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(54) Title: COMBINATION OF INOTUZUMAB OZOGAMICIN AND TORISEL FOR THE TREATMENT OF CANCER

(57) Abstract: The present invention relates to a therapeutic method for the treatment of cancer that comprises the use of a combination of inotuzumab ozogamicin (CMC-544) and temsirolimus. The enhanced antitumor of the combination therapy is particularly useful for patient population that are recalcitrant to inotuzumab ozogamicin or temsirolimus therapy, relapse after treatment with inotuzumab ozogamicin or temsirolimus or where enhanced antitumor effect reduces toxicities associated with treatment using inotuzumab ozogamicin or temsirolimus.

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COMBINATION OF INOTUZUMAB OZOGAMICIN AND TORISEL FOR THE TREATMENT OF CANCER

Related Application

This application claims the benefit of U.S. Provisional Application No. 61/576,831 filed December 16, 2011, which is hereby incorporated by reference in its entirety.

Field of the Invention

This invention relates to a method of treating abnormal cell growth such as cancer by administering a combination of inotuzumab ozogamicin (CMC-544) and temsirolimus (rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid; CCI-779). In a particular embodiment, the present invention relates to a product comprising inotuzumab ozogamicin and temsirolimus for simultaneous, separate, or sequential use thereof for the prevention, delay of progression, and/or treatment of a proliferative disease, especially cancer.

Background of the Invention

B cells are a critical component of the immune response in mammals, as they are the cells responsible for antibody production (humoral immunity). B cells are quite diverse, and this diversity is critical to the immune system. Each B cell within the host expresses a different antibody—thus, one B cell will express antibody specific for one antigen, while another B cell will express antibody specific for a different antigen. In humans, each B cell can produce an enormous number of antibody molecules (i.e., about 10^7 to 10^8). The maturation of B cells (and thus antibody production) most typically ceases or substantially decreases when the foreign antigen has been neutralized. Occasionally, however, proliferation of a particular B cell or plasma cell will continue unabated; such proliferation can result in a cancer referred to as “B cell lymphoma or multiple myeloma.”

B cell lymphomas include both Hodgkin's lymphoma and a broad class of non-Hodgkin's lymphoma. Cell lymphomas, such as the B-cell subtype of non-Hodgkin's lymphoma, are significant contributors to cancer mortality. The response of B-cell malignancies to various forms of treatment is mixed. For example, in cases in which adequate clinical staging of non-Hodgkin's lymphoma is possible, field radiation therapy

can provide satisfactory treatment. Still, about one-half of the patients die from the disease. Devesa et al., J. Nat'l Cancer Inst. 79:701 (1987).

Non Hodgkin's lymphomas (NHL) are the most common hematologic malignancies in adults representing the sixth most commonly diagnosed cancer in North America and in Europe. Approximately 85% of NHL are of B-cell origin and comprise a heterogeneous group of malignancies, ranging from slow growing indolent and usually incurable diseases, to more aggressive but potentially curable lymphomas. CD22 is expressed in ~60% to >90% of B-lymphoid malignancies of the majority of NHLs with B-cell origin.

Over the past two decades, major progress has been achieved in the management of NHL. The introduction of rituximab, a monoclonal antibody directed against the B-cell surface antigen CD20, has significantly improved treatment outcomes in most patients with NHL. Rituximab in combination with standard chemotherapy has improved response rate, progression free and overall survival in both indolent and aggressive lymphomas.

Despite therapeutic advances, treatment is still challenging for many patients with lymphomas. Traditional methods of treating B-cell malignancies, including chemotherapy and radiotherapy, have limited utility due to toxic side effects. Most lymphomas respond initially to any one of the current chemotherapeutic agents, but tumors typically recur and eventually become refractory. As the number of regimens patients receive increases, the more chemotherapy resistant the disease becomes. Average response to first line therapy is approximately 75%, 60% to second line, 50% to third line, and 35-40% to fourth line. Response rates with a single-agent in the multiple relapsed setting approaching 20% are considered positive and warrant further study.

Additionally, the period of remission following each treatment decreases. Patients with indolent lymphomas will invariably relapse and many will require additional treatments, while more than half of the patients with aggressive lymphomas will not be cured following standard treatments. In fact, many patients with diffuse large B-cell lymphoma (the most common subtype of aggressive lymphomas) are refractory to standard chemotherapy and/or chemoimmunotherapy regimens and relapses are frequent even in patients that achieve an initial response to treatment.

The prognosis for those affected by these diseases is poor, as the survival rates for lymphoma patients remain low. Salvage approaches based on high-dose chemotherapy with stem-cell transplantation are helpful only for selected patients and most patients succumb to their disease or to complications of intensive treatments. New methods for treating these diseases are needed.

Therefore, there is a need for the development of novel agents and treatment regimens with less toxicity and more specific targeting of tumor cells. Targeted therapies provide a promising alternative to standard cytotoxic chemotherapy. Unlike traditional chemotherapy, they affect specific targets present in the lymphoma cells and may spare normal tissues, thus minimize toxicity. The combination of agents that target specific components of pathways relevant to lymphomagenesis, with novel monoclonal antibodies represents a novel approach for the development of new treatment strategies in patients that are newly diagnosed, relapse or are refractory to Rituximab and standard chemotherapy.

Immunoconjugates comprising a member of the potent family of antibacterial and antitumor agents, known collectively as the calicheamicins or the LL-E33288 complex, (see U.S. Pat. No. 4,970,198 (1990)), were developed for use in the treatment of myelomas. The most potent of the calicheamicins is designated γ_1, which is herein referenced simply as gamma. These compounds contain a methyltrisulfide that can be reacted with appropriate thiols to form disulfides, at the same time introducing a functional group such as a hydrazide or other functional group that is useful in attaching a calicheamicin derivative to a carrier. (See U.S. Pat. No. 5,053,394). The use of the monomeric calicheamicin derivative/carrier conjugates in developing therapies for a wide variety of cancers has been limited both by the availability of specific targeting agents (carriers) as well as the conjugation methodologies which result in the formation of protein aggregates when the amount of the calicheamicin derivative that is conjugated to the carrier (i.e., the drug loading) is increased.Inotuzumab ozogamicin (CMC544) is a CD22-specific immunoconjugate of calicheamicin in which a humanized IgG4 anti-CD22 mAb, G5/44, is covalently linked via an acid-labile AcBut linker to CalichDMH (Blood 2004; 103:1807-1814). CalichDMH (N-acetyl gamma calicheamicin dimethylhydrazide) is a derivative of gamma calicheamicin, a DNA-damaging enediyne antibiotic (Bioconj Chem 2002;13:40-46). Gamma calicheamicin binds DNA in the minor groove and with the help of cellular thiols brings about double-strand DNA breaks (Science 1988; 240: 1198-1201) leading to cellular apoptosis and cell death. Antibody-

targeted chemotherapy enables a cytotoxic agent to be delivered specifically to tumor cells by conjugating the cytotoxic agent with a monoclonal antibody that binds to a tumor-associated antigen. This strategy preferentially delivers the cytotoxic agent to tumor cells, minimizes exposure of normal tissues (lacking the targeted agent) to the cytotoxic agent, and results in a significantly improved therapeutic index.

Temsirolimus is a specific inhibitor of the mammalian target of rapamycin (mTOR), an enzyme that regulates cell growth and proliferation. Temsirolimus prevents progression from the G1 phase to the S phase of the cell cycle through inhibition of mTOR. The mTOR is a kinase that propagates signalling through growth factor pathways and regulates metabolic pathways that allow tumors to adapt to a harsh microenvironment. Inhibitors of mTOR, therefore, have the potential to inhibit tumor cell growth on at least two levels, a direct inhibitory effect on mutated growth factor signaling pathways and an indirect effect through inhibition of mTOR-regulated tumor survival factors.

Temsirolimus (CCI-779, rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid) is a structural analog of sirolimus (rapamycin) that has been formulated for IV or oral administration for the treatment of various malignancies. Temsirolimus is an antineoplastic agent. Rapamycin is a macrocyclic triene antibiotic produced by *Streptomyces hygroscopicus*, which was found to have antifungal activity, particularly against *Candida albicans*, both in vitro and in vivo [C. Vezina et al., J. Antibiot. 28, 721 (1975); S. N. Sehgal et al., J. Antibiot. 28, 727 (1975); H. A. Baker et al., J. Antibiot. 31, 539 (1978); U.S. Pat. No. 3,929,992; and U.S. Pat. No. 3,993,749]. Additionally, rapamycin alone (U.S. Pat. No. 4,885,171) or in combination with picibanil (U.S. Pat. 4,401,653) has been shown to have antitumor activity.

Rapamycin is useful in preventing or treating adult T-cell leukemia/lymphoma [European Patent Application 525,960 A1] and malignant carcinomas [U.S. Pat. No. 5,206,018]. The preparation and use of hydroxyesters of rapamycin, including CCI-779, are disclosed in U.S. Pat. No. 5,362,718.

For patients with lymphomas relapsed or refractory to standard chemotherapy, improvements in outcomes may derive from the development of alternative treatment strategies with less toxicity and better targeting of the lymphoma cells. Basic and preclinical laboratory research have permitted to identify some of the pathways that are abnormally expressed in lymphomas and agents that target specific components of

these pathways have entered clinical evaluation in recent years. While some of these agents have proven to be effective and associated with a better toxicity profile than standard chemotherapy, resistance has been often observed, limiting their clinical use.

The increase of the antitumor efficacy of a known antitumor compound by administering the same in combination with one or more different antitumor drugs in order to reduce the toxic effects of the individual agents when used alone, and because the combination has greater efficacy than when either agent is used alone, is a strongly felt need in the field of anticancer therapy. Moreover, improved anti-cancer therapies comprise a large unmet medical need and the identification of novel systemic therapies and combination regimens are required to improve treatment outcome by targeting all types of B cell malignancies. In particular, there is a need for a therapy which can overcome the shortcomings of current treatments regimens by using combination of immunoconjugates and small molecules to treat a variety of malignancies including hematopoietic malignancies like non-Hodgkin's lymphoma (NHL), without inducing an immune response. Such improved therapy has the advantage of targeting a diverse group of B cell malignancies by using two agents with different mechanism of actions. Further, non-Hodgkin lymphomas are a diverse group of blood cell cancers derived from lymphocytes, a type of white blood cell. As such, patients with different types of B-cell non Hodgkins lymphomas would benefit from the combination therapy of the present invention.

Moreover, the combination therapy of the present invention is potentially more effective and less toxic; and thus allows repeated administration of comparatively low dosage levels of two or more agents targeting different types of B-cell malignancies and for longer periods of treatment.

In addition to treating newly diagnosed patients, the novel combination therapy using combinations of targeted agents, such as ADCs, with a cytotoxic agent represents possible approach to overcome resistance that may be developed to treatment. Further, the enhanced antitumor activity of the combination therapy is particularly useful for patient population that relapse after treatment with inotuzumab ozogamicin or temsirolimus alone or where enhanced antitumor effect reduces toxicities associated with treatment using inotuzumab ozogamicin or temsirolimus alone. Accordingly, the present invention provides methods for enhancing the antitumor activity of inotuzumab ozogamicin and temsirolimus by a novel combination and sequential therapy regimen.

Summary of the Invention

The present invention provides pharmaceutical composition comprising an amount of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof; an amount of temsirolimus or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent.

In one embodiment, the present invention provides a first pharmaceutical composition for use with a second pharmaceutical composition for achieving an anti-cancer effect in a mammal suffering from cancer, which anti-cancer effect is greater than the sum of the anti-cancer effects achieved by administering said first and second pharmaceutical compositions separately, and which second pharmaceutical composition comprises an amount of temsirolimus or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

In another embodiment, the present invention provides a first pharmaceutical composition for use with a second pharmaceutical composition for achieving an anti-cancer effect in a mammal suffering from cancer, which anti-cancer effect is greater than the sum of the anti-cancer effects achieved by administering said first and second pharmaceutical compositions separately, and which second pharmaceutical composition comprises an amount of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of temsirolimus or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

In yet another embodiment, the present invention provides a first pharmaceutical composition for use with a second pharmaceutical composition for achieving an anti-cancer effect in a mammal suffering from cancer, which anti-cancer effect is greater than the anti-cancer effects achieved by administering said first and second pharmaceutical compositions separately, and which second pharmaceutical composition comprises an amount of temsirolimus or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

In another embodiment, the present invention provides a first pharmaceutical composition for use with a second pharmaceutical composition for achieving an anti-cancer effect in a mammal suffering from cancer, which anti-cancer effect is greater than the anti-cancer effects achieved by administering said first and second pharmaceutical compositions separately, and which second pharmaceutical composition comprises an amount of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of temsirolimus or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

A method of treating cancer comprising administering to a patient in need thereof an effective amount of a combination of inotuzumab ozogamicin and temsirolimus.

In another embodiment, the first and second pharmaceutical compositions of the present invention, wherein said anti-cancer effects are achieved against a cancer selected from hematologic malignancies, non-Hodgkin's lymphoma (NHL) including follicular NHL or aggressive NHL (predominantly diffuse large B-cell lymphoma [DLBCL]).Acute Myeloid leukaemia (AML), Chronic myeloid leukemia (CML), Acute Lymphoblastic leukaemia (ALL), B cell malignancies, and myelodysplastic syndrome, Myelo-dysplastic syndrome (MDS), myelo-proliferative diseases (MPD), Chronic Myeloid Leukemia (CML), T-cell Acute Lymphoblastic leukaemia (T-ALL), B-cell Acute Lymphoblastic leukaemia (B-ALL), lung cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, glioblastoma, neuroblastoma, squamous cell cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, rectal cancer, cancer of the anal region, gastric cancer, stomach cancer, breast cancer, gynecological cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin’s Disease, cancer of the esophagus, cancer of the small intestine, cancer of the large intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (“CNS”), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary

adenoma, solid tumors of childhood or a combination of one or more of the foregoing cancers.

In yet another embodiment, the present invention provides for a kit for achieving a therapeutic effect in a mammal comprising a therapeutically effective amount of inotuzumab ozogamicin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent in a first unit dosage form; a therapeutically effective amount of and temsirolimus, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and container means for containing said first and second dosage forms.

In another embodiment, the present invention provides for a dosage form for achieving a therapeutic effect in a mammal comprising therapeutically effective amount of inotuzumab ozogamicin, or a pharmaceutically acceptable salt thereof; atherapeutically effective amount of temsirolimus, or a pharmaceutically acceptable salt thereof; and one or more pharmaceutically acceptable carriers or diluents.

In yet another embodiment, the kits and the dosage form is for the treatment of cancer wherein the cancer is selected from hematologic malignancies, non-Hodgkin's lymphoma (NHL) including follicular NHL or aggressive NHL (predominantly diffuse large B-cell lymphoma [DLBCL]).Acute Myeloid leukaemia (AML), Chronic myeloid leukemia (CML), Acute Lymphoblastic leukaemia (ALL), B cell malignancies, and myelodysplastic syndrome, Myelo-dysplastic syndrome (MDS), myelo-proliferative diseases (MPD), Chronic Myeloid Leukemia (CML), T-cell Acute Lymphoblastic leukaemia (T-ALL), B-cell Acute Lymphoblastic leukaemia (B-ALL), lung cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, glioblastoma, neuroblastoma, squamous cell cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, rectal cancer, cancer of the anal region, gastric cancer, stomach cancer, breast cancer, gynecological cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin’s Disease, cancer of the esophagus, cancer of the small intestine, cancer of the large intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder,

cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system ("CNS"), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, solid tumors of childhood or a combination of one or more of the foregoing cancers. A method of treating cancer, the method comprising the step of administering to a subject in need of such treatment, either simultaneously or sequentially, an effective amount of inotuzumab ozogamicin and temsirolimus.

In another embodiment, the present invention provides for a method of treating cancer, the method comprising the step of administering to a subject in need of such treatment, either simultaneously or sequentially, an effective amount of inotuzumab ozogamicin and temsirolimus.

In yet another embodiment, the present invention provides for a method for treating a subject in need of therapeutic treatment comprising administering to said subject an amount of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof; and an amount of a temsirolimus or a pharmaceutically acceptable salt thereof; wherein inotuzumab ozogamicin and temsirolimus are each independently administered, optionally together with one or more pharmaceutically acceptable carriers or diluents. In yet another embodiment, inotuzumab ozogamicin and temsirolimus are administered simultaneously. In yet another embodiment, inotuzumab ozogamicin and temsirolimus are administered concurrently.

In one embodiment, the present invention provides for a method of treating cancer wherein, inotuzumab ozogamicin is administered at a dose of 0.4 mg/m^2 to 1.8 mg/m^2 every 4 weeks for 6 cycles and temsirolimus is administered at a dose of 5 to 175 mg/week until disease progression. In one embodiment, the present invention provides for a method of treating cancer wherein inotuzumab ozogamicin and temsirolimus are administered up to 24 weeks. In another embodiment, the present invention provides for a method of treating cancer wherein the inotuzumab ozogamicin does is from 0.4 to 1.8 mg/m^2/dose. In another embodiment, the present invention provides for a method of treating cancer wherein the temsirolimus dose is from 10 to 175mg /dose. In another embodiment, the present invention provides for a method of treating cancer wherein the inotuzumab dose is from 0.4 to 0.8 mg/m2 every 4 weeks. In yet another embodiment, the present invention provides for a method of treating cancer wherein the temsirolimus dose is 5 mg to 25 mg every week. In yet another embodiment, the present invention

provides for a method of treating cancer wherein the temsirolimus dose starts on the day 8 of the treatment schedule.

In one embodiment, the present invention provides a pharmaceutical composition for treating cancer wherein the cancer is NHL or ALL.

In one embodiment, the present invention provides for a pharmaceutical composition suitable for treating cancer , comprising inotuzumab ozogamicin, and temsirolimus, in combination with one or more pharmaceutically acceptable carriers or vehicles, wherein the cancer is sensitive to the combination inotuzumab ozogamicin and temsirolimus, and wherein an anticancer effect is achieved with a combination of inotuzumab ozogamicin and temsirolimus which is larger than the anticancer effect achieved with either inotuzumab ozogamicin or temsirolimus alone and exceeds the sum of the effects of inotuzumab ozogamicin and temsirolimus.

In one embodiment, the present invention provides for a pharmaceutical composition suitable for treating cancer, comprising inotuzumab ozogamicin and temsirolimus in combination with one or more pharmaceutically acceptable carriers or vehicles, wherein inotuzumab ozogamicin and temsirolimus are combined or co-formulated in a single dosage form.

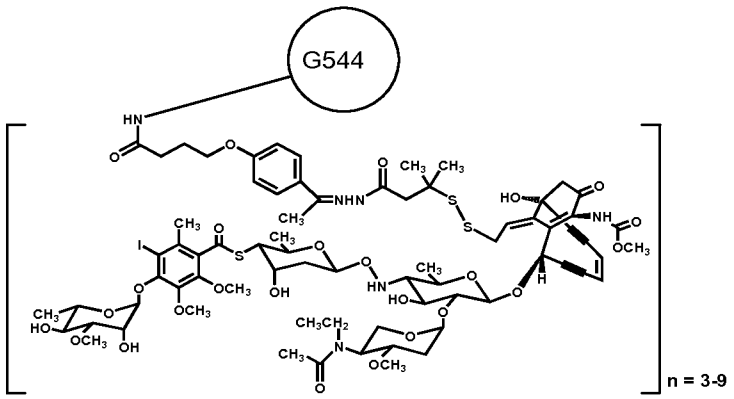
Detailed Description of the Invention

The present invention relates to combinations of inotuzumab ozogamicin (CMC-544) and temsirolimus (rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid; CCI-779), and to their use in the treatment of cancer. Additonally, the present invention also related to the combinations of of inotuzumab ozogamicin and sirolimus (rapamycin). In a particular embodiment, the present invention relates to a pharmaceutical composition comprising inotuzumab ozogamicin and temsirolimus and optionally at least one pharmaceutically acceptable carrier for simultaneous, separate, or sequential use, in particular, for the treatment of B cell malignancies; the use of such a combination for the preparation of a medicament for the delay of progression or treatment of a proliferative disease, such as B cell malignancies; a commercial package or product comprising such a combination; and to a method of treatment of a warm-blooded animal, especially a human.

In particular, the present invention provides methods and compositions related to combination of two agents with different mechanism of action for treatment of B malignancies. In the present invention, the mTOR inhibitor, temsirolimus is administered in combination with inotuzumab ozogamicin, an antibody-targeted chemotherapy. Both agents have shown significant clinical activity in patients with relapsed/refractory lymphomas that progressed after several lines of standard treatments.

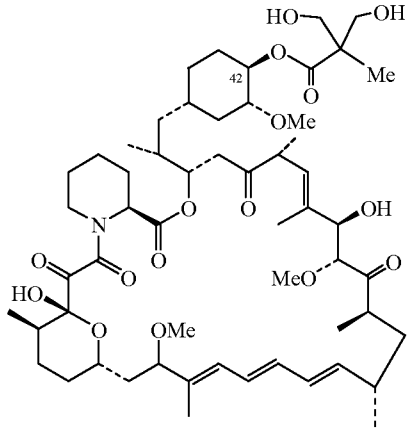
In certain embodiments, the combination therapy provides for the administration inotuzumab ozogamicin and temsirolimus.

Inotuzumab ozogamicin:



is described in U.S. Patent Application No. 10/428894.

Temsirolimus (CCI-779):



is described in US Patent No. 5,362,718 which are incorporated herein by reference.

The term “therapeutically effective amount” means an amount of a compound or combination of compounds that treats a disease; ameliorates, attenuates, or eliminates one or more symptoms of a particular disease; or prevents or delays the onset of one of more symptoms of a disease.

The term “pharmaceutically acceptable”, as used herein, means that a compound or combination of compounds is compatible with the other ingredients of a formulation, and not harmful for the patient or have acceptable risk benefit. .

The term “treating”, as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term “treatment”, as used herein, unless otherwise indicated, refers to the act of treating as “treating” is defined immediately above.

The phrase “a method of treating” or its equivalent, when applied to, for example, cancer refers to a procedure or course of action that is designed to reduce or eliminate the number of cancer cells in a patient, and/or to alleviate the symptoms of a cancer. “A method of treating” cancer or another proliferative disorder does not necessarily mean that the cancer cells or other disorder will, in fact, be eliminated, that the number of cells or disorder will, in fact, be reduced, or that the symptoms of a cancer or other disorder will, in fact, be alleviated. Often, a method of treating cancer will be performed even with a low likelihood of success, but which, given the medical history and estimated survival expectancy of a patient, is nevertheless deemed an overall beneficial course of action.

The term, "anticancer therapy" , as used herein, refers to all types of therapies for treating cancers or neoplasms or malignant tumors found in mammals comprising humans, including leukemia, lymphoma, melanoma, liver, breast, ovary, prostate, stomach, pancreas, lung, kidney, colon and central nervous system tumors.

The instant invention relates to a novel combination therapy using inotuzumab ozogamicin and temsirolimus which decrease cancer cell growth without increasing the toxicity profile compared to the individual drugs. Inotuzumab ozogamicin and temsirolimus produce the standard side effects of cancer chemotherapy when used alone at therapeutic doses. The novel combination therapy of the present invention provides a method where inotuzumab ozogamicin and temsirolimus are administered at lower doses with comparable efficacy and allow for more frequent dosing. Additionally,

the combination therapy of the present invention may lessen the severity or the occurrence of side effects and/or may reduce the chance of drug resistance.

"Combination therapy" or administration "in combination with" one or more further therapeutic agents includes simultaneous, concurrent, and consecutive administration in any order. The administration of the constituents of the combined preparations of the present invention can be made simultaneously, separately or sequentially.

According to the present invention there is provided a method for the treatment of cancers, comprising the simultaneous, concurrent or consecutive administration of inotuzumab ozogamicin and temsirolimus. For example, inotuzumab ozogamicin can be administered before or after or simultaneously with temsirolimus.

The term simultaneous administration as used herein in relation to the administration of medicaments refers to the administration of medicaments such that the individual medicaments are present within a subject at the same time. In addition to the concomitant administration of medicaments (via the same or alternative routes), simultaneous administration may include the administration of the medicaments (via the same or an alternative route) at different times.

Although the simultaneous administration of inotuzumab ozogamicin, and temsirolimus, may be maintained throughout a period of treatment or prevention, anti-cancer activity may also be achieved by subsequent administration of one compound in isolation (for example, temsirolimus without inotuzumab ozogamicin following combination treatment, or alternatively inotuzumab ozogamicin, without temsirolimus following combination treatment.

Thus, a further embodiment of the invention is provided which is a method for the treatment of a cancer, comprising: (a) an initial treatment phase comprising the simultaneous administration of inotuzumab ozogamicin and temsirolimus; and (b) a subsequent treatment phase comprising the administration of inotuzumab ozogamicin without temsirolimus. Further, there is provided a method for the treatment of cancer, comprising: (a) an initial treatment phase comprising the simultaneous administration of inotuzumab ozogamicin and temsirolimus; and (b) a subsequent treatment phase comprising the administration of temsirolimus without inotuzumab ozogamicin.

In one embodiment, the dosage regimen is tailored to the particular of the patient's conditions, response and associate treatments, in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

The patient can be any mammalian patient that suffers from a B cell malignancy. Preferably, the patient is a human or non-human primate, a dog, a cat, a horse, a cow, a goat, a sheep, a rabbit, or a rodent (e.g., mouse or rat). Those skilled in the medical art are readily able to identify individual patients who are afflicted with cancer and who are in need of treatment.

In one embodiment of this method, the abnormal cell growth is cancer, including, but not limited to, hematologic malignancies, non-Hodgkin's lymphoma (NHL), Acute Myeloid leukaemia (AML), Chronic myeloid leukemia (CML), Acute Lymphoblastic leukaemia (ALL), B cell malignancies, and myelodysplastic syndrome, Myelo-dysplastic syndrome (MDS), myelo-proliferative diseases (MPD), Chronic Myeloid Leukemia (CML), T-cell Acute Lymphoblastic leukaemia (T-ALL), B-cell Acute Lymphoblastic leukaemia (B-ALL), mesothelioma, hepatobilliary (hepatic and billiary duct), a primary or secondary CNS tumor, a primary or secondary brain tumor, lung cancer (NSCLC and SCLC), squamous cell cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal, and duodenal) cancers, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin’s Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, testicular cancer, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, multiple myeloma, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma, or a combination of one or more of the foregoing cancers.

This invention also relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of inotuzumab

ozogamicin or salts or solvates thereof that is effective in treating abnormal cell growth in combination with temsirolimus.

The Bliss independence combined response *C* for two single compounds with effects *A* and *B* is $C = A + B - A*B$, where each effect is expressed as a fractional inhibition between 0 and 1. (Reference: Bliss (1939) *Annals of Applied Biology)* The Bliss value, defined to be the difference between the experimental response and the calculated Bliss Independence value, indicates whether the two compounds in combination are additive or synergistic.

A Bliss value of zero (0) is considered additive. The term "additive" means that the result of the combination of the two targeted agents is the sum of each agent individually.

The terms "synergy" or "synergistic" are used to mean that the response of the combination of the two agents is more than the sum of each agent's individual response. More specifically, in the in vitro setting one measure of synergy is known as "Bliss synergy." Bliss synergy refers to "excess over Bliss independence", as determined by the Bliss value defined above.. When the Bliss value is greater than zero (0), or more preferably greater than 0.2, it is considered indicative of synergy. Of course, the use of "synergy" herein also encompasses in vitro synergy as measured by additional and/or alternate methods.

References herein to a combination's in vitro biological effects, including but not limited to anti-cancer effects, being greater than, or equal to, the sum of the combination's components individually, may be correlated to Bliss values. Again, the use of "synergy" herein, including whether a combination of components demonstrates activity equal to or greater than the sum of the components individually, may be measured by additional and/or alternate methods.

In measuring in vivo or therapeutic synergy one measure of synergy is known as "Excess over Highest Single Agent" Synergy. Excess over Highest Single Agent Synergy occurs where a combination of fixed doses is such that it is superior to both of its component doses then this is called "excess over highest single agent". (see FDA's policy at 21 CFR 300.50 which employs such method for approval of combination drug products; and, Borisy et al. (2003) *Proceedings of the National Academy of Science*). Of course, the use of "synergy" herein also encompasses in vivo synergy as measured by additional and/or alternate methods.

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In one embodiment, the method of the invention is related to a method of treating cancer comprising administering to a patient in need thereof an effective amount of: (i) inotuzumab ozogamicin or a pharmaceutically effective salt, derivative or metabolite thereof in combination with an effective amount of temsirolimus or a pharmaceutically effective salt thereof, in amounts sufficient to achieve synergistic effects. In this embodiment, the method of the invention is related to a synergistic combination of the targeted therapeutic agents, inotuzumab ozogamicin and temsirolimus.

Certain aspects of the invention relates to the administration of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof; and temsirolimus or a pharmaceutically acceptable salt thereof. The term "pharmaceutically acceptable salt", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the present invention. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like (see, for example, S.M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977;66:1-19 which is incorporated herein by reference); and. Handbook of Pharmaceutical Salts, P. Heinrich Stahl, Camille G. Wermuth (Eds.), Published jointly by VHCA (Zurich, Switzerland)&Wiley-VCH (Weinheim, Germany) 2002.

Additionally inotuzumab ozogamicin and temsirolimus, and pharmaceutically acceptable acid addition salts thereof, may occur as hydrates or solvates, acid hydrates and solvates are also within the scope of the invention.

An effective amount or dosage of inotuzumab ozogamicin or temsirolimus, may be understood to comprise an amount sufficient to prevent or inhibit the growth of tumor cells or the progression of cancer metastasis in the combination of the present invention. Therapeutic or pharmacological effectiveness of the doses and administration regimens may also be characterized as the ability to induce, enhance, maintain or prolong remission in patients experiencing specific tumors.

Inotuzumab ozogamicin and temsirolimus may be used as a fixed-dosed combination product, Such fixed-dosed combination products, with inotuzumab ozogamicin and temsirolimus combined or co-formulated in a single dosage form, offers simplified treatment regimens, improved clinical effectiveness, enhanced patient adherence and reduced administrative costs. The fixed-dose combination of the present invention may include additional agents such as chemotherapeutic agents and/or anti CD-20 antibodies. For example, Rituxan can be combined or co-formulated in a single dosage form with inotuzumab ozogamicin and temsirolimus as a fixed-dosed combination product.

The clinical utility of a cancer drug is based on the benefit of the drug under an acceptable risk profile to the patient. In cancer therapy survival has generally been the most sought after benefit, however there are a number of other well-recognized benefits in addition to prolonging life. These other benefits, where treatment does not adversely affect survival, include symptom palliation, protection against adverse events, prolongation in time to recurrence or disease-free survival, and prolongation in time to progression. These criteria are generally accepted and regulatory bodies such as the U.S. Food and Drug Administration (F.D.A.) approve drugs that produce these benefits (Hirschfeld et al. Critical Reviews in Oncology/Hematology 42:137-143 2002).

Continued eligibility is assessed throughout the treatment on the basis of a continued acceptable risk/benefit ratio and signs of disease progression. Acceptable risk/benefit ratio may be determined by the Principal Investigator (PI) with confirmation by the Medical Monitor and/or Medical Advisor. Conditions that may warrant termination include the discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the trial or failure to enroll subjects at an acceptable rate.

The appropriate effective amount or dosage of each compound, as used in the combination of the present invention, to administer to a patient, takes into account factors such as age, weight, general health, the compound administered, the route of administration, the nature and advancement of the cancer requiring treatment, and the presence of other medications.

Administration of the compounds of the combination of the present invention can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), Nasal / inhalational, topical, and rectal administration.

The compounds of the method or combination of the present invention may be formulated prior to administration. The formulation will preferably be adapted to the particular mode of administration. These compounds may be formulated with pharmaceutically acceptable carriers as known in the art and administered in a wide variety of dosage forms as known in the art. In making the pharmaceutical compositions of the present invention, the active ingredient will usually be mixed with a pharmaceutically acceptable carrier, complexed or diluted by a carrier or enclosed within a carrier. Such carriers include, but are not limited to, solid diluents or fillers, excipients, sterile aqueous media and various non-toxic organic solvents. Dosage unit forms or pharmaceutical compositions include tablets, capsules, such as gelatin capsules, pills, powders, granules, aqueous and nonaqueous oral solutions and suspensions, lozenges, troches, hard candies, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, injectable solutions, elixirs, syrups, and parenteral solutions packaged in containers adapted for subdivision into individual doses.

Parenteral formulations include pharmaceutically acceptable aqueous or nonaqueous solutions, dispersion, suspensions, emulsions, and sterile powders for the preparation thereof. Examples of carriers include water, ethanol, polyols (propylene glycol, polyethylene glycol), vegetable oils, and injectable organic esters such as ethyl oleate. Fluidity can be maintained by the use of a coating such as lecithin, a surfactant, or maintaining appropriate particle size. Exemplary parenteral administration forms include solutions or suspensions of the compounds of the invention in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefor, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

As used herein, a “pharmaceutically-acceptable carrier” is intended to include any and all material compatible with pharmaceutical administration including solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and other materials and compounds compatible with pharmaceutical administration. Except insofar as any conventional media or agent is incompatible with the active compound, uses thereof in the compositions of the invention are contemplated. Supplementary active compounds can also be incorporated into the compositions.

In making the pharmaceutical compositions of the present invention, the active ingredient will usually be mixed or complexed with a pharmaceutically acceptable carrier, or diluted by a carrier or enclosed within a carrier. Such carriers include, but are not limited to, solid diluents or fillers, excipients, sterile aqueous media and various non-toxic organic solvents. Dosage unit forms or pharmaceutical compositions include tablets, capsules, such as gelatin capsules, pills, powders, granules, aqueous and nonaqueous oral solutions and suspensions, lozenges, troches, hard candies, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, injectable solutions, elixirs, syrups, and parenteral solutions packaged in containers adapted for subdivision into individual doses.

In particular, a therapeutically effective amount of inotuzumab ozogamicin and temsirolimus may be administered simultaneously or sequentially and in any order, and

the components may be administered separately or as a fixed combination. For example, the method of delay of progression or treatment of a proliferative disease according to the invention may comprise: (a) administration of the inotuzumab ozogamicin in free or pharmaceutically acceptable salt form; and (b) administration of the temsirolimus in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts, e.g., in daily or weekly dosages corresponding to the amounts described herein.

Inotuzumab ozogamicin and temsirolimus can be administered separately at different times during the course of therapy or concurrently in divided, single combination forms or fixed-dosed combination. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

The effective dosage of inotuzumab ozogamicin and temsirolimus may vary depending on the pharmaceutical composition employed, the mode of administration, the condition being treated and the severity of the condition being treated. Thus, the dosage regimen the combination therapy using inotuzumab ozogamicin and temsirolimus is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the single active ingredients required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of the active ingredients within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the active ingredients' availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of the active ingredients.

Dosage units may be expressed in mg/kg (i.e. mg/kg of body weight) , mg/week or mg/m^2 . The mg/m^2 dosage units refer to the quantity in milligrams per square meter of body surface area. DLT refers to dose limiting toxicity.

The method according to the present invention may provide an improved level of anti-cancer activity suppression in comparison to conventional anti-cancer treatments comprising inotuzumab ozogamicin or temsirolimus alone. As such, it may be possible to utilize the anti-cancer agents of the invention at doses which would be insufficient (i.

e. sub-therapeutic) in the absence of the other anti-cancer agent while maintaining the same or an adequate level of anti-cancer activity with fewer side effects.

In the method of the present invention, inotuzumab ozogamicin may be administered orally ("PO") in a dosage of about 0.4 to about 5 mg once daily ("QD"). For example, inotuzumab ozogamicin may be administered orally ("PO") in a dosage of about 0.4 to about 3 mg once daily ("QD"). In an embodiment, inotuzumab ozogamicin may be administered orally ("PO") in a dosage of about 0.8 or 1.8 mg once daily ("QD"), for instance 0.8, 1.3, and 1.8 mg once daily. In another embodiment, inotuzumab ozogamicin may be administered via IV infusion.

In the method of the present invention, inotuzumab ozogamicin may be administered in a dosage of about 0.4 to about 5 mg /m^2 via IV infusion once every 1 to 8 weeks. In particular, in the method of the present invention, inotuzumab ozogamicin may be administered in a dosage of about 0.4 to about 1.8 mg /m^2 via IV infusion over about 60 minutes once every 1 to 4 weeks. For example, inotuzumab ozogamicin may be administered in a dosage of about 0.4 to about 1.8 mg /m^2 via IV infusion every 1 or 4 weeks. In an embodiment, inotuzumab ozogamicin may be administered in a dosage of about 0.4 to about 0.8 mg /m^2. In another embodiment, inotuzumab ozogamicin may be administered in a dosage of about 0.4 to about 0.8 mg /m^2 every 4 weeks.

In the method of the present invention, temsirolimus may be administered via IV in a dosage of about 5 to about 175 mg per week. For example, temsirolimus may be administered orally ("PO") in a dosage of about 5 to about 75 mg per week. In an embodiment, temsirolimus may be administered via IV 5, 10, 15, 25, 50, 75, 100, 125, 150, and 175 mg/week. In another embodiment, temsirolimus may be administered orally ("PO") in a dosage of about 5 or 25 mg per week. In yet another embodiment, temsirolimus may be administered orally ("PO") in a dosage of about 5 or 25 mg every week.

Inotuzumab ozogamicin can be administered before, during or after the administration of temsirolimus. In an embodiment, inotuzumab ozogamicin is co-administered with temsirolimus, in separate dosage forms.

In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed, as determined by those skilled in the art.

In some instances, inotuzumab ozogamicin and temsirolimus,is combined or co-formulated in a single dosage form.

The practice of the method of this invention may be accomplished through various administration regimens. In one aspect, the compounds may be administered in 1-week, 2-week, 3-week, 4-week, 5-week, 6-week, 7-week or 8-week cycles. In an embodiment, the compounds may be administered in 3-week cycles. Repetition of the administration regimens may be conducted as necessary to achieve the desired reduction or diminution of cancer cells. In a particular embodiment, temsirolimus is administered weekly and inotuzumab ozogamicin is administered every 4 weeks.

The present invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds and/or compositions of the present invention, including, one or more immunoconjugates and one or more chemotherapeutic agents. Such kits can also include, for example, other compounds and/or compositions, a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products. In particular, the invention relates to a kit comprising inotuzumab ozogamicin, temsirolimus, and written instructions for administration of the therapeutic agents. In one embodiment, the written instructions elaborate and qualify the modes of administration of the therapeutic agents, for example, for simultaneous or sequential administration of the therapeutic agents of the present invention. In another embodiment, the kit is for the treatment of cancer, including but not limited to hematologic malignancies, non-Hodgkin's lymphoma (NHL) including follicular NHL or aggressive NHL (predominantly diffuse large B-cell lymphoma [DLBCL]).Acute Myeloid leukaemia (AML), Chronic myeloid leukemia (CML), Acute Lymphoblastic leukaemia (ALL), B cell malignancies, and myelodysplastic syndrome, Myelo-dysplastic syndrome (MDS), myelo-proliferative diseases (MPD), Chronic Myeloid Leukemia (CML), T-cell Acute Lymphoblastic leukaemia (T-ALL), B-cell Acute Lymphoblastic leukaemia (B-ALL), lung cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, glioblastoma, neuroblastoma, squamous cell cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, rectal cancer, cancer of the anal region, gastric cancer, stomach cancer, breast cancer, gynecological cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the

cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the large intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, prostate cancer, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system ("CNS"), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, solid tumors of childhood or a combination of one or more of the foregoing cancers.

In one embodiment, the present invention provides a non-randomized, open-labeled phase I study of inotuzumab ozogamicin in combination with temsirolimus in patients with CD22 postive relapsed/refractory NHL. In another embodiment, the present invention provides for a study which consists of a dose escalation part where patients with any type of CD22 positive NHL are enrolled to find the highest doses of inotuzumab ozogamicin and temsirolimus that can be given in combination. Once the Recommended Phase II Dose (RP2D) of the combination is established, 4 additional patients with any type of CD22 positive NHL are treated at the RP2D without further dose escalation (expansion cohort).

The results from the above descriptions and examples provide an improved method of cancer therapy that is expected to find widespread clinical utility. In particular, the results suggest that combination of inotuzumab ozogamicin and temsirolimus increases the multiple signals in tumor tissues by contributing to modulation of multiple pathways. Such novel combination therapy leads to a significant clinical anti-tumor effect.

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

Example 1

Patient Selection

Patients have a histologically, and molecularly, and/or cytologically confirmed CD22 positive B-cell NHL, that is relapsed or refractory to standard treatments and for which standard curative or palliative measures do not exist or are no longer effective. Patients have measurable disease, defined as follows: clearly measurable (i.e. well defined boundaries) in at least two perpendicular dimensions on imaging scan; lymph node or nodal mass bi-dimensional measurement with > 1.5 cm in longest transverse diameter.

There are no limitations on prior therapy. Patients may be newly diagnosed cancer patients and receive the treatment of the present invention as the first line therapy. The patients may also be non-responsive or develop resistance to chemotherapy and then experience disease relapse. Additionally, the methods of the present invention may be used to treat patients with relapsed/progressed after of cessation of any treatment by any anti-cancer drug.

However patients have discontinued any previous anticancer and investigational therapy including radiation therapy for at least 21 days prior to study drug, and have recovered fully from the side effects of such treatment prior to beginning study drug. Exceptions are made however, for low dose, non-myelosuppressive radiotherapy for symptomatic palliation. Patient are 18 years or older.

Patients who have prior therapy with an mTOR inhibitor or prior treatment with calicheamicin *are* excluded from the treatment.

Example 2

Treatment Plan

Treatments are administered on an outpatient basis. Appropriate dose modifications for inotuzumab ozogamicin and temsirolimus are described in Example 3. No investigational or commercial agents or therapies other than those described below are administered with the intent to treat the patient's lymphoma.

Table 1: Treatment plan

Agent	Premedications; Precautions	Route	Schedule
Inotuzumab ozogamicin	No premedication required	IV infusion at a constant rate over a 1-hour (+/- 15 minutes) period using a programmable infusion pump.	Day1 q28d
Temsirolimus	diphenhydramine 25 to 50 mg (or equivalent) approximately 30 minutes before the start of each dose of infusion	IV infusion over 30 minutes using a programmable infusion pump.	Days 1,8,15, 22 q28d

Inotuzumab ozogamicin is administered as an intravenous infusion on Day 1 of a 28 day cycle. The reconstituted and diluted admixture solution of the drug is administered within 4 hours of reconstitution for the 1 mg/vial dosage form and within 8 hours of reconstitution for the 3 mg/vial and 4 mg/vial dosage forms. Patients receive the admixture solution (total dose) by IV infusion at a constant rate over a 1-hour (+/- 15 minutes) period using a programmable infusion pump. On day 1 of each cycle, inotuzumab ozogamicin is administered before the administration of temsirolimus.

No intrapatient dose escalation is permitted.

Temsirolimus is administered as an intravenous infusion on Days 1,8,15 and 22 of a 28 day cycle. Patients receive prophylactic medication of intravenous diphenhydramine 25 to 50 mg (or equivalent) approximately 30 minutes before the start of each dose of temsirolimus infusion. If a hypersensitivity/infusion reaction develops during the temsirolimus infusion, the infusion is stopped. Upon adequate resolution, and at the discretion of the physician, treatment is resumed with the administration of an H1-receptor antagonist (or equivalent), if not previously administered, and/or an H2-receptor antagonist (such as intravenous famotidine 20 mg or intravenous ranitidine 50 mg) approximately 30 minutes before restarting the temsirolimus infusion. The infusion is then be resumed at a slower rate (up to 60 minutes). Administration of the final diluted infusion solution is completed within six hours from the time that the concentrate diluent mixture is added to the sodium chloride injection. Temsirolimus concentrate-diluent

mixture for injection is infused over a 30-60 minute period once a week. Preferably, an infusion pump is used for the administration to ensure accurate delivery of the drug.

On day 1 of each cycle, temsirolimus is administered approximately 1 hour after the end of the infusion of inotuzumab ozogamicin. No intrapatient dose escalation is permitted.

Example 3

Subject Dose Escalation

The study starts at dose level 1 and dose escalation of both drugs occurs as reported in table 2. If dose level 1 exceeds the recommended phase II dose (RPTD), the study will proceed with dose level -1.

Table 2: dose escalation scheme

Dose Level	Inotuzumab Ozogamicin	Temsirolimus	Number of Patients
-1	0.8mg/m^2 d1q28	10mg d1,8,15,22q28	3-6
1	0.8mg/m^2 d1q28	15mg d1,8,15,22q28	3-6
2	1.3mg/m^2 d1q28	15mg d1,8,15,22q28	3-6
3	1.3mg/m^2 d1q28	25mg d1,8,15,22q28	3-6
4	1.8mg/m^2 d1q28	25mg d1,8,15,22q28	3-6
5	1.8mg/m^2 d1q28	50mg d1,8,15,22q28	3-6

Alternatively, the protocol is amended to skip the Day 1 dose of the temsirolimus.

Table 2B: Alternative dose escalation scheme

Dose Level	Inotuzumab Ozogamicin	Temsirolimus	Number of Patients
1	0.8mg/m^2 d1q28	15mg d 8,15,22q28	3-6

Based on the toxicities observed during the study, additional dose levels are explored, as reported in table 3.

Table 3: Additional dose levels

Dose Level	Inotuzumab Ozogamicin	Temsirolimus	Number of Patients
-2a	0.8mg/m^2 d1q28	25mg d1,8,15,22q28	3-6
-2b	0.8mg/m^2 d1q28	50mg d1,8,15,22q28	3-6
-2c	0.8mg/m^2 d1q28	75mg d1,8,15,22q28	3-6
-4a	1.3mg/m^2 d1q28	50mg d1,8,15,22q28	3-6
-4b	1.3mg/m^2 d1q28	75mg d1,8,15,22q28	3-6

Based on current knowledge and due to the risk of cumulative toxicity, patients receive inotuzumab ozogamicin up to a maximum of 6 cycles. However, treatment approach is re-evaluated during the course of the study if patients are found to potentially benefit from additional inotuzumab ozogamicin treatment.

There is no planned limit on the maximum number of treatment cycles with temsirolimus. Dose escalation will proceed according to the following rules.

Table 4. Conventional 3+3 Dose Escalation Rule.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level
$\geq$ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3

	patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

Patients are evaluated for DLT during the first 28 day cycle. All three patients treated on a dose level are observed for at least 28 days (one cycle) for any toxicity, and assessed for any DLT, before 3 other patients are entered on the same dose level or on next dose level. The RP2D is the dose at which ≤ 1/6 encountered DLT. Once the RP2D is established, 4 additional patients (up to a maximum of 10 patients) are treated in an expanded cohort at the RP2D. Intra-patient dose escalation is not permitted.

Example 4

Duration of Therapy

In the absence of treatment delays due to adverse events, treatment is continued until one of the following criteria applies: disease progression, inter-current illness that prevents further administration of treatment, unacceptable adverse events(s), patient decides to withdraw from the study, or general or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator. Based on current knowledge and due to the risk of cumulative toxicity, patients receive inotuzumab ozogamicin up to a maximum of 6 cycles. However, treatment approach is re-evaluated during the course of the study if patients are found to potentially benefit from additional inotuzumab ozogamicin treatment.

Example 5

Dosing Delays and Dose Modification

Additional cycles of therapy are administered provided that the patient meets the following criteria on Day 1 of each cycle:

- Absolute neutrophil count (ANC) ≥ $1x10^9$/L
- Platelets (PLT) ≥ $100x10^9$/L
- Non-hematologic toxicity recovered to ≤ grade (Gr) 1 (or tolerable grade 2)
- No evidence of progressive disease

Study starts at dose level (DL) 1 (Table 2). If dose level 1 exceeds the RP2D, then study proceeds with dose level -1. Should a patient require a dose reduction during the study, dose levels are applied following tables 5a and 5b for inotuzumab ozogamicin and temsirolimus respectively.

Table 5A. General Guidance for Dose Reductions and Modifications- Inotuzumab Ozogamicin

Current Inotuzumab Ozogamicin Dose	First Reduction	Second Reduction	Third Reduction
1.8 mg/m^2	1.3 mg/m^2	0.8 mg/m^2	Off Study
1.3 mg/m^2	0.8 mg/m^2	0.4 mg/m^2	Off study
0.8 mg/m^2	0.4 mg/m^2	Off study	-
0.4 mg/m^2	Off study	-	-

Table 5B. General Guidance for Dose Reductions and Modifications- Temsirolimus

Current Temsirolimus Dose	First Reduction	Second Reduction	Third Reduction
75 mg	50 mg	25 mg	Off Study
50 mg	25 mg	15 mg	Off study
25 mg	15 mg	10 mg	Off study
15 mg	10 mg	Off study	-
10 mg	Off study	-	-

Day 1 dose modifications: If on day 1 of a new cycle patient has ANC <1.0 and/or Platelets <100 and/or non-hematologic toxicity grade 2 or higher, the treatment is delayed by one-week intervals (up to two weeks of delay are permitted) until recovery, then treat with: same dose as day 1 of previous cycle for neutropenia gr 3 or gr 4 ≤ 7 days, thrombocytopenia gr 3 or gr 4 ≤ 7 days and non hematologic adverse events grade ≤2. With one dose-level reduction of both drugs in case of febrile neutropenia, grade 4 hematologic adverse events lasting >7 days, bleeding associated thrombocytopenia within previous cycle and grade ≥3 non hematologic toxicities.

If day 1 dose of CMC-544 and/or CCI-779 is reduced, no dose re-escalation is allowed for the remainder of the study. Up to two dose reductions on day 1 are permitted.

Day 8,15,22 dose reductions: For temsirolimus dosing on days 8, 15 and 22, the following rules will apply:

ANC ($x10^9$/L)	PLT ($x10^9$/L)	Non-hem AEs (see also Tables 6A-6C)	Dose
≥1.0	≥75	Gr 1	100%
≥0.5 to <1.0	≥50 to <75	Gr2 tolerable	Reduce by one DL
<0.5	<50	≥Gr2 intolerable	Hold

Patients requiring dose reductions should not have the dose re-escalated with subsequent treatments. However dose of temsirolimus may be re-escalated following a day 8,15,22 dose reduction, provided that ANC, Platelets and non hematologic adverse events have recovered to levels before day 1 of the previous cycle.

If a patient experiences several toxicities and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest dose level. If an adverse event is not covered in section 6.2, doses are reduced or held at the discretion of the investigator for the subject's safety. Subjects with toxicities that are manageable with supportive therapy may not require dose reductions (*e.g.*, nausea/vomiting may be treated with antiemetics). Subjects are withdrawn from the study if they fail to recover to common toxicity criteria (CTC) Grade 0-1 or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related toxicity within 14 days or they experience treatment-related adverse events requiring dose modification despite the number of permitted dose reductions (i.e. Tables 5a and 5b), unless the investigator agrees that the subject should remain in the study because of evidence that the patient is/may continue deriving benefit from continuing study treatment.

Specific Guidance for Dose Reductions and Modifications of temsirolimus based on Adverse Events is discussed in Tables 6A, 6B and 6C.

Table 6A. Specific dose modifications for Metabolic/Laboratory.

Adverse event	National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade	**Temsirolimus**
Metabolic/Laboratory	Cholesterol, serum high (hypercholesterolemia) ≥ Grade 3 Triglyceride, serum high (hypertriglyceridemia) Grade 1 and 2	May continue treatment. Start or adjust dosage of antihyperlipidemic agents. If baseline levels, < grade 2 hypertriglyceridemia, or ≤ grade 2 hypercholesterolemia, whichever is higher, are not achieved after 8 weeks, discontinue agent.
	Triglyceride, serum high (hypertriglyceridemia) > Grade 3	Omit temsirolimus for 1 week. Therapy with a triglyceridelowering agent will be initiated. Triglycerides will be reassessed at the end of the week, and temsirolimus will be resumed if the triglycerides level is reduced to Grade ≤ 2. If triglycerides remain at grade 3 or 4 levels, temsirolimus will be omitted another week, with serum triglycerides re-assessed one week later. If a patient's triglyceride levels remain at CTCAE grade 3-4 for two weeks despite triglyceride-lowering therapy, discontinue agent. If Grade 3 or 4 hypertriglyceridemia recurs after re-challenge, dose interruption will be managed as above, and the patient will resume therapy at a dose reduction of 2 dose levels if the hypertriglyceridemia resolves to a Grade ≤ 2 level within 2 weeks.

Table 6B. Specific Dose Modifications for Pneumonitis.

Adverse Event	**NCI CTCAE grade**	**Temsirolimus**
Polmunary/Upper Respiratory	Pneumonitis	Patients with cough and dyspnea should have temsirolimus omitted pending investigation and permanently discontinued if the diagnosis is confirmed and thought to be related to temsirolimus

Table 6C. Specific dose modifications for Hypersensitivity Reactions.

Adverse Event	NCI CTCAE grade	Temsirolimus
Hypersensitivity Reactions	Grades 0-2 (eg flushing, skin rash, asymptomatic broncospasm	Slow or hold infusion. Give supportive treatment. Upon symptom resolution, may resume infusion-rate escalation at the investigator's discretion
	Grade 3 (eg symptomatic bronchospasm, requiring parenteral treatment, allergy related edema or angioedema	Discontinue infusion. Give supportive treatment. Upon symptom resolution, may resume infusion rate escalation, at investigator discretion. Note: If the same adverse event recurs with same severity, treatment must be permanently discontinued.
	Grade 4 (life threatening anaphylaxis)	Discontinue infusion immediately, treat symptoms aggressively, and do not restart drug.

Example 6

TREAMENT CALENDAR

Baseline (pre-study) evaluations are to be conducted within 7 days prior to start of protocol therapy. Scans are done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations are repeated within 48 hours prior to initiation of the next cycle of therapy. A cycle is 28days long.

	Pre-study	**Treatment Cycle (28 days)**				**Off study**
		Day 1	Day 8	Day 15	Day 22	
Inotuzumab Ozogamicin		X				
Temsirolimus		X	X	X	X	
CD22 evaluation	X					
Demographics	X					
Medical history	X					
B-HCG[b]	X[b]					
Serological testing for Hepatitis B and C	X					
Concurrent meds	X[c]	X----------X				
Physical exam	X	X	X	X	X	X
Vital signs (BP, Pulse, Respiration Rate)	X	X	X	X	X	X
Height	X					X
Weight	X	X				X

Performance status	X	X				X
CBC w/diff, plts	X	X	X	X	X	X
PT, INR, PTT	X	X				
Serum chemistry[d]	X	X	X[e]	X[e]	X[e]	X
Hemoglobin A1C	X					
EKG	X	X				
Adverse event evaluation		X---------- X				X
Tumor measurements	X	Tumor measurements are repeated every 2 cycles Documentation (radiologic) must be provided for patients removed from study for progressive disease.				X[f]
Radiologic evaluation	X	Radiologic measurements should be performed every 2 cycles.				X[f]

a: Patients must be consented at least 4 weeks prior to study entry (registration) as they are required to use two forms of contraception as of 4 weeks prior to registration.
b: One serum pregnancy test (with a sensitivity of at least 25 mIU/mL) within 7 days prior to the first dose of study therapy
c: Concurrent medications recorded as of 30 days pre registration.
d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium, cholesterol, triglycerides.
e: Serum chemistry on days 8,15 and 22 only on C1.
f: CT scans to be performed at baseline and every two cycles thereafter. Bone marrow aspirate and biopsy should be perfomed only in patients with known bone marrow lymphoma involvement.

Example 7

MEASUREMENT OF EFFECT

Antitumor Effect: For the purposes of this study, patients are re-evaluated for response every two cycles. Response and progression are evaluated in this study using the new Modified Response Criteria for Malignant Lymphoma. All patients are evaluabled for toxicity from the time of their first treatment with inotuzumab ozogamicin and temsirolimus. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated are considered evaluable for response. These patients have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 are also considered evaluable.)

Disease Parameters: Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

1. Clearly measurable in at least two perpendicular dimensions at baseline. All nodal lesions are measured: > 1.5 cm in greatest transverse diameter (GTD) regardless of short axis measurement, or, > 1.0 cm in short axis regardless of the GTD measurement.
2. All extranodal lesions are measured ≥ 10 mm in the GTD and twice the reconstruction interval of the scan.
3. If possible, they are from disparate regions of the body.
4. They include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
5. Extranodal lesions within the liver or spleen are at least 1.0 cm in two perpendicular dimensions.

Non-target lesions are qualitatively assessed at each subsequent time point. All of the sites of disease present at baseline and not classified as target lesions are classified as non-target lesions, including any measurable lesions that were not chosen as target lesions. Examples of non-target lesions include: all bone lesions, irrespective of the modality used to assess them; lymphangitis of the skin or lung; cystic lesions; splenomegaly and hepatomegaly; irradiated lesions; measurable lesions beyond the maximum number of six; groups of lesions that are small and numerous; and pleural/pericardial effusions and/or ascites

For the study of the present invention, a significant increase in existing pleural effusions, ascites, or other fluid collections are considered sufficient evidence of progression and do not require cytological proof of malignancy. Effusions, ascites or other fluid collections are followed as non-target lesions.

Further, the existing effusions/ascites such as effusions, ascites or other fluid collections are followed as non-target lesions. At each time point, radiologists check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression is assessed. Significant new effusions, ascites or other fluid collections, which are radiographically suggestive of malignancy are recorded as new lesions.

Unable to Evaluate (UE) lesion category is reserved for target and non-target lesions that are deemed un-evaluable because 1) subsequent (post-baseline) exams had not been performed, 2) lesions could not be evaluated due to poor radiographic technique or poorly defined margins, or 3) lesions identified at baseline were not at a

subsequent time point. Examples of UE lesions are a lung lesion in the hilum obstructing the bronchus and causing atelectasis of the lobe, or a hypodense liver lesion that becomes surrounded by fatty infiltration. In both examples the boundaries of the lesion can be difficult to distinguish. Every effort is made to assign measurements to lesions that develop less distinct margins because they become much smaller. Another example is the instance when lesions identified at baseline were not imaged at a subsequent time point unless the lesions are not imaged because of complete resolution. Lesions that cannot be measured or evaluated will be classified for that time point as UE. If a target lesion is classified as UE post-baseline, the SPD/area (whichever applies) of the target lesions cannot accurately be determined for that time point a response of CR, PR, or SD cannot be assigned for that time point and the response assessment will be UE unless unequivocal progression is determined on the basis of non-target or new lesions, or the evaluable target lesions. PD can be determined without evaluation of all sites of disease based on the GTD, area or SPD for target lesions, evaluation of unequivocal progression in non-target lesions or observation of a new lesion within the available radiographic or clinical assessments.

Any target lesion findings identified on baseline images, which at a subsequent time point decreases in size to < 5 mm in any dimension, are categorized as Too Small To Measure (TSTM). The lesion, node or mass are assigned measurements of 5 mm × 5 mm (for the GTD and the short axis) on the Source Document for the purpose of calculating the area. If that lesion increases in size to ≥ 5 mm in any dimension afterwards, its true size (GTD and short axis) should be recorded. The purpose of the assigned value for the measurement is the acknowledgment that small findings are not accurately measured.

Example 8

Response Criteria and Evaluation of Target Lesions

Complete Response (CR): complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present prior to therapy. Further, the spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable

because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (> 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Partial Response (PR): 1. a ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; (b) if possible they should be from disparate regions of the body; (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved. 2. No increase in the size of the other nodes, liver, or spleen. 3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter. 4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified (e.g. large-cell lymphoma or small neoplastic B cells). Patients who achieve a complete remission by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. 6. No new sites of disease should be observed (e.g., nodes > 1.5 cm in any axis). In patients with follicular lymphoma, a FDG-PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be FDG-PET negative and should be considered partial responders. At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Stable Disease (SD): 1. Failing to attain the criteria needed for a CR or PR, but not fulfilling those for progressive disease (see below).

Progressive Disease (PD): Lymph nodes are considered abnormal in the long axis is > 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1−1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 cm by ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease. 1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. 2. At least a 50% increase from nadir in the sum of the product of the diameters (SPD) of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 × 1.5 cm or more than 1.5 cm in the long axis. 3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis. Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Claims

We claim:

1. A pharmaceutical composition comprising:

a. an amount of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof;
b. an amount of temsirolimus or a pharmaceutically acceptable salt thereof; and
c. a pharmaceutically acceptable carrier or diluent.

2. The pharmaceutical composition of claim 1 comprising inotuzumab ozogamicin.

3. The pharmaceutical composition of claim 1 comprising temsirolimus.

4. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an anti-cancer effect in a mammal suffering from cancer, which anti-cancer effect is greater than the sum of the anti-cancer effects achieved by administering said first and second pharmaceutical compositions separately, and which second pharmaceutical composition comprises an amount of temsirolimus or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

5. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an anti-cancer effect in a mammal suffering from cancer, which anti-cancer effect is greater than the sum of the anti-cancer effects achieved by administering said first and second pharmaceutical compositions separately, and which second pharmaceutical composition comprises an amount of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of temsirolimus

or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

6. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an anti-cancer effect in a mammal suffering from cancer, which anti-cancer effect is greater than the anti-cancer effects achieved by administering said first and second pharmaceutical compositions separately, and which second pharmaceutical composition comprises an amount of temsirolimus or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

7. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an anti-cancer effect in a mammal suffering from cancer, which anti-cancer effect is greater than the anti-cancer effects achieved by administering said first and second pharmaceutical compositions separately, and which second pharmaceutical composition comprises an amount of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of temsirolimus or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

8. The first and second pharmaceutical compositions of claim 4, 5, 6 or 7, wherein said anti-cancer effects are achieved against a cancer selected from hematologic malignancies, non-Hodgkin's lymphoma (NHL) including follicular NHL or aggressive NHL (predominantly diffuse large B-cell lymphoma [DLBCL]).Acute Myeloid leukaemia (AML), Chronic myeloid leukemia (CML), Acute Lymphoblastic leukaemia (ALL), B cell malignancies, and myelodysplastic syndrome, Myelo-dysplastic syndrome (MDS), myelo-proliferative diseases (MPD), Chronic Myeloid Leukemia (CML), T-cell Acute Lymphoblastic leukaemia (T-ALL), B-cell Acute Lymphoblastic leukaemia (B-ALL), lung cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, glioblastoma, neuroblastoma, squamous cell cancer, bone cancer,

pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, rectal cancer, cancer of the anal region, gastric cancer, stomach cancer, breast cancer, gynecological cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the large intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system ("CNS"), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, solid tumors of childhood or a combination of one or more of the foregoing cancers.

9. A kit for achieving a therapeutic effect in a mammal comprising:
a. a therapeutically effective amount of inotuzumab ozogamicin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;
b. a therapeutically effective amount of and temsirolimus, or a pharmaceutically
acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and
c. container means for containing said first and second dosage forms.

10. The kit of claim 9 wherein said therapeutic effect is the treatment of cancer.

11. The kit of claim 10 wherein the cancer is selected from hematologic malignancies, non-Hodgkin's lymphoma (NHL) including follicular NHL or aggressive NHL (predominantly diffuse large B-cell lymphoma [DLBCL]).Acute Myeloid leukaemia (AML), Chronic myeloid leukemia (CML), Acute Lymphoblastic leukaemia (ALL), B cell malignancies, and myelodysplastic syndrome, Myelo-dysplastic syndrome (MDS), myelo-proliferative diseases (MPD), Chronic Myeloid Leukemia (CML), T-cell Acute Lymphoblastic leukaemia (T-ALL), B-cell Acute Lymphoblastic leukaemia (B-

ALL), lung cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, glioblastoma, neuroblastoma, squamous cell cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, rectal cancer, cancer of the anal region, gastric cancer, stomach cancer, breast cancer, gynecological cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the large intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system ("CNS"), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, solid tumors of childhood or a combination of one or more of the foregoing cancers.

12. A dosage form for achieving a therapeutic effect in a mammal comprising:
    a. a therapeutically effective amount of inotuzumab ozogamicin, or a pharmaceutically acceptable salt thereof;
    b. a therapeutically effective amount of temsirolimus, or a pharmaceutically acceptable salt thereof; and
    c. one or more pharmaceutically acceptable carriers or diluents.

13. The dosage form of claim 12 wherein said therapeutic effect is the treatment of cancer.

14. The dosage form of claim 13 wherein the cancer is selected from hematologic malignancies, non-Hodgkin's lymphoma (NHL) including follicular NHL or aggressive NHL (predominantly diffuse large B-cell lymphoma [DLBCL]).Acute Myeloid leukaemia (AML), Chronic myeloid leukemia (CML), Acute Lymphoblastic leukaemia (ALL), B cell malignancies, and myelodysplastic syndrome, Myelo-dysplastic syndrome (MDS), myelo-proliferative diseases (MPD), Chronic Myeloid Leukemia (CML), T-cell Acute Lymphoblastic leukaemia (T-ALL), B-cell Acute Lymphoblastic leukaemia (B-

ALL), lung cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, glioblastoma, neuroblastoma, squamous cell cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, rectal cancer, cancer of the anal region, gastric cancer, stomach cancer, breast cancer, gynecological cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the large intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system ("CNS"), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, solid tumors of childhood or a combination of one or more of the foregoing cancers. A method of treating cancer, the method comprising the step of administering to a subject in need of such treatment, either simultaneously or sequentially, an effective amount of inotuzumab ozogamicin and temsirolimus.

15. A method of treating cancer, the method comprising the step of administering to a subject in need of such treatment, either simultaneously or seqeuncetially, an effective amount of inotuzumab ozogamicin and temsirolimus.

16. A method for treating a mammal in need of therapeutic treatment comprising administering to said mammal:

a. an amount of inotuzumab ozogamicin or a pharmaceutically acceptable salt thereof; and

b. an amount of a temsirolimus or a pharmaceutically acceptable salt thereof;

wherein inotuzumab ozogamicin and temsirolimus are each independently administered, optionally together with one or more pharmaceutically acceptable carriers or diluents.

17. The method of claim 16 wherein inotuzumab ozogamicin and temsirolimus are administered simultaneously.

18. The method of claim 16 wherein said inotuzumab ozogamicin and temsirolimus are administered concurrently.

19. The method of claim 16 wherein inotuzumab ozogamicin and temsirolimus are administered sequentially in either order.

20. The method of claim 16 wherein said therapeutic treatment comprises cancer treatment.

21. The method of claim 15, wherein the subject is a human patient.

22. The method of claim15, wherein inotuzumab ozogamicin is administered at a dose of 0.4 mg/m^2 to 1.8 mg/m^2 every 4 weeks for 6 cycles and temsirolimus is administered at a dose of 5 to 175 mg/week until disease progression.

23. The method of claim 15, wherein inotuzumab ozogamicin and temsirolimus are administered up to 24 weeks.

24. The method of claim 15, wherein the inotuzumab ozogamicin does is from 0.4 to 1.8 mg/m^2/dose.

25. The method of claim 15, wherein the temsirolimus does is from 5 to 175 mg per week.

26. The method of claim 15, wherein the temsirolimus dose is 5 mg per week.

27. The method of claim 15, wherein the cancer is NHL.

28. The method of claim 15, comprising administering to said patient a pharmaceutically acceptable formulation of inotuzumab ozogamicin at a unit dosage of about 0.4 mg/m^2 to about 1.8 mg/m^2 and concurrently administering to said patient temsirolimus at a unit dosage of from about 5 mg per week to about 175 mg per week.

29. A pharmaceutical composition suitable for treating cancer , comprising inotuzumab ozogamicin, and temsirolimus, in combination with one or more pharmaceutically acceptable carriers or vehicles, wherein the cancer is sensitive to the combination inotuzumab ozogamicin and temsirolimus, and wherein an anticancer effect is achieved with a combination of inotuzumab ozogamicin and temsirolimus which is larger than the anticancer effect achieved with either inotuzumab ozogamicin or temsirolimus alone and exceeds the sum of the effects of inotuzumab ozogamicin and temsirolimus.

30. A pharmaceutical composition suitable for treating cancer, comprising inotuzumab ozogamicin and temsirolimus in combination with one or more pharmaceutically acceptable carriers or vehicles, wherein inotuzumab ozogamicin and temsirolimus are combined or co-formulated in a single dosage form.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/056958

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 A61K47/48 C07K16/28
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/124252 A2 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; BURKE GREGORY [US]; LANE) 1 November 2007 (2007-11-01) pages 28-30; claim 12	1-30
X	WO 2007/131689 A2 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; LANE HEIDI [CH] NOVARTIS) 22 November 2007 (2007-11-22) pages 2-3, 52; claims 1-14	1-30

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

[X] 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
14 May 2013	22/05/2013

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/056958

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Y. KOBAYASHI: "Molecular Target Therapy in Hematological Malignancy: Front-runners and Prototypes of Small Molecule and Antibody Therapy", JAPANESE JOURNAL OF CLINICAL ONCOLOGY, vol. 41, no. 2, 1 February 2011 (2011-02-01), pages 157-164, XP055056258, ISSN: 0368-2811, DOI: 10.1093/jjco/hyq189 page 161; table 1	1-30
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/056958

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权利要求书3页 说明书22页

(54)发明名称

用于癌症治疗的伊珠单抗奥佐米星和TORISEL的组合

(57)摘要

本发明涉及用于治疗癌症的治疗方法，其包括使用伊珠单抗奥佐米星(CMC-544)和替西罗莫司的组合。该组合疗法的增强的抗肿瘤效应对于对伊珠单抗奥佐米星或替西罗莫司治疗有抗性、用伊珠单抗奥佐米星或替西罗莫司治疗后复发的患者人群是特别有用的，或者所述增强的抗肿瘤效应降低了与使用伊珠单抗奥佐米星或替西罗莫司的治疗有关的毒性。

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1. 药物组合物，其包含：

a. 一定量的伊珠单抗奥佐米星或其药学上可接受的盐；

b. 一定量的替西罗莫司或其药学上可接受的盐；以及

c. 药学上可接受的载体或稀释剂。

2. 权利要求 1 的药物组合物，其包含伊珠单抗奥佐米星。

3. 权利要求 1 的药物组合物，其包含替西罗莫司。

4. 用于在患有癌症的哺乳动物中实现抗癌效应的与第二药物组合物联合使用的第一药物组合物，所述抗癌效应大于通过单独给药所述第一药物组合物和所述第二药物组合物所实现的抗癌效应的总和，并且所述第二药物组合物包含一定量的替西罗莫司或其药学上可接受的盐和药学上可接受的载体或稀释剂，所述第一药物组合物包含一定量的伊珠单抗奥佐米星或其药学上可接受的盐和药学上可接受的载体或稀释剂。

5. 用于在患有癌症的哺乳动物中实现抗癌效应的与第二药物组合物联合使用的第一药物组合物，所述抗癌效应大于通过单独给药所述第一药物组合物和所述第二药物组合物所实现的抗癌效应的总和，并且所述第二药物组合物包含一定量的伊珠单抗奥佐米星或其药学上可接受的盐和药学上可接受的载体或稀释剂，所述第一药物组合物包含一定量的替西罗莫司或其药学上可接受的盐和药学上可接受的载体或稀释剂。

6. 用于在患有癌症的哺乳动物中实现抗癌效应的与第二药物组合物联合使用的第一药物组合物，所述抗癌效应大于通过单独给药所述第一药物组合物和所述第二药物组合物所实现的抗癌效应，并且所述第二药物组合物包含一定量的替西罗莫司或其药学上可接受的盐和药学上可接受的载体或稀释剂，所述第一药物组合物包含一定量的伊珠单抗奥佐米星或其药学上可接受的盐和药学上可接受的载体或稀释剂。

7. 用于在患有癌症的哺乳动物中实现抗癌效应的与第二药物组合物联合使用的第一药物组合物，所述抗癌效应大于通过单独给药所述第一药物组合物和所述第二药物组合物所实现的抗癌效应，并且所述第二药物组合物包含一定量的伊珠单抗奥佐米星或其药学上可接受的盐和药学上可接受的载体或稀释剂，所述第一药物组合物包含一定量的替西罗莫司或其药学上可接受的盐和药学上可接受的载体或稀释剂。

8. 权利要求 4、5、6 或 7 的第一药物组合物和第二药物组合物，其中所述抗癌效应是针对选自下列的癌症所实现的：恶性血液病、包括滤泡性 NHL 或侵袭性 NHL（主要是弥漫性大 B 细胞淋巴瘤 [DLBCL]）的非霍奇金淋巴瘤 (NHL)、急性髓性白血病 (AML)、慢性髓性白血病 (CML)、急性淋巴母细胞白血病 (ALL)、B 细胞恶性肿瘤、骨髓增生异常综合征、骨髓增生异常综合征 (MDS)、骨髓增生性疾病 (MPD)、慢性髓性白血病 (CML)、T 细胞急性淋巴母细胞白血病 (T-ALL)、B 细胞急性淋巴母细胞白血病 (B-ALL)、肺癌、小细胞肺癌、非小细胞肺癌、脑癌、胶质母细胞瘤、神经母细胞瘤、鳞状细胞癌、骨癌、胰腺癌、皮肤癌、头颈癌、皮肤黑色素瘤或眼内黑色素瘤、子宫癌、卵巢癌、结直肠癌、结肠癌、直肠癌、肛区癌、胃癌、胃癌、乳腺癌、妇科癌症、输卵管癌、子宫内膜癌、宫颈癌、阴道癌、外阴癌、霍奇金病、食管癌、小肠癌、大肠癌、内分泌系统癌症、甲状腺癌、甲状旁腺癌、肾上腺癌、软组织肉瘤、尿道癌、阴茎癌、睾丸癌、前列腺癌、慢性白血病或急性白血病、淋巴细胞性淋巴瘤、膀胱癌、肾癌或输尿管癌、肾细胞癌、肾盂癌、中枢神经系统（“CNS”）肿瘤、原发性 CNS 淋巴瘤、脊柱肿瘤、脑干神经胶质瘤、垂体腺瘤、儿童实体瘤、或者上述癌症中的一种或多种的组合。

9. 用于在哺乳动物中实现疗效的药盒，其包含：

a. 在第一单位剂型中的治疗有效量的伊珠单抗奥佐米星或其药学上可接受的盐和药学上可接受的载体或稀释剂；

b. 在第二单位剂型中的治疗有效量的替西罗莫司或其药学上可接受的盐和药学上可接受的载体或稀释剂；以及

c. 用于容纳所述第一剂型和第二剂型的容器装置。

10. 权利要求 9 的药盒，其中所述疗效为对癌症的治疗。

11. 权利要求 10 的药盒，其中所述癌症选自：恶性血液病、包括滤泡性 NHL 或侵袭性 NHL（主要是弥漫性大 B 细胞淋巴瘤 [DLBCL]）的非霍奇金淋巴瘤 (NHL)、急性髓性白血病 (AML)、慢性髓性白血病 (CML)、急性淋巴母细胞白血病 (ALL)、B 细胞恶性肿瘤、骨髓增生异常综合征、骨髓增生异常综合征 (MDS)、骨髓增生性疾病 (MPD)、慢性髓性白血病 (CML)、T 细胞急性淋巴母细胞白血病 (T-ALL)、B 细胞急性淋巴母细胞白血病 (B-ALL)、肺癌、小细胞肺癌、非小细胞肺癌、脑癌、胶质母细胞瘤、神经母细胞瘤、鳞状细胞癌、骨癌、胰腺癌、皮肤癌、头颈癌、皮肤黑色素瘤或眼内黑色素瘤、子宫癌、卵巢癌、结直肠癌、结肠癌、直肠癌、肛区癌、胃癌、胃癌、乳腺癌、妇科癌症、输卵管癌、子宫内膜癌、宫颈癌、阴道癌、外阴癌、霍奇金病、食管癌、小肠癌、大肠癌、内分泌系统癌症、甲状腺癌、甲状旁腺癌、肾上腺癌、软组织肉瘤、尿道癌、阴茎癌、睾丸癌、前列腺癌、慢性白血病或急性白血病、淋巴细胞性淋巴瘤、膀胱癌、肾癌或输尿管癌、肾细胞癌、肾盂癌、中枢神经系统（“CNS”）肿瘤、原发性 CNS 淋巴瘤、脊柱肿瘤、脑干神经胶质瘤、垂体腺瘤、儿童实体瘤、或者上述癌症中的一种或多种的组合。

12. 用于在哺乳动物中实现疗效的剂型，其包含：

a. 治疗有效量的伊珠单抗奥佐米星或其药学上可接受的盐；

b. 治疗有效量的替西罗莫司或其药学上可接受的盐；以及

c. 一种或多种药学上可接受的载体或稀释剂。

13. 权利要求 12 的剂型，其中所述疗效为对癌症的治疗。

14. 权利要求 13 的剂型，其中所述癌症选自：恶性血液病、包括滤泡性 NHL 或侵袭性 NHL（主要是弥漫性大 B 细胞淋巴瘤 [DLBCL]）的非霍奇金淋巴瘤 (NHL)、急性髓性白血病 (AML)、慢性髓性白血病 (CML)、急性淋巴母细胞白血病 (ALL)、B 细胞恶性肿瘤、骨髓增生异常综合征、骨髓增生异常综合征 (MDS)、骨髓增生性疾病 (MPD)、慢性髓性白血病 (CML)、T 细胞急性淋巴母细胞白血病 (T-ALL)、B 细胞急性淋巴母细胞白血病 (B-ALL)、肺癌、小细胞肺癌、非小细胞肺癌、脑癌、胶质母细胞瘤、神经母细胞瘤、鳞状细胞癌、骨癌、胰腺癌、皮肤癌、头颈癌、皮肤黑色素瘤或眼内黑色素瘤、子宫癌、卵巢癌、结直肠癌、结肠癌、直肠癌、肛区癌、胃癌、胃癌、乳腺癌、妇科癌症、输卵管癌、子宫内膜癌、宫颈癌、阴道癌、外阴癌、霍奇金病、食管癌、小肠癌、大肠癌、内分泌系统癌症、甲状腺癌、甲状旁腺癌、肾上腺癌、软组织肉瘤、尿道癌、阴茎癌、睾丸癌、前列腺癌、慢性白血病或急性白血病、淋巴细胞性淋巴瘤、膀胱癌、肾癌或输尿管癌、肾细胞癌、肾盂癌、中枢神经系统（“CNS”）肿瘤、原发性 CNS 淋巴瘤、脊柱肿瘤、脑干神经胶质瘤、垂体腺瘤、儿童实体瘤、或者上述癌症中的一种或多种的组合。

15. 治疗癌症的方法，所述方法包括向需要此类治疗的个体同时或按序给药有效量的伊珠单抗奥佐米星和替西罗莫司的步骤。

16. 治疗需要治疗性治疗的哺乳动物的方法，其包括向所述哺乳动物给药：

a. 一定量的伊珠单抗奥佐米星或其药学上可接受的盐；以及

b. 一定量的替西罗莫司或其药学上可接受的盐；

其中将伊珠单抗奥佐米星和替西罗莫司各自独立地给药，任选地连同一种或多种药学上可接受的载体或稀释剂。

17. 权利要求 16 的方法，其中将伊珠单抗奥佐米星和替西罗莫司同时给药。

18. 权利要求 16 的方法，其中将伊珠单抗奥佐米星和替西罗莫司并行给药。

19. 权利要求 16 的方法，其中将伊珠单抗奥佐米星和替西罗莫司以任意顺序按序给药。

20. 权利要求 16 的方法，其中所述治疗性治疗包括癌症治疗。

21. 权利要求 15 的方法，其中所述个体为人类患者。

22. 权利要求 15 的方法，其中将伊珠单抗奥佐米星以每 4 周 0.4mg/m^2-1.8mg/m^2 的剂量给药并持续 6 个周期，并且将替西罗莫司以 5-175mg/ 周的剂量给药直到疾病进展。

23. 权利要求 15 的方法，其中将伊珠单抗奥佐米星和替西罗莫司给药达 24 周。

24. 权利要求 15 的方法，其中所述伊珠单抗奥佐米星的剂量为 0.4-1.8mg/m^2/ 剂。

25. 权利要求 15 的方法，其中所述替西罗莫司的剂量为每周 5-175mg。

26. 权利要求 15 的方法，其中所述替西罗莫司的剂量为每周 5mg。

27. 权利要求 15 的方法，其中所述癌症为 NHL。

28. 权利要求 15 的方法，其包括向所述患者以约 0.4mg/m^2 至约 1.8mg/m^2 的单位剂量给药伊珠单抗奥佐米星的药学上可接受的制剂，并且向所述患者以每周约 5mg 至每周约 175mg 的单位剂量并行给药替西罗莫司。

29. 适用于治疗癌症的药物组合物，其包含伊珠单抗奥佐米星和替西罗莫司与一种或多种药学上可接受的载体或媒介物，其中所述癌症对伊珠单抗奥佐米星和替西罗莫司的组合敏感，并且其中用伊珠单抗奥佐米星和替西罗莫司的组合实现的抗癌效应大于单独用伊珠单抗奥佐米星或替西罗莫司所实现的抗癌效应，并且超过伊珠单抗奥佐米星和替西罗莫司的效应的总和。

30. 适用于治疗癌症的药物组合物，其包含伊珠单抗奥佐米星和替西罗莫司与一种或多种药学上可接受的载体或媒介物，其中伊珠单抗奥佐米星和替西罗莫司被组合或复合配制在单一剂型中。

用于癌症治疗的伊珠单抗奥佐米星和 TORISEL 的组合

[0001] 相关申请

[0002] 本申请要求 2011 年 12 月 16 日提交的第 61/576,831 号美国临时申请的优先权，其整体援引加入本文。

发明领域

[0003] 本发明涉及通过给药伊珠单抗奥佐米星 (inotuzumab ozogamicin,CMC-544) 与替西罗莫司 (temsirolimus,与 3- 羟基 -2-(羟甲基)-2- 甲基丙酸形成的雷帕霉素 42- 酯；CCI-779) 的组合治疗异常细胞生长 (如癌症) 的方法。在一具体实施方案中，本发明涉及包含用于同时、单独或按序使用的伊珠单抗奥佐米星和替西罗莫司的产品，其用于对增殖性疾病 (特别是癌症) 进行预防、延迟其进展和 / 或治疗。

[0004] 发明背景

[0005] B 细胞是哺乳动物中免疫应答的关键组分，因为它们是负责产生抗体 (体液免疫) 的细胞。B 细胞是相当多样的，并且这种多样性对于免疫系统是关键的。宿主内每种 B 细胞表达不同的抗体——因此，一种 B 细胞会表达对一种抗原具有特异性的抗体，而另一种 B 细胞会表达对不同的抗原具有特异性的抗体。在人体中，每种 B 细胞可产生大量的抗体分子 (即约 10^7-10^8 个)。当外源性抗原被中和时，B 细胞的成熟通常停止或实质上减少 (从而抗体产生也停止或减少)。然而，特定 B 细胞或浆细胞的增殖会偶然地持续不减弱；这样的增殖可导致癌症，其被称作“B 细胞淋巴瘤”或“多发性骨髓瘤”。

[0006] B 细胞淋巴瘤包括霍奇金淋巴瘤和多种非霍奇金淋巴瘤。细胞淋巴瘤 (如非霍奇金淋巴瘤的 B 细胞亚型) 是造成癌症死亡率的显著原因。B 细胞恶性肿瘤对不同治疗形式的应答是混杂的。例如，在可进行适当的临床分期的非霍奇金淋巴瘤的病例中，野放射疗法 (field radiation therapy) 可提供令人满意的治疗。然而，仍有约一半的患者死于该疾病。Devesa 等人，J.Nat'l Cancer Inst.79:701(1987)。

[0007] 非霍奇金淋巴瘤 (NHL) 是在成年人中最常见的恶性血液病，在北美洲和欧洲，其为第六大最常被诊断出的癌症。大约 85％的 NHL 是 B 细胞来源，并且其包括从缓慢生长的无痛且通常不能治愈的疾病至更具侵袭性但有可能治愈的淋巴瘤的恶性肿瘤的多相群。在大多数为 B 细胞来源的 NHL 中，约 60％至 >90％的 B 淋巴样恶性肿瘤表达 CD22。

[0008] 在过去的 20 年，在 NHL 的控制中取得重大进展。利妥昔单抗 (一种针对 B 细胞表面抗原 CD20 的单克隆抗体) 的引入显著改善了大多数患有 NHL 的患者的治疗结果。在缓慢进展淋巴瘤和侵袭性淋巴瘤二者中，与标准化学疗法联合的利妥昔单抗具有改善的应答率、无进展和提高的总生存数。

[0009] 尽管有了治疗进步，但是对于许多患有淋巴瘤的患者，治疗仍然是有挑战的。由于其毒副作用，治疗 B 细胞恶性肿瘤的传统方法 (包括化学疗法和放射疗法) 的实用性有限。大多数淋巴瘤最初对当前化学治疗剂中的任一种都有应答，但是肿瘤通常会复发并最终成为顽固性的。随着患者接受的治疗方案的数目的增加，疾病对化学疗法变得更有抵抗性。对一线疗法的平均应答为大约 75％，对二线疗法为 60％，对三线疗法为 50％，对四线疗

法为 35-40％。在多次复发的情况中对单一药剂的应答率接近 20％被认为是阳性的，并且确保进一步研究。

[0010] 此外，每次治疗后缓解的时间减少。患有缓慢进展淋巴瘤的患者常常会复发，并且许多人会需要另外的治疗，同时超过一半的患有侵袭性淋巴瘤的患者在标准治疗后不会被治愈。实际上，许多患有弥漫性大 B 细胞淋巴瘤（侵袭性淋巴瘤的最常见亚型）的患者对于标准化学治疗和 / 或化学免疫治疗方案是顽固性的，并且经常复发，甚至是在对治疗实现初步应答的患者中也是如此。

[0011] 受这些疾病影响的患者的预后较差，因此淋巴瘤患者的生存率仍然较低。基于高剂量化学疗法与干细胞移植的补救方法仅仅对于选择的患者有帮助，并且大多数患者死于他们的疾病或强力治疗的并发症。需要治疗这些疾病的新方法。

[0012] 因此，需要研发具有低毒性和更加特异性靶向肿瘤细胞的新型药剂和治疗方案。靶向治疗提供标准细胞毒性化学治疗的有前景的替代疗法。不同于传统的化学疗法，它们影响存在于淋巴瘤细胞中的特异性靶点，并且可避开正常组织，从而将毒性降至最低。靶向与淋巴瘤生成相关的通路的特异性组分的药剂与新型单克隆抗体的组合代表了用于在新诊断的、复发的或对于利妥昔单抗和标准化学疗法是顽固性的患者中研发新治疗策略的新方法。

[0013] 研发包含抗菌和抗肿瘤药剂的有效家族成员的免疫交联物（统称为卡奇霉素或 LL-E33288 复合物，参见第 4,970,198 号美国专利 (1990)）在治疗骨髓瘤中的用途。将最有效的卡奇霉素命名为 γ_1，在本文中简单地称作 γ。这些化合物包含甲基三硫 (methyltrisulfide)，其可与适合的硫醇反应以形成二硫化物，同时引入如酰肼的官能团或用于将卡奇霉素衍生物连接至载体的其它官能团（参见第 5,053,394 号美国专利）。在对于多种癌症的疗法的研发中，单体卡奇霉素衍生物 / 载体缀合物的用途既受到特异性靶向剂（载体）的有效性的限制，又受到缀合方法（当缀合至载体的卡奇霉素衍生物的量（即药物负载）增加时，导致蛋白质聚集体的形成）的限制。伊珠单抗奥佐米星 (CMC544) 是卡奇霉素的 CD22- 特异性免疫交联物，其中人源化的 IgG4 抗 -CD22mAb(G5/44) 通过对酸敏感的 AcBut 连接基共价连接至 CalichDMH(Blood2004 ;103:1807-1814)。CalichDMH(N- 乙酰基 γ 卡奇霉素二甲基酰肼）是 γ 卡奇霉素（一种 DNA 损伤烯二炔 (enediyne) 抗生素）的衍生物 (Bioconj Chem2002 ;13:40-46)。γ 卡奇霉素在小沟 (small groove) 中与 DNA 结合，并且在细胞硫醇的帮助下使双链 DNA 断裂 (Science1988 ;240:1198-1201)，从而导致细胞凋亡和细胞死亡。抗体靶向的化学疗法使细胞毒素剂能够通过细胞毒素剂与单克隆抗体（与肿瘤相关的抗原结合）的缀合而被特异性地递送至肿瘤细胞。这一策略优先将细胞毒素剂递送至肿瘤细胞，将正常组织（缺少靶向物质）对细胞毒素剂的暴露降至最低，并得到显著改善的治疗指数。

[0014] 替西罗莫司是哺乳动物雷帕霉素靶点 (mTOR)（调节细胞生长和增殖的酶）的特异性抑制剂。替西罗莫司通过抑制 mTOR 来防止细胞周期从 G1 期进展至 S 期。mTOR 是一种通过生长因子通路进行信号转导并且调节使肿瘤适应苛刻微环境的代谢通路的激酶。因此，mTOR 的抑制剂具有至少在两个水平上（对突变的生长因子信号转导通路的直接抑制作用和通过抑制 mTOR- 调节的肿瘤存活因子的间接作用）的抑制肿瘤细胞生长的潜力。

[0015] 替西罗莫司 (CCI-779，与 3- 羟基 -2-（羟甲基）-2- 甲基丙酸形成的雷帕霉

素 42- 酯）是西罗莫司（雷帕霉素）的结构类似物，已将替西罗莫司配制用于静脉注射或口服给药来治疗多种恶性肿瘤。替西罗莫司是抗肿瘤药。雷帕霉素是由吸水链霉菌 (Streptomyces hygroscopicus) 产生的大环三烯抗生素，其被发现在体外和体内均具有抗真菌活性，特别是抗白念珠菌 (Candida albicans) 活性 [C. Vezina 等人，J. Antibiot. 28, 721(1975) ；S. N. Sehgal 等 人 ，J. Antibiot. 28, 727(1975) ；H. A. Baker 等人，J. Antibiot. 31, 539(1978) ；第 3,929,992 号美国专利 ；和第 3,993,749 号美国专利]。此外，已证明单独的雷帕霉素（第 4,885,171 号美国专利）或其与毕西巴尼 (picibanil) 的组合（第 4,401,653 号美国专利）具有抗肿瘤活性。

[0016] 雷帕霉素用于预防或治疗成年 T 细胞白血病 / 淋巴瘤 [欧洲专利申请 525,960A1] 和恶性肿瘤 [第 5,206,018 号美国专利]。在第 5,362,718 号美国专利中公开了雷帕霉素的羟基酯（包括 CCI-779) 的制备和用途。

[0017] 对于患有对标准化学疗法复发的或顽固性的淋巴瘤的患者，可从研发具有更低毒性和更好地靶向淋巴瘤细胞的替代治疗策略来得到结果的改善。基础和临床前的实验研究已能够识别一些在淋巴瘤中异常表达的通路，并且在近些年，靶向这些通路的特异性组分的药剂已进入临床评价。同时已证明这些药剂中的一些是有效的且具有比标准化学疗法更好的毒性谱，经常观察到耐药性，这限制了它们的临床使用。

[0018] 通过给药已知的抗肿瘤化合物与一种或多种不同抗肿瘤药物的组合使所述已知的抗肿瘤化合物的抗肿瘤效力增加，以降低当单独使用时各药剂的毒性作用，并且由于所述组合具有比当各药剂单独使用时更高的效力，它们在抗癌治疗领域中是非常需要的。此外，改进的抗癌疗法构成很大的未满足的医疗需求，并且需要发现新的全身疗法和组合方案以通过靶向全部类型的 B 细胞恶性肿瘤来改善治疗结果。具体而言，需要可通过使用免疫交联物和小分子的组合来克服当前治疗方案的缺点的疗法，以治疗多种恶性肿瘤（包括恶性血液病，如非霍奇金淋巴瘤 (NHL)) 而不引发免疫应答。此类改进的疗法通过使用两种具有不同作用机制的药剂而具有靶向多种 B 细胞恶性肿瘤的优点。此外，非霍奇金淋巴瘤是一大类源自淋巴细胞（一种白细胞）的血细胞癌症。因此，患有不同类型的 B 细胞非霍奇金淋巴瘤的患者会受益于本发明的组合疗法。

[0019] 此外，本发明的组合疗法潜在地更有效并具有更低的毒性 ；从而使得能够重复给药较低剂量水平的两种或更多种靶向不同类型的 B 细胞恶性肿瘤的药剂，并持续较长的治疗时间。

[0020] 除了治疗新诊断的患者外，使用靶向药剂（如 ADC) 与细胞毒素剂的组合的新型组合疗法代表了克服可能在治疗中出现的耐药性的可能途径。此外，该组合疗法的增强的抗肿瘤活性对于在单独使用伊珠单抗奥佐米星或替西罗莫司治疗后复发的患者人群特别有用，或者增强的抗肿瘤效应降低了与单独使用伊珠单抗奥佐米星或替西罗莫司治疗有关的毒性。因此，本发明提供通过新的组合和序贯治疗方案来增强伊珠单抗奥佐米星和替西罗莫司的抗肿瘤活性的方法。

[0021] 发明概述

[0022] 本发明提供包含一定量的伊珠单抗奥佐米星或其药学上可接受的盐、一定量的替西罗莫司或其药学上可接受的盐以及药学上可接受的载体或稀释剂的药物组合物。

[0023] 在一个实施方案中，本发明提供用于在患有癌症的哺乳动物中实现抗癌效应的与

第二药物组合物联合使用的第一药物组合物，所述抗癌效应大于通过单独给药所述第一药物组合物和所述第二药物组合物所实现的抗癌效应的总和，并且所述第二药物组合物包含一定量的替西罗莫司或其药学上可接受的盐和药学上可接受的载体或稀释剂，所述第一药物组合物包含一定量的伊珠单抗奥佐米星或其药学上可接受的盐和药学上可接受的载体或稀释剂。

[0024] 在另一实施方案中，本发明提供用于在患有癌症的哺乳动物中实现抗癌效应的与第二药物组合物联合使用的第一药物组合物，所述抗癌效应大于通过单独给药所述第一药物组合物和所述第二药物组合物所实现的抗癌效应的总和，并且所述第二药物组合物包含一定量的伊珠单抗奥佐米星或其药学上可接受的盐和药学上可接受的载体或稀释剂，所述第一药物组合物包含一定量的替西罗莫司或其药学上可接受的盐和药学上可接受的载体或稀释剂。

[0025] 在另一实施方案中，本发明提供用于在患有癌症的哺乳动物中实现抗癌效应的与第二药物组合物联合使用的第一药物组合物，所述抗癌效应大于通过单独给药所述第一药物组合物和所述第二药物组合物所实现的抗癌效应，并且所述第二药物组合物包含一定量的替西罗莫司或其药学上可接受的盐和药学上可接受的载体或稀释剂，所述第一药物组合物包含一定量的伊珠单抗奥佐米星或其药学上可接受的盐和药学上可接受的载体或稀释剂。

[0026] 在另一实施方案中，本发明提供用于在患有癌症的哺乳动物中实现抗癌效应的与第二药物组合物联合使用的第一药物组合物，所述抗癌效应大于通过单独给药所述第一药物组合物和所述第二药物组合物所实现的抗癌效应，并且所述第二药物组合物包含一定量的伊珠单抗奥佐米星或其药学上可接受的盐和药学上可接受的载体或稀释剂，所述第一药物组合物包含一定量的替西罗莫司或其药学上可接受的盐和药学上可接受的载体或稀释剂。

[0027] 治疗癌症的方法，其包括向有此需要的患者给药有效量的伊珠单抗奥佐米星和替西罗莫司的组合。

[0028] 在另一实施方案中，本发明的第一药物组合物和第二药物组合物，其中所述抗癌效应是针对选自下列的癌症所实现的：恶性血液病、包括滤泡性 NHL 或侵袭性 NHL（主要是弥漫性大 B 细胞淋巴瘤 [DLBCL]）的非霍奇金淋巴瘤 (NHL)、急性髓性白血病 (AML)、慢性髓性白血病 (CML)、急性淋巴母细胞白血病 (ALL)、B 细胞恶性肿瘤、骨髓增生异常综合征 (myelodysplastic syndrome)、骨髓增生异常综合征 (Myelo-dysplastic syndrome,MDS)、骨髓增生性疾病 (MPD)、慢性髓性白血病 (CML)、T 细胞急性淋巴母细胞白血病 (T-ALL)、B 细胞急性淋巴母细胞白血病 (B-ALL)、肺癌、小细胞肺癌、非小细胞肺癌、脑癌、胶质母细胞瘤、神经母细胞瘤、鳞状细胞癌、骨癌、胰腺癌、皮肤癌、头颈癌、皮肤黑色素瘤或眼内黑色素瘤、子宫癌、卵巢癌、结直肠癌、结肠癌、直肠癌、肛区癌、胃癌 (gastric cancer)、胃癌 (stomach cancer)、乳腺癌、妇科癌症、输卵管癌、子宫内膜癌、宫颈癌、阴道癌、外阴癌、霍奇金病、食管癌、小肠癌、大肠癌、内分泌系统癌症、甲状腺癌、甲状旁腺癌、肾上腺癌、软组织肉瘤、尿道癌、阴茎癌、睾丸癌、前列腺癌、慢性白血病或急性白血病、淋巴细胞性淋巴瘤、膀胱癌、肾癌或输尿管癌、肾细胞癌、肾盂癌、中枢神经系统（“CNS”）肿瘤、原发性 CNS 淋巴瘤、脊柱 (spinal axis) 肿瘤、脑干神经胶质瘤、垂体腺瘤、儿童实体瘤 (solid tumors of

childhood)、或者上述癌症中的一种或多种的组合。

[0029] 在另一实施方案中，本发明提供用于在哺乳动物中实现疗效的药盒，其包含在第一单位剂型中的治疗有效量的伊珠单抗奥佐米星或其药学上可接受的盐和药学上可接受的载体或稀释剂；在第二单位剂型中的治疗有效量的替西罗莫司或其药学上可接受的盐和药学上可接受的载体或稀释剂；以及用于容纳所述第一剂型和第二剂型的容器装置。

[0030] 在另一实施方案中，本发明提供用于在哺乳动物中实现疗效的剂型，其包含治疗有效量的伊珠单抗奥佐米星或其药学上可接受的盐、治疗有效量的替西罗莫司或其药学上可接受的盐、以及一种或多种药学上可接受的载体或稀释剂。

[0031] 在另一实施方案中，所述药盒和所述剂型用于治疗癌症，其中所述癌症选自：恶性血液病、包括滤泡性 NHL 或侵袭性 NHL（主要是弥漫性大 B 细胞淋巴瘤 [DLBCL]）的非霍奇金淋巴瘤 (NHL)、急性髓性白血病 (AML)、慢性髓性白血病 (CML)、急性淋巴母细胞白血病 (ALL)、B 细胞恶性肿瘤、骨髓增生异常综合征、骨髓增生异常综合征 (MDS)、骨髓增生性疾病 (MPD)、慢性髓性白血病 (CML)、T 细胞急性淋巴母细胞白血病 (T-ALL)、B 细胞急性淋巴母细胞白血病 (B-ALL)、肺癌、小细胞肺癌、非小细胞肺癌、脑癌、胶质母细胞瘤、神经母细胞瘤、鳞状细胞癌、骨癌、胰腺癌、皮肤癌、头颈癌、皮肤黑色素瘤或眼内黑色素瘤、子宫癌、卵巢癌、结直肠癌、结肠癌、直肠癌、肛区癌、胃癌、胃癌、乳腺癌、妇科癌症、输卵管癌、子宫内膜癌、宫颈癌、阴道癌、外阴癌、霍奇金病、食管癌、小肠癌、大肠癌、内分泌系统癌症、甲状腺癌、甲状旁腺癌、肾上腺癌、软组织肉瘤、尿道癌、阴茎癌、睾丸癌、前列腺癌、慢性白血病或急性白血病、淋巴细胞性淋巴瘤、膀胱癌、肾癌或输尿管癌、肾细胞癌、肾盂癌、中枢神经系统（“CNS”）肿瘤、原发性 CNS 淋巴瘤、脊柱肿瘤、脑干神经胶质瘤、垂体腺瘤、儿童实体瘤、或者上述癌症中的一种或多种的组合。治疗癌症的方法，所述方法包括向需要此类治疗的个体同时或按序给药有效量的伊珠单抗奥佐米星和替西罗莫司的步骤。

[0032] 在另一实施方案中，本发明提供治疗癌症的方法，所述方法包括向需要此类治疗的个体同时或按序给药有效量的伊珠单抗奥佐米星和替西罗莫司的步骤。

[0033] 在另一实施方案中，本发明提供治疗需要治疗性治疗的个体的方法，其包括向所述个体给药一定量的伊珠单抗奥佐米星或其药学上可接受的盐；以及一定量的替西罗莫司或其药学上可接受的盐；其中将伊珠单抗奥佐米星和替西罗莫司各自独立地给药，任选地连同一种或多种药学上可接受的载体或稀释剂。在另一实施方案中，将伊珠单抗奥佐米星和替西罗莫司同时 (simultaneously) 给药。在另一实施方案中，将伊珠单抗奥佐米星和替西罗莫司并行 (concurrently) 给药。

[0034] 在一个实施方案中，本发明提供治疗癌症的方法，其中将伊珠单抗奥佐米星以每 4 周 0.4mg/m^2-1.8mg/m^2 的剂量给药并持续 6 个周期，并且将替西罗莫司以 5-175mg/ 周的剂量给药直到疾病进展。在一个实施方案中，本发明提供治疗癌症的方法，其中将伊珠单抗奥佐米星和替西罗莫司给药达 24 周。在另一实施方案中，本发明提供治疗癌症的方法，其中伊珠单抗奥佐米星的剂量为 0.4-1.8mg/m^2/ 剂。在另一实施方案中，本发明提供治疗癌症的方法，其中替西罗莫司的剂量为 10-175mg/ 剂。在另一实施方案中，本发明提供治疗癌症的方法，其中伊珠单抗奥佐米星 (inotuzumab) 的剂量为每 4 周 0.4-0.8mg/m^2。在另一实施方案中，本发明提供治疗癌症的方法，其中替西罗莫司的剂量为每周 5mg-25mg。在另一实施方案中，本发明提供治疗癌症的方法，其中在治疗方案的第 8 天开始替西罗莫司的剂量。

[0035] 在一个实施方案中，本发明提供用于治疗癌症的药物组合物，其中所述癌症为 NHL 或 ALL。

[0036] 在一个实施方案中，本发明提供适用于治疗癌症的药物组合物，其包含伊珠单抗奥佐米星和替西罗莫司与一种或多种药学上可接受的载体或媒介物，其中所述癌症对伊珠单抗奥佐米星和替西罗莫司的组合敏感，并且其中用伊珠单抗奥佐米星和替西罗莫司的组合实现的抗癌效应大于单独用伊珠单抗奥佐米星或替西罗莫司所实现的抗癌效应，并且超过伊珠单抗奥佐米星和替西罗莫司的效应的总和。

[0037] 在一个实施方案中，本发明提供适用于治疗癌症的药物组合物，其包含伊珠单抗奥佐米星和替西罗莫司与一种或多种药学上可接受的载体或媒介物的组合，其中伊珠单抗奥佐米星和替西罗莫司被组合或复合配制 (co-formulated) 在单一剂型中。

[0038] 发明详述

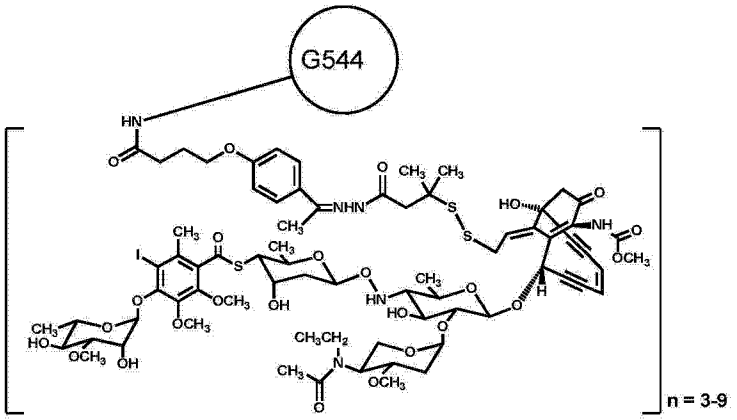
[0039] 本发明涉及伊珠单抗奥佐米星 (CMC-544) 和替西罗莫司 (与 3- 羟基 -2-(羟甲基)-2- 甲基丙酸形成的雷帕霉素 42- 酯 ;CCI-779) 的组合以及它们在癌症治疗中的用途。此外，本发明还涉及伊珠单抗奥佐米星和西罗莫司 (雷帕霉素) 的组合。在一个具体实施方案中，本发明涉及包含用于同时、单独或按序使用的伊珠单抗奥佐米星和替西罗莫司以及任选存在的至少一种药学上可接受的载体的药物组合物，其特别用于治疗 B 细胞恶性肿瘤 ;这样的组合在制备用于延迟增殖性疾病 (如 B 细胞恶性肿瘤) 的进展或对其治疗的药物中的用途 ;包含这样的组合的市售包 (package) 或产品 ;以及治疗温血动物 (特别是人) 的方法。

[0040] 特别地，本发明提供用于治疗 B 细胞恶性肿瘤的涉及两种具有不同作用机制的药剂的组合的方法和组合物。在本发明中，将替西罗莫司 (mTOR 抑制剂) 与伊珠单抗奥佐米星 (抗体靶向的化学治疗剂) 联合给药。这两种药剂在患有进行数种标准治疗后复发 / 顽固性的淋巴瘤的患者中均表现出显著的临床活性。

[0041] 在特定实施方案中，所述组合疗法提供伊珠单抗奥佐米星和替西罗莫司的给药。

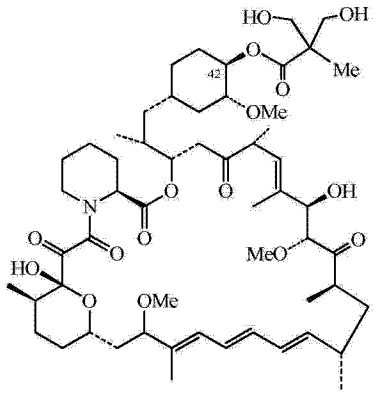
[0042] 第 10/428894 号美国专利申请中记载了伊珠单抗奥佐米星。

[0043]



[0044] 第 5,362,718 号美国专利 (其援引加入本文) 中记载了替西罗莫司 (CCI-779)。

[0045]



[0046] 术语“治疗有效量”意指治疗疾病；改善、减少或消除特定疾病的一种或多种症状；或者预防或延迟疾病的一种或多种症状的发作的化合物或化合物的组合的量。

[0047] 如本文使用的术语“药学上可接受的”意指化合物或化合物的组合与制剂的其它成分相容，并且对于患者无害或具有可接受的风险利益。

[0048] 除非另外说明，如本文使用的术语“治疗（treating）”意指对此类术语所应用的病症或病状或者此类病症或病状的一种或多种症状进行逆转、缓解、抑制其进展或者预防。除非另外说明，如本文使用的术语“治疗（treatment）”指上文所限定的“治疗”的治疗行为。

[0049] 当将短语“治疗方法（治疗……的方法）”或其等同物应用于例如癌症时，其指设计用于减少或消除患者中的癌细胞数目和/或减轻癌症的症状的操作或作用过程。癌症或其他增殖性病症的“治疗方法”不一定意味着癌细胞或其它病症实际上会被消除、细胞数目或病症实际上会减少、或者癌症或其它病症的症状实际上会减轻。通常，即使成功的可能性较低也会进行癌症的治疗方法，但是在考虑到患者的医疗史和估计的存活预期下所述方法被认为是总体上有益的作用过程。

[0050] 如本文使用的术语“抗癌疗法/治疗”指所有类型的用于治疗在哺乳动物（包括人）中发现的癌症或新生物或恶性肿瘤（包括白血病、淋巴瘤、黑色素瘤、肝、乳腺、卵巢、前列腺、胃、胰腺、肺、肾、结肠和中枢神经系统的肿瘤）的疗法。

[0051] 本发明涉及使用伊珠单抗奥佐米星和替西罗莫司的新型组合疗法，其与单个药物相比使癌细胞生长减少而不增加毒性谱。当将伊珠单抗奥佐米星和替西罗莫司以治疗剂量单独使用时，其产生癌症化学疗法的标准副作用。本发明的新型组合疗法提供以更低剂量给药伊珠单抗奥佐米星和替西罗莫司的方法，其具有相当的效力并且可以更频繁地给药。此外，本发明的组合疗法可以减轻副作用的严重性或减少副作用的发生，和/或可降低耐药性的可能性。

[0052] “组合疗法”或与一种或多种其它治疗剂“联合”给药包括同时、并行和以任意顺序相继给药。可同时、单独或按序给药本发明的组合制剂的组分。

[0053] 本发明提供治疗癌症的方法，其包括同时、并行或相继给药伊珠单抗奥佐米星和替西罗莫司。例如，可在给药替西罗莫司之前或之后或与其同时给药伊珠单抗奥佐米星。

[0054] 如本文使用的涉及多种药物给药的术语“同时给药”指将多种药物给药以使得各药物在个体内同时存在。除了将多种药物伴随（concomitant）给药（通过相同或其它途径）外，同时给药还可包括在不同时间将多种药物给药（通过相同或其它途径）。

[0055] 尽管可在整个治疗或预防期间保持伊珠单抗奥佐米星和替西罗莫司的同时给药，

但也可通过随后单独给药一种化合物（例如联合治疗后给药替西罗莫司而不给药伊珠单抗奥佐米星，或者联合治疗后给药伊珠单抗奥佐米星而不给药替西罗莫司）来实现抗癌活性。

[0056] 因此，本发明的另一实施方案提供治疗癌症的方法，其包括：(a) 包括同时给药伊珠单抗奥佐米星和替西罗莫司的初始治疗期；和 (b) 包括给药伊珠单抗奥佐米星而不给药替西罗莫司的后续治疗期。此外，本发明提供治疗癌症的方法，其包括：(a) 包括同时给药伊珠单抗奥佐米星和替西罗莫司的初始治疗期；和 (b) 包括给药替西罗莫司而不给药伊珠单抗奥佐米星的后续治疗期。

[0057] 在一个实施方案中，使给药方案以对于任意疗法常规的方式适应患者的特定病况、反应和相关的治疗，并且给药方案可能需要根据病况的变化和 / 或根据其它临床病况进行调整。

[0058] 所述患者可以是患有 B 细胞恶性肿瘤的任意哺乳动物患者。优选地，所述患者为人或非人灵长类动物、狗、猫、马、牛、山羊、绵羊、兔或啮齿类动物（例如小鼠或大鼠）。医药领域的技术人员能够容易地鉴定受癌症的折磨且需要治疗的患者个体。

[0059] 在该方法的一个实施方案中，所述异常细胞生长是癌症，所述癌症包括但不限于：恶性血液病、非霍奇金淋巴瘤 (NHL)、急性髓性白血病 (AML)、慢性髓性白血病 (CML)、急性淋巴母细胞白血病 (ALL)、B 细胞恶性肿瘤、骨髓增生异常综合征、骨髓增生异常综合征 (MDS)、骨髓增生性疾病 (MPD)、慢性髓性白血病 (CML)、T 细胞急性淋巴母细胞白血病 (T-ALL)、B 细胞急性淋巴母细胞白血病 (B-ALL)、间皮瘤、肝胆管癌 (hepatobilliary)（肝和胆管）、原发性或继发性 CNS 肿瘤、原发性或继发性脑瘤、肺癌 (NSCLC 和 SCLC)、鳞状细胞癌、骨癌、胰腺癌、皮肤癌、头颈癌、皮肤黑色素瘤或眼内黑色素瘤、卵巢癌、结肠癌、直肠癌、肛区癌、胃癌、胃肠（胃的、结肠直肠的和十二指肠的）癌、乳腺癌、子宫癌、输卵管癌、子宫内膜癌、宫颈癌、阴道癌、外阴癌、霍奇金病、食管癌、小肠癌、内分泌系统癌症、甲状腺癌、甲状旁腺癌、肾上腺癌、软组织肉瘤、尿道癌、阴茎癌、前列腺癌、睾丸癌、肾癌或输尿管癌、肾细胞癌、肾盂癌、中枢神经系统（“CNS”）肿瘤、原发性 CNS 淋巴瘤、脊柱肿瘤、脑干神经胶质瘤、垂体腺瘤、肾上腺皮质癌症、胆囊癌、多发性骨髓瘤、胆管上皮癌、纤维肉瘤、神经母细胞瘤、视网膜母细胞瘤、或者上述癌症中的一种或多种的组合。

[0060] 本发明还涉及治疗哺乳动物中异常细胞生长的方法，其包括向所述哺乳动物给药有效治疗异常细胞生长的量的伊珠单抗奥佐米星或其盐或溶剂合物与替西罗莫司的组合。

[0061] 对于具有效果 A 和 B 的两种单独化合物的 Bliss 独立联合反应 C 为 C = A+B-A*B，其中各个效果以 0-1 的相对抑制的形式来表示（参考文献：Bliss(1939)Annals of Applied Biology）。Bliss 值（定义为实验反应与计算的 Bliss 独立值之间的差）表明组合的两种化合物是加和或协同。

[0062] Bliss 值为零 (0) 被认为是加和。术语“加和”意指两种目标药剂的组合的结果为各个单独药剂的总和。

[0063] 术语“协同”或“协同的”用于意指两种药剂的组合的反应大于各个药剂单独反应的总和。更特别地，在体外环境中，一种协同测量结果称作“Bliss 协同”。Bliss 协同指如通过如上所定义的 Bliss 值测定的“超过 Bliss 独立”。当 Bliss 值大于零 (0)，或更优选地大于 0.2 时，认为其表明是协同的。当然，本文中使用的“协同”也包括如通过另外的和

/ 或其它方法测量的体外协同。

[0064] 可将本文所提及的组合的体外生物学效果（包括但不限于大于或等于所述组合的各组分的总和的抗癌效应）与 Bliss 值相关联。再次重申，本文中使用的“协同”（包括证明组分的组合的活性等于或大于各组分的总和）可通过另外的和 / 或其它方法测量。

[0065] 在测量体内协同或治疗协同时，一种协同测量结果被称作“超过最高单独药剂”协同。在固定剂量的组合使得其优于这两种组分的剂量时发生超过最高单独药剂的协同，则将其称作“超过最高单独药剂”（参见在 21CFR300.50 中的 FDA 的政策，其应用这样的方法来批准药品的组合，以及 Borisy 等人 (2003)Proceedings of the National Academy of Science)。当然，本文中使用的“协同”也包括如通过另外的和 / 或其它方法测量的体内协同。

[0066] 在测量体内协同时，一种协同测量结果被称作“超过最高单独药剂”协同。在固定剂量的组合使得其优于这两种组分的剂量时发生超过最高单独药剂的协同，则将其称作“超过最高单独药剂”（参见在 21CFR300.50 中的 FDA 的政策，其应用这样的方法来批准药品的组合，以及 Borisy 等人 (2003)Proceedings of the National Academy of Science)。当然，本文中使用的“协同”也包括如通过另外的和 / 或其它方法测量的体内协同。

[0067] 在一个实施方案中，本发明的方法涉及治疗癌症的方法，其包括向有此需要的患者给药有效量的 :(i) 与有效量的替西罗莫司或其药学上有效的组合的足以实现协同效应的量的伊珠单抗奥佐米星或其药学上有效的盐、衍生物或代谢产物。在该实施方案中，本发明的方法涉及目标治疗剂（伊珠单抗奥佐米星和替西罗莫司）的协同组合。

[0068] 本发明的特定方面涉及给药伊珠单抗奥佐米星或其药学上可接受的盐和替西罗莫司或其药学上可接受的盐。除非另外说明，如本文使用的术语“药学上可接受的盐”包括可能存在于本发明的化合物中的酸基团或碱基团的盐。代表性的盐包括氢溴酸盐、盐酸盐、硫酸盐、硫酸氢盐、硝酸盐、乙酸盐、草酸盐、戊酸盐、油酸盐、棕榈酸盐、硬脂酸盐、月桂酸盐、硼酸盐、苯甲酸盐、乳酸盐、磷酸盐、甲苯磺酸盐、柠檬酸盐、马来酸盐、延胡索酸盐、琥珀酸盐、酒石酸盐、萘甲酸盐、甲磺酸盐、葡庚糖酸盐、乳糖酸盐和十二烷基磺酸盐等。这些可包括碱金属和碱土金属（如钠、锂、钾、钙、镁等）系阳离子，以及非毒性铵、季铵和胺阳离子，包括但不限于铵、四甲基铵、四乙基铵、甲胺、二甲胺、三甲胺、三乙胺、乙胺等（参见例如，S.M.Berge 等人，“Pharmaceutical Salts,”J.Pharm.Sci.,1977 ;66:1-19，将其援引加入本文，以及 Handbook of Pharmaceutical Salts,P.Heinrich Stahl,Camille G.Wermuth(Eds.)，由 VHCA(Zurich,Switzerland)&Wiley-VCH(Weinheim,Germany) 联合出版，2002)。

[0069] 此外，伊珠单抗奥佐米星和替西罗莫司及其药学上可接受的酸加成盐可以水合物或溶剂合物的形式存在，酸的水合物和溶剂合物也在本发明的范围内。

[0070] 有效量或有效剂量的伊珠单抗奥佐米星或替西罗莫司可理解为本发明的组合中包含足以预防或抑制肿瘤细胞的生长或癌症转移的进展的量。剂量或给药方案的治疗有效性或药理有效性也可表征为诱导、增强、维持或延长在经历特定肿瘤的患者中缓解的能力。

[0071] 伊珠单抗奥佐米星和替西罗莫司可以固定剂量组合产品的形式使用。这样的具有被组合或复合配制在单一剂型中的伊珠单抗奥佐米星和替西罗莫司的固定剂量组合产品提供简化的治疗方案、改善临床有效性、增强的患者依从性 (adherence) 和降低的给药成

本。本发明的固定剂量组合可包含另外的药剂，例如化学治疗剂和 / 或抗 CD-20 抗体。例如，可将 Rituxan 与伊珠单抗奥佐米星和替西罗莫司组合或复合配制在单一剂型中，作为固定剂量组合产品。

[0072] 癌症药物的临床效用基于在可接受的风险预测下药物对患者的益处。在癌症中，治疗存活率通常是最受追求的益处，然而除了延长寿命外，还有很多其它公认的益处。这些其它益处（其中治疗不会不利地影响存活）包括症状缓解、针对不良事件的保护、延长复发或无疾病存活的时间，以及延长进展的时间。这些标准通常是可接受的，并且管理部门（如美国食品药品监督管理局 (F.D.A.)）批准产生这些益处的药物 (Hirschfeld 等人，Critical Reviews in Oncology/Hematology42:137-1432002)。

[0073] 在整个治疗过程中，基于连续的可接受的风险 / 益处比以及疾病进展的标志来评估持续合格性 (continued eligibility)。可由主要研究者 (Principal Investigator,PI) 来测定可接受的风险 / 益处比，并由医疗监护仪器 (Medical Monitor) 和 / 或医学咨询家 (Medical Advisor) 确证。可确保终止的条件包括发现对参与试验的个体的出乎预料的、显著的或不可接受的风险，或者不能以可接受的比率登记患者。

[0074] 如本发明的组合中使用的向患者给药的各化合物的合适的有效量或有效剂量考虑到如年龄、体重、一般健康状况、所给药的化合物、给药途径、需要治疗的癌症的性质和进展以及其它药物疗法的存在。

[0075] 本发明的组合的化合物的给药可通过任意能够将所述化合物递送至作用部位的方法来实现。这些方法包括口服途径、十二指肠内途径、肠胃外注射（包括静脉内、皮下、肌内、血管内或者输注）、经鼻 / 吸入、局部和直肠给药。

[0076] 本发明的方法或组合的化合物可在给药前配制。制剂会优选适应于特定的给药模式。可将这些化合物与本领域已知的药学上可接受的载体配制，并以本领域已知的多种剂型给药。在本发明的药物组合物的制备中，通常会将活性成分与药学上可接受的载体混合，用载体复合或稀释，或者包封入载体内。这样的载体包括但不限于固体稀释剂或填充剂、赋形剂、无菌水性介质和多种无毒有机溶剂。剂量单位形式或药物组合物包括片剂、胶囊剂（如明胶胶囊剂）、丸剂、散剂、颗粒剂、水性和非水性口服溶液剂和混悬剂、锭剂 (lozenge)、含锭剂 (troche)、硬糖剂 (hard candy)、喷雾剂、乳膏剂、油膏剂 (salve)、栓剂、胶冻剂、凝胶剂、糊剂、洗剂、软膏剂、注射溶液剂、酏剂、糖浆剂、以及在容器中包装的适合再分为单个剂量的肠胃外溶液剂。

[0077] 肠胃外制剂包括药学上可接受的水性或非水性溶液剂、分散剂、混悬剂、乳剂以及用于制备其的无菌粉末。载体的实例包括水、乙醇、多元醇（丙二醇、聚乙二醇）、植物油和可注射有机酯（如油酸乙酯）。可通过使用包衣（如卵磷脂，一种表面活性剂）或者保持适合的粒度来保持流动性。示例性肠胃外给药形式包括本发明的化合物在无菌水溶液（例如丙二醇水溶液或右旋糖水溶液）中的溶液剂或混悬剂。如果需要，可将这样的剂型适合地缓冲。

[0078] 此外，为了压片的目的，经常使用润滑剂，如硬脂酸镁、十二烷基硫酸钠和滑石。相似类型的固体组合物还可应用于软填充明胶胶囊剂和硬填充明胶胶囊剂。为此，优选的物质包括乳糖 (lactose) 或乳糖 (milk sugar) 和高分子量聚乙二醇。当期望水性混悬剂或酏剂用于口服给药时，可将其中的活性化合物与多种甜味剂或芳香剂、着色剂或染料以及

（如果需要）乳化剂或助悬剂，连同稀释剂（如水、乙醇、丙二醇、甘油或其组合）组合。

[0079] 制备多种含有特定量的活性化合物的药物组合物的方法对于本领域技术人员而言是已知的或会是清楚的。例如，参见 Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975)。

[0080] 如本文中所使用，“药学上可接受的载体”意图包括任意和全部与药学给药相容的物质，其包括溶剂、分散介质、包衣、抗菌剂和抗真菌剂、等渗剂和吸收延迟剂、以及其它与药物给药相容的物质和化合物。除了到了任何常规介质和物质与所述活性化合物不相容的程度外，本发明还包括其在本发明的组合物中的使用。还可将补充活性化合物掺入所述组合物中。

[0081] 在本发明的药物组合物的制备中，通常会将活性成分与药学上可接受的载体混合或复合，或者用载体稀释，或者包封入载体内。这样的载体包括但不限于固体稀释剂或填充剂、赋形剂、无菌水性介质和多种无毒有机溶剂。剂量单位形式或药物组合物包括片剂、胶囊剂（如明胶胶囊剂）、丸剂、散剂、颗粒剂、水性和非水性口服溶液剂和混悬剂、锭剂、含锭剂、硬糖剂、喷雾剂、乳膏剂、油膏剂、栓剂、胶冻剂、凝胶剂、糊剂、洗剂、软膏剂、注射溶液剂、酏剂、糖浆剂以及在容器中包装的适合再分为单个剂量的肠胃外溶液剂。

[0082] 具体而言，可将治疗有效量的伊珠单抗奥佐米星和替西罗莫司同时给药或以任意顺序按序给药，并且可将所述组分单独给药或以固定的组合形式给药。例如，本发明的延迟增殖性疾病的进展或对其治疗的方法可包括：以共同治疗有效量，优选以协同有效量（例如以对应于本文中描述的量的每日或每周剂量）同时地或以任意顺序按序地 (a) 给药游离形式或药学上可接受的盐的形式的伊珠单抗奥佐米星；以及 (b) 给药游离形式或药学上可接受的盐的形式的替西罗莫司。

[0083] 在治疗过程中，可在不同时间单独给药伊珠单抗奥佐米星和替西罗莫司，或者以分开的单一组合形式或固定剂量组合并行给药。因此，本发明应理解为包括所有这样的同时或交替治疗方案，并且应相应地解释术语“给药”。

[0084] 伊珠单抗奥佐米星和替西罗莫司的有效剂量可根据所用的药物组合物、给药模式、所治疗的病况和所治疗病况的严重性而变化。因此，根据包括给药途径以及患者的肾功能和肝功能在内的多种因素选择使用伊珠单抗奥佐米星和替西罗莫司的组合疗法的剂量方案。本领域内科医师、临床医师或兽医可容易地确定预防、对抗或阻止病况进展所需要的单一活性成分的有效量并开处方。实现使活性成分浓度在产生效力而不产生毒性的范围内的最佳精度需要基于活性成分对靶点的有效性的动力学的方案。这涉及对于活性成分分布、平衡和消除的考虑。

[0085] 剂量单位可以 mg/kg（即 mg/kg 体重）、mg/ 周或 mg/m^2 的形式表示。mg/m^2 剂量单位指每平方米体表面积的量（以毫克计）。DLT 指剂量限制性毒性。

[0086] 本发明的方法可提供与包含单独的伊珠单抗奥佐米星或替西罗莫司的常规抗癌治疗相比改善的抗癌活性抑制水平。因而，可以在另一抗癌剂不存在时不足的（即亚治疗的）剂量使用本发明的抗癌剂，同时保持具有更少副作用的相同或足够的抗癌活性水平。

[0087] 在本发明的方法中，可以每天一次（“QD”）约 0.4mg 至约 5mg 的剂量口服（“PO”）给药伊珠单抗奥佐米星。例如，可以每天一次（“QD”）约 0.4mg 至约 3mg 的剂量口服（“PO”）给药伊珠单抗奥佐米星。在一个实施方案中，可以每天一次（“QD”）约 0.8mg 或 1.8mg（例

如每天一次 0.8mg、1.3mg 和 1.8mg) 的剂量口服 (“PO”) 给药伊珠单抗奥佐米星。在另一实施方案中,可通过静脉输注给药伊珠单抗奥佐米星。

[0088] 在本发明的方法中,可每 1-8 周通过静脉输注给药一次约 0.4mg/m^2 至约 5mg/m^2 剂量的伊珠单抗奥佐米星。特别地,在本发明的方法中,可每 1-4 周通过静脉输注给药一次约 0.4mg/m^2 至约 1.8mg/m^2 剂量的伊珠单抗奥佐米星 (在约 60 分钟内)。例如,可每 1-4 周通过静脉输注给药约 0.4mg/m^2 至约 1.8mg/m^2 剂量的伊珠单抗奥佐米星。在一个实施方案中,可给药约 0.4mg/m^2 至约 0.8mg/m^2 剂量的伊珠单抗奥佐米星。在另一实施方案中,可每四周给药约 0.4mg/m^2 至约 0.8mg/m^2 剂量的伊珠单抗奥佐米星。

[0089] 在本发明的方法中,可通过静脉注射给药约 5mg/ 周至约 175mg/ 周剂量的替西罗莫司。例如,可口服 (“PO”) 给药约 5mg/ 周至约 75mg/ 周剂量的替西罗莫司。在一个实施方案中,可通过静脉注射给药 5mg/ 周、10mg/ 周、15mg/ 周、25mg/ 周、50mg/ 周、75mg/ 周、100mg/ 周、125mg/ 周、150mg/ 周和 175mg/ 周的替西罗莫司。在另一实施方案中,可口服 (“PO”) 给药约 5mg/ 周或 25mg/ 周剂量的替西罗莫司。在另一实施方案中,可口服 (“PO”) 给药约 5mg/ 周或 25mg/ 周剂量的替西罗莫司。

[0090] 可在给药替西罗莫司之前、期间或之后给药伊珠单抗奥佐米星。在一个实施方案中,将伊珠单抗奥佐米星与替西罗莫司以单独的剂型共同给药。

[0091] 如由本领域技术人员所测定,在一些情况中,低于之前所述范围的下限值的剂量水平可能更为合适,而在其它情况中仍可应用较大剂量。

[0092] 在一些情况中,将伊珠单抗奥佐米星和替西罗莫司组合或复合配制在单一剂型中。

[0093] 可通过多种给药方案实施本发明的方法。在一个方面,可将所述化合物以 1 周、2 周、3 周、4 周、5 周、6 周、7 周或 8 周的周期给药。在一个实施方案中,可将所述化合物以 3 周的周期给药。为了实现期望的癌细胞减少或减小,可视需要重复进行给药方案。在一个具体实施方案中,将替西罗莫司每周给药,并且将伊珠单抗奥佐米星每 4 周给药。

[0094] 本发明还提供包含一种或多种容器的药盒,所述容器装有一种或多种药物化合物和 / 或组合物的成分,其包含一种或多种免疫交联物和一种或多种化学治疗剂。这样的药盒还可包含例如其它化合物和 / 或组合物、一种或多种用于给药所述化合物和 / 或组合物的装置、以及政府机构规定的形式的规定药品或生物制品的生产、使用或销售的书面说明。本发明特别涉及包含伊珠单抗奥佐米星、替西罗莫司和用于给药所述治疗剂的书面说明的药盒。在一个实施方案中,所述书面说明详细说明并限定所述治疗剂的给药模式,例如将本发明的治疗剂同时或按序给药。在另一实施方案中,所述药盒用于治疗癌症,所述癌症包括但不限于恶性血液病、包括滤泡性 NHL 或侵袭性 NHL(主要是弥漫性大 B 细胞淋巴瘤 [DLBCL]) 的非霍奇金淋巴瘤 (NHL)、急性髓性白血病 (AML)、慢性髓性白血病 (CML)、急性淋巴母细胞白血病 (ALL)、B 细胞恶性肿瘤、骨髓增生异常综合征、骨髓增生异常综合征 (MDS)、骨髓增生性疾病 (MPD)、慢性髓性白血病 (CML)、T 细胞急性淋巴母细胞白血病 (T-ALL)、B 细胞急性淋巴母细胞白血病 (B-ALL)、肺癌、小细胞肺癌、非小细胞肺癌、脑癌、胶质母细胞瘤、神经母细胞瘤、鳞状细胞癌、骨癌、胰腺癌、皮肤癌、头颈癌、皮肤黑色素瘤或眼内黑色素瘤、子宫癌、卵巢癌、结直肠癌、结肠癌、直肠癌、肛区癌、胃癌、胃癌、乳腺癌、妇科癌症、输卵管癌、子宫内膜癌、宫颈癌、阴道癌、外阴癌、霍奇金病、食管癌、小肠癌、大肠

癌、内分泌系统癌症、甲状腺癌、甲状旁腺癌、肾上腺癌、软组织肉瘤、尿道癌、阴茎癌、睾丸癌、前列腺癌、膀胱癌、肾癌或输尿管癌、肾细胞癌、肾盂癌、中枢神经系统（“CNS”）肿瘤、原发性 CNS 淋巴瘤、脊柱肿瘤、脑干神经胶质瘤、垂体腺瘤、儿童实体瘤、或者上述癌症中的一种或多种的组合。

[0095] 在一个实施方案中，本发明提供在患有 CD22 阳性复发 / 顽固性 NHL 的患者中的伊珠单抗奥佐米星与替西罗莫司的组合的非随机、开放性 (open-labeled) I 期研究。在另一实施方案中，本发明提供由剂量递增部分 (dose escalation part) 组成的研究，其中招募患有任意类型的 CD22 阳性 NHL 的患者以发现可联合给予的伊珠单抗奥佐米星和替西罗莫司的最高剂量。一旦确定所述组合的推荐的 II 期剂量 (RP2D)，则将另外 4 位患有任意类型的 CD22 阳性 NHL 的患者在所述 RP2D 下治疗而不进一步剂量递增（人群扩展，expansion cohort）。

[0096] 从以上说明和实例得到的结果提供改善的癌症治疗方法，其被预期会具有广泛的临床应用。特别地，该结果表明伊珠单抗奥佐米星和替西罗莫司的组合通过有助于调节多条通路使肿瘤组织中的多种信号增加。这样的新型组合疗法产生显著的临床抗肿瘤效应。

[0097] 以下实施例举例说明以上描述的发明；但是，它们不意图以任何方式限制本发明的范围。也可通过相关领域技术人员已知的其它测试模型来测定使用所述组合疗法的有利作用。

[0098] 实施例 1

[0099] 患者选择

[0100] 患者患有组织学和分子学和 / 或细胞学确证的 CD22 阳性 B 细胞 NHL，所述 NHL 是对于标准治疗复发的或顽固性的，并且没有对于其的标准治疗方法或姑息疗法，或者这些标准治疗方法或姑息疗法不再有效。患者患有可测量疾病，所述可测量疾病定义如下：在成像扫描时在至少两个垂直维度上明确可测量（即边界清晰）；最长横径 >1.5cm 的淋巴结或结块 (nodal mass) 二维测量值。

[0101] 对于之前的疗法没有限制。患者可以是新诊断的癌症患者并且接受本发明的治疗作为一线疗法。所述患者也可以是对化学疗法无应答或对其有耐药性，然后经历疾病复发的患者。此外，本发明的方法还可用于治疗患有在停止通过任意抗癌药物的任意治疗后复发 / 进展的患者。

[0102] 然而，患者已经中断了任何之前的抗癌治疗和研究性治疗，包括药物研究之前的持续至少 21 天的放射治疗，并且在药物研究开始之前已从这样的治疗的副作用中完全恢复。然而例外是用于缓解症状的低剂量非骨髓移植性放射疗法。患者为 18 岁或更大。

[0103] 从治疗中排除接受用 mTOR 抑制剂的先前治疗或用卡奇霉素的先前治疗的患者。

[0104] 实施例 2

[0105] 治疗计划

[0106] 在门诊患者基础上给药治疗剂。在实施例 3 中描述对伊珠单抗奥佐米星和替西罗莫司的适当剂量更改。不给药除了以下描述的那些之外的意图治疗患者的淋巴瘤的研究性或市售药剂或治疗剂。

[0107] 表 1：治疗计划

[0108]

药剂	术前用药；注意	途径	计划
伊珠单抗奥佐米星	不需要术前用药	使用程控输液泵在 1 小时(+/- 15 分钟)时间内以恒定速率静脉输注。	第 1 天 q28d
替西罗莫司	在每个输注剂量开始之前约 30 分钟给药 25-50 mg 的苯海拉明(或等同物)。	使用程控输液泵在 30 分钟内静脉输注。	第 1、8、15、22 天 q28d

[0109] 在 28 天周期的第 1 天以静脉输注的形式给药伊珠单抗奥佐米星。对于 1mg/ 瓶的剂型，将复原或稀释的药物的混合溶液 (admixture solution) 在复原的 4 小时内给药；并且对于 3mg/ 瓶和 4mg/ 瓶的剂型，在复原的 8 小时内给药。患者接受使用程控输液泵在 1 小时 (+/-15 分钟) 时间内以恒定速率静脉输注的混合溶液 (总剂量)。在每个周期的第 1 天，在给药替西罗莫司之前给药伊珠单抗奥佐米星。

[0110] 不允许患者体内的剂量递增。

[0111] 在 28 天周期的第 1、8、15 和 22 天以静脉输注的形式给药替西罗莫司。在每个替西罗莫司的输注剂量开始之前约 30 分钟，患者接受静脉内给药 25-50mg 的苯海拉明 (或等同物) 的预防服药。如果在输注替西罗莫司期间发生过敏反应 / 输液反应，则停止输注。在充分消退后并在医师慎重考虑下恢复治疗，并在再次开始输注替西罗莫司之前约 30 分钟给药 H1- 受体拮抗剂 (或等同物)(如果之前未给药) 和 / 或 H2- 受体拮抗剂 (例如静脉内给药法莫替丁 20mg 或静脉内给药雷尼替丁 50mg)。然后以较低的速率恢复输注 (至多 60 分钟)。从将浓缩物稀释剂混合物加入至氯化钠注射液中起 6 小时内完成最终稀释输注溶液的给药。将用于注射的替西罗莫司浓缩物 - 稀释混合物在 30-60 分钟内输注，每周一次。优选使用输液泵用于给药以确保所述药物的准确递送。

[0112] 在每个周期的第 1 天，在伊珠单抗奥佐米星的输注结束后约 1 小时给药替西罗莫司。不允许患者体内的剂量递增。

[0113] 实施例 3

[0114] 个体剂量递增

[0115] 该研究以剂量水平 1 开始，并以表 2 中所示进行两种药物的剂量递增。如果剂量水平 1 超过推荐的 II 期剂量 (RPTD)，则该研究会以剂量水平 -1 进行。

[0116] 表 2 ：剂量递增方案

[0117]

剂量水平	伊珠单抗奥佐米星	替西罗莫司	患者数目
-1	0.8mg/m^2d1q28	10mg d1、8、15、22q28	3-6
1	0.8mg/m^2d1q28	15mg d1、8、15、22q28	3-6
2	1.3mg/m^2d1q28	15mg d1、8、15、22q28	3-6

3	1.3mg/m^2d1q28	25mg d1、8、15、22q28	3-6
4	1.8mg/m^2d1q28	25mg d1、8、15、22q28	3-6
5	1.8mg/m^2d1q28	50mg d1、8、15、22q28	3-6

[0118] 或者，将该方案修改为跳过第 1 天的替西罗莫司剂量。

[0119] 表 2B：另一种剂量递增方案

[0120]

剂量水平	伊珠单抗奥佐米星	替西罗莫司	患者数目
1	0.8mg/m^2d1q28	15mg d8、15、22q28	3-6

[0121] 基于研究期间观察的毒性，研究其他剂量水平，如表 3 中所示。

[0122] 表 3：其他剂量水平

[0123]

剂量水平	伊珠单抗奥佐米星	替西罗莫司	患者数目
-2a	0.8mg/m^2d1q28	25mg d1、8、15、22q28	3-6
-2b	0.8mg/m^2d1q28	50mg d1、8、15、22q28	3-6
-2c	0.8mg/m^2d1q28	75mg d1、8、15、22q28	3-6
-4a	1.3mg/m^2d1q28	50mg d1、8、15、22q28	3-6
-4b	1.3mg/m^2d1q28	75mg d1、8、15、22q28	3-6

[0124] 基于目前的认识并且由于累积毒性的风险，患者至多接受 6 个周期的伊珠单抗奥佐米星。然而，如果发现患者潜在地受益于额外的伊珠单抗奥佐米星治疗，则在研究期间对治疗方法重新评估。

[0125] 对于用替西罗莫司的最大治疗周期数没有计划限制。根据以下规则进行剂量递增。

[0126] 表 4. 常规的 3+3 剂量递增规则

[0127]

在给定剂量水平下的具有 DLT 的患者数	递增决策规则(Escalation Decision Rule)
3 人中的 0 人	使 3 位患者进入下一剂量水平
≥ 2	停止剂量递增。将该剂量水平称作最大给药剂量(给药的最高剂量)。只有当 3 位患者之前以该剂量治疗时，另外三(3)位患者才会进入下一最低剂量水平。
3 人中的 1 人	使至少另外 3 位患者进入该剂量水平。 • 如果这 3 位患者中的 0 位经受 DLT，则进行至下一剂量水平。 • 如果该组中的 1 位或多位经受 DLT，则停止剂量递增，并将该剂量称作最大给药剂量。只有当 3 位患者之前以该剂量治疗时，另外三(3)位患者才会进入下一最低剂量水平。
在低于最大给药剂量的最高剂量水平下，6 人中的≤1 人	这通常是推荐的 2 期剂量。必须至少 6 位患者进入推荐的 2 期剂量。

[0128] 在最初的 28 天周期内评价患者的 DLT。观察所有三位用一定剂量水平治疗的患者中的任何毒性，持续至少 28 天（一个周期），并在另外 3 位患者进入相同剂量水平或下一剂量水平之前评估任意 DLT。RP2D 为≤ 1/6 位遭受 DLT 时的剂量。一旦确定 RP2D，在扩展人群中在 RP2D 下治疗另外 4 位患者（至多 10 位患者）。不允许患者体内的剂量递增。

[0129] 实施例 4

[0130] 治疗持续时间

[0131] 在不存在由于不良事件的治疗延迟的情况下，持续治疗直到符合以下标准之一：疾病进展、阻止进一步给药治疗的间发疾病 (intercurrent illness)、一种或多种不可接受的不良事件、患者决定从研究中退出、或者研究者判断患者病况的一般性变化或特定变化导致患者不可接受进一步治疗。基于目前的认识并且由于累积毒性的风险，患者至多接受 6 个周期的伊珠单抗奥佐米星。然而，如果发现患者潜在地受益于额外的伊珠单抗奥佐米星治疗，则在研究期间对治疗方法重新评估。

[0132] 实施例 5

[0133] 给药延迟和剂量更改

[0134] 给药另外的治疗周期，条件是在各周期的第 1 天患者符合以下标准：

[0135] 绝对中性粒细胞计数 (ANC) ≥ $1x10^9/L$

[0136] 血小板 (PLT) ≥ $100x10^9/L$

[0137] 非血液学毒性恢复至≤ 1 级 (Gr)（或者可耐受的 2 级）

[0138] 无进行性疾病的迹象

[0139] 在剂量水平 (DL)1 下开始研究（表 2）。如果剂量水平 1 超过 RP2D，则该研究以剂量水平 -1 进行。如果在研究期间患者需要降低剂量，则分别对伊珠单抗奥佐米星和替西罗莫司施用下表 5a 和 5b 的剂量水平。

[0140] 表 5A. 降低和更改剂量的通用指南 - 伊珠单抗奥佐米星

[0141]

当前的伊珠单抗奥佐米星剂量	第一次降低	第二次降低	第三次降低
1.8 mg/m^2	1.3 mg/m^2	0.8 mg/m^2	退出研究
1.3 mg/m^2	0.8 mg/m^2	0.4 mg/m^2	退出研究
0.8 mg/m^2	0.4 mg/m^2	退出研究	-
0.4 mg/m^2	退出研究	-	-

[0142] 表 5B. 降低和更改剂量的通用指南 - 替西罗莫司

[0143]

当前的替西罗莫司剂量	第一次降低	第二次降低	第三次降低
75 mg	50 mg	25 mg	退出研究
50 mg	25 mg	15 mg	退出研究
25 mg	15 mg	10 mg	退出研究
15 mg	10 mg	退出研究	-
10 mg	退出研究	-	-

[0144] 第 1 天的剂量更改 :如果在新周期的第 1 天,患者的 ANC<1.0 和 / 或血小板 <100 和 / 或非血液学毒性为 2 级或更高,则将治疗延迟一周的间隔 (至多允许两周的延迟) 直至恢复,然后用以下治疗 :与中性粒细胞减少 3 级或 4 级≤ 7 天、血小板减少 3 级或 4 级≤ 7 天和非血液学不良事件级别≤ 2 的之前周期的第 1 天相同的剂量。在发热性中性粒细胞减少、4 级血液学不良事件持续 >7 天、与之前周期内的血小板减少相关的出血以及≥ 3 级的非血液学毒性的情况中,这两种药物降低一个剂量水平。

[0145] 如果第 1 天降低了 CMC-544 和 / 或 CCI-779 的剂量,则在其余的研究阶段不允许剂量再次递增。在第 1 天允许至多两次剂量降低。

[0146] 第 8、15、22 天的剂量降低 :对于替西罗莫司在第 8、15 和 22 天的给药,会适用以下规则 :

[0147]

ANC (x10^9/L)	PLT (x10^9/L)	非血液学不良事件(Non-hem AE) (也参见表 6A-6C)	剂量
≥1.0	≥75	1 级	100%
≥0.5 至<1.0	≥50 至<75	2 级 可耐受	降低一个 DL
<0.5	<50	≥2 级 不可耐受	保持

[0148] 需要降低剂量的患者不应在随后的治疗中剂量再次递增。然而,在第 8、15、22 天的剂量降低后,替西罗莫司的剂量可再次递增,条件是 ANC、血小板和非血液学不良事件已恢复至之前周期的第 1 天之前的水平。

[0149] 如果患者经受数种毒性并且有冲突的推荐,请使用使剂量降低至最低剂量水平的

推荐的剂量调整。如果不良事件未涵盖在第 6.2 章中，则根据研究者对于患者安全的慎重考虑降低或保持剂量。经受可用支持疗法控制的毒性（例如恶心 / 呕吐可用止吐药治疗）的患者可能不需要降低剂量。如果患者不能在 14 天内从治疗相关的毒性中恢复至通常毒性标准 (CTC)0-1 级或可耐受的 2 级（或者已存在的实验室异常情况的起始值的 1 级内），或者他们经受了治疗相关的不良事件（不管允许的剂量降低数（即表 5a 和 5b）如何，其需要进行剂量更改），则所述患者从研究中退出，除非由于有证据表明所述患者从持续的研究治疗中确实 / 可能继续获得益处，使得研究者同意应将患者保留在研究中。

[0150] 在表 6A、6B 和 6C 中讨论基于不良事件的降低和更改替西罗莫司的剂量的特定指南。

[0151] 表 6A. 对于代谢 / 实验室的特定剂量更改。

[0152]

不良事件	国家癌症研究所(NCI)对于不良事件的通用术语标准(CTCAE)级别	替西罗莫司
代谢/实验室	高血清胆固醇(高胆固醇血症) ≥3级高血清甘油三酯(高甘油三酯血症) 1级和2级	可继续治疗。开始或调整抗高血脂药的剂量。如果基线水平在8周后未达到<2级的高甘油三酯血症或者≤2级的高胆固醇血症(不管哪个更高)，则中断药剂。
	高血清甘油三酯(高甘油三酯血症) >3 级	不使用替西罗莫司，持续1周。开始用降甘油三酯药的疗法。在一周结束时再次评估甘油三酯，如果甘油三酯水平降至≤2级，则恢复使用替西罗莫司。如果甘油三酯保持在3级或4级水平，则再次不使用一周的替西罗莫司，并在一周后再次评估血清甘油三酯。如果尽管使用降甘油三酯疗法，但患者的甘油三酯水平保持在CTCAE 3-4级持续两周，则中断药剂。如果激发试验后复发3或4级的高甘油三酯血症，则会进行如上所述的剂量中断，如果在2周内高甘油三酯血症消退至≤2级水平，则患者会以降低2个剂量水平的剂量恢复治疗。

[0153] 表 6B. 对于肺炎的特定剂量更改。

[0154]

不良事件	NCI CTCAE 级别	替西罗莫司
肺/上呼吸道	肺炎	患有咳嗽和呼吸困难的患者应在研究期间不使用替西罗莫司，并且如果确诊并且认为其与替西罗莫司相关，则应永久中止。

[0155] 表 6C. 对于超敏反应的特定剂量更改。

[0156]

不良事件	NCI CTCAE 级别	替西罗莫司
超敏反应	0-2 级(例如潮红、皮疹、无症状性支气管痉挛(broncospasm))	减慢或保持输注。 给予支持治疗。 在症状消退后，经研究者慎重考虑可恢复输注速率递增。
	3 级(例如需要肠胃外治疗的症状性支气管痉挛、变态反应相关的水肿或血管性水肿)	中断输注 给予支持治疗。 在症状消退后，经研究者慎重考虑可恢复输注速率递增。 注意：如果相同的不良事件复发并具有相同的严重性，则必须永久中止治疗。
	4 级(危害生命的过敏反应)	立即中断输注，积极地治疗症状，并且不重新开始给药。

[0157] 实施例 6

[0158] 治疗日程

[0159] 在开始方案治疗之前的 7 天内进行基线（预研究）评估。在治疗开始前≤ 4 周进行扫描。在患者的病况正在恶化的情况中，在开始下一治疗周期前的 48 小时内重复实验室评估。周期长 28 天。

[0160]

	预研究	治疗周期(28 天)				退出研究
		第 1 天	第 8 天	第 15 天	第 22 天	
伊珠单抗奥佐米星		X				
替西罗莫司		X	X	X	X	
CD22评估	X					
人口统计学	X					
医疗史	X					
B-HCG[b]	X[b]					
对于B型和C型肝炎的血清学检测	X					
并行医疗	X[c]	X----------X				
体格检查	X	X	X	X	X	X
生命体征(BP、脉搏、呼吸率)	X	X	X	X	X	X
身高	X					X
体重	X	X				X
体力状态	X	X				X
CBC w/diff, plts	X	X	X	X	X	X
PT、INR、PTT	X	X				

[0161]

血清化学[d]	X	X	X[e]	X[e]	X[e]	X
血红蛋白A1C	X					
EKG	X	X				
不良事件评估		X---------- X				X
肿瘤测量	X	每 2 个周期重复肿瘤测量。对于由于进行性疾病而从研究中移除的患者必须提供文件记录(放射学的)。				X[f]
放射学评估	X	应每 2 个周期进行放射学测量。				X[f]

[0162] a: 患者必须在进入研究（注册）之前至少 4 周得到许可，因为自注册前 4 周起需要他们使用两种形式的避孕。

[0163] b: 在研究治疗的首次剂量之前 7 天内的一种血清妊娠试验（灵敏度至少为 25mIU/mL）。

[0164] c: 自注册前 30 天起记录并行药物治疗。

[0165] d: 白蛋白、碱性磷酸酶、总胆红素、碳酸氢盐、BUN、钙、氯化物、肌酸酐、葡萄糖、LDH、镁、磷、钾、总蛋白质、SGOT[AST]、SGPT[ALT]、钠、胆固醇、甘油三酯。

[0166] e: 第 8、15 和 22 天的血清化学，仅对于 C1。

[0167] f: 在基线时和之后的每两个周期时进行 CT 扫描。应仅在患有已知骨髓淋巴瘤的患者中进行骨髓抽吸和活组织检查。

[0168] 实施例 7

[0169] 效果测量

[0170] 抗肿瘤效果：为了本研究的目的，每两个周期重新评估患者的反应。在本研究中使用新的修改的对恶性淋巴瘤的反应标准 (Modified Response Criteria) 来评估反应和进展。从所有患者首次用伊珠单抗奥佐米星和替西罗莫司治疗的时间起评估他们中的毒性。只有那些在基线时存在可测量疾病、已接受至少一个周期的治疗、并且将他们的疾病重新评估的患者被认为可评估反应。这些患者的反应按照以下所述定义分类。（注意：在第 1 周期结束之前表现出客观疾病进展的患者也被认为是可评估的。）

[0171] 疾病参数：根据所有下述标准选择至多六个最大的主要节点或肿块：

[0172] 1. 基线时在至少两个垂直维度上明确可测量。测量所有结节病损：不管短轴测量值如何，最大横径 (GTD)>1.5cm，或者不管 GTD 测量值如何，短轴 >1.0cm。

[0173] 2. 测量的所有结节外病损的 GTD ≥ 10mm 并为重构扫描间隔的 2 倍。

[0174] 3. 如果可能，它们来自身体的不同区域。

[0175] 4. 无论何时累及这些部位，它们包括疾病的纵隔区域和腹膜后区域。

[0176] 5. 肝或脾内的结节外病损在两个垂直维度上为至少 1.0cm。

[0177] 在各个随后的时间点定性评价非目标病损。将所有在基线时存在的并且未被归类为目标病损的疾病部位归类为非目标病损，其包括任意未被选作目标病损的可测量病损。非目标病损的实例包括：所有的骨病损（不考虑评价它们所使用的形式）、皮肤或肺的淋巴管炎、胆囊病损、脾肿大和肝肿大、受辐射的病损、超过最大数六的可测量病损、小且数目众多的病损的组、以及胸腔 / 心包积液和 / 或腹水。

[0178] 对于本发明的研究，认为现有的胸腔积液、腹水或其它液体聚集的显著增加是进

展的充足证明，并且不需要恶性肿瘤的细胞学证据。作为非目标病损而产生积液、腹水或其它液体聚集。

[0179] 此外，作为非目标病损而产生现有的积液 / 腹水，如积液、腹水或其它液体聚集。在各时间点，放射线学者检查是否存在积液 / 腹水。如果在不存在良性的病因的情况下体积显著增加，则评价为进展。将显著的新积液、腹水或其它液体聚集（其为恶性肿瘤的放射照相提示）记录为新病损。

[0180] 为由于以下原因而被认为是不能评价的目标和非目标病损保留不能评价 (UE) 的病损类别，所述原因为 :1) 未进行随后（基线后）检查，2) 由于较差的放射照相技术或模糊的边界而不能评估的病损，或者 3) 在基线时鉴定的病损在随后的时间点未鉴定。UE 病损的实例为阻塞支气管并导致肺叶肺不张的肺病损，或者变得被脂肪浸润包围的低密度肝病损。在这两个实例中，病损的边界难以区分。尽全力对由于它们变得更小而产生不明确边界的病损进行测量。另一实例为在基线时鉴定的病损在随后的时间点未成像的情况，除非所述病损是由于完全消退而未成像。对于那个时间点，不能测量或评估的病损会被归类为 UE。如果基线后目标病损被归类为 UE，则对于那个时间点不能准确测定目标病损的 SPD/ 面积（无论应用哪个），对于那个时间点不能归属 CR、PR 或 SD 的反应，并且反应的评估会是 UE，除非在非目标病损或新病损或可评估的目标病损的基础上测定明确的进展。可在不评估所有疾病部位的情况下，基于 GTD、目标病损的面积或 SPD、非目标病损中明确进展的评估或在可用的放射照相或临床评价内对新病损的观察来测定 PD。

[0181] 将任何在基线成像中鉴定的，在随后的时间点尺寸在任意维度上减少至 <5mm 的目标病损发现归类为太小而不能测量 (TSTM)。为了计算面积的目的，在源文件中将病损、节点或肿块赋予 5mm×5mm 的量度（对于 GTD 和短轴）。如果之后所述病损的尺寸在任意维度上增加至≥ 5mm，则应记录它的真实尺寸 (GTD 和短轴）。对测量结果赋予的值的目的是承认小的发现未准确测量。

[0182] 实施例 8

[0183] 目标病损的反应标准和评估

[0184] 完全反应 (CR) :所有治疗之前的可检测的疾病的临床证据和疾病相关的症状（如果存在）完全消失。此外，如果治疗之前基于体格检查或 CT 扫描认为脾和 / 或肝是增大的，则其在体格检查时应是不明显的并且通过成像研究应认为是正常尺寸，并且与淋巴瘤相关的结节应消失。然而，对脾病症的测定并不总是可靠的，因为被认为是正常尺寸的脾仍然可能包含淋巴瘤，而增大的脾可能反映解剖学、血量、造血生长因子的使用、或者不同于淋巴瘤的原因的变化。如果治疗前淋巴瘤累及骨髓，则在重复骨髓活组织检查时浸润必须已被清除。进行该项测定的活组织检查样品必须是足够的 (>20mm 的单侧核 (unilateral core))。如果样品的形态是不确定的，则它就免疫组织化学而言应是阴性的。就免疫组织化学而言是阴性的但是通过流式细胞术证明有少量的同源淋巴细胞 (clonal lymphocyte) 的样品会被认为是 CR，直到可用数据证明患者结果中的明显差异。

[0185] 部分反应 (PR) :1. 至多 6 个最大的主要节点或结块的直径乘积的总和 (sum of the product of the diameters，SPD) 减少≥ 50％。应根据以下标准选择这些节点或肿块 :(a) 它们应在至少 2 个垂直维度上明确可测量 ;(b) 如果可能，它们应来自身体的不同区域 ;(c) 无论何时累及这些部位，它们应包括疾病的纵隔区域和腹膜后区域。2. 其它节点、肝或脾

的尺寸不增加。3. 脾或肝的结节就它们的 SPD 而言（或者对于单一结节，其最大横径）必须消退≥ 50％。4. 除了脾和肝的结节，其它器官病症通常是可评价的，并且不应存在可测量的疾病。如果治疗之前样品是阳性的，则对于 PR 的测定，骨髓评价是无关的。然而，如果是阳性的，则细胞类型应是特定的（例如大细胞淋巴瘤或小肿瘤 B 细胞）。就上述标准而言取得完全缓解，但是具有持续形态学的骨髓病症的患者会被认为是部分反应者。6. 不应观察到新的疾病部位（例如在任意轴上 >1.5cm 的节点）。在患有滤泡型淋巴瘤的患者中，FDG-PET 扫描仅表明在 CT 上一个或至多两个消退超过 50％的残留肿块；带有多于两个残留病损的患者不太可能是 FDG-PET 阴性的，并且应被认为是部分反应者。参照基线直径总和，目标病损的直径总和至少减少 30％。

[0186] 稳定的疾病 (SD)：1. 未能达到对于 CR 或 PR 所需的标准，但是不满足那些对于进行性疾病的标准（参见以下）。

[0187] 进行性疾病 (PD)：不管短轴如何，长轴 >1.5cm 的淋巴结被认为是异常的。如果淋巴结的长轴为 1.1-1.5cm，则只有它的短轴 >1.0 时，其被认为是异常的。对于复发或进行性疾病，≤ 1.0cm 的淋巴结不会被认为是异常的。1. 在治疗期间或治疗结束时，即使其它病损的尺寸减少，但在任何轴上出现大于 1.5cm 的任何新病损。2. 任意之前累及的节点或在单个累及的节点中或其它病损（例如脾或肝结节）的尺寸的直径乘积的总和 (SPD) 从最低值增加至少 50％。短轴直径小于 1.0cm 的淋巴结必须增加≥ 50％，并且其尺寸变为 1.5×1.5cm 或长轴大于 1.5cm 才被认为是进行性疾病。3. 任何单独的之前鉴定的其短轴大于 1cm 的节点的最长直径增加至少 50％。可测量的结节外疾病应以与结节疾病相似的方式进行评价。对于这些建议，将脾认为是结节疾病。参照研究时最小的直径总和，既未足以缩小至对于 PR 是合格的，又未足以增大至对于 PD 是合格的。

Abstract

The present invention relates to a therapeutic method for the treatment of cancer that comprises the use of a combination of inotuzumab ozogamicin (CMC-544) and temsirolimus. The enhanced antitumor of the combination therapy is particularly useful for patient population that are recalcitrant to inotuzumab ozogamicin or temsirolimus therapy, relapse after treatment with inotuzumab ozogamicin or temsirolimus or where enhanced antitumor effect reduces toxicities associated with treatment using inotuzumab ozogamicin or temsirolimus.