51(18):5522-5532; US 2008/0076768; Belvin et al, American Association for Cancer Research Annual Meeting 2008, 99th:April 15, Abstract 4004; Folkes et al, American Association for Cancer Research Annual Meeting 2008, 99th:April 14, Abstract LB-146; Friedman et al, American Association for Cancer Research Annual Meeting 2008, 99th:April 14, Abstract LB-110). The exemplary Formula I compound, GDC-0941, shows synergistic activity in vitro and in vivo in combination with certain chemotherapeutic agents against solid tumor cell lines (US Ser. No. 12/208,227, Belvin et al "Combinations Of Phosphoinositide 3-Kinase Inhibitor Compounds And Chemotherapeutic Agents, And Methods Of Use", filed 10 Sept 2008).

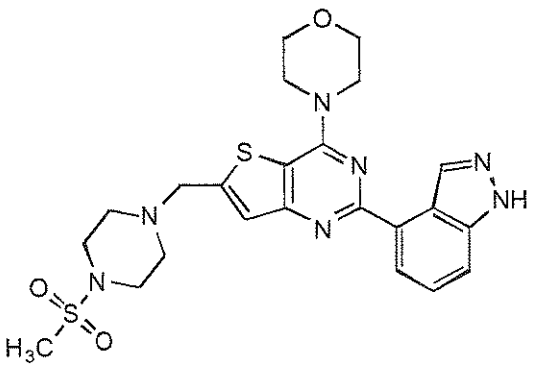
[0018] SUMMARY ~~OF THE INVENTION~~

[0019] The ~~invention~~disclosure relates generally to thienopyrimidine compounds of Formula **I** with anti-cancer activity, and more specifically with PI3 kinase or mTOR inhibitory activity, administered in combination with monoclonal antibody agents or chemotherapeutic agents to inhibit the growth of hematopoietic malignancies. Certain combinations of Formula I compounds with chemotherapeutic agents show synergistic effects in inhibiting the growth of hematopoietic cancer cells in vitro and in vivo. The combinations and methods of the ~~invention~~disclosure may be useful in the treatment of hematopoietic malignancies. The compositions may inhibit tumor growth in mammals and may be useful for treating human cancer patients.

[0019a] In one aspect, there is provided the use of therapeutically effective amount of a compound having Formula I, and a therapeutically effective amount of one or more chemotherapeutic agents selected from dexamethasone, thioTEPA, doxorubicin, vincristine, rituximab, cyclophosphamide, prednisone, melphalan, lenalidomide, bortezomib, rapamycin, and cytarabine, in the manufacture of a therapeutic combination for the treatment of a hematopoietic malignancy, wherein said therapeutic combination is to be administered as a combined formulation or by alternation to a mammal; and

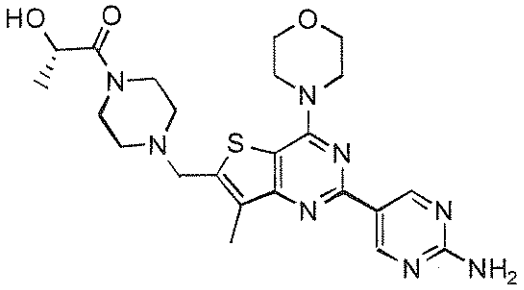
where Formula I compounds are selected from the group consisting of:

4-(2-(1H-indazol-4-yl)-6-((4-(methylsulfonyl)piperazin-1-yl)methyl)thieno[3,2-d]pyrimidin-4-yl)morpholine having Formula **Ia**:



Ia ; and

(S)-1-(4-((2-(2-aminopyrimidin-5-yl)-7-methyl-4-morpholinothieno[3,2-d]pyrimidin-6-yl)methyl)piperazin-1-yl)-2-hydroxypropan-1-one having Formula **Ib**:



Ib; and

pharmaceutically acceptable salts thereof.

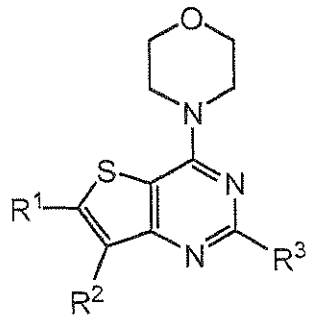
[0019b] In another aspect, there is provided the use of a therapeutic combination as defined above in the manufacture of a medicament for the treatment of a hematopoietic malignancy selected from non-Hodgkin's lymphoma, diffuse large hematopoietic lymphoma, follicular lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia, multiple myeloma, AML, and MCL.

[0019c] In another aspect, there is provided an article of manufacture for treating a hematopoietic malignancy comprising:

a) a therapeutic combination as defined above; and

b) instructions for use.

[0020] ~~In one aspect, the invention includes~~Disclosed is a method for the treatment of a hematopoietic malignancy comprising administering a therapeutic combination as a combined formulation or alternation to a mammal, wherein the therapeutic combination comprises a therapeutically effective amount of a compound having Formula I, and a therapeutically effective amount of a chemotherapeutic agent selected from dexamethasone, thioTEPA, doxorubicin, vincristine, rituximab, cyclophosphamide, prednisone, melphalan, lenalidomide, bortezomib, rapamycin, and cytarabine.

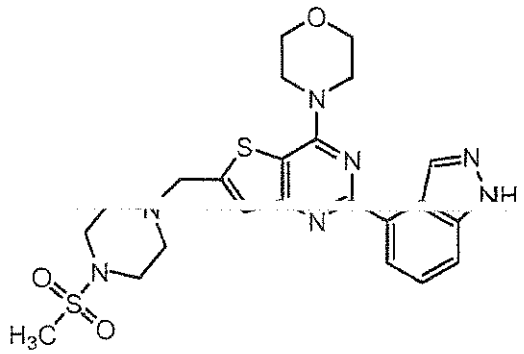


I

[0021] ~~The invention also relates to~~Disclosed are methods of using the therapeutic combinations

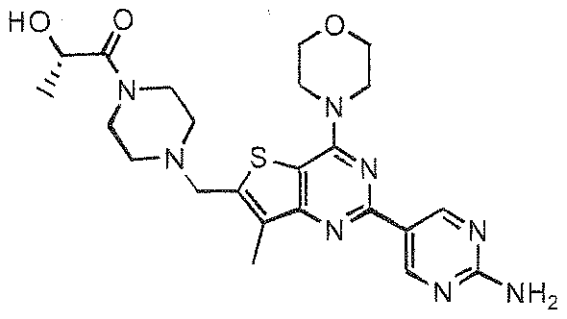
for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, organisms, or associated pathological conditions related to the hematopoietic malignancies.

[0022] ~~An aspect of the invention provides~~Also disclosed are therapeutic combinations comprising 4-(2-(1H-indazol-4-yl)-6-((4-(methylsulfonyl)piperazin-1-yl)methyl)thieno[3,2-d]pyrimidin-4-yl)morpholine (US 2008/0076768; US 2008/0207611; Folkes et al (2008) Jour. of Med. Chem. 51(18):5522-5532), also known as GDC-0941 (Genentech, Inc.) and having Formula Ia and a therapeutically effective amount of a chemotherapeutic agent selected from dexamethasone, thioTEPA, doxorubicin, vincristine, rituximab, cyclophosphamide, prednisone, melphalan, lenalidomide, bortezomib, rapamycin, and cytarabine.



Ia

[0023] ~~An aspect of the invention provides~~Disclosed are therapeutic combinations comprising (S)-1-(4-((2-(2-aminopyrimidin-5-yl)-7-methyl-4-morpholinothieno[3,2-d]pyrimidin-6-yl)methyl)piperazin-1-yl)-2-hydroxypropan-1-one (US 2008/0242665) having Formula Ib and a therapeutically effective amount of a chemotherapeutic agent selected from dexamethasone, thioTEPA, doxorubicin, vincristine, rituximab, cyclophosphamide, prednisone, melphalan, lenalidomide, bortezomib, rapamycin, and cytarabine.



Ib

[0024] Formula I compounds include all stereoisomers, geometric isomers, tautomers, metabolites, and pharmaceutically acceptable salts thereof. Certain Formula I compounds are potent inhibitors of PI3K with drug-like physicochemical and pharmacokinetic properties. Certain Formula I compounds exhibit selectivity for class Ia PI3Ks over class Ib, in particular

for the P110 alpha subtype. Formula Ia and Ib compounds are orally bioavailable and have single agent anti-tumor activity in multiple human cancer models.

[0025] Pharmaceutical compositions and therapeutic combinations of the ~~invention~~disclosure comprise a chemotherapeutic agent selected from dexamethasone, thioTEPA, doxorubicin, vincristine, rituximab, cyclophosphamide, prednisone, melphalan, lenalidomide, bortezomib, rapamycin, and cytarabine.

[0026] Pharmaceutical compositions of the ~~invention~~disclosure may further comprise a pharmaceutically acceptable carrier.

[0027] ~~Another aspect of the invention provides~~Disclosed are methods of treating a hematopoietic malignancy modulated by PI3 kinases, comprising administering to a mammal in need of such treatment effective amounts of a Formula I compound and a chemotherapeutic agent. The Formula I compound and the chemotherapeutic agent may be co-formulated for administration in a combination as a pharmaceutical composition or they may be administered separately in alternation (sequentially, consecutively) as a therapeutic combination.

[0028] ~~Another aspect of the invention provides~~Disclosed are methods of treating a hematopoietic malignancy, comprising administering to a mammal in need of such treatment effective amounts of the Formula I compound and a chemotherapeutic agent.

[0029] ~~In a further aspect of the present invention provides~~Disclosed is a method of using a pharmaceutical composition of the ~~invention~~disclosure to treat a hematopoietic malignancy disease or condition modulated by PI3 kinase in a mammal.

[0030] ~~An additional aspect of the invention~~Also disclosed is the use of a pharmaceutical composition of the ~~invention~~disclosure in the preparation of a medicament for the treatment of a hematopoietic malignancy disease or condition modulated by PI3 kinase in a mammal.

[0031] ~~Another aspect of the invention includes~~Also disclosed are articles of manufacture or kits comprising a Formula I compound, a chemotherapeutic agent, a container, and optionally a package insert or label indicating a treatment for a hematopoietic malignancy.

[0032] ~~Another aspect of the invention~~Also disclosed is a product comprising a Formula I compound, and a chemotherapeutic agent selected from dexamethasone, thioTEPA, doxorubicin, vincristine, rituximab, cyclophosphamide, prednisone, melphalan, lenalidomide, bortezomib, rapamycin, and cytarabine; as a combined preparation for separate, simultaneous or sequential use in the treatment of a hematopoietic malignancy.

[0033] ~~Another aspect of the invention includes~~Disclosed is a method for determining compounds to be used in combination for the treatment of cancer comprising: a) administering a

therapeutic combination comprising a Formula I compound, and a chemotherapeutic agent to an in vitro hematopoietic malignancy cell line with one or more mutations, and b) measuring a synergistic or non-synergistic effect.

[0034] ~~Another aspect of the invention is~~Also disclosed are methods of therapeutically treating a mammal having a hematopoietic malignancy, wherein the method comprises administering to the mammal a therapeutically effective amount of the therapeutic combination, thereby resulting in the effective therapeutic treatment of the hematopoietic malignancy, such as non-Hodgkin's lymphoma, diffuse large hematopoietic lymphoma, follicular lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia, multiple myeloma, AML, and MCL. In one embodiment, the therapeutic combination inhibits one or more isoforms of PI3K. In one embodiment, the therapeutic combination inhibits mTOR.

[0035] ~~In one aspect, the invention provides~~Disclosed is a method of inhibiting the growth of a non-Hodgkin's lymphoma comprising administering the therapeutic combination to a patient with a non-Hodgkin's lymphoma, whereby growth of the lymphoma is inhibited.

[0036] ~~In one aspect, the invention provides~~Also disclosed is a method of inhibiting the growth of a non-Hodgkin's lymphoma comprising administering the therapeutic combination to a lymphoma cell, or to a cell present in and/or adjacent to the lymphoma, whereby growth of the lymphoma is inhibited. In one embodiment, said cell is not a non-Hodgkin's lymphoma cell (e.g., it is not a T or B cell) for example, said cell may be a stromal cell.

[0037] BRIEF DESCRIPTION OF THE DRAWINGS

[0038] Figure 1 shows reduction of pharmacodynamic (PD) markers measured by flow cytometry with Formula Ia (GDC-0941) treated (right column) and untreated (left column) cells, DoHH2, WSU-DLCL2, OPM2, and U266. Cells were treated in vitro with 5 μM GDC-0941 for 4 hrs.

[0039] Figure 2 shows reduction of pharmacodynamic (PD) markers p-AKT, p-S6RP, p-Bad, and beta-actin in cells DoHH2, WSU-DLCL2, OPM2, and U266 as measured by SDS-polyacrylamide gel electrophoresis and western blotting in cell lines treated in vitro with 5 μM GDC-0941 for 4 hrs.

[0040] Figure 3 shows the effect of PI3K single agent inhibitor, Formula Ia (GDC-0941), and in combinations with dexamethasone (Dex) and doxorubicin (Dox), on B-NHL cell line DoHH2. In vitro cell survival and proliferation assays (Cell-Titer Glo, Promega) measured viable cells over varying inhibitor concentrations (10^{-5} to 10 Relative Units of the previously (approximately) determined IC50, Formula Ia, dexamethasone, doxorubicin and