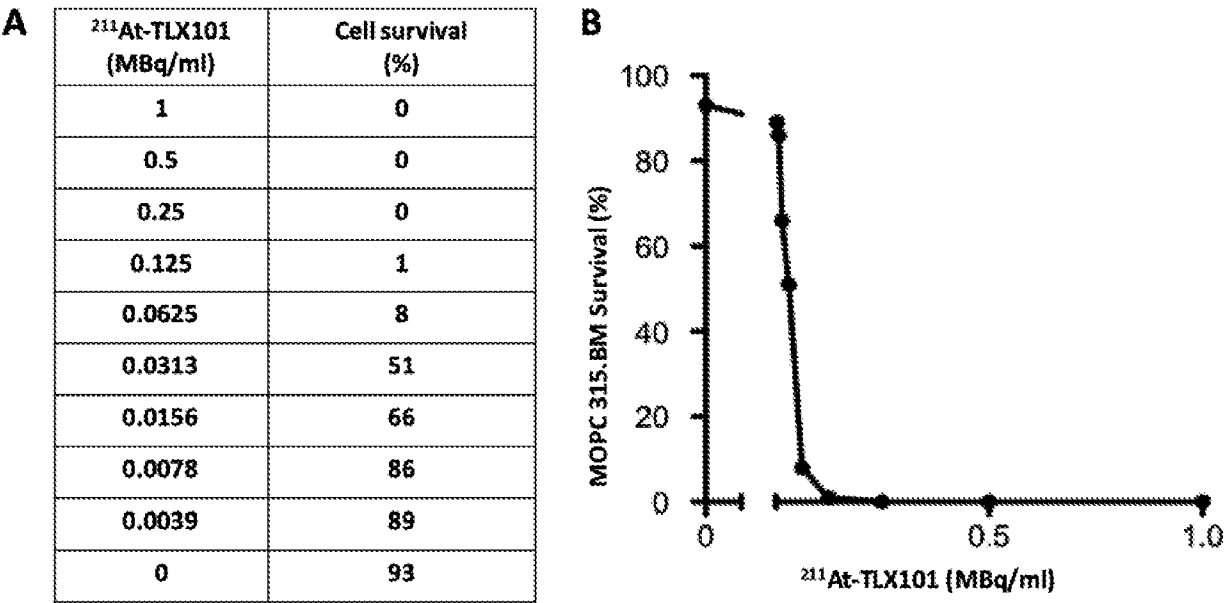


Figure 5.



A. CLASSIFICATION OF SUBJECT MATTER

A61K 51/04 (2006.01) A61P 35/00 (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

Databases consulted: PATENW, CAPLUS, Embase, Biosis, Medline, REGISTRY, Google and PubMed.

Search terms: Myeloma, Monoclonal gammopathy of undetermined significance, MGUS, Kahler's disease, Smoldering multiple myeloma, Plasma cell myeloma, Plasmacytoma, Myelomatosis, A61K51/0406, 73538-17-7, 4-[211At]Astat-L-phenylalanine, L-phenylalanine, TLX-102, Astat-L-phenylalanine, astatinated phenylalanine, astatine-211, At-211, 211-At, targeted alpha therapy, alpha emitter, alpha emitting radioisotope, radiotherapy, alpha-emitting radionuclides, LAT1 and like terms.

Inventor and Applicant name searches conducted in Auspat, Espacenet, PubMed, DOCDB, DWPI and Non-OPI IP Australia internal databases.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Documents are listed in the continuation of Box C		



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"D" document cited by the applicant in the international application	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
19 August 2021

Date of mailing of the international search report
19 August 2021

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/AU2021/050798
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WATANABE S, et al., "A convenient and reproducible method for the synthesis of astatinated 4-[211At]astato-L-phenylalanine via electrophilic desilylation", Org. Biomol Chem., 2019, 17, 165-171 Title, Abstract, Introduction, Results and Discussion and Scheme 2	1-4
X	US 20070128108 A1 (Samuel Samnick) 07 June 2007 Abstract, [0010]-[0017], [0030], Examples 1, 6-7 and 15	1-4
X	MEYER G J., et al., "Synthesis and analysis of 2-[211At]-L-phenylalanine and 4-[211At]-L-phenylalanine and their uptake in human glioma cell cultures in-vitro", Applied Radiation and Isotopes, 2010, 68, 1060-1065 Title, Abstract, Introduction, Results and Section 4.3 - Cell Uptake	1-4
X	BORRMANN N, et al., "Systemic treatment with 4-211At-L-phenylalanine enhances survival of rats with intracranial glioblastoma", Nuklearmedizin, 2013, Vol. 52, No. 6, 212-221 Title, Summary, Discussion and Animals and methods	1-4
X	WATABE T, et al., "Targeted alpha therapy using astatine (211At)-labeled phenylalanine: A preclinical study in glioma bearing mice" Oncotarget, 2020, Vol. 11, No. 15, 1388-1398 Abstract, Results, Materials and Methods, Discussion and Figures 1-3 and 6	1-4
X	O'STEEN S, et al., "The α -emitter astatine-211 targeted to CD38 can eradicate multiple myeloma in a disseminated disease model", Blood, 2019, Vol. 134, Num. 15, 1247-1256 Abstract, Introduction, Discussion and Figures 1-6	1-4
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