(54) Title: COMBINATION OF RO5503781 AND CAPECITABINE FOR CANCER THERAPY

(57) Abstract:
There are provided pharmaceutical products comprising a) a first component comprising the compound of formula (A); and b) a second component comprising capecitabine for the simultaneous or sequential treatment of cancer, kits comprising said product as well as methods for treating cancer patients by administering said product.
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COMBINATION OF RO5503781 AND CAPECITABINE FOR CANCER THERAPY

FIELD OF THE INVENTION

The present invention is directed to a method of cancer therapy by administering (i) a pharmaceutical composition containing (i) a compound of formula

![Chemical Structure](image)

4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-methoxy-benzoic acid (Compound A) an antagonist of the p53/MDM2 interaction and (ii) a pharmaceutical composition containing capecitabine which is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil intracellularly, an antineoplastic agent. Capecitabine is marketed in the United States by Roche Laboratories under the brand name Xeloda®. The chemical name for capecitabine is 5’-deoxy-5-fluoro-N-[(pentyloxy)-carbonyl]-cytidine and has the following structural formula:

![Chemical Structure](image)

Capecitabine is covered in US patents, including US Pat. No. 4,966,891 and 5,472,949. Improved methods for the manufacture of capecitabine are also taught by US Pat. No. 5,453,497
and 5,476,932, and application USSN 60/532,266, filed December 22, 2003. Compound A is disclosed in WO2011/098398 and US Patent No. 8,354,444. Specific pharmaceutical preparations comprising Compound A are also disclosed in International Patent Application No. PCT/EP2014/050974. To the extent necessary, any and all of the foregoing patents and applications are herein incorporated by reference. The invention is also directed to a kit containing both of the above compositions.

BACKGROUND OF THE INVENTION

p53 is a transcription factor that can activate a panel of genes implicated in the regulation of cell cycle and apoptosis. p53 is a potent cell cycle inhibitor which is tightly regulated by MDM2 at the cellular level. MDM2 and p53 form a feedback control loop. MDM2 can bind p53 and inhibit its ability to transactivate p53-regulated genes. In addition, MDM2 mediates the ubiquitin-dependent degradation of p53. p53 can activate the expression of the MDM2 gene, thus raising the cellular level of MDM2 protein. This feedback control loop insures that both MDM2 and p53 are kept at a low level in normal proliferating cells. MDM2 is also a cofactor for E2F, which plays a central role in cell cycle regulation.

The ratio of MDM2 to p53 (E2F) is dysregulated in many cancers. Frequently occurring molecular defects in the p16INK4/p19ARF locus, for instance, have been shown to affect MDM2 protein degradation. Inhibition of MDM2-p53 interaction in tumor cells with activation of the p53-MDM2 pathway should lead to accumulation of p53, cell cycle arrest and/or apoptosis. The feasibility of p53/MDM2 antagonism as a strategy has been shown by the use of different macromolecular tools for inhibition of MDM2-p53 interaction (e.g. small molecules, antisense oligonucleotides, peptides).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method of treating a patient suffering with cancer comprising administering to the patient, either concomitantly or sequentially, a first component consisting of a pharmaceutical composition containing as an active ingredient a therapeutically effective amount of a compound of 4-[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-methoxy-benzoic acid (Compound A) or a pharmaceutically acceptable salt or ester of said compound and a second component consisting of a pharmaceutical composition containing a therapeutically effective amount of capecitabine.
This combination of chemotherapeutic compounds is particularly useful in the treatment of colon cancer.

It was unexpectedly found that administration of the two components in accordance with the present invention results in improved antineoplastic effects that are significantly superior to the results obtained with each compound alone. Namely, administration of the two components in accordance with the present invention resulted in an improved therapeutic index (that is, superior efficacy) in comparison to either component alone without a significant increase in toxicity.

Alternatively the invention permits reduction of the amount of at least one component (in comparison the amount typically given in monotherapy) while retaining a desirable therapeutic index. In preferred embodiments, the amount of both components (in comparison the amount typically given in monotherapy) is reduced affording reduced toxicity while still retaining a desirable therapeutic index.

In one embodiment, the present invention relates to a pharmaceutical product comprising a) a first component comprising Compound A; and b) a second component comprising capecitabine for the simultaneous or sequential treatment of cancer, in particular solid and/or hematological tumors such as breast, colon, colorectal, lung and pancreatic tumors, sarcoma or leukemias such as acute myelocytic leukemia (AML).

In another embodiment there is provided Compound A and capecitabine for the simultaneous or sequential use in the treatment of cancer, in particular solid and/or hematological tumors such as breast, colon, colorectal, lung and pancreatic tumors, sarcoma or leukemias such as acute myelocytic leukemia (AML).

In another embodiment, the present invention relates to a method of treating a patient suffering with cancer comprising administering to the patient Compound A in an amount of from about 400 to about 3200 mg/day, or from about 400 to about 1600 mg/day, or from about 1000 to about 2500 mg/day, or from about 1250 to about 1800 mg/day, for an administration period of up to about 7 days, preferably once per week or up to about 5 days, more preferably once per week, on days 1-3, or on days 1-5, of a 28 day treatment cycle, followed by a rest period of from about 21 to about 23 days, preferably up to about 23 days together with, in combination with
Compound A, capecitabine in an amount of about 800-1500 mg/m² twice daily over a period of 14 days.

The course of a preferred treatment cycle is about 28 days, though cycles anywhere between about 14 and about 28 days are contemplated. This treatment cycle is repeated for as long as the tumor remains under control and the regimen is clinically tolerated.

Dosages of Compound A can be applied either as a body surface area ("BSA") adapted dose (mg/m²/day) or following flat dosing (mg/day). Compound A may be administered as a single dose daily or divided into multiple daily doses.

A patient's body measurement in square meters ("m²") typically ranges from about 1.4 m² to about 2.2 m². Thus, the total amount of Compound A to be delivered in a treatment cycle (mg) using a BSA adapted dose would be calculated as follows:

[Dose intensity (mg/m²/week)] x [BSA(m²)] x [number of weeks in treatment cycle].

For capecitabine in combination with Compound A the preferred dose is 800-1500 mg/m² twice daily over a period of 14 days.

In an embodiment, Compound A is administered daily for about 5 days, on days 1-5 of a weekly treatment cycle, followed by a rest period of 23 days ("5+/23-."). Compound A is administered daily, either once or twice (bid) daily, preferably once daily. The compound is administered to the patient in an oral unit dosage form, most preferably in tablet form.

Preferably, the 5 day per week treatment schedule is repeated every twenty-eight days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control or regressing and the patient tolerates the regimen. Preferably, these treatment cycles are repeated for a total of up to about 12 cycles.

In an embodiment, Compound A is administered daily in an amount from about 400 to about 3000 mg/day for up to about 3 days on days 1-5 of a weekly 28 day cycle.

In an embodiment, Compound A is administered daily in an amount from about 400 to about 1500 mg/day for up to about 5 days on days 1-5 of a weekly 28 day cycle.
In an embodiment, Compound A is administered daily in an amount from about 800 to about 3000 mg/day for up to about 5 days on days 1-5 of a weekly 28 day cycle.

In another embodiment, Compound A is administered daily in an amount from about 800 to about 3200 mg/day weekly on days 1, 7, 15 of a weekly 28 day cycle.

In another embodiment, Compound A is administered daily in an amount from about 1250 to about 1800 mg/day weekly on days 1, 7, 15 of a weekly 28 day cycle.

In an embodiment, Compound A is administered daily in an amount from about 400 to about 1600 mg/day for up to about 7 days on days 1-7 of a weekly 28 day cycle.

In an embodiment, Compound A is administered in an amount from about 400 mg/day to about 1600 mg/day, daily, for up to about 7 days, followed by a rest period of up to about 21 days, said administration starting on the first day of a 28 day treatment cycle.

In an embodiment, Compound A is administered in an amount from about 400 mg/day to about 3200 mg/day, daily, for up to about 3 days, followed by a rest period of up to about 23 days, said administration starting on the first day of a 28 day treatment cycle.

In an embodiment, Compound A is administered in an amount from about 800 mg/day to about 3000 mg/day once per week, followed by a rest period of up to about 23 days, said administration starting on the first day of a 28 day treatment cycle.

In an embodiment, Compound A is administered from about 400 mg/day to about 1500 mg/day.

In an embodiment, Compound A is administered from about 1000 mg/day to about 2500 mg/day.

In an embodiment, Compound A is administered from about 1250 mg/day to about 1800 mg/day.

In an embodiment, Compound A and capecitabine are administered, simultaneously or sequentially, according to treatment groups 6, 7, 8 or 9 according to Example 1.
In an embodiment there is provided a kit comprising: (a) a first component containing one or more oral unit dosage forms of an active ingredient comprising capecitabine and (b) a second component comprising 4-[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-methoxy-benzoic acid. Within this embodiment, preferably the first component contains a sufficient number of units so that a patient can administer about 800 -1500 mg/m^2 of capecitabine twice daily over a period of 14 days and the second component contains a sufficient number of doses so that a patient can administer about 400-3000 mg per day of 4-[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-methoxy-benzoic acid for a period of up to 5 days.

Abbreviations used herein are as follows:
x times
po orally
bid twice daily
wk week
qd once daily
qdx5 once daily for five days
qweekly or
1x/wk once a week
BWL body weight loss
SD standard deviation

The LoVo cell line was selected for implantation in mice as it is a p53 wildtype cell line that lacks MDM2 amplification or overexpression and therefore is felt to be more reflective of clinical reality of the colorectal cancer patient population of interest.

The present invention may be exemplified by controlled preclinical animal studies as shown in the Examples below, which illustrates the invention without limitation.
EXAMPLES

Example 1

Compound A and the capecitabine formulations were as follows. If not explicitly indicated otherwise, the amounts provided below are concentrations [mg/ml]. Compound A is used at concentrations of 10 mg/ml and 12.5 mg/ml. Capecitabine is used at concentrations of 12.5 mg/ml, 25mg/ml and 50mg/ml. The vehicle solutions for compound A and capecitabine are as follows:

Vehicle solution for Compound A

Klucel LF: 20.0 mg/mL
Tween 80: 1.0 mg/mL
Methylparaben: 0.9 mg/mL
Propylparaben: 0.1 mg/mL
Water for Injection: Qs to 1.0ml

Vehicle solution for oral suspension of capecitabine

Klucel LF: 20.0 mg/mL
Polysorbate 80: 1.0 mg/mL
Methylparaben: 0.9 mg/mL
Propylparaben: 0.1 mg/mL
Purified Water: Qs to 1.0 ml

Compound A is provided as powder for constitution prior to dosing. The powder can be kept at room temperature. The vehicle solution is prepared immediately prior to constitution or, if prepared earlier, kept at 2-8 °C.

Constitution instructions:

1. Take out the vehicle from the storage refrigerator.
2. Take one vial of the Compound A Powder for Constitution. Add the amount of vehicle indicated on the label. For easier constitution, it is recommended to add a small portion to wet the powder first and then add the remaining amount of vehicle. Mix the suspension using a magnetic bar at low speed for 30 minutes or vortex it till the powder is fully wet and suspended
before dosing. If needed, use a spatula to help wet the powder periodically during the course of mixing.

3. Continue mixing while withdraw for dosing.

5 The capecitabine suspension should be stored at 2-8 °C after preparation. While preparing this suspension good mixing (stir for at least 30 min) is required. Stirring should be continued while dosing the suspension.

10 The following treatment groups were used in the study

1. Vehicle Control qd x 5 po + qd x 14 po
2. Compound A 80 mg/kg qd x 5 po
3. Compound A 100 mg/kg qweekly x 3 po
4. Capecitabine 200 mg/kg qd x 14 po
5. Capecitabine 400 mg/kg qd x 14 po
6. Compound A 80 mg/kg qd x 5 + Capecitabine 200 mg/kg qd x 14
7. Compound A 80 mg/kg qd x 5 + Capecitabine 400 mg/kg qd x 14
8. Compound A 100 mg/kg qweekly x 3 + Capecitabine 200 mg/kg qd x 14
9. Compound A 100 mg/kg qweekly x 3 + Capecitabine 400 mg/kg qd x 14
Table 1.: Efficacy Summary

<table>
<thead>
<tr>
<th>Group</th>
<th>Schedule</th>
<th>Mean Tumor Volume</th>
<th>%T/C (EOS)</th>
<th>%Inhibition (EOS)</th>
<th>%Increased Life Span</th>
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<tbody>
<tr>
<td>Vehicle</td>
<td>qdx5</td>
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<td>-----</td>
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<tr>
<td></td>
<td>qdx14</td>
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<td>5</td>
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<tr>
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<tr>
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<td>80 mg/kg</td>
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<td>400 mg/kg</td>
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</tr>
</tbody>
</table>

All dosing above is per os.

**Tumor Growth Inhibition (TGI) and Assessment of Survival/increase in Life Span (ILS)**

Efficacy data was graphically represented as the mean tumor volume ± standard error of the mean (SEM). In addition, tumor volumes of treated groups were presented as percentages of tumor volumes of the control groups (%T/C), using the formula: 100 x ((T - T₀)/(C - C₀)), where T represented mean tumor volume of a treated group on a specific day during the experiment, T₀ represented mean tumor volume of the same treated group on the first day of treatment; C
represented mean tumor volume of a control group on the specific day during the experiment, and \( C_0 \) represented mean tumor volume of the same treated group on the first day of treatment.

Tumor volume (in cubic millimeters) was calculated using the ellipsoid formula: \((D \times (d^2))/2\), where "D" represents the large diameter of the tumor and "d" represents the small diameter. In some cases, tumor regression and/or percent change in tumor volume was calculated using the formula: \((T - T_0)/ T_0 \) x 100, where ‘T’ represents mean tumor volume of the treated group at a particular day, and ‘T_0’ represents mean tumor volume of the same treated group at initiation of treatment.

Statistical analysis was determined by the rank sum test and One Way Anova and a post-hoc Bonferroni t-test (SigmaStat, version 2.0, Jandel Scientific, San Francisco, CA, USA). Differences between groups were considered to be significant when the probability value \((p)\) was \(\leq0.05\).

For survival assessment, the percent of increased life space (ILS) was calculated as: 100 x [(median survival day of treated group - median survival day of control group)/median survival day of control group]. Median survival was determined utilizing Kaplan Meier survival analysis. Survival in treated groups was statistically compared with the vehicle group and survival comparisons were done between groups using the log-rank test (Graph Pad Prism, La Jolla, CA, USA). Differences between groups were considered significant when the probability value \((p)\) was \(\leq0.05\).

For the 80mg/kg Cpd A + 400mg/kg capecitabine arm there were 2 partial tumor regressions; for the 100mg/kg Cpd A + 200 mg/kg capecitabine arm 2 partial tumor regressions and for the 100 mg/kg Cpd A + 400 mg/kg capecitabine arm 6 partial tumor regressions and one total tumor regressions.

Discussion of Results

In the above study Compound A gave monotherapy antitumor activity and survival of 62% \((p<0.001)\), 23% \((p<0.0001)\) and 55% \((p<0.001)\), 17% \((p<0.0001)\) for the 80 mg/kg qdx5 and the 100 mg/kg qweekly regimens, respectively. Capecitabine had single agent antitumor activity \(([TGI and survival (ILS)]\) with 72% \((p<0.001)\), 40% \((p<0.0001)\) and 88% \((p<0.001)\), 49% \((p<0.0001)\) for 200 mg/kg qd and 400 mg/kg qd regimens, respectively.
In combination, the Compound A at 80 mg/kg qdx5 plus capecitabine 200 mg/kg qd gave 87% TGI (p<0.001) and 40% ILS (p<0.0001) results. Compound A in combination with capecitabine 400 mg/kg qd gave 95% with 2/10 partial regressions (p<0.001) and 49% (p<0.0001) survival was rendered.

Compound A at 100 mg/kg qweekly plus capecitabine 200 mg/kg qd gave 94% TGI with 2/10 partial regressions (p<0.001) and 77% ILS (p<0.0001). For compound A at 200mg/kgin combination with capecitabine 400mg/kg qd regression predominated (>100%) with 6/10 partial and 1/10 complete regressions (p<0.001) and 109% ILS (p<0.0001) survival

Statistical cross comparisons for the above study show the TGI and ILS for both 80 mg/kg qdx5 Compound A + capecitabine doublets are not significantly better than their correlative capecitabine monotherapy arms. The TGI and ILS for 100 mg/kg qweekly Compound A + capecitabine 200mg/kg doublet are significantly better than both correlative monotherapy arms. The TGI in the 100 mg/kg qweekly Compound A + capecitabine 400mg/kg doublet was not significantly better than the correlative capecitabine monotherapy arm, however, ILS was significantly better than both correlative monotherapy arms.

Although TGI was equivalent in both 100 mg/kg qweekly Compound A + capecitabine doublets, ILS was significantly better in the 100 mg/kg qweekly Compound A + capecitabine 400mg/kg doublet alluding to a more sustained regressive effect for this group.
CLAIMS

1. A pharmaceutical product comprising a) a first component comprising Compound A; and b) a second component comprising capecitabine for the simultaneous or sequential treatment of cancer, in particular solid and/or hematological tumors such as breast, colon, colorectal, lung and pancreatic tumors, sarcoma or leukemias such as acute myelocytic leukemia (AML).

2. The product of claim 1 wherein the capecitabine is dosed at about 800 to about 1500 mg/m² twice daily over a period of 14 days.

3. The product of claim 2 wherein the dosage of 4-[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrroloidine-2- carbonyl]-amino]-3-methoxy-benzoic acid in an amount from about 400 mg/day to about 1600 mg/day, daily, for up to about 7 days, followed by a rest period of up to about 21 days, said administration starting on the first day of a 28 day treatment cycle.

4. The product of claim 2 wherein the dosage of 4-[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrroloidine-2- carbonyl]-amino]-3-methoxy-benzoic acid is in an amount from about 400 mg/day to about 3200 mg/day, daily, for up to about 3 days, followed by a rest period of up to about 23 days, said administration starting on the first day of a 28 day treatment cycle.

5. The product of claim 2 wherein the dosage of 4-[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrroloidine-2- carbonyl]-amino]-3-methoxy-benzoic acid is in an amount from about 800 mg/day to about 3000 mg/day once per week, followed by a rest period of up to about 23 days, said administration starting on the first day of a 28 day treatment cycle.

6. The product of claim 2 wherein 4-[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrroloidine-2-carbonyl]-amino]-3-methoxy-benzoic acid is administered in an amount of from about 400 mg/day to about 1500 mg/day.
7. The product of claim 2 wherein 4-\{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}\}3-methoxy-benzoic acid is administered in an amount of from about 1000 mg/day to about 2500 mg/day.

8. The product of claim 2 wherein 4-\{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}\}3-methoxy-benzoic acid is administered in an amount of from about 1250 mg/day to about 1800 mg/day.

9. The product of claim 3 wherein the treatment cycle is repeated every 28 days for up to about 12 cycles.

10. The product of any one of claims 2 to 8 wherein 4-\{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}\}3-methoxy-benzoic acid is administered weekly on days 1, 7, 15 of a weekly 28 day cycle.

11. The product of any one of claims 2 to 8 wherein 4-\{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino\}3-methoxy-benzoic acid is administered once daily for 5 days weekly every 28 days.

12. A kit comprising: (a) a first component containing one or more oral unit dosage forms of an active ingredient comprising capcitabine and (b) a second component comprising 4-\{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino\}3-methoxy-benzoic acid.

13. The kit of claim 12, wherein the first component contains a sufficient number of units so that a patient can administer about 800-1500 mg/m² of capcitabine twice daily over a period of 14 days and the second component contains a sufficient number of doses so that a patient can administer about 400-3000 mg per day of 4-\{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino\}3-methoxy-benzoic acid for a period of up to 5 days.
14. A method of treating a patient suffering from cancer comprising administering to said patient a therapeutically effective amount of a pharmaceutical product according to any one of claims 1 to 11.

15. The novel combinations, compositions and uses substantially as described herein.