Title: SMAC MIMETIC METHOD OF TREATMENT

Abstract: A method of treating a patient suffering from a proliferative disorder that comprises administering a Smac mimetic to a patient in accordance with an ascending dose protocol. A method relates to administration at a selected dose, including a high dose relative to previously understood doses, of birinapant, referred to herein as Compound 15, which is N-[1S-[2R-(6,6’-Difluoro-3’-{4S-hydroxy-1-[2S(2S)-methylamino-propionylaminoj-butyryl] -pyrrolidin-2R-ylmethyl } -IH,1H[2,2’]biindolyl-3-ylmethyl)-4S-hydroxy-pyrrolidine-1-carbonyl] -propyl} -2S-methylamino-propionamide or a pharmaceutically acceptable salt thereof.
SMAC MIMETIC METHOD OF TREATMENT

Cross-Reference to Related Applications

[001] This application claims priority to and benefit of U.S. Provisional Application No. 61/760,465, filed February 4, 2013; the entire contents of which are hereby incorporated by reference in their entirety.

Field of the Invention

[002] This invention is in the field of Smac mimetics and compositions and uses thereof to treat proliferative disorders including cancers.

Background of the Invention

[003] Inhibitors of Apoptosis Proteins (IAPs) are naturally occurring intra-cellular proteins that suppress caspase-dependent apoptosis. Smac, also known as DIABLO, is another intracellular protein that functions to antagonize, i.e., inhibit the activity of IAPs. In normal healthy cells, Smac and IAPs function together to maintain the viability of healthy cells. However, in certain disease states, e.g., cancers and other proliferative disorders, IAPs are not adequately antagonized and therefore prevent apoptosis and cause or exacerbate abnormal proliferation and survival.

[004] Smac mimetics, also known as IAP antagonists, are synthetic small molecules that mimic the structure and IAP antagonist activity of the four N-terminal amino acids of Smac. (Smac mimetics are sometimes referred to as Smac peptidomimetics.) When administered to animals suffering proliferative disorders, the Smac mimetics antagonize IAPs, causing an increase in apoptosis among abnormally proliferating cells.

Summary of the Invention

[006] This invention, in one aspect, is a method of treating a patient suffering a proliferative disorder that comprises administering a Smac mimic to a patient in accordance with an ascending dose protocol.

[007] In one aspect, the invention relates to reducing the risk of an adverse event, i.e., an unwanted side effect, associated with treatment with a Smac mimic, such as an inflammatory neuropathy, such as Bell's palsy, by following an ascending dose protocol.

[008] In a particular embodiment, this invention relates to administration at a selected dose, including a high dose relative to previously understood doses, of birinapant, referred to herein as Compound 15, which is N-[1S-[2R-((6,6'-Difluoro-3'-{4S-hydroxy-1-[2S-(2S-methylamino-propionylamino)-butyryl]-pyrroloidin-2R-ylmethyl]-1H,1'H-[2,2']biindolyl-3-ylmethyl)-4S-hydroxy-pyrrolidine-1-carbonyl]-propyl]-2S-methylamino-propionamide or a pharmaceutically acceptable salt thereof, as well as various forms of such compound and salts thereof as further described herein below.

[009] This compound is disclosed in US8283372, the entire disclosure of which is hereby incorporated by reference as though fully set forth herein, and the compound has the following structure:

![Chemical Structure](image)

wherein R5 is –CH2CH3 and Me is methyl. This compound is also referred to herein as Compound 15. It is also known as birinapant.
The invention, in related aspects, comprises a pharmaceutical composition in a dosage unit for intravenous infusion (or for other route of administration e.g., subcutaneous administration) comprising such compound in a dose as hereinafter described and a method of treating a proliferative disorder in a human or non-human mammalian subject in need thereof that comprises internally administering to the subject an effective amount of said compound or a pharmaceutically acceptable salt thereof wherein the effective amount is a dose as defined more fully hereinafter, in accordance with an ascending dose protocol.

In additional illustrative embodiments, the invention comprises a method of potentiating apoptosis of abnormally proliferating cells in a human or non-human mammalian subject that comprises internally administering, e.g., by intravenous infusion or subcutaneously, a hereinafter defined dose of Compound 15, in accordance with an ascending dose protocol.

In additional illustrative embodiments, the invention comprises any one or more of the above methods that further comprises administering a second cancer-related therapy, such as, e.g., radiation, chemotherapy, immunotherapy, photodynamic therapy, and combinations thereof.

In a further illustrative embodiment, the invention comprises a method of treating an autoimmune disease, in which the condition is caused or exacerbated by abnormal regulation of apoptosis, in a mammal in need thereof, including, for example, systemic lupus erythematosus, psoriasis, and immune thrombocytopenic purpura that comprises internally administering to the animal a hereinafter defined dose of Compound 15 or a pharmaceutically acceptable salt thereof, in accordance with an ascending dose protocol.

Thus, this invention is, in illustrative embodiments, a method of administering a Smac mimetic to a patient that comprises internally administering the Smac mimetic to the patient according to an ascending dose protocol, a method of treating a proliferative disorder in a patient that comprises internally administering to the patient a Smac mimetic according to an ascending dose protocol, and a method of reducing the risk of adverse events resulting from internal administration of a Smac mimetic to a patient that comprises administering the Smac mimetic in accordance with an ascending dose protocol.

In illustrative embodiments, the Smac mimetic is administered intravenously, such as by infusion over a period of 1 to 120 minutes, and/or the initial dose is sub-therapeutic.
and the dose is increased each administration, every other administration, or weekly until a target dose is reached, and/or the risk of the patient suffering a neuropathy, e.g., an inflammatory neuropathy such as Bell's palsy, as a consequence of administration of the Smac mimetic is reduced by treating the patient in accordance with the ascending dose protocol, and/or the Smac mimetic is administered once, twice, or thrice per week in accordance with a treatment cycle of one, two, three or four weeks on and one week off, and/or the Smac mimetic is Compound 15. In illustrative embodiments, the Smac mimetic is administered subcutaneously and in such instances the invention comprises pharmaceutical compositions, dosage units, and methods, as described herein, for subcutaneous administration.

Detailed Description of the Invention

[0016] In accordance with this invention, a Smac mimetic is administered in accordance with an ascending dose protocol. An ascending dose protocol is one in which the drug is initially administered at a dose lower than the target dose and is administered at increasingly higher doses in subsequent administrations until a target dose is reached. The initial dose is a dose that is unlikely to result in an adverse event and may be subtherapeutic. The target dose is the dose that has been determined through clinical studies to be a safe and effective dose. Dose escalation is typically carried out by increasing the dose incrementally over 3 or more administrations.

[0017] Dosing protocols, including target doses, of birinapant are illustrated hereinbelow. In accordance with this invention, an initial low dose is administered and the dose is increased over the course of three or more administrations until the target dose is achieved.

[0018] The compound administered in accordance with the present invention is a Smac mimetic that can be used in the treatment of proliferative disorders, e.g.: various benign tumors or malignant tumors (cancer), benign proliferative diseases (e.g., psoriasis, benign prostatic hypertrophy, and restenosis), or autoimmune diseases (e.g., autoimmune proliferative glomerulonephritis, lymphoproliferative autoimmune responses). Cancers which potentially can be treated with Smac mimetics, i.e., IAP antagonists, include, but are not limited to, one or more of the following: lung adenocarcinoma, pancreatic cancer, colon cancer, ovarian cancer, breast cancer, mesothelioma, peripheral neuroma, bladder cancer, glioblastoma, melanoma,

Some embodiments of the invention include inducing apoptosis of cells, particularly pathologically proliferating cells. The methods can be carried out in vitro or in vivo.

The methods of the invention can include administration of a Smac mimetic alone, administration of a combination of IAP antagonists, or administration of a Smac mimetic, with or without one or more additional IAP antagonists, and one or more additional chemotherapeutic agents. Administration of multiple agents can be simultaneous or sequential. Useful chemotherapeutic agents include, but are not limited to, alkylating agents (e.g., cyclophosphamide, mechlorethamine, chlorambucil, melphalan), anthracyclines (e.g., daunorubicin, doxorubicin, epirubicin,
idarubicin, mitoxantrone, valrubicin), cytoskeletal disruptors (e.g., paclitaxel, docetaxel), epothilones (e.g., epothilone A, epothilone B, epothilone D), inhibitors of topoisomerase I and II (e.g., irinotecan, topotecan, etoposide, teniposide, tafluposide), nucleotide analogs precursor analogs (e.g., azacytidine, azathioprine, capecitabine, cytarabine, doxifluridine, fluorouracil, gemcitabine, mercaptopurine, methotrexate, tioguanine), peptide antibiotics (e.g., bleomycin), platinum-based agents (e.g., carboplatin, cisplatin, oxaliplatin), retinoids (e.g., all-trans retinoic acid), and vinca alkaloids and derivatives (e.g., vinblastine, vincristine, vindesine, vinorelbine). In some embodiments, chemotherapeutic agents include fludarabine, doxorubicin, paclitaxel, docetaxel, camptothecin, etoposide, topotecan, irinotecan, cisplatin, carboplatin, oxaliplatin, amsacrine, mitoxantrone, 5-fluoro-uracil, or gemcitabine.

Smac mimetics are IAP antagonists that generally have the formula: \([P_1-P_2-P_3-P_4]\) and bivalent Smac mimetics generally have the formula: \([P_1-P_2-P_3-P_4]-L-[P_1'-P_2'-P_3'-P_4']\) wherein \(P_1-P_2-P_3-\) and \(P_1'-P_2'-P_3'\) correspond to, i.e., mimic, the N-terminal Ala-Val-Pro- of mature Smac and \(P_4\) and \(P_4'\) correspond to Phe, Tyr, Ile, or Val and \(L\) is a linking group, or bond, covalently linking \([P_1-P_2-P_3-P_4]\) to \([P_1'-P_2'-P_3'-P_4']\).

An illustrative genus of bivalent Smac mimetics has the generic structure of formula I, which follows:

\[ [P_1-P_2-P_3-P_4]-L-[P_1'-P_2'-P_3'-P_4'] \]

wherein

\(P_1\) and \(P_1'\) are \(NHR^1-CHR^2-C(O)-\);

\(P_2\) and \(P_2'\) are \(-NH-CHR^3-C(O)-\);

\(P_3\) and \(P_3'\) are pyrrolidine, pyrrolidine fused to a cycloalkyl, or pyrrolidine fused to a heterocycloalkyl having a \(-N-\) heteroatom, and wherein the pyrrolidine of \(P_3/P_3'\) is bound to \(P_2/P_2'\) by an amide bond;

\(P_4\) and \(P_4'\) are \(-M- \text{Q}_p \text{R}^7\);

\(R^1\) is \(-H\) or \(-\text{CH}_3\);

\(R^2\) is \(-\text{CH}_3\) or \(-\text{CH}_2\text{CH}_3\);

\(R^3\) is C2-6 alkyl, C2-6 alkoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, optionally substituted in each case;
M is a covalent bond, C1-6 alkylene, substituted C1-C6 alkylene such as but not limited to -C(O)-;

Q is a covalent bond, C1-6 alkylene, substituted C1-C6 alkylene, -O- or -NR^7-, provided that M is not a covalent bond if: (1) M- is bound directly to the 2 position of a P3/P3' pyrrolidine or to a heteroatom in a P3/P3' pyrrolidine-heterocycloalkyl bicycle and (2) Q is -O- or -NR^7-;

p is 0 or 1;

R^7 is cycloalkyl, cycloalkylaryl, aryl or heteroaryl, optionally substituted in each case;

R^8 is -H or C1-6 alkyl;

L is a linking group, or bond, covalently linking [P1-P2-P3-P4] to [P1'-P2'-P3'-P4'].

For the avoidance of doubt, when Q is absent, i.e., p is 0, and M is a covalent bond, then R7 is bound directly to P3/P3'.

In some embodiments of the invention, pharmaceutical compositions comprising a Smac mimetic such as Compound 15, alone or in combination with one or more other active pharmaceutical ingredients, are administered to a human or veterinary subject. The pharmaceutical compositions typically comprise at least one pharmaceutically acceptable excipient, e.g., a carrier or diluent, and can be administered in the conventional manner by routes including systemic, topical, or oral routes. Administration is normally by intravenous injection, either as a bolus or infusion, but other routes of administration are not precluded including, e.g., subcutaneous, intramuscular, intraperitoneal, intrapleural, intrathecal, intraorbital, or intraarterial injection. An intravenous formulation can contain, e.g., from 1 mg/mL up to and including 5 mg/mL of Compound 15 in sterile 0.05M citrate buffered saline, pH 5. For intravenous infusion, Compound 15, e.g., 1 mg/mL or 5 mg/mL in 0.05M citrate buffered saline, can be added to sterile saline in an infusion bag in an amount calculated to deliver the desired dose.

Typically, Compound 15 will be administered by intravenous infusion, including, e.g., by infusion over an infusion period of about 1 to about 120 minutes, or 1 to about 60 minutes, e.g., about 30 minutes.

The pharmaceutical composition of the invention is a composition in which the active pharmaceutical ingredient, i.e., Compound 15, is pure enough, and the composition is otherwise suitable, for internal administration to a human or other mammal. It can be
prepared in unit dose form, i.e., a form suitable for single administration to a subject such as by infusion. So, e.g., a pharmaceutical composition in intravenous unit dose form may comprise a vial or pre-filled syringe, or an infusion bag or device, each comprising a sufficient amount of Compound 15 to supply the desired dose (or a convenient fraction of such dose), as described hereinafter, such that the contents of one vial or syringe (or a small number of multiple vials, depending upon the fraction of dose in each) are administered at a time.

Administration can be repeated up to about 4 times per day over a period of time, if necessary to achieve a cumulative effective dose, e.g., a cumulative dose effective to produce tumor stasis or regression. A dosing regimen can be, e.g., daily, twice-weekly, or three times weekly (i.e., thrice weekly) intravenous injections, or, e.g., once weekly injections in cycles of three weeks on and one week off, or continuously, for as long as the treatment is effective, e.g., until disease progresses or the drug is not tolerated. The effective dose administered in each injection is an amount that is effective and tolerated.

An effective dose is one that over the course of therapy, which may be, e.g., 1 or more weeks, e.g., multiple courses of 3 weeks on/1 week off, results in treatment of the proliferative disorder, i.e., a decrease in the rate of disease progression, termination of disease progression, or regression or remission.

It has been found as an aspect of this invention that Compound 15 is unexpectedly well tolerated. In some embodiments of the invention, Compound 15 can therefore, in general, be administered in doses that are higher than previously understood (see, e.g., US8283372). In some embodiments of the invention, Compound 15 can, in general, be administered in doses that are generally higher than other synthetic small molecules that mimic the structure and IAP antagonist activity of the four N-terminal amino acids of Smac (i.e., other Smac mimetics). Other Smac mimetics have lower maximum tolerated doses (MTD) and have not shown meaningful clinical efficacy below such MTDs.

Doses employed in the practice of this invention can be effective in potentiating apoptosis of abnormally proliferating cells in a patient suffering a proliferative disorder or certain other disorders, e.g., certain autoimmune disorders. For example, Compound 15 can be administered intravenously, e.g., by infusion, at a dose of 1 to 80 mg/m² of patient body surface area (BSA) per day of treatment, e.g., 2 to 80, 2 to 65, 5 to 65, 10 to 65, 20 to 65, 30 to 65, 30 or >30 to 80, 30 or >30 to 65, 30 or >30 to
60, 30 or >30 to 55, or 30 or >30 to 50 mg/m², administered, e.g., by infusion over about 1 to about 120 minutes, e.g., about 30 minutes. The dose in most cases will be more than 5 mg/m². For example, the dose can be in the range 5 or >5 to 80, 5 or >5 to 60 mg/m². Current clinical studies employ about 5 mg/m² to about 50 mg/m², specifically, 5.6 to 47 mg/m². In two patients who received 63 mg/m², weekly / 3 weeks on, /1 week off, Compound 15 was not well tolerated.

[0031] It will be understood that there are different formulae for calculating BSA. Most commonly used are the Mosteller formula (Mosteller RD. "Simplified calculation of body-surface area". N Engl J Med 317:1098 (1987)) and the Dubois & Dubois formula (Du Bois & Du Bois, Arch Intern Med 17:863 (1916)). Doses recited herein are meant to apply to BSA calculated as per any such accepted methodologies notwithstanding that such different methodologies may result in slightly different BSA calculations, e.g., depending upon the number of decimal places used. It is generally sufficient to round off BSA calculations to 1 decimal place with allowance for a reasonable margin of error, e.g., 1.6 m² (+/- 0.1) or 1.9 m² (+/- 0.1). For purposes of this invention, BSA can also be estimated, e.g., using relevant population averages.

[0032] Doses recited herein as mg/m² BSA can, of course, be converted to mg/kg body weight. So, for example, assuming a given patient has a BSA of 1.6 m² and a body weight of 77 kg, a dose of 40 mg/m² is equal to a dose of 64 mg, i.e., about 0.8 mg/kg. By way of further example, using an average adult BSA of 1.7 m² and an average adult body weight of 70 kg, a dose of 40 mg/m² is equal to a dose of 68 mg, i.e., also about 0.8 mg/kg. Similarly, a dose range of >30 to 60 mg/m² equates to a dose range of > 0.7 mg/kg to approximately 1.5 mg/kg, in such person of average BSA and weight.

[0033] It has also been discovered that Compound 15 has a long half-life in the patient and therefore can be administered less often than once per day. In general, Compound 15 can be administered once, twice or three times per week for one to four weeks (or longer). In some situations a treatment interval may be followed by a rest interval. A suitable rest interval includes but is not limited to one week. Such treatment cycle of one, two, three or four weeks “on” and one week “off” can be continued for as long as Compound 15 shows effectiveness and is tolerated. It should be understood that the “on” weeks are consecutive weeks, i.e., two consecutive weeks on drug, three consecutive weeks on drug, and four consecutive weeks (or more) on drug.
An illustrative dosing regimen for Compound 15 is one ~30 minute infusion/week for one to four weeks, e.g., once a week for 2 or 3 consecutive weeks, followed by a week off. Specific illustrative dosing regimens include, without limitation, one administration by, e.g., intravenous infusion, of drug per week, in accordance with one of the following treatment cycles:

1) two weeks on/one week off, e.g., in combination with chemotherapies;
2) one week on/one week off, e.g., in patients with AML;
3) two weeks on/one week off, e.g., in patients with AML;
4) three weeks on/one week off, e.g., in patients with AML;
5) continuously (i.e., without a rest interval).

An illustrative dosing regimen for Compound 15 is one 30 minute infusion/week for 2 to 4 weeks, e.g., once a week for 2 or 3 consecutive weeks, followed by a week off. Such treatment cycle of two, three or four weeks on and one week off can be continued for as long as Compound 15 shows effectiveness and is tolerated.

In an alternative dosing regimen, Compound 15 is administered weekly, twice weekly, or three times per week, without a rest interval, i.e., continuously, for as long as Compound 15 shows effectiveness and is tolerated.

It is noteworthy and a priori unpredictable that a dose of > 30 mg/m², e.g., >30 to 65, >30 to 60 or >30 to 50 mg/m², can be tolerated and effective when administered by intravenous infusion during a period of about 30 minutes once per week for three or four weeks on and one week off or continuously.

Typically, higher doses will be employed when Compound 15 is used in monotherapy, i.e., single agent therapy, then in combination therapy. Such monotherapy dose can be, e.g., about 40 to about 55 mg/m², or about 45 to about 50 mg/m², weekly for three weeks on/one week off or weekly continuously. An illustrative dosing regimen for Compound 15 in single agent therapy is 45 to 50 mg/m², e.g., 47 mg/m², weekly for three weeks on/one week off or weekly continuously.

When Compound 15 is used in combination therapy, the dose can be, e.g., about 5 to about 50 mg/m², or about 5 to about 40 mg/m², weekly for three weeks on/one week off or weekly continuously. An illustrative dosing regimen for Compound 15 in combination therapy is about 5 to about 35 mg/m², weekly for three weeks on/one week off or weekly continuously.
In patients in whom Compound 15 is less well tolerated, lower doses can be administered more frequently. For example, in AML patients, Compound 15 can be administered in single agent therapy at about 15 to about 20 mg/m², e.g., 17 mg/m², twice/week (e.g., Mondays and Thursdays, Tuesdays and Fridays, etc.) or 17 mg/m², thrice/week (e.g., Mondays, Wednesdays, Fridays). three weeks on/one week off or continuously.

The phrase "pharmaceutical composition" refers to a composition suitable for administration in a medical use, i.e., internal administration to a patient. Compositions suitable for infusion in accordance with the method of this invention conveniently comprise a sterile aqueous preparation of Compound 15, which is preferably isotonic with the blood of the recipient. This aqueous preparation may be formulated according to known methods using suitable carriers or diluents which may include a buffer. Thus, in one illustrative aspect, this invention comprises a pharmaceutical dosage unit comprising Compound 15 and one or more pharmaceutically acceptable excipients in an aqueous solvent for use in intravenous or subcutaneous administration for the treatment of a cancer or an autoimmune disorder.

When practicing the conjoint or combination therapy described in more detail below, the administration of Compound 15 can occur simultaneous with, subsequent to, or prior to the combination therapy, such as chemotherapy or radiation, so long as the chemotherapeutic agent or radiation sensitizes the system to the method and compositions of the present invention.

The present invention also is directed to the use of Compound 15 as a chemopotentiating agent with other treatment approaches. The term "chemopotentiating agent" refers to an agent that acts to increase the sensitivity of an organism, tissue, or cell to a chemical compound, or treatment namely "chemotherapeutic agents" or "chemo drugs" or to radiation treatment. Thus, the methods and compositions of the present invention can be used for inhibiting tumor growth in vivo by administering them in combination with a biologic or chemotherapeutic agent or by using them in combination with radiation. In these applications, the administration of Compound 15 in accordance with the present invention may occur prior to, and with sufficient time, to cause sensitization of the site to be treated. Alternatively, Compound 15 may be used contemporaneously with radiation and/or additional anti-cancer chemical agents (infra).
Biological and chemotherapeutics/anti-neoplastic agents and radiation induce apoptosis by activating the extrinsic or intrinsic apoptotic pathways, and, since the method and compositions of the present invention relieve antagonists of apoptotic proteins (IAPs) and, thus, remove the block in apoptosis, the combination of chemotherapeutics/anti-neoplastic agents and radiation with the method and compositions of the present invention should work additively or synergistically to facilitate apoptosis.

A combination of the compound of the present invention and a biological or chemotherapeutic/anti neoplastic agent and/or radiation therapy of any type that activates the extrinsic or intrinsic pathway may provide a more effective approach to destroying tumor cells. The compound of the present invention interacts with IAP's, such as XIAP, cIAP-1, cIAP-2, ML-IAP, etc., and removes the IAP mediated block of apoptosis. Most chemotherapeutics/anti neoplastic agents and/or radiation therapy kills actively dividing cells by activating the intrinsic apoptotic pathway leading to apoptosis and cell death. Biological antitumor agents such as TRAIL (TNF-related apoptosis inducing ligand) activate extrinsic apoptotic pathways. As is described in more detail below, embodiments of the invention provide combinations of the compound of the present invention and a biological or chemotherapeutic/anti-neoplastic agent and/or radiation which provide a synergistic action against unwanted cell proliferation. This synergistic action between the compound of the present invention and a biological or chemotherapeutic/anti-neoplastic agent and/or radiation therapy can improve the efficiency of the biological or chemotherapeutic/anti-neoplastic agent and/or radiation therapies. This will allow for an increase in the effectiveness of current biological or chemotherapeutic/anti-neoplastic agents or radiation treatments allowing a higher percentage of tumors to respond to the therapy, an improved tumor response, and, potentially, a reduction in the dose of the biological or chemotherapeutic/anti-neoplastic agent needed to treat a tumor, thereby providing the use of a more tolerable dose of biological or chemotherapeutic/anti-neoplastic agent and/or radiation.

In an embodiment of the present invention, the patient is treated by administering the compound or a pharmaceutical composition of the present invention at a time the patient is subject to concurrent or antecedent radiation or chemotherapy for treatment of a neoproliferative pathology of a tumor such as, but not limited to, bladder cancer, breast cancer, prostate cancer, lung cancer, pancreatic cancer, gastric cancer, colon
cancer, ovarian cancer, renal cancer, hepatoma, melanoma, lymphoma, sarcoma, and combinations thereof.

In another embodiment of the present invention, the compound or a composition of the present invention can be administered in combination with a biological or chemotherapeutic and/or for use in combination with radiotherapy, immunotherapy, and/or photodynamic therapy, promoting apoptosis and enhancing the effectiveness of the chemotherapeutic, radiotherapy, immunotherapy, and/or photodynamic therapy.

As discussed above, embodiments of the invention also include a method of treating a patient afflicted with cancer by the contemporaneous or concurrent administration of a biological or chemotherapeutic agent additional to Compound 15. Such biological or chemotherapeutic agents include but are not limited to the chemotherapeutic agents described in "Modern Pharmacology with Clinical Applications", Sixth Edition, Craig & Stitzel, Chpt. 56, pg 639-656 (2004), herein incorporated by reference in its entirety. The chemotherapeutic agent can be, but is not limited to, alkylating agents, antimetabolites, anti-tumor antibiotics, plant-derived products such as taxanes, enzymes, hormonal agents, miscellaneous agents such as cisplatin, monoclonal antibodies, glucocorticoids, mitotic inhibitors, topoisomerase I inhibitors, topoisomerase II inhibitors, immunomodulating agents such as interferons, cellular growth factors, cytokines, and nonsteroidal anti-inflammatory compounds (NSAID), cellular growth factors and kinase inhibitors. Other suitable classifications for chemotherapeutic agents include mitotic inhibitors, and anti-estrogenic agents.

Specific examples of suitable biological and chemotherapeutic agents include, but are not limited to, carboplatin, cisplatin, carmustine (BCNU), bendamustine, 5-fluorouracil (5-FU), cytarabine (Ara-C), clofarabine, decitabine, 5-azacytidine, gemcitabine, methotrexate, daunorubicin, doxorubicin, dexamethasone, irinotecan, topotecan, etoposide, paclitaxel, docetaxel, vincristine, tamoxifen, TNF-alpha, TRAIL and other members, i.e., other than TRAIL and TNF-alpha, of the TNF superfamily of molecules, interferon (in both its alpha and beta forms), GM-CSF, IL-2, thalidomide, thalidomide derivatives such as lenalidomide, melphalan, inhibitors of kinase enzymes such as EGFR, Her-2, B-RAF, ALK, Met encompassing both small molecules and antibodies, and PARP inhibitors. Other specific examples of suitable chemotherapeutic agents include nitrogen mustards such as cyclophosphamide, alkyl sulfonates, nitrosoureas, ethylenimines, triazenes, folate antagonists, purine analogs, pyrimidine analogs, anthracyclines, bleomycins, mitomycins, dactinomycins,
plicamycin, vinca alkaloids, epipodophyllotoxins, taxanes, glucocorticoids, L-asparaginase, estrogens, androgens, progestins, luteinizing hormones, octreotide acetate, hydroxyurea, procarbazine, mitotane, hexamethylmelamine, carboplatin, mitoxantrone, monoclonal antibodies, levamisole, interferons, interleukins, and supportive care agents such as erythropoietin, romiplostim, eltrombopag, filgrastim and sargramostim.

Another embodiment of the present invention relates to the use of the compound or a composition of the present invention in combination with topoisomerase inhibitors to potentiate their apoptotic inducing effect. Topoisomerase inhibitors inhibit DNA replication and repair, thereby promoting apoptosis and are used as chemotherapeutic agents. Topoisomerase inhibitors promote DNA damage by inhibiting the enzymes that are required in the DNA repair process. Therefore, export of Smac from the mitochondria into the cell cytosol is provoked by the DNA damage caused by topoisomerase inhibitors. Topoisomerase inhibitors of both the Type I class (camptothecin, topotecan, SN-38 (irinotecan active metabolite) and the Type II class (etoposide) are expected to show potent synergy with compounds of the present invention. Further examples of topoisomerase inhibiting agents that may be used include, but are not limited to, irinotecan, topotecan, etoposide, amsacrine, exatecan, gimatecan, etc. Other topoisomerase inhibitors include, for example, Aclacinomycin A, camptothecin, daunorubicin, doxorubicin, ellipticine, epirubicin, and mitaxantrone.

Another embodiment of the present invention relates to the use of the compound or a composition of the present invention in combination with nonsteroidal antiinflammatory drugs (NSAIDs).

In another embodiment of the invention, the chemotherapeutic/anti-neoplastic agent for use in combination with the method and compositions of the present invention may be a platinum containing compound. In one embodiment of the invention, the platinum containing compound is cisplatin. Cisplatin can synergize with a compound of the present invention and potentiate the inhibition of an IAP, such as but not limited to XIAP, cIAP-1, c-IAP-2, ML-IAP, etc. In another embodiment a platinum containing compound is carboplatin. Carboplatin can synergize with a compound of the present invention and potentiate the inhibition of an IAP, including, but not limited to, XIAP, cIAP-1, c-IAP-2, ML-IAP, etc. In another embodiment a platinum containing compound is oxaliplatin. The oxaliplatin can synergize with a compound
of the present invention and potentiate the inhibition of an IAP, including, but not limited to, XIAP, cIAP-1, c-IAP-2, ML-IAP, etc.

Platinum chemotherapy drugs belong to a general group of DNA modifying agents. DNA modifying agents may be any highly reactive chemical compound that bonds with various nucleophilic groups in nucleic acids and proteins and cause mutagenic, carcinogenic, or cytotoxic effects. DNA modifying agents work by different mechanisms, disruption of DNA function and cell death; DNA damage/the formation of cross-bridges or bonds between atoms in the DNA; and induction of mispairing of the nucleotides leading to mutations, to achieve the same end result. Three non-limiting examples of a platinum containing DNA modifying agents are cisplatin, carboplatin and oxaliplatin.

Yet another embodiment of the present invention is the therapeutic combination or the therapeutic use in combination of the compound or compositions of the present invention with TRAIL or TRAIL agonist antibodies, or other chemical or biological agents which bind to and activate the TRAIL receptor(s). Many cancer cell types are sensitive to TRAIL-induced apoptosis, while most normal cells appear to be resistant to this action of TRAIL. TRAIL-resistant cells may arise by a variety of different mechanisms including loss of the receptor, presence of decoy receptors, overexpression of cFLIP, which competes for zymogen caspase-8 binding during DISC formation and inhibition of activated caspase-3 and/or caspase-9 by XIAP. In TRAIL resistance, a compound or composition of the present invention may increase tumor cell sensitivity to TRAIL leading to enhanced cell death, the clinical correlations of which are expected to be increased apoptotic activity in TRAIL resistant tumors, improved clinical response, increased response duration, and ultimately, enhanced patient survival rate.

In another embodiment of the invention, Compound 15 is administered in combination with a cytokine, e.g., TNFα, IFN, IL-2, or GM-CSF.

The method and compositions of the present invention also can be used to augment radiation therapy (or radiotherapy), i.e., the medical use of ionizing radiation as part of cancer treatment to control malignant cells. Although radiotherapy is often used as part of curative therapy, it is occasionally used as a palliative treatment, where cure is not possible and the aim is for symptomatic relief. Radiotherapy is commonly used for the treatment of tumors. It may be used as the primary therapy. It is also common to combine radiotherapy with surgery and/or chemotherapy. The most common
tumors treated with radiotherapy are breast cancer, prostate cancer, rectal cancer, head & neck cancers, gynecological tumors, bladder cancer and lymphoma. Radiation therapy is commonly applied just to the localized area involved with the tumor. Often the radiation fields also include the draining lymph nodes. It is possible but uncommon to give radiotherapy to the whole body, or entire skin surface. Radiation therapy is usually given daily for up to 35-38 fractions (a daily dose is a fraction). These small frequent doses allow healthy cells time to grow back, repairing damage inflicted by the radiation. Three main divisions of radiotherapy are external beam radiotherapy or teletherapy, brachytherapy or sealed source radiotherapy and unsealed source radiotherapy, which are all suitable examples of treatment protocol in the present invention. The differences relate to the position of the radiation source; external is outside the body, while sealed and unsealed source radiotherapy has radioactive material delivered internally. Brachytherapy sealed sources are usually extracted later, while unsealed sources are injected into the body.

Compound 15 is capable of forming pharmaceutically acceptable salts, including but not limited to acid addition and/or base addition salts. Such salts are included within all aspects of the invention.

The present invention can also be practiced using isotopically-enriched compounds, which are identical to Compound 15 but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be included in the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as $^2$H, $^3$H, $^{13}$C, $^{14}$C, $^{15}$N, $^{16}$O, $^{17}$O, $^{31}$P, $^{32}$P, $^{33}$S, $^{18}$F, and $^{36}$Cl. Substitution with heavier isotopes such as deuterium, i.e., $^2$H, are also included. Isotopically enriched compounds can generally be prepared by substituting a readily available isotopically labelled reagent for a non-isotopically enriched reagent. For example, incorporation of deuterium can be accomplished by substituting sodium borohydride with $d_4$-sodium borohydride, or by replacing iodomethane with $d_3$-iodomethane. Representative examples of specific deuterated analogs and their preparation are described in US8283372.

Compound 15 may exist in unsolvated forms as well as solvated forms, including hydrated forms. Furthermore, Compound 15 may exist in various solid states including crystalline, semi-crystalline and amorphous (noncrystalline) forms, and in the form of clathrates, prodrugs, polymorphs, bio-hydrolyzable esters, racemic
mixtures, non-racemic mixtures, or as purified stereoisomers including, but not limited to, optically pure enantiomers and diastereomers. In general, all of these and other such forms are intended to be encompassed within the scope of the term, "Compound 15".

References to Compound 15 in this specification and in the claims, are intended to include not only the compound of formula (I), but also pharmaceutically acceptable salts of Compound 15, as well as various forms of said compound or salts thereof such as those that are described above and below.

Examples

Data from various experiments with Compound 15 (i.e., TL32711 also known as birinapant) are provided in the following Examples.

Example 1 - Dose Scheduling and Efficacy Analysis of the SMAC Mimetic TL32711 in Primary Melanoma Tumor Xenotransplant Models

Initial pharmacokinetics modeling of TL32711 in mice bearing the MDA-MB-231 tumor indicated a potential efficacy benefit may be possible with a biweekly dosing schedule. The objectives of the current study were to 1) evaluate the efficacy of TL32711 as a single agent in primary human melanoma tumor xenograft models, 2) assess the efficacy and tolerability of TL32711 in combination with carboplatin and paclitaxel and 3) determine if a biweekly dosing schedule is more effective than weekly administration.

Significant tumor growth inhibition was observed in 5 of 6 of the primary melanoma tumor xenografts evaluated following treatment with single agent TL32711 (30 mg/kg IP). Combining TL32711 with carboplatin and paclitaxel resulted in a further enhancement in anti-tumor efficacy with tumor regressions noted in 4 of the 6 models without any marked changes in tolerability (<14% reduction in bodyweight). Based on the initial PK modeling a follow up study was conducted to assess the activity of TL32711 in a primary melanoma model when the dose was fractionated (15 mg/kg twice/week versus 30 mg/kg once/week). Surprisingly, the biweekly dosing schedule did not result in enhanced anti-tumor activity and demonstrated equivalent suppression of cIAP1 in tumors compared to the weekly dosing schedule.

Pharmacokinetic analysis of the TL32711 in tumor tissue at 15, 30 and 60 mg/kg revealed that TL32711 exhibits a greater than dose proportional relationship in that a
4-fold increase in dose, resulted in a 14-fold increase in exposure. This increase in exposure led to a change in the TL32711 tumor half-life from 56 to 166 hrs, possibly due to the saturation of an efflux transporter at higher dose levels.

Together, these data show that TL32711 is highly active in primary human melanoma xenografts and that efficacy can be enhanced by combination therapy with carboplatin and paclitaxel without reducing tolerability. These data also demonstrate that biweekly dosing confers no advantage over the current clinical weekly dosing regimen due to the dose dependent changes in TL32711 half-life and exposure observed in tumor tissue.

Example 2 - Phase 1 PK/PD Analysis of the Smac Mimetic TL32711 Demonstrates Potent and Sustained cIAP1 Suppression in Patient PBMCs and Tumor Biopsies

The pharmacokinetics (PK) and pharmacodynamics (PD) of TL32711 have been studied in human tumor xenografts, patient plasma/PBMCs and Phase 1 tumor biopsy samples. In mice bearing the MDA-MB-231 xenograft, TL32711 is rapidly and extensively taken up into the tumor (tumor/plasma AUC ratio >22) and is eliminated slowly with a half-life of 96 hrs (20 hrs in plasma). A PK/PD link model was used to characterize the relationship between TL32711 tumor concentrations and cIAP1 suppression. cIAP1 suppression was dose and time dependent with cIAP1 levels reduced to <20% baseline within 30 minutes and with >70% inhibition maintained 7-14 days post treatment following a single IV bolus dose (5 mg/kg). TL32711 had a potent effect on tumor cIAP1 levels (EC50 24 ng/g) and caused significant tumor growth inhibition and regressions at doses ≥2.5 mg/kg q3D. Efficacy has also been evaluated in primary human melanoma tumors, recently derived from patients and transplanted into nude mice. Significant tumor growth inhibition was observed in 5/6 primary melanoma tumor xenografts with mean Day 7 tumor concentrations of 187, 579 and 2658 ng/g at 15, 30 and 60 mg/kg respectively. TL32711 PK/PD (drug concentration analysis and cIAP1 degradation in PBMCs and tumor biopsies) has also been investigated in patients as part of the single agent Phase I study. Following weekly, 30 min IV infusions TL32711 plasma PK was dose proportional and non-accumulating (0.18 to 47 mg/m2). Plasma PK was tri-exponential with a long terminal t1/2 (73-79 hrs). The target AUC in plasma for therapeutic activity (71 h.ng/mL) based on the MDA-MB-231 model was achieved in patients at dose >2.88 mg/m2 (Mean AUC 86 h.ng/mL). This exposure was associated with marked uptake and retention in PBMCs (t1/2 = 29-35 hrs) and resulted in prolonged cIAP1
suppression over 7 days. A dose related increase in PBMC PARP cleavage and plasma caspase-3 activity was also observed indicative of apoptosis pathway activation. TL32711 PK/PD was also assessed in tumor biopsy samples from patients 4 hrs to 6 days post treatment (11.5 to 17.2 mg/m²). TL32711 is extensively taken up into the tumor with levels >350 ng/g on day 6, significantly in excess of the EC₅₀ for cIAP1 inhibition. Estimated tumor exposure at 35 to 47 mg/m² was also in excess of the measured drug levels observed at 15 to 30 mg/kg in the primary human tumor xenograft models in mice. Together these PK/PD data show that TL32711 results in potent and sustained cIAP1 suppression over 7 days at tolerable dose levels with evidence of apoptosis pathway activation and promising early signs of anti-tumor activity in patients. Selected results and conclusions of these studies are summarized in the following list:

1) To date, TL32711 has been well tolerated in patients and Phase 1 dose escalation continues to define the single agent maximum tolerated dose (MTD).

2) TL32711 is rapidly taken up into tumor tissue with a long terminal half-life of 96hrs (MDA-MB-231 xenograft) or 52hrs (human tumor biopsies).

3) TL32711 rapidly (within 4hrs) and potently inhibits cIAP1 in MDA-MB-231 tumor tissue (IC50 24 ng/g; IC75 135 ng/g) in a dose dependent manner.

4) PK/PD analyses in mice indicated that tumor tissue was approximately 2x to 100x more sensitive to the cIAP1 inhibition compared to other normal tissues.

5) Significant tumor growth delay and regressions were observed when cIAP1 levels in tumors was inhibited by >75% throughout the dosing interval in mice bearing the MDA-MB-231 xenograft.

6) TL32711 PK was dose proportional over the dose range 0.18 to 47 mg/m² in Phase 1 patients.

7) The PK/PD response in patient biopsies and PBMCs were very similar to the response observed in the MDA-MB-231 xenograft.

8) PK/PD modeling of the cIAP1 response in patients indicates that the current dose level of 47 mg/m² results in >75% cIAP1 inhibition throughout the weekly dosing interval.

9) In summary, TL32711 causes potent and sustained cIAP1 suppression over 7 days at tolerable dose levels, apoptosis pathway activation and promising early signs of anti-tumor activity in patients.
Example 3 - Phase 1 Study of the Smac Mimetic TL32711 in Adult Subjects with Advanced Solid Tumors & Lymphoma to Evaluate Safety, Pharmacokinetics, Pharmacodynamics and Anti-tumor Activity.

A clinical study was conducted having the following primary objective: To determine the maximum tolerated dose and characterize the safety and tolerability of TL32711 when administered as a 30 minute intravenous infusion once weekly for 3 consecutive weeks followed by one week off (Cycle) repeated every 4 weeks as tolerated in patients with refractory solid tumors or lymphoma. The secondary objective was to assess the pharmacokinetics, pharmacodynamic effects and anti-tumor activity of TL32711.

Relevant information pertaining to the design of the clinical study is summarized in Tables 1-3.

Table 1

<table>
<thead>
<tr>
<th>Eligibility</th>
</tr>
</thead>
</table>

**Inclusion Criteria:**
- Confirmed advanced metastatic or unresectable malignancy that is refractory to currently available standard therapies
- ECOG performance status of ≤ 2; life expectancy > 3 mo
- Adequate renal, hepatic and bone marrow function

**Exclusion Criteria:**
- Received standard or investigational anti-cancer therapy within 4 weeks prior to first dose of TL32711
- Symptomatic or uncontrolled brain metastases requiring current treatment
- Clinically significant auto-immune, cardiac or pulmonary disease
Table 2

<table>
<thead>
<tr>
<th>Trial Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Phase 1, multi-centered, open-label, dose-escalation 3+3 design, with dose expansion at recommended Phase 2 dose</td>
</tr>
<tr>
<td>• Dose levels escalated by 100%. If CTCAE v.4 drug-related AE Grade ≥2 or &gt;1 change above baseline, subsequent cohorts escalated by 50% or 33%</td>
</tr>
<tr>
<td>• TL32711 administered as a 30min IV infusion once weekly for 3 consecutive weeks followed by one week off (Cycle) repeated every 4 weeks IV until progression/ toxicity/ voluntary withdrawal.</td>
</tr>
<tr>
<td>• Weekly study assessments (+C1D2, C1D16) until treatment discontinued</td>
</tr>
<tr>
<td>• PK/PD markers (IAPs, apoptosis activation) - pre-dose and 4 and 24 hours post dose on Day 1 and 15, and pre-dose and 4 hours post-dose on Day 8 dose</td>
</tr>
<tr>
<td>• Restaging was done at the end of Cycle 2</td>
</tr>
</tbody>
</table>
Safety and Anti-tumor activity results are summarized in Tables 4 - 5.

Table 3

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Cancer Type</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Treated (Cohorts 1-8)</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Age, yrs (range)</td>
<td>56.5 (31-80 yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, n (%) Male</td>
<td>15 (62.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9 (37.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status, n (%)</td>
<td>13 (54%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (46%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Safety Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Grade 3 or Grade 4 Adverse Events attributed to study drug</td>
</tr>
</tbody>
</table>

Most Common Drug-Related Adverse Events with incidence ≥ 2

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of Grade 1 or 2 Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Fever</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>
The following conclusions were drawn from this study:

1) TL3271 is well tolerated in patients with solid tumors and lymphoma with no dose-limiting toxicities and the MTD has not been reached.

2) TL3271 displays dose proportional PK, moderate to low inter-patient variability in Cmax and AUC, and a long terminal half-life in plasma (35 hours) with high uptake and retention in tumor tissues (49 hours).

3) TL3271 causes rapid (within 4 hours) and sustained (for 7 days) suppression of cIAPI that is dose-dependent as measured in both PBMCs and tumor biopsies.

4) TL3271 causes dose-related activated serum caspase-3/7 and cleaved cytokeratin-18 levels.

5) Evidence of anti-tumor activity observed.

Example 4 - Anti-tumor Efficacy in Primary Pancreatic Adenocarcinoma Model.

Pancreatic cancer is highly resistant to chemotherapeutic drugs and radiation. Inhibitors of apoptosis (IAPs) were overexpressed in pancreatic cancer cells and IAPs downregulation were shown to induce sensitivity to death receptor signaling, cytotoxic agents and radiation. A study was conducted to investigate the efficacy of
TL32711 using a patient-derived primary pancreatic cancer explant model that mirrors the disease’s biological heterogeneity.

Methods. Effect of TL32711 alone and with TRAIL was evaluated in Panc1 by immunoblotting and Trypan blue staining. Dose escalation studies were performed in 2 primary pancreatic tumors at i.p. 30 mg/kg, 45 mg/kg and 60 mg/kg every twice weekly and tumor volume were measured for 28 days. No significant toxicity was observed in the tumor-bearing mice at all dose levels. An additional 6 primary pancreatic tumors were evaluated at 60 mg/kg. H&E slides of donor patients for these tumors were evaluated and untreated tumors were analyzed by gene microarrays to explore for potential efficacy biomarkers. Tumor, plasma and liver samples were obtained from the dose escalation studies for pharmacokinetic analysis.

Results. TL32711 treatment resulted in rapid cIAP1 degradation leading to caspase-3 activation in Panc1, and exerted a dose-dependent pro-apoptotic effect that was synergized with TRAIL co-incubation in in vitro studies. In primary tumor explant studies, TL32711 dosed at 60 mg/kg exerted significant growth arrest/inhibition in 6 primary tumors (T/C range -0.1 to 0.2) and suboptimal growth inhibition in 2 (T/C ~0.4). H&E slides of resected pancreatic cancer specimens for 7 donor patients were available for evaluation, and there was no relationship between histological findings (inflammatory infiltrate, stroma, neutrophil/lymphocyte ratio and necrosis) and in vivo TL32711 efficacy. Dose escalation studies showed a dose-dependent growth inhibitory effect of TL32711 in 2 primary tumors: 30mg/kg achieved significant growth inhibition in #17624 but not #12872. Significant growth inhibition was achieved in both at >= 45 mg/kg. Pharmacokinetic analysis showed that TL32711 efficacy correlated with tumor drug exposure and that tumor concentrations at the effective doses are in the range of what is achievable in tumors in patients at tolerated doses.

Conclusions. TL32711 demonstrated significant single agent efficacy in pancreatic cancer that correlated with tumor drug exposure that were at exposure levels achievable in tumors at tolerated doses in clinical studies.

Example 5 - Ascending Dose Protocol.

Phase 2 Clinical Activity and Tolerability of the SMAC-mimetic Birinapant (TL32711) plus Irinotecan in Irinotecan-relapsed/refractory Metastatic Colorectal Cancer

Authors: N. Senzer, P. LoRusso, L. Martin, R. Schilder, R. Amaravadi, K.
Papadopoulos, E. Segota, D. Weng, M. Graham, A. Adjei;

Affiliations: Mary Crowley Cancer Research Center, Dallas TX; Barbara Ann Karmanos Cancer Center, Detroit MI; Fox Chase Cancer Center, Philadelphia PA; Jefferson Kimmel Cancer Center, Philadelphia PA; Holy Cross Hospital, Ft. Lauderdale FL; Abramson Cancer Center University of Pennsylvania, Philadelphia PA; South Texas Accelerated Research Therapeutics, San Antonio TX; TetraLogic Pharmaceuticals, Inc., Malvern PA; Roswell Park Cancer Institute, Buffalo NY

(CRC means colorectal cancer, CR means complete response, PR means partial response, SD means stable disease, and PD means progressive disease.)

Background: Birinapant (B) is a SMAC-mimetic that inhibits IAPs and has potent preclinical anti-tumor synergy combined with TNFα-inducing chemotherapies [i.e. irinotecan (I)]. B and I combination is well-tolerated and has encouraging activity in phase 1 study. This study intended to test B+I for further clinical work and test an ascending dose strategy of B to mitigate Bell’s palsy (BP) risk, an unusual and reversible side effect of SMAC mimetics.

Methods: I at 350mg/m² IV q3weeks was administered with B weekly (2 of 3 weeks). For Cycle 1 (C1), of the dose of B was increased during Cycle 1 (C1D1 at 5.6mg/m²; C1D8 at 11mg/m²). For Cycle 2 (C2) and ongoing treatment, B was 22mg/m² or 35mg/m², which were the MTD and DLT (BP) dose levels when combined with I from Ph 1 study. Safety and clinical activity for KRAS mutant (KRAS-MT) and wildtype (KRAS-WT) was assessed in 3 cohorts - (1) C2 at 22mg/m2 for CRC KRAS MT; (2) C2 at 22mg/m2 for CRC KRAS WT; (3) C2 at 35mg/m2 for CRC KRAS MT.

Results: 51 patients (pts) with CRC had a median number of 4 prior regimens with 47 refractory/relapsed to irinotecan (92%). Tolerability was comparable to I alone. There were 2 PRs (4%), 27 SD (>2 cycles; 53%), 17 PD (< 2 cycles; 33%), and 5 pts (9%) were not evaluable, with overall clinical benefit (CR+PR+SD) of 57%. Median progression-free survival (PFS) was 2.1 months, and 6 mo PFS was 20%. KRAS MT CRC (20 pts) with prior I had a median PFS of 2.9 mo and 6 mo PFS of 25%. KRAS WT CRC (18pts) with prior I had a median PFS of 1.4 mo and 6 mo PFS of 17%. No BP events occurred among 40 pts (22mg/m² with C1 ascending dose), compared to 1 of 7 pts (22mg/m2 without C1 ascending dose). In the 35mg/m2 cohort, 1 BP event occurred among 12 pts (with C1 ascending dose), compared to 3 of 6 (without C1
Conclusions: B + I demonstrated clinical benefit in pts refractory/relapsed to irinotecan, with greatest benefit in KRAS MT CRC. C1 ascending dose may provide a mitigation strategy for BP risk. Prior studies with I retreatment have showed no benefit in KRAS MT CRC. Comparable CRC pts have 6 mo PFS of 2%. Clinical activity supports the hypothesis for therapeutic synergy of B +I, with I as a TNFα-inducing chemotherapy combination.

Explanations of mechanisms of action herein are intended to facilitate understanding of the invention but are not meant to be binding or limiting. It is to be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims. All references cited hereinabove are incorporated herein by reference as though fully set forth.
Claims:

1. A method of administering a Smac mimetic to a patient that comprises internally administering the Smac mimetic to the patient according to an ascending dose protocol.

2. The method of claim 1 wherein the Smac mimetic is Compound 15.

3. The method of claim 2 that comprises internally administering to the patient Compound 15 in an amount of 1 to 80 mg/m$^2$ of patient body surface area (BSA) by intravenous infusion over a period of 1 to 120 minutes.

4. The method of claim 3 wherein the amount of Compound 15 administered per dose is 2 to 65 mg/m$^2$ and the period of infusion is 1 to 60 minutes.

5. The method of claim 3 wherein the amount of Compound 15 administered per dose is 5 to 65 mg/m$^2$ and the period of infusion is 1 to 60 minutes.

6. The method of claim 3 wherein the amount of Compound 15 administered per dose is >30 to 65 mg/m$^2$ and the period of infusion is 1 to 60 minutes.

7. The method of claim 3 wherein the amount of Compound 15 administered per dose is 45 to 50 mg/m$^2$ and the period of infusion is 1 to 60 minutes.

8. The method of claim 3, 4, 5, 6, or 7 wherein Compound 15 is administered once, twice, or thrice per week for two or more successive weeks.

9. The method of claim 8 that comprises weekly intravenous infusion of Compound 15 during multiple treatment cycles of one, two, or three weeks on and one week off, wherein the dose is incrementally increased from an initial dose of about 2 to about 10 mg/m$^2$ to a target dose that is about 30, or >30, to about 65 mg/m$^2$. 
10. The method of claim 8 wherein the amount of Compound 15 administered per dose is > 30 mg/m², and the compound is administered by intravenous infusion during a period of about 30 minutes once per week for three or four weeks on and one week off or continuously.

11. The method of claim 8 wherein the amount of Compound 15 administered per dose is > 30 to 65 mg/m², and the compound is administered by intravenous infusion during a period of about 30 minutes once per week, twice weekly, or three times weekly, for three or four weeks on and one week off or continuously.

renal pelvis and ureter, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, and Wilm's tumor and other childhood kidney tumors.

13. The method of claim 12 wherein the proliferative disorder is a cancer selected from the group consisting of: sarcomas, bladder cancer, ovarian cancer, breast cancer, brain cancer, pancreatic cancer, colon cancer, blood cancer, skin cancer, lung cancer, and bone cancer.

14. The method of claim 12 wherein the cancer is selected from colorectal cancer, renal carcinoma, pancreatic carcinoma, prostate carcinoma, melanoma, glioblastoma, acute myeloid leukemia, small cell lung cell carcinoma, non-small cell lung carcinoma, rhabdomyosarcoma, and basal cell carcinoma.

15. The method of claim 12 wherein the cancer is selected from chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy cell leukemia, leukemia, acute lymphoblastic leukemia (ALL), and acute myeloid leukemia (AML).

16. The method of claim 15 wherein the proliferative disorder is AML and Compound 15 is administered at a dose of 15 to 20 mg/m², twice per week.

17. The method of any of claims 1 through 16 that further comprises administering a second cancer therapy selected from radiation, chemotherapy, immunotherapy, photodynamic therapy, and combinations thereof.

18. Compound 15 for use in the manufacture of a pharmaceutical dosage unit for treatment in accordance with any of the preceding claims.

# INTERNATIONAL SEARCH REPORT

**International application No.**

PCT/US 14/14380

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/40; C09B 7/02 (2014.01)
USPC - 514/414; 548/458

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

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## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 31/40; C09B 7/02 (2014.01)
USPC - 514/414; 548/458

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

Patents and NPL (classification, keyword, search terms below)

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


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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>Amaravadi et al., &quot;Phase 1 Study of the Smac Mimetic TL32711 in Adult Subjects with Advanced Solid Tumors &amp; Lymphoma to Evaluate Safety, Pharmacokinetics, Pharmacodynamics and Anti-tumor Activity&quot; AACR 102nd Annual Meeting, 2011, Exhibit Hall A4-C, Poster Section 40, poster # LB-406, 05 April 2011 (05/04/2011) [retrieved from internet: &lt;URL: <a href="http://www.tetralogicpharma.com%3E">http://www.tetralogicpharma.com&gt;</a>; please see Amaravadi-pubdate-abstract.pdf attached for the publication date of the poster] col 1, in 1-2; col 2, in 1-7; col 3, in 1-10.</td>
<td>1-5, 8(3,4,5)</td>
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<td>Y</td>
<td>US 2011/0301151 A1 (Condron et al.) 8 December 2011 (08.12.2011), para [0153]-[0158], [0209]-[0211]</td>
<td>6, 7, 8(6,7), 9-11</td>
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<td>A</td>
<td>US 2008/0253966 A1 (Bonavida et al.) 16 October 2008 (16.10.2008), para [0007], [0199], [0197], [0206]</td>
<td>6, 7, 8(6,7), 9-11</td>
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<td>WO 2013/049351 A1 (Weng et al.) 4 April 2013 (04.04.2013), para [0006]-[0010], [0017], [0019], [0020], [0022], [0024]-[0033], [0084], [0086], [0092]</td>
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**Date of the actual completion of the international search**

16 April 2014 (16 04 2014)

**Date of mailing of the international search report**

07 MAY 2014

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**Name and mailing address of the ISA/US**

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No 571-273-3201

**Authorized officer**

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)
### Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos: because they relate to subject matter not required to be searched by this Authority, namely:

2. □ Claims Nos: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos: 12-19 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.

**Remark on Protest**

□ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

□ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

□ No protest accompanied the payment of additional search fees.