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(71) Applicant: **ACTINIUM PHARMACEUTICALS, INC.** [US/US]; 275 Madison Avenue, 7th Floor, New York, NY 10016 (US).

(72) Inventor: **CICIC, Dragan**; 393 17th Street, Apartment 1A, Brooklyn, NY 11215 (US).

(74) Agent: **MORRISON, Alan, J.**; Law Offices of Alan J. Morrison, 85 Broad Street, 17th Floor, New York, NY 10004 (US).

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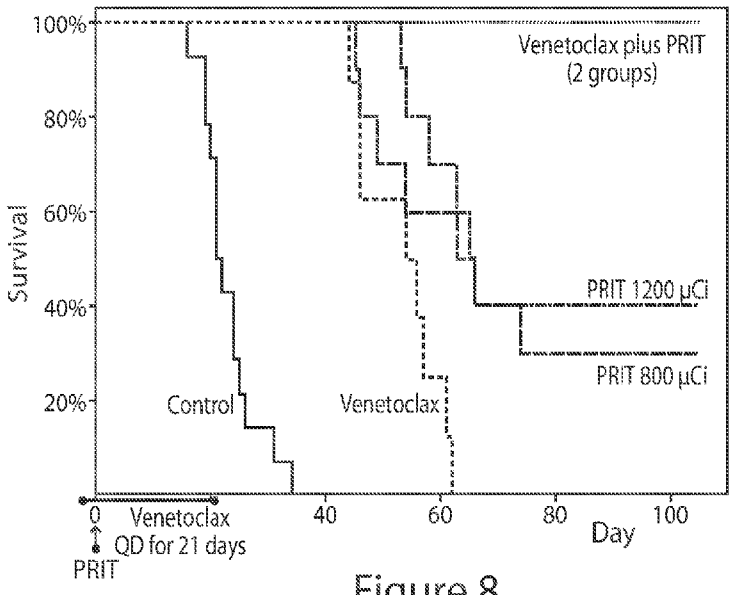

Figure 8

(57) Abstract: This invention provides a method for treating a subject afflicted with cancer, comprising administering to the subject (i) a BCL-2 inhibitor in conjunction with (ii) an alpha-emitting isotope-labeled agent that targets cancer cells in the subject, wherein the amounts of the BCL-2 inhibitor and labeled agent, when administered in conjunction with one another, are therapeutically effective. This invention also provides a method for inducing the death of a cancer cell, comprising contacting the cell with (i) a BCL-2 inhibitor in conjunction with (ii) an alpha-emitting isotope-labeled agent that targets the cancer cell, wherein the amounts of BCL-2 inhibitor and labeled agent, when concurrently contacted with the cell, are effective to induce the cell's death.

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METHOD FOR TREATING CANCER USING A BCL-2 INHIBITOR IN CONJUNCTION WITH AN ALPHA-EMITTING RADIOIMMUNOTHERAPEUTIC

This application claims the benefit of U.S. Provisional Application No. 62/491,803, filed April 28, 2017, the contents of which are incorporated herein by reference.

Throughout this application, various publications are cited. The disclosure of these publications is hereby incorporated by reference into this application to describe more fully the state of the art to which this invention pertains.

Field of the Invention

The present invention relates to treating a subject afflicted with cancer using a therapeutically effective regimen of a BCL-2 inhibitor in conjunction with an alpha-emitting isotope-labeled agent that targets cancer cells in the subject.

Background of the Invention

BCL-2 Inhibitors

BCL-2 inhibitors have potential for treating malignancies. One such BCL-2 inhibitor is venetoclax, a drug that has been approved for treating chronic lymphocytic leukemia ("CLL") (1). Venetoclax binds to the BH3-binding groove of BCL-2, displacing pro-apoptotic proteins like BIM to initiate mitochondrial outer membrane permeabilization ("MOMP"), the release of cytochrome c, and caspase activation, ultimately resulting in programmed cancer cell death (i.e., apoptosis) (2).

Apoptosis is a mechanism of cell death in cancer cells, in addition to necrosis and autophagy (3). Ideally, by changing the balance between pro-apoptotic and anti-apoptotic stimuli, venetoclax would facilitate programed cell death of cancer cells and thus improve cancer patient outcomes.

5

However, apoptosis is a complex pathway. Cancer cells can develop various mechanisms to circumvent and/or abrogate a given treatment strategy intended to cause apoptotic death (4) (as presented in Figure 1 of that reference). For example, X-linked XIAP can abrogate the blocking of BCL-2.
10 XIAP is a well-characterized inhibitor of apoptosis proteins (IAPs) (5). Indeed, the majority of human cancers harbor high levels of IAPs such as XIAP (6).

Other possible mechanisms of circumventing the effect of BCL-2 inhibitors can be seen in Figure 7. These include blocking activation of caspase 8 to
15 prevent the downstream activity of venetoclax on the BAX/BCL-2 axis. Also, stimulating or un-blocking one part of the apoptotic pathway may not be sufficient to cause apoptosis, as pro-apoptotic stimuli are still needed to trigger an apoptotic pathway (7), (8).

20 Consequently, not all cancer cells respond to BCL-2 inhibitors. In one venetoclax trial, for example, the complete response rate (including complete responses with incomplete marrow recovery) was 7.5%, even though a majority of patients (79.4%) had some level of response to venetoclax (2). In addition, venetoclax has a significant myelosuppressive effect on neutrophils,
25 with 40% of patients experiencing grade 3 and/or 4 neutropenia (2).

Radiation

Radiation is a recognized way to treat cancer. It is known that cellular effects
30 of radiation include cell cycle arrest, mutation, apoptosis, necrosis and autophagy (9). Radiation-related mediators of cellular damage include: (i) direct LED (linear energy deposition); (ii) ROS (reactive oxygen species); and (iii) RNS (reactive nitrogen species) (9).

These mediators lead to cell damage/kill/arrest via the following mechanisms: (i) DNA damage (9) (e.g., double-strand DNA breaks (most efficient), single-strand DNA breaks (less efficient, repairable), DNA base damage (least efficient, repairable), and DNA crosslinks); (ii) direct effects on the apoptotic cascade (e.g., direct activation of caspases, and damage to IAPs) (10); and (iii) bystander effects (i.e., damage or killing of cells not directly damaged by radiation, which damage or killing occurs through mediation via gap junction communication and/or cytokines from target cells) (11).

The Unpredictability of Combination Therapies

In a mouse xenograft model of venetoclax and radiation synergy (12), mice treated with a combination of venetoclax and ^{90}Y-based radioimmunotherapy had better survival rates compared to mice treated with either venetoclax or the radioimmunotherapy alone. Survival outcomes in xenografted mouse cohorts are shown in Figure 8.

Importantly, however, these mouse results may not be applicable to humans. Indeed, there are various factors that could render infeasible the treatment of cancer in humans using radiation in conjunction with venetoclax.

One such factor is oxygenation. Xenografted mice had small tumor masses in Fred Hutchinson Cancer Research Center experiments. Diffuse large B-cell lymphoma ("DLBCL") tumor xenografts were treated at a volume of 50 mm^3, implying a tumor diameter of under 0.5 cm. For DLBCL patients in an MD Anderson study, ~25% of patients had tumor diameters greater than 7 cm (13). In large xenografted tumors in rats, it was found that in tumors larger than 3.5 cm^3, baseline hypoxia was greater than 80%, while tumors smaller than 2.5 cm^3 had baseline hypoxia of ~20% (14). Hypoxia confers resistance to irradiation by lowering the creation of ROS (15), (16), (17). High tumor burden with hypoxic areas in human disease would significantly abrogate beta radiation-induced ROS and RNS.

Another such factor is the range of feasible dose levels. In mouse experiments on candidate therapeutics, the mice typically receive doses of drug weight per body weight that cannot be applied to humans. For example, in the ^{90}Y / venetoclax combination experiment described above, mice were treated with doses of 800 µCi and 1,200 µCi per mouse (whereby 800 µCi was used in combination with venetoclax). Eight hundred µCi in a mouse would correspond to 3,000 mCi in an average human. By comparison, Zevalin® (^{90}Y-RIT, ibritumomab tiuxetan) can be administered to patients at a dose not exceeding 32 mCi (18).

There remains a need for a cancer therapy that solves the problems seen with BCL-2 inhibitors such as venetoclax and radiation therapies such as ^{90}Y-based therapies.

Summary of the Invention

This invention provides a method for treating a subject afflicted with cancer, comprising administering to the subject (i) a BCL-2 inhibitor in conjunction with (ii) an alpha-emitting isotope-labeled agent that targets cancer cells in the subject, wherein the amounts of the BCL-2 inhibitor and labeled agent, when administered in conjunction with one another, are therapeutically effective.

This invention also provides a method for treating a human subject afflicted with acute myeloid leukemia, comprising administering to the subject (i) venetoclax in conjunction with (ii) ^{225}Ac-labeled HuM195, wherein the amounts of venetoclax and ^{225}Ac-labeled HuM195, when administered in conjunction with one another, are therapeutically effective.

This invention further provides a method for inducing the death of a cancer cell, comprising contacting the cell with (i) a BCL-2 inhibitor in conjunction with (ii) an alpha-emitting isotope-labeled agent that targets the cancer cell, wherein the amounts of BCL-2 inhibitor and labeled agent, when concurrently contacted with the cell, are effective to induce the cell's death.

Finally, this invention also provides a method for inducing the death of an acute myeloid leukemic cell, comprising contacting the cell with (i) venetoclax in conjunction with (ii) ^{225}Ac-labeled HuM195, wherein the amounts of venetoclax and ^{225}Ac-labeled HuM195, when concurrently contacted with the cell, are effective to induce the cell's death.

Brief Description of the Figures

Figure 1

This figure shows a schematic diagram of the expression plasmids for HuM195. The humanized VL and VH exons of HuM195 are flanked by XbaI sites. The VL exon was inserted into mammalian expression vector pVk, and the VH exon into pVg1 (Co, et al., J. Immunol. 148:1149-1154, 1992).

Figure 2

This figure shows the complete sequence of the HuM195 light chain gene cloned in pVk between the XbaI and BamHI sites. The nucleotide number indicates its position in the plasmid pVk-HuM195. The VL and CK exons are translated in single letter code; the dot indicates the translation termination codon. The mature light chain begins at the double-underlined aspartic acid (D). The intron sequence is in italics. The polyA signal is underlined.

Figure 3

This figure shows the complete sequence of the HuM195 heavy chain gene cloned in pVg1 between the XbaI and BamHI sites. The nucleotide number indicates its position in the plasmid pVg1-HuM195. The VH, CH1, H, CH2 and CH3 exons are translated in single letter code; the dot indicates the translation termination codon. The mature heavy chain begins at the double-underlined glutamine (Q). The intron sequences are in italics. The polyA signal is underlined.

Figure 4

This figure shows the structure of ^{225}Ac-Lintuzumab (^{225}Ac-HuM195).

Figure 5

This figure shows a flowchart for the production of ^{225}Ac-HuM195.

Figure 6

This figure shows a dosing protocol for ^{225}Ac-Lintuzumab (^{225}Ac-HuM195) treatment of AML.

Figure 7

This figure shows a schematic of apoptotic cell death and mechanisms of cancer cells resistance to apoptosis (modified from (4)).

Figure 8

This figure shows a diagram of survival of xenografted mice treated with venetoclax alone, targeted beta radioimmunotherapy alone, and a combination of venetoclax and targeted beta radioimmunotherapy. In Rec-1-bearing mice, venetoclax had no effect alone ($p = .12$), 800μCi PRIT lengthened survival time 111% beyond controls ($p = .0001$), while the combination extended survival 483% beyond controls and cured 40% ($p = .001$, combination group > PRIT alone). In the U2932 xenograft model, venetoclax alone doubled survival time compared to controls ($p < .0001$) and 800μCi PRIT alone doubled survival and cured 30%. Combination treatments cured 100% (12).

Figure 9

This figure shows a comparison between beta and alpha radiation mechanisms of apoptotic cell killing. As the figure shows, alpha radiation is significantly more potent than beta radiation (~700 times); causes more dsDNA breaks than beta radiation; does not depend on tissue oxygenation and the cell division phase; and can overcome cellular resistance to beta and gamma radiation and cytotoxic chemotherapy. These findings are collectively supported by (9)-(11) and (22)-(24).

Detailed Description of the Invention

This invention provides methods for treating a subject afflicted with cancer. These methods comprise administering to the subject two types of agents in conjunction with one another. The first type of agent is a BCL-2 inhibitor such as venetoclax. The second type is an alpha-emitting isotope-labeled agent, such as ^{225}Ac-labeled HuM195, that targets cancer cells in the subject.

Definitions

In this application, certain terms are used which shall have the meanings set forth as follows.

As used herein, “administer”, with respect to an agent, means to deliver the agent to a subject’s body via any known method. Specific modes of administration include, without limitation, intravenous, oral, sublingual, transdermal, subcutaneous, intraperitoneal, intrathecal and intra-tumoral administration.

In addition, in this invention, the various antibodies and other antigen-targeting agents used can be formulated using one or more routinely used pharmaceutically acceptable carriers. Such carriers are well known to those skilled in the art. For example, injectable drug delivery systems include solutions, suspensions, gels, microspheres and polymeric injectables, and can comprise excipients such as solubility-altering agents (e.g., ethanol, propylene glycol and sucrose) and polymers (e.g., polycaprylactones and PLGA's).

As used herein, the term “agent”, whether in reference to a BCL-2 inhibitor or an alpha-emitting isotope-labeled agent, can be any type of compound or composition useful for such purpose. Types of agents include, without limitation, antibodies, other protein-based drugs, peptides, nucleic acids, carbohydrates and small molecules drugs.

As used herein, the term “alpha-emitting isotope” includes, without limitation, ^{225}Ac, ^{213}Bi and ^{213}Po. Methods for affixing an alpha-emitting isotope to an antibody (i.e., “labeling” an antibody with an alpha-emitting isotope) are well known.

As used herein, the term “antibody” includes, without limitation, (a) an immunoglobulin molecule comprising two heavy chains and two light chains and which recognizes an antigen; (b) polyclonal and monoclonal

immunoglobulin molecules; (c) monovalent and divalent fragments thereof, and (d) bi-specific forms thereof. Immunoglobulin molecules may derive from any of the commonly known classes, including but not limited to IgA, secretory IgA, IgG and IgM. IgG subclasses are also well known to those in the art and include, but are not limited to, human IgG1, IgG2, IgG3 and IgG4. Antibodies can be both naturally occurring and non-naturally occurring. Furthermore, antibodies include chimeric antibodies, wholly synthetic antibodies, single chain antibodies, and fragments thereof. Antibodies may be human, humanized or nonhuman.

As used herein, an "anti-CD33 antibody" is an antibody that binds to any available epitope of CD33. In one embodiment, the anti-CD33 antibody binds to the epitope recognized by the antibody HuM195.

As used herein, the term "burden", when used in connection with a cancerous cell, means quantity. So, a cancerous cell "burden" means the quantity of cancerous cells. Cancerous cells have a burden with respect to their tissue of origin (i.e., the primary site of disease), such as the "bone marrow blast burden" in the case of AML. Cancerous cells also have a burden with respect to one or more tissues other than those of origin, such as the blast burden in blood, liver and spleen in the case of AML. The term "peripheral burden" relates to such cells. The peripheral burden of cancerous cells, such as blasts in the case of AML, can be measured in different ways with different outcomes. For example, in the case of AML, the "peripheral blast burden" can be measured as the total blast population outside of the bone marrow, or the total blast population of the blood, spleen and liver combined, or simply the blast population of the blood as measured in cells per unit volume. As used herein in connection with AML and other cancers originating in the bone marrow, and unless stated otherwise, the term "peripheral cancerous cell burden" (e.g., peripheral blast burden) refers to the cancerous cell population of the blood as measured in cells per unit volume (e.g., cells/μl). This blood-based measurement is a useful proxy for the more cumbersome measurements of spleen and liver burdens, for example.

Herein, a peripheral cancerous cell burden in a subject is "high" if, when the subject is administered an agent (e.g., an antibody) targeting a hematologic malignancy-associated antigen at the maximum safe dose, the agent does not reach the primary site of disease in a sufficient amount to bind to more than 90% of its target antigens at that site. Conversely, a peripheral cancerous cell burden in a subject is "low" if, when the subject is administered an agent (e.g., an antibody) targeting a hematologic malignancy-associated antigen at the maximum safe dose, the agent reaches the primary site of disease in a sufficient amount to bind to more than 90% of its target antigens at that site. In the case of AML, examples of low peripheral blast burden are those yielding blood blast burdens at or below 1,000 blast cells/μl, at or below 500 blast cells/μl, at or below 400 blast cells/μl, at or below 300 blast cells/μl, at or below 200 blast cells/μl, at or below 100 blast cells/μl, and at or below 50 blast cells/μl.

A "hematologic malignancy", also known as a blood cancer, is a cancer that originates in blood-forming tissue, such as the bone marrow or other cells of the immune system. Hematologic malignancies include, without limitation, leukemias (such as AML, acute promyelocytic leukemia, acute lymphoblastic leukemia, acute mixed lineage leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, hairy cell leukemia and large granular lymphocytic leukemia), myelodysplastic syndrome (MDS), myeloproliferative disorders (polycythemia vera, essential thrombocytosis, primary myelofibrosis and chronic myeloid leukemia), lymphomas, multiple myeloma, and MGUS and similar disorders.

As used herein, a "hematologic malignancy-associated antigen" can be, for example, a protein and/or carbohydrate marker found exclusively or predominantly on the surface of a cancer cell associated with that particular malignancy. Examples of hematologic malignancy-associated antigens include, without limitation, CD20, CD33, CD38, CD45, CD52, CD123 and CD319.

The antibody "HuM195" (also known as lintuzumab) is known, as are methods of making it. Likewise, methods of labeling HuM195 with ^{225}Ac are known. These methods are exemplified, for example, in Scheinberg, et al., U.S. Patent No. 6,683,162. This information is also exemplified in the examples and figures below.

As used herein, administering to a subject a BCL-2 inhibitor "in conjunction with" an alpha-emitting isotope-labeled agent that targets cancer cells in the subject means administering the BCL-2 inhibitor before, during or after administration of the labeled agent. This administration includes, without limitation, the following scenarios: (i) the BCL-2 inhibitor is administered first (e.g., orally once per day for 21 days, 28 days, 35 days, 42 days, 49 days, or a longer period during which the cancer being treated does not progress and during which the BCL-2 inhibitor does not cause unacceptable toxicity), and the labeled agent is administered second (e.g., intravenously in a single dose or a plurality of doses over a period of weeks); (ii) the BCL-2 inhibitor is administered concurrently with the labeled agent (e.g., the BCL-2 inhibitor is administered orally once per day for n days, and the labeled agent is administered intravenously in a single dose on one of days 2 through n-1 of the BCL-2 inhibitor regimen); (iii) the BCL-2 inhibitor is administered concurrently with the labeled agent (e.g., the BCL-2 inhibitor is administered orally for a duration of greater than one month (e.g., orally once per day for 35 days, 42 days, 49 days, or a longer period during which the cancer being treated does not progress and during which the BCL-2 inhibitor does not cause unacceptable toxicity), and the labeled agent is administered intravenously in a single dose on a day within the first month of the BCL-2 inhibitor regimen); and (iv) the labeled agent is administered first (e.g., intravenously in a single dose or a plurality of doses over a period of weeks), and the BCL-2 inhibitor is administered second (e.g., orally once per day for 21 days, 28 days, 35 days, 42 days, 49 days, or a longer period during which the cancer being treated does not progress and during which the BCL-2 inhibitor does not cause unacceptable toxicity). Additional permutations are provided below in the Examples section.

As used herein, the term "subject" includes, without limitation, a mammal such as a human, a non-human primate, a dog, a cat, a horse, a sheep, a goat, a cow, a rabbit, a pig, a rat and a mouse. Where the subject is human, the subject can be of any age. For example, the subject can be 60 years or older, 65 or older, 70 or older, 75 or older, 80 or older, 85 or older, or 90 or older. Alternatively, the subject can be 50 years or younger, 45 or younger, 40 or younger, 35 or younger, 30 or younger, 25 or younger, or 20 or younger. For a human subject afflicted with AML, the subject can be newly diagnosed, or relapsed and/or refractory, or in remission.

As used herein, a "sub-saturating dose" of an agent targeting an antigen (e.g., CD33) or marker (e.g., BCL-2) is one that introduces into the subject's body fewer target antigen-binding sites (e.g., Fab's) than there are target antigens, or fewer target marker-binding sites (e.g., venetoclax molecules) than there are target markers, as applicable. By way of example, for an anti-CD33 antibody, a sub-saturating dose is one that introduces into the subject's body fewer CD33-binding sites than there are CD33 molecules. In one embodiment, a sub-saturating dose of an agent targeting a hematologic malignancy-associated antigen is one where the ratio of target antigen-binding sites to target antigens is less than or equal to 9:10. In another embodiment, the ratio of target antigen-binding sites to target antigens is less than or equal to 1:2, less than or equal to 1:5, less than or equal to 1:10, less than or equal to 1:20, or less than or equal to 1:100. By way of additional example, for a BCL-2 inhibitor, a sub-saturating dose is one that introduces into the subject's body fewer BCL-2-binding sites than there are BCL-2 proteins. In one embodiment, a sub-saturating dose of a BCL-2 inhibitor is one where the ratio of inhibitor to BCL-2 protein is less than or equal to 9:10. In another embodiment, the ratio of target antigen-binding sites to target antigens is less than or equal to 1:2, less than or equal to 1:5, less than or equal to 1:10, less than or equal to 1:20, or less than or equal to 1:100. In a further embodiment, a "sub-saturating dose" of a BCL-2 inhibitor (e.g., venetoclax) is a dose lower than the inhibitor's maximum approved dose in humans (e.g., below 400 mg per day, below 300 mg per day, below 200 mg

per day, below 100 mg per day, below 50 mg per day, or below 10 mg per day).

For an agent such as an antibody labeled with an alpha-emitting isotope, the majority of the drug administered to a subject typically consists of non-labeled antibody, with the minority being the labeled antibody. Thus, in one embodiment, a sub-saturating dose of an agent targeting a hematologic malignancy-associated antigen is one where the ratio of total (i.e., labeled and unlabeled) target antigen-binding sites to target antigens is less than or equal to 9:10 (and can be less than or equal to 1:2, less than or equal to 1:5, less than or equal to 1:10, less than or equal to 1:20, or less than or equal to 1:100). In another embodiment, a sub-saturating dose of an agent targeting a hematologic malignancy-associated antigen is one where the ratio of labeled target antigen-binding sites to target antigens is less than or equal to 9:10 (and can be less than or equal to 1:2, less than or equal to 1:5, less than or equal to 1:10, less than or equal to 1:20, or less than or equal to 1:100).

Sub-saturating doses of labeled agent used in connection with this invention include, for example, a single administration, and two or more administrations (i.e., fractions). The amount administered in each dose can be measured, for example, by labeled radiation activity (e.g., μCi/kg) or antibody weight (e.g., μg/kg or μg/m^2). In the case of ^{225}Ac-HuM195 for treating AML, human dosing regimens include the following, without limitation: (i) 2 x < 0.5 μCi/kg, 2 x 0.5 μCi/kg, 2 x 1.0 μCi/kg, 2 x 1.5 μCi/kg, or 2 x 2.0 μCi/kg, where the fractions are administered one week apart; (ii) < 0.5 μCi/kg, or from 0.5 μCi/kg to 10 μCi/kg; (iii) 2 x < 7.5 μg/kg, 2 x 7.5 μg/kg, 2 x 10 μg/kg, or 2 x 12.5 μg/kg, where the fractions are administered one week apart; or (iv) < 15 μg/kg, or from 15 μg/kg to 50 μg/kg.

As used herein, an amount of BCL-2 inhibitor and an amount of alpha-emitting isotope-labeled agent that targets cancer cells in the subject, when administered in conjunction with each other, are “therapeutically effective” if the subject is treated.

As used herein, “treating” a subject afflicted with a disorder shall include, without limitation, (i) slowing, stopping or reversing the disorder's progression, (ii) slowing, stopping or reversing the progression of the disorder’s symptoms, (iii) reducing the likelihood of the disorder’s recurrence, and/or (iv) reducing the likelihood that the disorder’s symptoms will recur. In the preferred embodiment, treating a subject afflicted with a disorder means (i) reversing the disorder's progression, ideally to the point of eliminating the disorder, and/or (ii) reversing the progression of the disorder’s symptoms, ideally to the point of eliminating the symptoms, and/or (iii) reducing or eliminating the likelihood of relapse (i.e., consolidation, which is a common goal of post-remission therapy for AML and, ideally, results in the destruction of any remaining leukemia cells).

The treatment of hematologic malignancy, such as the treatment of AML, can be measured according to a number of clinical endpoints. These include, without limitation, survival time (such as weeks, months or years of improved survival time, e.g., one, two or more months’ of additional survival time), and response status (such as complete remission (CR), complete remission with incomplete platelet recovery (CRp), complete remission with incomplete peripheral blood recovery (CRi), morphologic leukemia-free state (MLFS) and partial remission (PR)).

In one embodiment, treatment of hematologic malignancy, such as the treatment of AML, can be measured in terms of remission. Included here are the following non-limiting examples. (1) Morphologic complete remission (“CR”): ANC ≥ 1,000/mcl, platelet count ≥ 100,000/mcl, < 5% bone marrow blasts, no Auer rods, no evidence of extramedullary disease. (No requirements for marrow cellularity, hemoglobin concentration). (2) Morphologic complete remission with incomplete blood count recovery (“CRi”): Same as CR but ANC may be < 1,000/mcl and/or platelet count < 100,000/mcl. (3) Partial remission (PR): ANC ≥ 1,000/mcl, platelet count > 100,000/mcl, and at least a 50% decrease in the percentage of marrow aspirate blasts to 5-25%, or marrow blasts < 5% with persistent Auer rods. These criteria and others are known, and are described, for example, in

SWOG Oncology Research Professional (ORP) Manual Volume I, Chapter 11A, Leukemia (2014).

Embodiments of the Invention

This invention employs the use of alpha particles. These particles induce apoptosis in target cells, e.g., leukemic cells (10), (19). Alpha-emitters and beta-emitters induce apoptosis with different efficiencies at comparable activities in leukemic cells (10). Alpha particles can overcome doxorubicin-resistance, CD95-resistance, and radio-resistance to beta-irradiation and gamma-irradiation in leukemic cells (10). The particles induce apoptosis via: (i) double-strand DNA breaks (20), (21); (ii) activation of caspases; (iii) the fact that [^{213}Bi]anti-CD45 activates caspases 2, 3, 8 and 9 through the mitochondrial pathway independent of the CD95 ligand/receptor system (10), (19); and (iv) inactivation of XIAP and Bcl-XL (19).

Specifically, this invention provides a first therapeutic method. This first method is for treating a subject afflicted with cancer, comprising administering to the subject (i) a BCL-2 inhibitor in conjunction with (ii) an alpha-emitting isotope-labeled agent that targets cancer cells in the subject, wherein the amounts of the BCL-2 inhibitor and labeled agent, when administered in conjunction with one another, are therapeutically effective.

This invention also provides a second therapeutic method. This second method is for treating a human subject afflicted with acute myeloid leukemia, comprising administering to the subject (i) venetoclax in conjunction with (ii) ^{225}Ac-labeled HuM195, wherein the amounts of venetoclax and ^{225}Ac-labeled HuM195, when administered in conjunction with one another, are therapeutically effective.

Preferably in the first and second therapeutic methods, the subject is human. In one embodiment of the first and second therapeutic methods, the cancer is a hematologic malignancy, and preferably is a leukemia such as acute myeloid leukemia.

In the preferred embodiment of the first and second therapeutic methods, the BCL-2 inhibitor is venetoclax. Also in the preferred embodiment of the first and second therapeutic methods, the alpha-emitting isotope-labeled agent is an anti-CD33 antibody labeled with an alpha-emitting isotope, ideally ^{225}Ac-labeled HuM195. In these methods, the BCL-2 inhibitor, the labeled agent, or both, are preferably administered (i) in sub-saturating doses, and/or (ii) in doses that are less than (and/or shorter duration than) those presently prescribed on their respective labels. Also in these methods, the subject's peripheral blast burden is preferably low, and the methods preferably do not cause unacceptable levels of neutropenia.

This invention provides a third method. This third method is for inducing the death of a cancer cell, comprising contacting the cell with (i) a BCL-2 inhibitor in conjunction with (ii) an alpha-emitting isotope-labeled agent that targets the cancer cell, wherein the amounts of BCL-2 inhibitor and labeled agent, when concurrently contacted with the cell, are effective to induce the cell's death.

Preferably, the cancer cell is a human cancer cell. In one embodiment, the cancer cell is a hematologic cell, and preferably is a leukemic cell such as an acute myeloid leukemic cell.

In the preferred embodiment, the BCL-2 inhibitor is venetoclax. Also in the preferred embodiment, the alpha-emitting isotope-labeled agent is an anti-CD33 antibody labeled with an alpha-emitting isotope, ideally ^{225}Ac-labeled HuM195.

This invention also provides a fourth method. This fourth method is for inducing the death of an acute myeloid leukemic cell, comprising contacting the cell with (i) venetoclax in conjunction with (ii) ^{225}Ac-labeled HuM195, wherein the amounts of venetoclax and ^{225}Ac-labeled HuM195, when concurrently contacted with the cell, are effective to induce the cell's death.

Finally, this invention provides two articles of manufacture. The first article comprises (i) a BCL-2 inhibitor (e.g., venetoclax) and (ii) a label instructing the user (e.g., the patient or healthcare provider) to treat a subject afflicted with cancer (e.g., acute myeloid leukemia) by administering the BCL-2 inhibitor to the subject in conjunction with an alpha-emitting isotope-labeled agent that targets cancer cells in the subject (e.g., ^{225}Ac-labeled HuM195), wherein the amounts of the BCL-2 inhibitor and labeled agent, when administered in conjunction with one another, are therapeutically effective. The second article comprises (i) an alpha-emitting isotope-labeled agent that targets cancer cells (e.g., ^{225}Ac-labeled HuM195) and (ii) a label instructing the user to treat a subject afflicted with cancer (e.g., acute myeloid leukemia) by administering the labeled agent to the subject in conjunction with a BCL-2 inhibitor (e.g., venetoclax), wherein the amounts of the BCL-2 inhibitor and labeled agent, when administered in conjunction with one another, are therapeutically effective.

Wherever applicable, the methods of the subject invention may also be performed using pre-targeted radioimmunotherapy (PRIT). A PRIT-based method comprises the steps of (i) administering a monoclonal antibody labeled with a marker (e.g., streptavidin), (ii) then administering a suitable clearing agent (e.g., a biotin galactose clearing agent), and (iii) administering an alpha-emitting isotope-labeled agent that specifically binds to the marker (e.g., ^{225}Ac-labeled biotin). Therefore, the various embodiments of the invention relating to non-PRIT-based methods for administering an alpha-emitting isotope-labeled agent apply, *mutatis mutandis*, to these PRIT-based methods.

This invention will be better understood by reference to the examples which follow, but those skilled in the art will readily appreciate that the specific examples detailed are only illustrative of the invention as described more fully in the claims which follow thereafter.

Examples

Example 1 – Structure of ^{225}Ac-Lintuzumab (^{225}Ac-HuM195)

^{225}Ac-Lintuzumab includes three key components; humanized monoclonal antibody HuM195 (generic name, lintuzumab), the alpha-emitting radioisotope ^{225}Ac, and the bi-functional chelate 2-(p-isothiocyanatobenzyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (p-SCN-Bn-DOTA). As depicted in Figure 4, HuM195 is radiolabeled using the bi-functional chelate p-SCN-Bn-DOTA that binds to ^{225}Ac and that is covalently attached to the IgG via a lysine residue on the antibody.

Example 2 – p-SCN-Bn-DOTA

DOTA, 2-(4-Isothiocyanatobenzyl)-1,4,7,10-tetraazacyclododecane tetraacetic acid (Macrocyclics item code B205-GMP) is synthesized by a multi-step organic synthesis that is fully described in U.S. Patent No. 4,923,985.

Example 3 – Preparation of ^{225}Ac-Lintuzumab (^{225}Ac-HuM195)

The procedure for preparing ^{225}Ac-Lintuzumab is based on the method described by Michael R. McDevitt, "Design and synthesis of ^{225}Ac radioimmuno-pharmaceuticals, Applied Radiation and Isotope", 57 (2002), 841-847. The procedure involves radiolabeling the bi-functional chelate, p-SCN-Bn-DOTA, with the radioisotope ^{225}Ac, followed by binding of the radiolabeled p-SCN-Bn-DOTA to the antibody (HuM195). The construct, ^{225}Ac-p-SCN-Bn-DOTA-HuM195, is purified using 10 DG size exclusion chromatography and eluted with 1% human serum albumin (HSA). The resulting drug product, Ac^{225}-Lintuzumab, is then passed through a 0.2 μm sterilizing filter.

Example 4 – Process Flow for Preparation of ^{225}Ac-Lintuzumab (^{225}Ac-HuM195)

The procedure, shown in Figure 5, begins with confirming the identity of all components and the subsequent QC release of the components to production. The ^{225}Ac is assayed to confirm the level of activity and is reconstituted to the desired activity concentration with hydrochloric acid. A vial of lyophilized p-SCN-Bn-DOTA is reconstituted with metal-free water to a concentration of 10 mg/mL. To the actinium reaction vial, 0.02 ml of ascorbic acid solution (150 mg/mL) and 0.05 ml of reconstituted p-SCN-Bn-DOTA are added and the pH adjusted to between 5 and 5.5 with 2M tetramethylammonium acetate (TMAA). The mixture is then heated at 55 ± 4°C for 30 minutes.

To determine the labeling efficiency of the ^{225}Ac-p-SCN-Bn-DOTA, an aliquot of the reaction mixture is removed and applied to a 1 ml column of Sephadex C25 cation exchange resin. The product is eluted in 2-4 ml fractions with a 0.9% saline solution. The fraction of ^{225}Ac activity that elutes is ^{225}Ac-p-SCN-Bn-DOTA and the fraction that is retained on the column is un-chelated, unreactive ^{225}Ac. Typically, the labeling efficiency is greater than 95%.

To the reaction mixture, 0.22 ml of previously prepared HuM195 in DTPA (1 mg HuM195) and 0.02 ml of ascorbic acid are added. The DTPA is added to bind any trace amounts of metals that may compete with the labeling of the antibody. The ascorbic acid is added as a radio-protectant. The pH is adjusted with carbonate buffer to pH 8.5-9. The mixture is heated at 37 ± 3 ^{0}C for 30 minutes.

The final product is purified by size exclusion chromatography using 10DG resin and eluted with 2 ml of 1% HSA. Typical reaction yields are 10%.

Example 5 – Venetoclax And Its Normal Dosing Regimen

Venetoclax is sold by Genentech (San Francisco, CA) under the brand name Venclexta™. According to the FDA's Venclexta™ label, this drug "is a BCL-2 inhibitor indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion … who have received at least one prior

therapy." Venclexta™ is sold in tablet form at 10 mg, 50 mg and 100 mg. Therapy is to be initiated "at 20 mg once daily for 7 days, followed by a weekly ramp-up dosing schedule to the recommended daily dose of 400 mg." The ramp-up dosing schedule is as follows: week 1, 20mg/day; week 2, 50mg/day; week 3, 100mg/day; week 4, 200mg/day; and week 5 and beyond, 400mg/day. This dosing regimen is referred to herein as the "normal" human dosing regimen for venetoclax, regardless of the disorder treated. Any dosing regimen having a shorter duration (e.g., 21 days) or involving the administration of less venetoclax (e.g., 20mg/day for a total of 21 days) is referred to herein as a "reduced" human dosing regimen. The terms "normal" human dosing regimen and "reduced" human dosing regimen also apply, *mutatis mutandis*, to any other BCL-2 inhibitor with respect to its approved or otherwise customary dosing regimen.

Also envisioned is a "normal" murine dosing regimen and a "reduced" murine dosing regimen, each being commensurate with mouse body weight and tumor xenograft size. Moreover, the "normal" murine dosing regimen has a duration of at least 21 days.

Example 6 – ^{225}Ac-HuM195 And Its Normal Dosing Regimen

In the case of ^{225}Ac-HuM195, the "normal" human dosing regimen (regardless of the disorder treated), as this term is used herein, includes either of the following: (i) 2 x 2.0 μCi/kg, where the fractions are administered one week apart; and (ii) 4.0 μCi/kg when delivered in a single administration. Any dosing regimen involving the administration of less ^{225}Ac-HuM195 (e.g., 2.0 μCi/kg when delivered in a single administration) is referred to herein as a "reduced" human dosing regimen (which may also be considered a sub-saturating dose). The terms "normal" human dosing regimen and "reduced" human dosing regimen also apply, *mutatis mutandis*, to any other alpha-emitting isotope-labeled agent with respect to its approved or otherwise customary dosing regimen.

Also envisioned is a “normal” murine dosing regimen and a “reduced” murine dosing regimen, each being commensurate with mouse body weight and tumor xenograft size.

Example 7 – Dosing Scenario I for ^{225}Ac-HuM195 and Venetoclax

A human AML patient is treated according to the following regimen. Venetoclax is orally administered according to its normal dosing regimen (i.e., for at least five weeks), followed by intravenous administration of ^{225}Ac-HuM195 according to its normal dosing regimen (either single or fractional administration). In one embodiment, the first (and only, if applicable) dose of ^{225}Ac-HuM195 is administered on the same day as, or one day following, the last dose of venetoclax.

Also envisioned is the treatment of an experimental mouse model according to the treatment regimen in this scenario, whereby the appropriate dosing regimens are commensurate with mouse body weight and tumor xenograft size.

Example 8 – Dosing Scenario II for ^{225}Ac-HuM195 and Venetoclax

A human AML patient is treated according to the following regimen. Venetoclax is orally administered according to its normal dosing regimen (i.e., for at least five weeks), followed by intravenous administration of a reduced dosing regimen of ^{225}Ac-HuM195 (either single or fractional administration). In one embodiment, the first (and only, if applicable) dose of ^{225}Ac-HuM195 is administered on the same day as, or one day following, the last dose of venetoclax. In another embodiment, the reduced dosing regimen of ^{225}Ac-HuM195 is (i) 2 x 0.5 μCi/kg, 2 x 1.0 μCi/kg, or 2 x 1.5 μCi/kg, where the fractions are administered one week apart; or (ii) 1 x 0.5 μCi/kg, 1 x 1.0 μCi/kg, 1 x 2.0 μCi/kg, or 1 x 3.0 μCi/kg, for a single administration.

Also envisioned is the treatment of an experimental mouse model according to the treatment regimen in this scenario, whereby the appropriate dosing

regimens are commensurate with mouse body weight and tumor xenograft size.

Example 9 – Dosing Scenario III for ^{225}Ac-HuM195 and Venetoclax

A human AML patient is treated according to the following regimen. Venetoclax is orally administered according to a reduced dosing regimen, followed by intravenous administration of the normal dosing regimen of ^{225}Ac-HuM195 (either single or fractional administration). In one embodiment, the first (and only, if applicable) dose of ^{225}Ac-HuM195 is administered on the same day as, or one day following, the last dose of venetoclax. In another embodiment, the reduced dosing regimen of venetoclax is one of the following: (i) 20 mg once daily for 7 days; (ii) 20 mg once daily for 14 days; (iii) 20 mg once daily for 21 days; (iv) 50 mg once daily for 7 days; (v) 50 mg once daily for 14 days; (vi) 50 mg once daily for 21 days; (vii) 100 mg once daily for 7 days; (viii) 100 mg once daily for 14 days; (ix) 100 mg once daily for 21 days; (x) 200 mg once daily for 7 days; (xi) 200 mg once daily for 14 days; (xii) 200 mg once daily for 21 days; (xiii) 400 mg once daily for 7 days; and (xiv) week 1 at 20mg/day, week 2 at 50mg/day and week 3 at 100mg/day.

Also envisioned is the treatment of an experimental mouse model according to the treatment regimen in this scenario, whereby the appropriate dosing regimens are commensurate with mouse body weight and tumor xenograft size.

Example 10 – Dosing Scenario IV for ^{225}Ac-HuM195 and Venetoclax

A human AML patient is treated according to the following regimen. Venetoclax is orally administered according to a reduced dosing regimen, followed by intravenous administration of a reduced dosing regimen of ^{225}Ac-HuM195 (either single or fractional administration). In one embodiment, the first (and only, if applicable) dose of ^{225}Ac-HuM195 is administered on the same day as, or one day following, the last dose of venetoclax. In another embodiment, (a) the reduced dosing regimen of venetoclax is one of (i) 20 mg

once daily for 7 days; (ii) 20 mg once daily for 14 days; (iii) 20 mg once daily for 21 days; (iv) 50 mg once daily for 7 days; (v) 50 mg once daily for 14 days; (vi) 50 mg once daily for 21 days; (vii) 100 mg once daily for 7 days; (viii) 100 mg once daily for 14 days; (ix) 100 mg once daily for 21 days; (x) 200 mg once daily for 7 days; (xi) 200 mg once daily for 14 days; (xii) 200 mg once daily for 21 days; (xiii) 400 mg once daily for 7 days; and (xiv) week 1 at 20mg/day, week 2 at 50mg/day and week 3 at 100mg/day; and (b) the reduced dosing regimen of ^{225}Ac-HuM195 is one of (i) 2 x 0.5 μCi/kg, 2 x 1.0 μCi/kg, or 2 x 1.5 μCi/kg, where the fractions are administered one week apart; or (ii) 1 x 0.5 μCi/kg, 1 x 1.0 μCi/kg, 1 x 2.0 μCi/kg, or 1 x 3.0 μCi/kg, for a single administration.

Also envisioned is the treatment of an experimental mouse model according to the treatment regimen in this scenario, whereby the appropriate dosing regimens are commensurate with mouse body weight and tumor xenograft size.

Example 11 – Dosing Scenario V for ^{225}Ac-HuM195 and Venetoclax

A human AML patient is treated according to the following regimen. Venetoclax is orally administered according to its normal dosing regimen (i.e., for at least five weeks), and ^{225}Ac-HuM195 is intravenously administered according to its normal single dose regimen during the course of the venetoclax dosing regimen. In one embodiment, the single dose of ^{225}Ac-HuM195 is administered (a) on day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 of the venetoclax dosing regimen, or (b) on the last day of, the penultimate day of, or 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 days prior to the last day of, the venetoclax dosing regimen.

Also envisioned is the treatment of an experimental mouse model according to the treatment regimen in this scenario, whereby the appropriate dosing regimens are commensurate with mouse body weight and tumor xenograft size.

Example 12 – Dosing Scenario VI for ^{225}Ac-HuM195 and Venetoclax

A human AML patient is treated according to the following regimen. Venetoclax is orally administered according to its normal dosing regimen (i.e., for at least five weeks), and ^{225}Ac-HuM195 is intravenously administered according to a reduced single dose regimen during the course of the venetoclax dosing regimen. In one embodiment, the single dose of ^{225}Ac-HuM195 is administered (a) on day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 of the venetoclax dosing regimen, or (b) on the last day of, the penultimate day of, or 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 days prior to the last day of, the venetoclax dosing regimen. In another embodiment, the reduced dosing regimen of ^{225}Ac-HuM195 is (i) 2 x 0.5 μCi/kg, 2 x 1.0 μCi/kg, or 2 x 1.5 μCi/kg, where the fractions are administered one week apart; or (ii) 1 x 0.5 μCi/kg, 1 x 1.0 μCi/kg, 1 x 2.0 μCi/kg, or 1 x 3.0 μCi/kg, for a single administration.

Also envisioned is the treatment of an experimental mouse model according to the treatment regimen in this scenario, whereby the appropriate dosing regimens are commensurate with mouse body weight and tumor xenograft size.

Example 13 – Dosing Scenario VII for ^{225}Ac-HuM195 and Venetoclax

A human AML patient is treated according to the following regimen. Venetoclax is orally administered according to a reduced dosing regimen, and ^{225}Ac-HuM195 is intravenously administered according to its normal single dose regimen during the course of the venetoclax dosing regimen. In one embodiment, the single dose of ^{225}Ac-HuM195 is administered (a) on day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 of the venetoclax dosing regimen, or (b) on the last day of, the penultimate day of, or 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 days prior to the last day of, the venetoclax dosing regimen. In another embodiment, the reduced dosing regimen of venetoclax is one of the following: (i) 20 mg once daily for 7 days; (ii) 20 mg once daily for 14 days; (iii) 20 mg once daily for 21

days; (iv) 50 mg once daily for 7 days; (v) 50 mg once daily for 14 days; (vi) 50 mg once daily for 21 days; (vii) 100 mg once daily for 7 days; (viii) 100 mg once daily for 14 days; (ix) 100 mg once daily for 21 days; (x) 200 mg once daily for 7 days; (xi) 200 mg once daily for 14 days; (xii) 200 mg once daily for 21 days; (xiii) 400 mg once daily for 7 days; and (xiv) week 1 at 20mg/day, week 2 at 50mg/day and week 3 at 100mg/day.

Also envisioned is the treatment of an experimental mouse model according to the treatment regimen in this scenario, whereby the appropriate dosing regimens are commensurate with mouse body weight and tumor xenograft size.

Example 14 – Dosing Scenario VIII for ^{225}Ac-HuM195 and Venetoclax

A human AML patient is treated according to the following regimen. Venetoclax is orally administered according to a reduced dosing regimen, and ^{225}Ac-HuM195 is intravenously administered according to a reduced single dose regimen during the course of the venetoclax dosing regimen. In one embodiment, the single dose of ^{225}Ac-HuM195 is administered (a) on day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 of the venetoclax dosing regimen, or (b) on the last day of, the penultimate day of, or 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 days prior to the last day of, the venetoclax dosing regimen. In another embodiment, (a) the reduced dosing regimen of venetoclax is one of (i) 20 mg once daily for 7 days; (ii) 20 mg once daily for 14 days; (iii) 20 mg once daily for 21 days; (iv) 50 mg once daily for 7 days; (v) 50 mg once daily for 14 days; (vi) 50 mg once daily for 21 days; (vii) 100 mg once daily for 7 days; (viii) 100 mg once daily for 14 days; (ix) 100 mg once daily for 21 days; (x) 200 mg once daily for 7 days; (xi) 200 mg once daily for 14 days; (xii) 200 mg once daily for 21 days; (xiii) 400 mg once daily for 7 days; and (xiv) week 1 at 20mg/day, week 2 at 50mg/day and week 3 at 100mg/day; and (b) the reduced dosing regimen of ^{225}Ac-HuM195 is one of (i) 2 x 0.5 μCi/kg, 2 x 1.0 μCi/kg, or 2 x 1.5 μCi/kg, where the fractions are administered one week apart; or (ii) 1 x 0.5 μCi/kg, 1 x 1.0 μCi/kg, 1 x 2.0 μCi/kg, or 1 x 3.0 μCi/kg, for a single administration.

Also envisioned is the treatment of an experimental mouse model according to the treatment regimen in this scenario, whereby the appropriate dosing regimens are commensurate with mouse body weight and tumor xenograft size.

5

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What is claimed is:

1. A method for treating a subject afflicted with cancer, comprising administering to the subject (i) a BCL-2 inhibitor in conjunction with (ii) an alpha-emitting isotope-labeled agent that targets cancer cells in the subject, wherein the amounts of the BCL-2 inhibitor and labeled agent, when administered in conjunction with one another, are therapeutically effective.

2. The method of claim 1, wherein the subject is human.

3. The method of claim 1, wherein the cancer is a hematologic malignancy.

4. The method of claim 3, wherein the hematologic malignancy is a leukemia.

5. The method of claim 4, wherein the leukemia is acute myeloid leukemia.

6. The method of claim 1, wherein the BCL-2 inhibitor is venetoclax.

7. The method of claim 1, wherein the alpha-emitting isotope-labeled agent is an anti-CD33 antibody labeled with an alpha-emitting isotope.

8. The method of claim 7, wherein the anti-CD33 antibody labeled with an alpha-emitting isotope is ^{225}Ac-labeled HuM195.

9. A method for treating a human subject afflicted with acute myeloid leukemia, comprising administering to the subject (i) venetoclax in conjunction with (ii) ^{225}Ac-labeled HuM195, wherein the amounts of venetoclax and ^{225}Ac-labeled HuM195, when administered in conjunction with one another, are therapeutically effective.

10. A method for inducing the death of a cancer cell, comprising contacting the cell with (i) a BCL-2 inhibitor in conjunction with (ii) an alpha-emitting isotope-labeled agent that targets the cancer cell, wherein the amounts of BCL-2 inhibitor and labeled agent, when concurrently contacted with the cell, are effective to induce the cell's death.

11. The method of claim 10, wherein the cancer cell is a human cancer cell.

12. The method of claim 10, wherein the cancer cell is a hematologic cell.

13. The method of claim 12, wherein the cancer cell is a leukemic cell.

14. The method of claim 13, wherein the leukemic cell is an acute myeloid leukemic cell.

15. The method of claim 10, wherein the BCL-2 inhibitor is venetoclax.

16. The method of claim 10, wherein the alpha-emitting isotope-labeled agent is an anti-CD33 antibody labeled with an alpha-emitting isotope.

17. The method of claim 16, wherein the anti-CD33 antibody labeled with an alpha-emitting isotope is ^{225}Ac-labeled HuM195.

18. A method for inducing the death of an acute myeloid leukemic cell, comprising contacting the cell with (i) venetoclax in conjunction with (ii) ^{225}Ac-labeled HuM195, wherein the amounts of venetoclax and ^{225}Ac-labeled HuM195, when concurrently contacted with the cell, are effective to induce the cell's death.

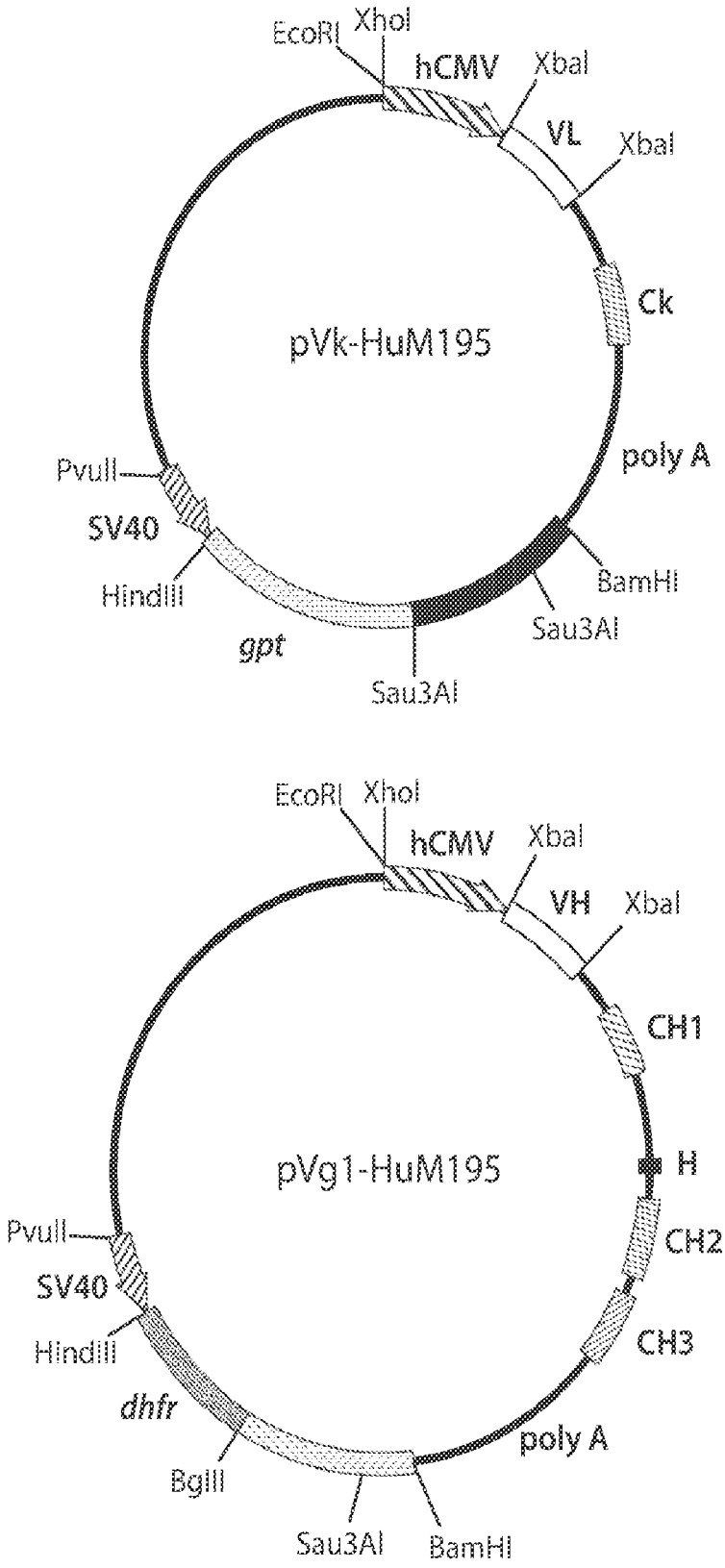
EcoRI
XhoI
hCMV
XbaI
VL
XbaI
Ck
pVk-HuM195
poly A
PvuII
SV40
HindIII
gpt
Sau3AI
BamHI
Sau3AI
EcoRI
XhoI
hCMV
XbaI
VH
XbaI
CH1
pVg1-HuM195
H
CH2
CH3
PvuII
SV40
HindIII
dhfr
BglII
poly A
Sau3AI
BamHI

Figure 1

624 TCTAGACCACCATGGAGAAAGACACACTCCTGCTATGGGTCCTACTTCTCTGGGTTCCAGGTTCCACAGGTGACATTCAG
M E K D T L L L W V L L L W V P G S T G D I Q
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M T Q S P S S L S A S V G D R V T I T C R A S E S V D
784 CAATTATGGCATTAGCTTTATGAACTGGTTCCAACAGAAACCCGGGAAGGCTCCTAAGCTTCTGATTTACGCTGCATCCA
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K R
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1664 CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAGAGGGAGAAGTGCCCCCACCTGCTCCTCAGTTCCA
L S S P V T K S F N R G E C ·
1744 GCCTGACCCCCTCCCATCCTTTGGCCTCTGACCCTTTTTCCACAGGGGACCTACCCCTATTGCGGTCCTCCAGCTCATCT

1824 TTCACCTCACCCCCCTCCTCCTCCTTGGCTTTAATTATGCTAATGTTGGAGGAGAATGAATAAATAAAGTGAATCTTTGC

1904 ACCTGTGGTTTCTCTCTTTCCTCATTTAATAATTATTATCTGTTGTTTTACCAACTACTCAATTTCTCTTATAAGGGACT

1984 AAATATGTAGTCATCCTAAGGCGCATAACCATTTATAAAAATCATCCTTCATTCTATTTTACCCTATCATCCTCTGCAAG

2064 ACAGTCCTCCCTCAAACCCACAAGCCTTCTGTCCTCACAGTCCCCTGGGCCATGGTAGGAGAGACTTGCTTCCTTGTTTT

2144 CCCCTCCTCAGCAAGCCCTCATAGTCCTTTTTAAGGGTGACAGGTCTTACAGTCATATATCCTTTGATTCAATTCCCTGA

2224 GAATCAACCAAAGCAAATTTTTCAAAAGAAGAAACCTGCTATAAAGAGAATCATTCATTGCAACATGATATAAAATAACA

2304 ACACAATAAAAGCAATTAAATAAACAAACAATAGGGAAATGTTTAAGTTCATCATGGTACTTAGACTTAATGGAATGTCA

2384 TGCCTTATTTACATTTTTAAACAGGTACTGAGGGACTCCTGTCTGCCAAGGGCCGTATTGAGTACTTTCCACAACCTAAT

2464 TTAATCCACACTATACTGTGAGATTAAAAACATTCATTAAAATGTTGCAAAGGTTCTATAAAGCTGAGAGACAAATATAT

2544 TCTATAACTCAGCAATCCCACTTCTAGGATCC

Figure 2

624 TCTAGACCACCATGGGATGGAGCTGGATCTTTCTCTTCCTCCTGTCAGGAACTGCTGGCGTCCACTCTCAGGTTCAGCTG
M G W S W I F L F L L S G T A G V H S Q V Q L
704 GTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGAGCTCAGTGAAGGTTTCCTGCAAAGCTTCTGGCTACACCTTCACTGA
V Q S G A E V K K P G S S V K V S C K A S G Y T F T D
784 CTACAACATGCACTGGGTGAGGCAGGCTCCTGGCCAACGGCCTGGAATGGATTGGATATATTTATCCTTACAATGGTGGTA
Y N M H W V R Q A P G Q G L E W I G Y I Y P Y N G G
864 CCGGCTACAACCAGAAGTTCAAGAGCAAGGCCACAATTACAGCAGACGAGAGTACTAACACAGCCTACATGGAACTCTCC
T G Y N Q K F K S K A T I T A D E S T N T A Y M E L S
944 AGCCTGAGGTCTGAGGACACTGCAGTCTATTACTGCGCAAGAGGGCGCCCCGCTATGGACTACTGGGGCCAAGGGACTCT
S L R S E D T A V Y Y C A R G R P A M D Y W G Q G T L
1024 GGTCACTGTCTCTTCAG*GTAAGAATGGCCTCTAGACCACCATGGGATGGAGCTTTCTGGGGCAGGCCAGGCCTGACCTTG*
V T V S S
1104 *GCTTTGGGGCAGGGAGGGGGCTAAGGTGAGGCAGGTGGCGCCAGCCAGGTGCACACCCAATGCCCATGAGCCCAGACACT*

1184 *GGACGCTGAACCTCGCGGACAGTTAAGAACCCAGGGGCCTCTGCGCCCTGGGCCCAGCTCTGTCCCACACCGCGGTCACA*

1264 TGGCACCACCTCTCTTGCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGG
A S T K G P S V F P L A P S S K S T S G
1344 GCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACC
G T A A L G C L V K D Y F P E P V T V S W N S G A L T
1424 AGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAG
S G V H T F P A V L Q S S G L Y S L S S V V T V P S S
1504 CAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGGTGAGA
S L G T Q T Y I C N V N H K P S N T K V D K K V
1584 *GGCCAGCACAGGGAGGGAGGGTGTCTGCTGGAAGCCAGGCTCAGCGCTCCTGCCTGGACGCATCCCGGCTATGCAGCCCC*

1664 *AGTCCAGGGCAGCAAGGCAGGCCCCGTCTGCCTCTTCACCCGGAGGCCTCTGCCCGCCCCACTCATGCTCAGGGAGAGGG*

1744 *TCTTCTGGCTTTTTCCCCAGGCTCTGGGCAGGCACAGGCTAGGTGCCCCTAACCCAGGCCCTGCACACAAAGGGGCAGGT*

1824 *GCTGGGCTCAGACCTGCCAAGAGCCATATCCGGGAGGACCCTGCCCCTGACCTAAGCCCACCCCAAAGGCCAAACTCTCC*

1904 *ACTCCCTCAGCTCGGACACCTTCTCTCCTCCCAGATTCCAGTAACTCCCAATCTTCTCTCTGCAGAGCCCAAATCTTGTG*
E P K S C
1984 *ACAAAACTCACACATGCCCACCGTGCCCAGGTAAGCCAGCCCAGGCCTCGCCCTCCAGCTCAAGGCGGGACAGGTGCCCT*
D K T H T C P P C P
2064 *AGAGTAGCCTGCATCCAGGGACAGGCCCCAGCCGGGTGCTGACACGTCCACCTCCATCTCTTCCTCAGCACCTGAACTCC*
A P E L
2144 TGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC
L G G P S V F L F P P K P K D T L M I S R T P E V T C
2224 GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAA
V V V D V S H E D P E V K F N W Y V D G V E V H N A K
2304 GACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA
T K P R E E Q Y N S T Y R V V S V L T V L H Q D W L
2384 ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGT
N G K E Y K C K V S N K A L P A P I E K T I S K A K
2464 *GGGACCCGTGGGGTGCGAGGGCCACATGGACAGAGGCCGGCTCGGCCCACCCTCTGCCCTGAGAGTGACCGCTGTACCAA*

Figure 3

2544 CCTCTGTCCCTACAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAG
G Q P R E P Q V Y T L P P S R D E L T K N Q
2624 GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAA
V S L T C L V K G F Y P S D I A V E W E S N G Q P E N
2704 CAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCA
N Y K T T P P V L D S D G S F F L Y S K L T V D K S
2784 GGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCC
R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S
2864 CTGTCTCCGGGTAAATGAGTGCGACGGCCGGCAAGCCCCCGCTCCCCGGGCTCTCGCGGTCGCACGAGGATGCTTGGCAC
L S P G K *
2944 GTACCCCCTGTACATACTTCCCGGGCGCCCAGCATGGAAATAAAGCACCCAGCGCTGCCCTGGGCCCCTGCGAGACTGTG

3024 ATGGTTCTTTCCACGGGTCAGGCCGAGTCTGAGGCCTGAGTGGCATGAGGGAGGCAGAGCGGGTCCCACTGTCCCCACAC

3104 TGGCCCAGGCTGTGCAGGTGTGCCTGGGCCGCCTAGGGTGGGGCTCAGCCAGGGGCTGCCCTCGGCAGGGTGGGGGATTT

3184 GCCAGCGTGGCCCTCCCTCCAGCAGCACCTGCCCTGGGCTGGGCCACGGGAAGCCCTAGGAGCCCCTGGGGACAGACACA

3264 CAGCCCCTGCCTCTGTAGGAGACTGTCCTGTTCTGTCAGCGCCCTGTCCTCCGACCTCCATGCCCACTCGGGGGCATGCC

3344 TAGTCCATGTGCGTAGGGACAGGCCCTCCCTCACCCATCTACCCCCACGGCACTAACCCCCTGGCTGCCCTGCCCAGCCTC

3424 GCACCCGCATGGGGACACAACCGACTCCGGGGACATGCACTCTCGGGCCCTGTGGAGGGACTGGTGCAGATGCCCACACA

3504 CACACTCAGCCCAGACCCGTTCAACAAACCCCCGCACTGAGGTTGGCCGGCCACACGGCCACCACACACACACGTGCACGC

3584 CTCACACACGGAGCCTCACCCGGGCGAACTGCACAGCACCCAGACCAGAGCAAGGTCCTCGCACACGTGAACACTCCTCG

3664 GACACAGGCCCCCACGAGCCCCACGCGGCACCTCAAGGCCCACGAGCCTCTCGGCAGCTTCTCCACATGCTGACCTGCTC

3744 AGACAAACCCAGCCCTCCTCTCACAAGGGTGCCCCTGCAGCCGCCACACACACACAGGGGATCACACACCACGTCACGTC

3824 CCTGGCCCTGGCCCACTTCCCAGTGCCGCCCTTCCCTGCAGGATCC

Figure 3 Cont'd

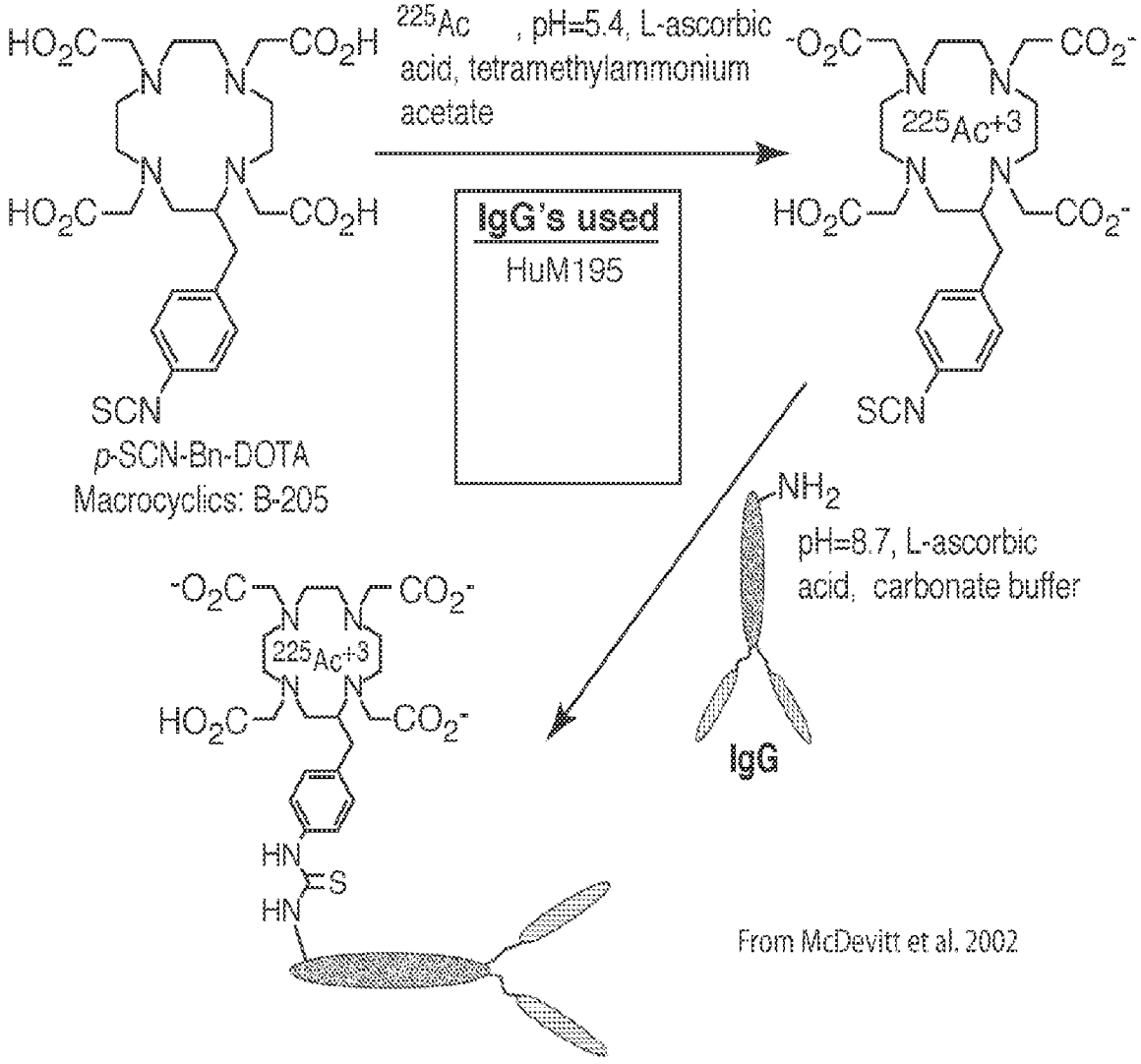
^{225}Ac , pH=5.4, L-ascorbic acid, tetramethylammonium acetate
IgG's used
HuM195
SCN
p-SCN-Bn-DOTA
Macrocyclics: B-205
^{225}Ac+3
NH2
pH=8.7, L-ascorbic acid, carbonate buffer
IgG
From McDevitt et al. 2002

Figure 4

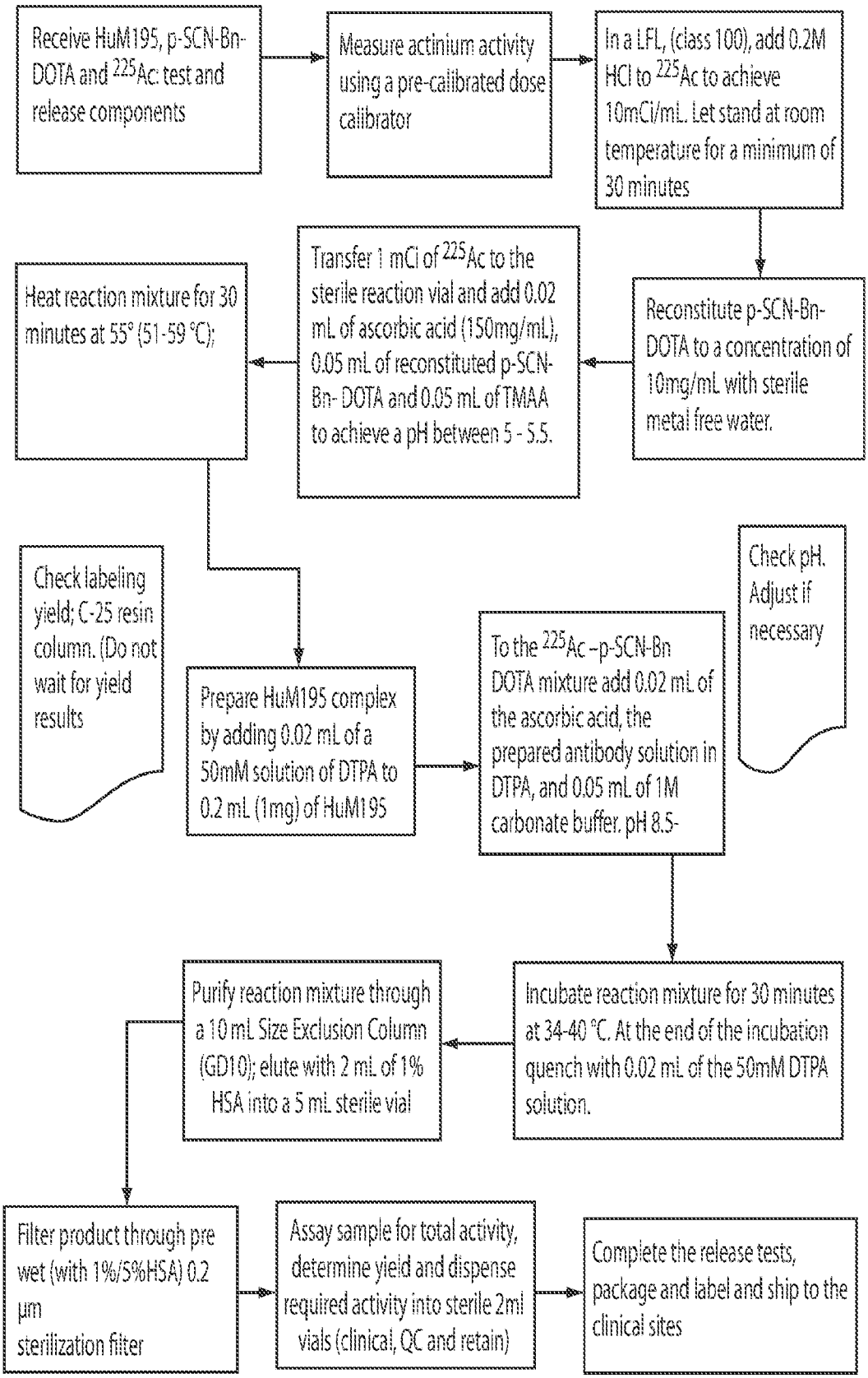
Receive HuM195, p-SCN-Bn-DOTA and 225Ac test and release components
Measure actinium activity using a pre-calibrated dose calibrator
In a LFL, (class 100), add 0.2M HCl to 225Ac to achieve 10mCi/mL. Let stand at room temperature for a minimum of 30 minutes
Reconstitute p-SCN-Bn-DOTA to a concentration of 10mg/mL with sterile metal free water.
Transfer 1 mCi of 225Ac to the sterile reaction vial and add 0.02 mL of ascorbic acid (150mg/mL), 0.05 mL of reconstituted p-SCN-Bn- DOTA and 0.05 mL of TMAA to achieve a pH between 5 - 5.5.
Heat reaction mixture for 30 minutes at 55° (51-59 °C);
Check labeling yield; C-25 resin column. (Do not wait for yield results
Prepare HuM195 complex by adding 0.02 mL of a 50mM solution of DTPA to 0.2 mL (1mg) of HuM195
To the 225Ac –p-SCN-Bn DOTA mixture add 0.02 mL of the ascorbic acid, the prepared antibody solution in DTPA, and 0.05 mL of 1M carbonate buffer. pH 8.5-
Check pH. Adjust if necessary
Incubate reaction mixture for 30 minutes at 34-40 °C. At the end of the incubation quench with 0.02 mL of the 50mM DTPA solution.
Purify reaction mixture through a 10 mL Size Exclusion Column (GD10); elute with 2 mL of 1% HSA into a 5 mL sterile vial
Filter product through pre wet (with 1%/5%HSA) 0.2 µm sterilization filter
Assay sample for total activity, determine yield and dispense required activity into sterile 2ml vials (clinical, QC and retain)
Complete the release tests, package and label and ship to the clinical sites

Figure 5

Protocol Schema

Phase I Dose Escalation Component (3+3 Design)

Low Dose Ara-C (LDAC) 20 mg subQ q 12 hrs x 100 Cycle 1

D-1

D-10

Fractionated Doses

Dose 1	Dose 2
Lintuzumab-Ac225	Lintuzumab-Ac225
D-14-17	D-18-24

plus furosemide and spitonolactone

LDAC Cycle 2-12 every 28 D beginning 4 weeks after dose 2 of Lintuzumab-Ac225

Phase II Component (Simon 2-stage Design)

Low Dose Ara-C (LDAC) 20 mg subQ q 12 hrs X 10D Cycle 1

D-1

D-10

Fractionated Doses

Dose 1	Dose 2
Lintuzumab-Ac225	Lintuzumab-Ac225
D-14-17	D-18-24

plus furosemide and spitonolactone

LDAC Cycle 2-12 every 28 D

Dose Escalation Schedule

Dose Level	Ac-225 Activity per fractionated dose (μCi/Kg)	Total Dose (μCi/Kg)	HuM195 per fractionated dose (μCi/Kg)	Total HuM195 dose (μCi/Kg)
1	0.5	1.0	7.5	15
2	1	2	10	20
3	1.5	3	10	20
4	2	4	12.5	25

Statistics

Historical CR for this population = 20%

Target CR rate of 35% (p=.05, power = 80%)
Need 7 CRs in first 31 subjects to proceed to stage 2
Total sample size in the Phase II portion = up to 53 subjects

Primary endpoint: Response rate (CR + CRp)

Eligibility

Patients age ≥ 60 years with newly diagnosed AML with 20% blasts who decline or are considered unfit for intensive induction therapy because of poor risk factors or co-morbid conditions, or subjects ≥ 70 years old with newly diagnosed AML.

Figure 6

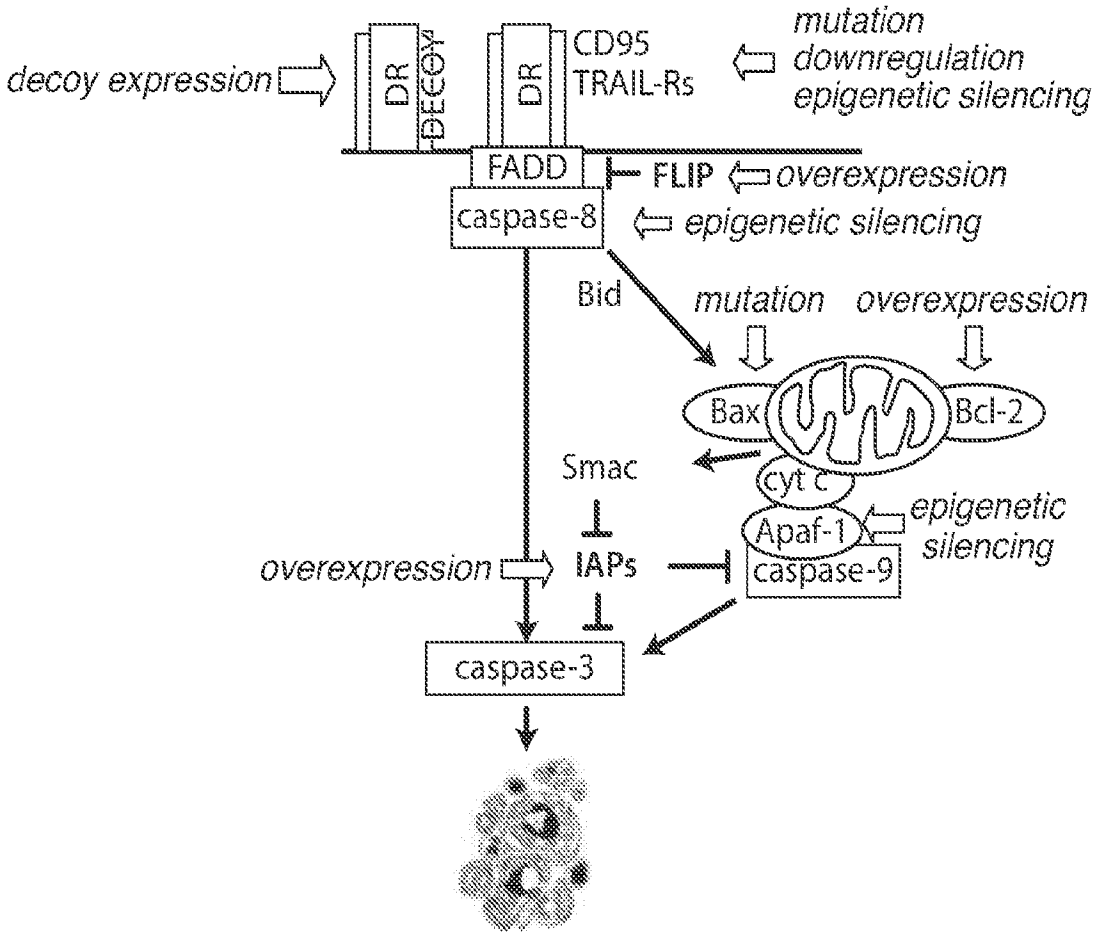
decoy expression
DR
DECOY
DR
CD95
TRAIL-Rs
mutation
downregulation
epigenetic silencing
FADD
FLIP
overexpression
caspase-8
epigenetic silencing
Bid
mutation
overexpression
Bax
Bcl-2
Smac
cyt c
Apaf-1
epigenetic
silencing
overexpression
IAPs
caspase-9
caspase-3

Figure 7

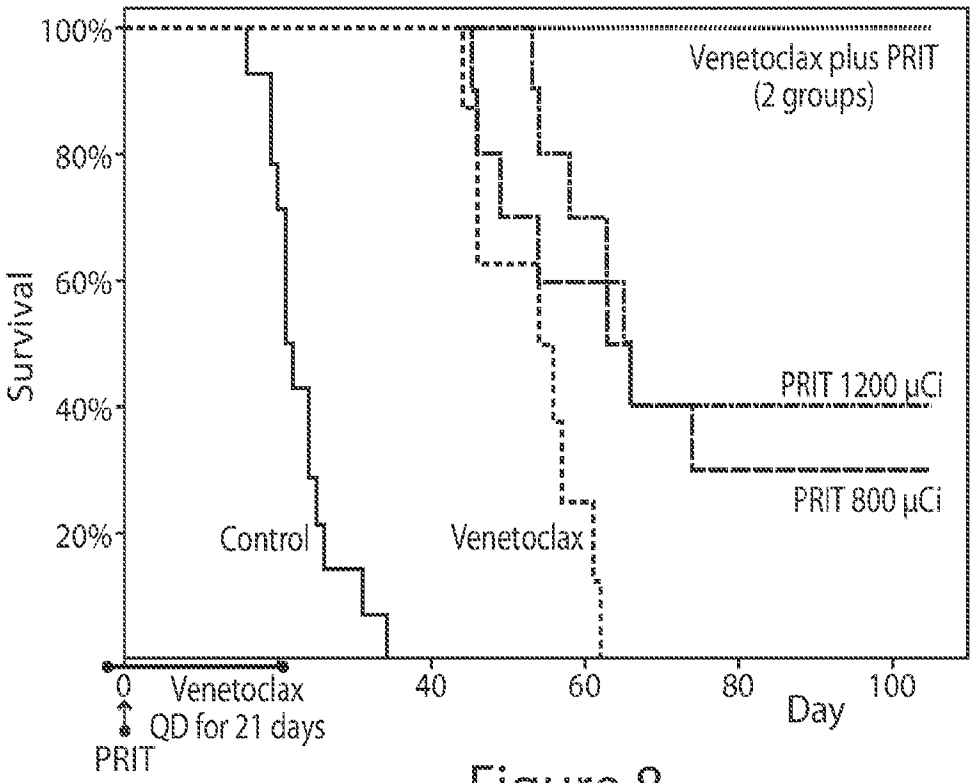
100%
80%
60%
40%
20%
Survival
Venetoclax plus PRIT
(2 groups)
PRIT 1200 µCi
PRIT 800 µCi
Control
Venetoclax
0
Venetoclax
QD for 21 days
PRIT
40
60
80
100
Day

Figure 8

MoA	Beta (low LED)	Alpha (high LED)
dsDNA breaks (1), (2), (3), (4)	+/-	++
ssDNA breaks (1), (4)	+	+
Direct effect on apoptotic cascade (5), (6)	+/-	++
Bystander effect (5)	+	+
Dependence on tissue oxygenation (5)	+	-
Dependence on cell cycle phase (5)	+	-

Figure 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/029607

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 35/17; A61K 39/00; A61P 35/00; C07K 14/705; C07K 14/725; C07K 16/28 (2018.01)

CPC - A61K 38/00; A61K 2039/505; A61K 2039/5156; C07K 14/7051; C07K 16/30; C07K 2317/24; C07K 2317/622; C07K 2319/03 (2018.05)

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)

See Search History document

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

USPC - 424/134.1; 424/185.1; 435/328; 435/455; 435/320.1 (keyword delimited)

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/0096892 A1 (BROGDON et al) 07 April 2016 (07.04.2016) entire document	1-18
A	WO 2016/044605 A1 (BEATTY et al) 24 March 2016 (24.03.2016) entire document	1-18
A	US 2016/0362472 A1 (BITTER et al) 15 December 2016 (15.12.2016) entire document	1-18
A	JURCIC et al. "Targeted α Particle immunotherapy for Myeloid Leukemia," Blood Journal, 15 August 2002 (15.08.2002), Vol. 100, Iss. 4, Pgs. 1233-39. entire document	1-18
A	US 8,546,399 B2 (BRUNCKO et al) 01 October 2013 (01.10.2013) entire document	1-18
A	MIEDERER et al. "Pharmacokinetics, Dosimetry, and Toxicity of the Targetable Atomic Generator, 225Ac-HuM195, in Nonhuman Primates," Journal of Nuclear Medicine, 01 January 2004 (01.01.2004), Vol. 45, Iss. 1, Pgs. 129-137. entire document	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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

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

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2018	10 SEP 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)