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(54) **METHOD FOR ADMINISTRATION**

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(63) Continuation of application No. 14/596,747, filed on Jan. 14, 2015, which is a continuation of application No. 13/759,647, filed on Feb. 5, 2013, now abandoned.

(60) Provisional application No. 61/612,429, filed on Mar. 19, 2012.

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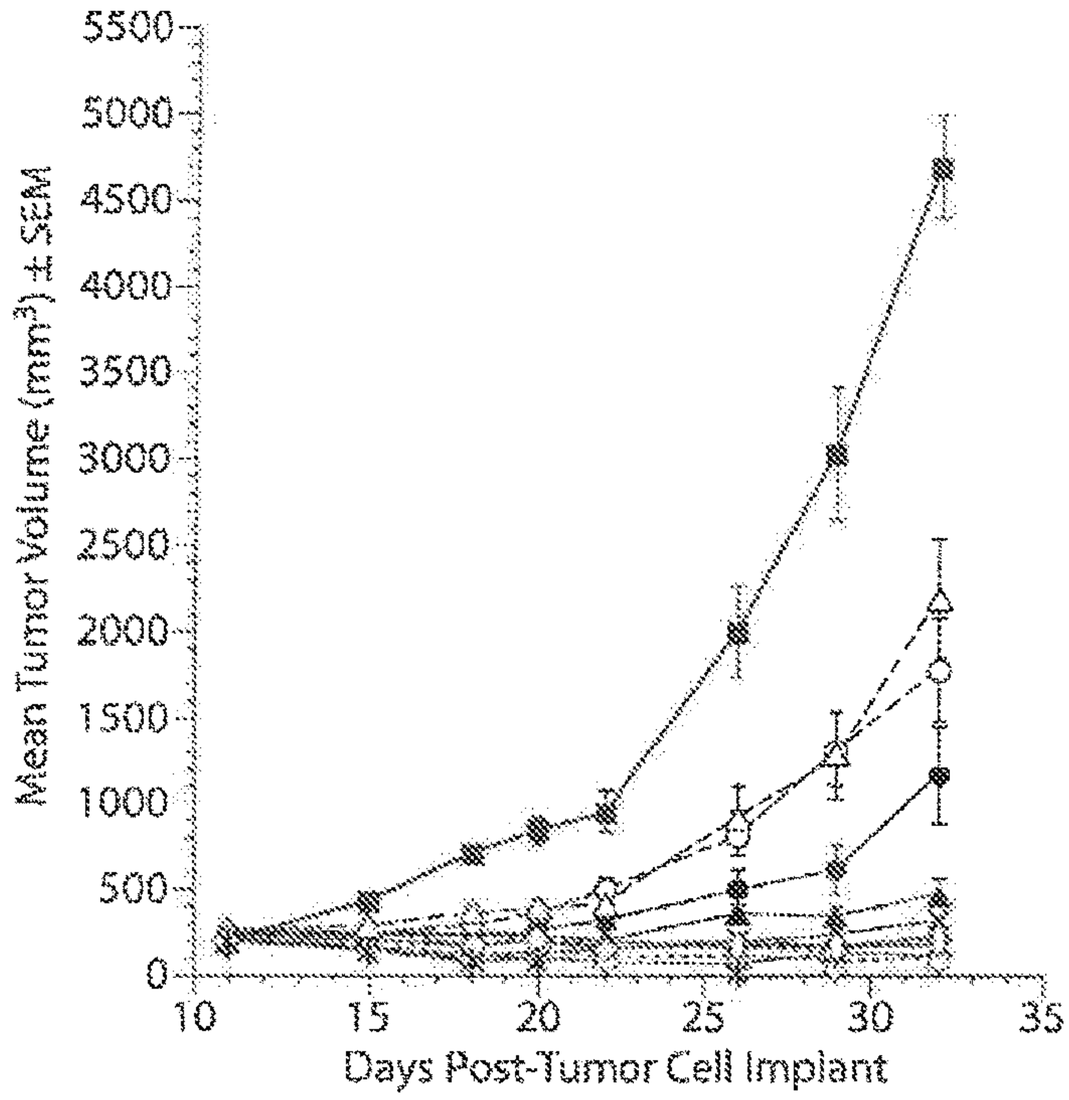
(52) **U.S. Cl.**

CPC ***A61K 31/401*** (2013.01); ***A61K 9/146*** (2013.01); ***A61K 31/40*** (2013.01)

(57) **ABSTRACT**

There is provided a new dosage regimen for Compound A which maximizes anti-tumor activity while maintaining acceptable toxicity levels.


Mean Tumor Volume (mm³) ± SEM
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10
15
20
25
30
35
Days Post-Tumor Cell Implant

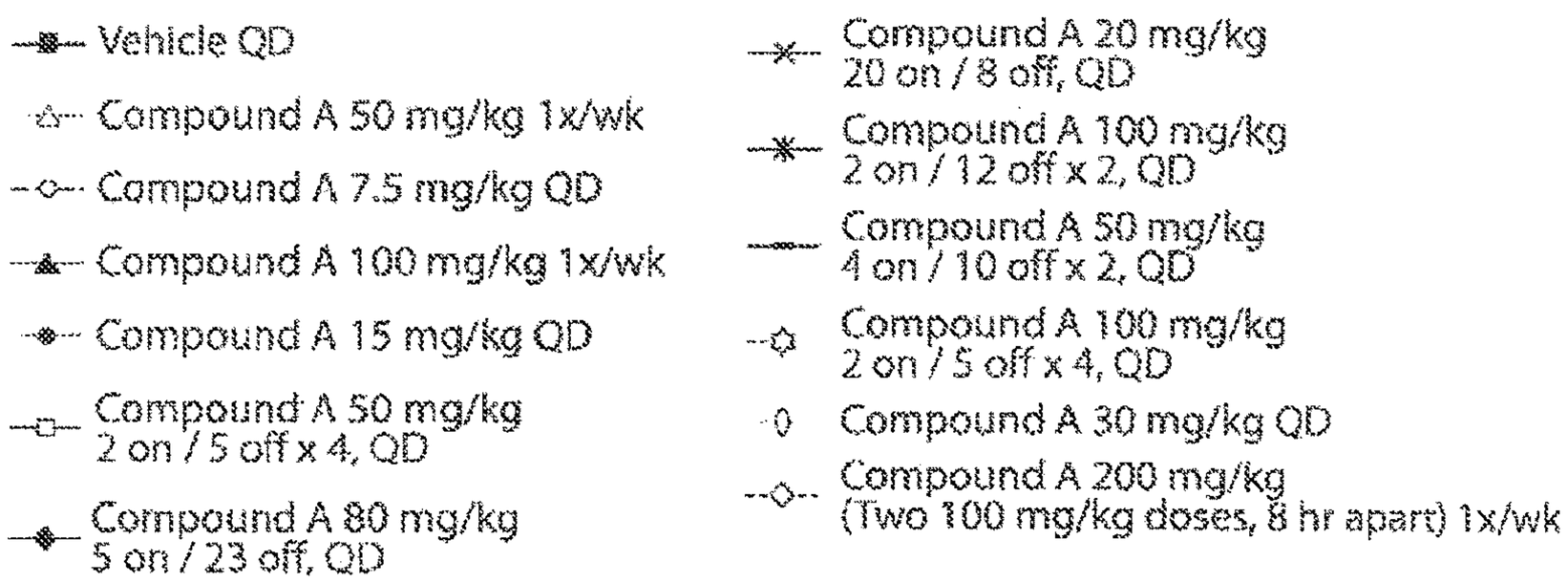
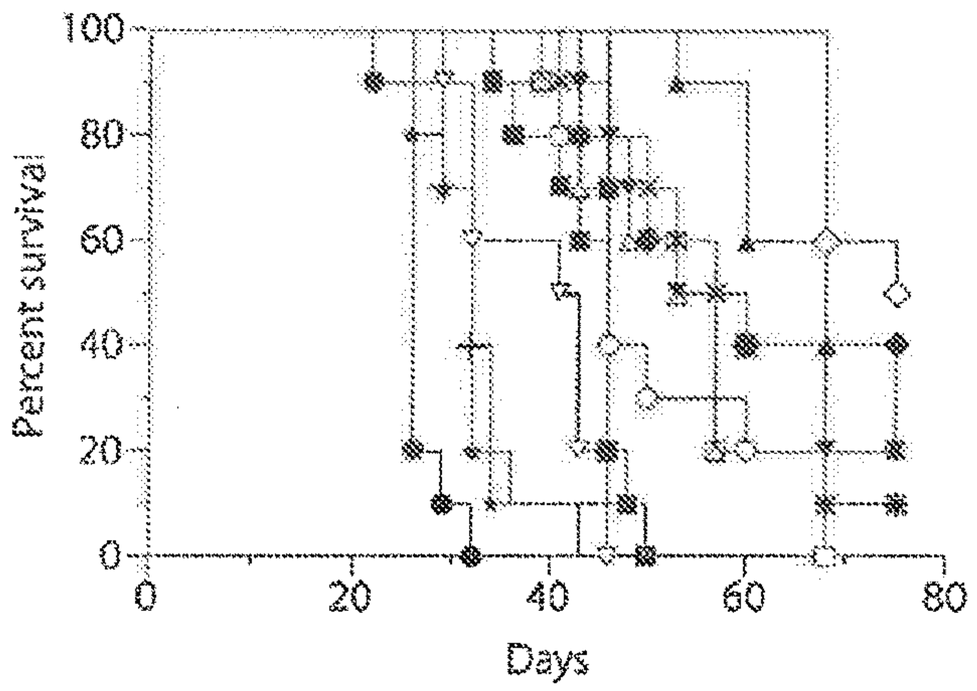

Vehicle QD
Compound A 50 mg/kg 1x/wk
Compound A 7.5 mg/kg QD
Compound A 100 mg/kg 1x/wk
Compound A 15 mg/kg QD
Compound A 50 mg/kg 2 on / 5 off x 4, QD
Compound A 80 mg/kg 5 on / 23 off, QD
Compound A 20 mg/kg 20 on / 8 off, QD
Compound A 100 mg/kg 2 on / 12 off x 2, QD
Compound A 50 mg/kg 4 on / 10 off x 2, QD
Compound A 100 mg/kg 2 on / 5 off x 4, QD
Compound A 30 mg/kg QD
Compound A 200 mg/kg (Two 100 mg/kg doses, 8 hr apart) 1x/wk

Fig. 1



- Vehicle, qd
- Compound A 50 mg/kg 1x/wk
- Compound A 7.5 mg/kg qd
- Compound A 100 mg/kg 1x/wk
- Compound A 15 mg/kg qd
- Compound A 50 mg/kg 2 on/5off x 4, qd
- Compound A 80 mg/kg 5 on/23 off, qd
- Compound A 20 mg/kg 20 on/8 off, qd
- Compound A 100 mg/kg 2 on/12 off x 2, qd
- Compound A 50 mg/kg 4 on/10 off x 2, qd
- Compound A 100 mg/kg 2 on/5 off x 4, qd
- Compound A 30 mg/kg qd
- Compound A 200 mg/kg (Two 100 mg/kg doses, 8 hr apart) 1x/wk

Fig. 2

METHOD FOR ADMINISTRATION

PRIORITY TO RELATED APPLICATION(S)

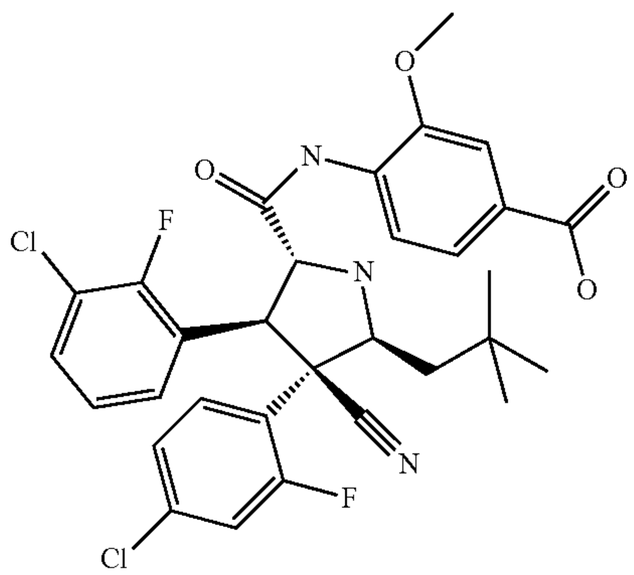
[0001] This application claims the benefit of U.S. Provisional Application No. 61/612,429, filed Mar. 19, 2012, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention is related to improved methods of administration 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 (referred to herein as Compound A) in the treatment of cancer. In particular, the invention relates to improved methods of administration of Compound A that provide desirable antineoplastic effects with a tolerable level of toxicity. The methods of the invention are characterized by administering less frequent doses comprising relatively high concentrations of Compound A. This protocol is expected to be safer and at least as effective as, possibly more effective than, administering more frequent doses at lower concentrations or larger doses at intermittent periods.

BACKGROUND OF THE INVENTION

[0003] Compound A is an orally administered pyrrolidine that inhibits the binding of MDM2 to p53 and is thus useful in the treatment of cancer. It has the following chemical structure:



Molecular Weight = 616.4973
Molecular Formula = C31H29Cl2F2N3O4

[0004] Compound A recently entered into phase I clinical trials for the treatment of solid tumors. See ClinicalTrials.gov, identifier NCT01462175. This compound is disclosed in US Pub 2010/0152190 A1. To the extent necessary, this patent publication is herein incorporated by reference.

[0005] Applicants have discovered that Compound A is especially effective, and best tolerated, in cancer therapy when administered in the specific doses and pursuant to the specific protocols herein described.

SUMMARY OF THE INVENTION

[0006] The present invention relates to a method of treating a patient suffering with cancer, in particular colon, breast, prostate, lung or kidney cancer or osteosarcoma, comprising administering to the patient Compound A in an amount of from about 800 to about 3000 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 up to about 5 days, on days 1-7, or preferably 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] FIG. **1** illustrates the antitumor activity, as demonstrated by the change in mean tumor volume over time, of Compound A monotherapy for a number of different dosing schedules, including a continuous 5 day dosing schedule.

[0008] FIG. **2** shows the increased lifespan of mice treated with Compound A for the different dosing schedules also reflected in FIG. **1**.

DETAILED DESCRIPTION OF THE INVENTION

[0009] "Tumor control" means that the perpendicular diameters of measurable lesions have not increased by 25% or more from the last measurement. See, e.g., World Health Organization ("WHO") Handbook for Reporting Results of Cancer Treatment, Geneva (1979). The determination of tumor control or shrinkage (also referred to as "regression") is made by known methods. For example, by evaluation of patient symptoms, physical examination, X-ray, MRI or CAT scan or other commonly accepted evaluation modalities.

[0010] The present invention relates to a method of treating a patient suffering with cancer, in particular colon, breast, prostate or kidney cancer as well as osteo or tissue sarcoma, comprising administering to the patient Compound A in an amount of from about 800 to about 3000 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 up to about 5 days, on days 1-7, or preferably 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. The course of a preferred 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.

[0011] Dosages of Compound A can be applied either as a body surface area ("BSA") adapted dose (mg/m^2/day) or following flat dosing (mg/day). Compound A may be administered as a single dose daily or divided into multiple daily doses.

[0012] A patient's body measurement in square meters ("m^2") typically ranges from about 1.4 m^2 to about 2.2 m^2, 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/m^2/week)]×[BSA(m^2)]×[number of weeks in treatment cycle].

[0013] In an embodiment, Compound A is administered daily for about 5 days, on days 1-5 of a treatment cycle, followed by a rest period of 23 days ("5+/23−"). The 5+/23− treatment schedule is expected to be superior to interim schedules or to longer schedules as currently on-going Phase I studies indicate that in solid tumors, maximal apoptosis occurs only after about 48 hours of continuous exposure and

longer schedules seem to present occurrence of delayed thrombocytopenia ("TCP"). Thus, a 3-5 daily treatment schedule is expected to provide the best benefit ratio taking into consideration efficacy and toxicity

[0014] 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.

[0015] Preferably, the 5 day 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.

[0016] 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 28 day cycle.

[0017] In another embodiment, Compound A is administered daily in an amount from about 1000 to about 2500 mg/day for up to about 5 days on days 1-5 of a 28 day cycle.

[0018] In another embodiment, Compound A is administered daily in an amount from about 1250 to about 1800 mg/day for up to about 5 days on days 1-5 of a 28 day cycle.

[0019] The present invention may be exemplified by controlled preclinical animal studies as shown in the Examples below, which illustrates the invention without limitation.

EXAMPLES

[0020] The superiority of the 5 day regimen of the present invention on solid tumors is demonstrated by the following experiments.

[0021] 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

Toxicity

[0022] In the examples below, weight loss was graphically represented as percent change in mean group body weight, using the formula: $((W-W_0)/W_0)\times 100$, where 'W' represents mean body weight of the treated group at a particular day, and 'W_0' represents mean body weight of the same treated group at initiation of treatment. Maximum weight loss was also represented using the above formula, and indicated the maximum percent body weight loss that was observed at any time during the entire experiment for a particular group. Toxicity is defined as ≥20% of mice in a given group demonstrating ≥20% body weight loss and/or death.

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

[0023] 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: $100\times((T-T_0)/(C-C_0))$, where T represented mean tumor volume of a treated group on a specific day during the experiment, T_0 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.

[0024] 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: $((T-T_0)/T_0)\times 100$, 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.

[0025] 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, Calif., USA). Differences between groups were considered to be significant when the probability value (p) was ≤0.05.

[0026] For survival assessment, the percent of increased life space (ILS) was calculated as: 100×[(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, Calif., USA). Differences between groups were considered significant when the probability value (p) was ≤0.05.

Example 1

[0027] The antitumor activity of Compound A in the human osteosarcoma cancer xenograft model SJASA1 in immunocompromized mice using a variety of different schedules was assessed.

A. Test Compound A

[0028] Compound A was formulated as an amorphous solid dispersion micro-bulk precipitate (MBP) powder containing 30% drug substance and 70% HPMC-AS polymer was reconstituted immediately before administration as a suspension in Klucel/Tween, and remaining suspension was discarded after dosing. All dose levels are reported as the actual dosage of Compound A rather than including drug plus polymer.

B: In Vivo Assays

Animals

[0029] Female athymic Crl:NU-Foxn1nu mice (10/group), obtained from Charles River Laboratories (Wilmington, Del.) were utilized when they were approximately 10-12 weeks of age and weighed 23-25 g. The health of the mice was assessed daily by gross observation and analyses of blood samples taken from sentinel animals housed on shared shelf racks. All animals were allowed to acclimate and recover from any shipping-related stress for a minimum of 72 hours prior to experimental use. Autoclaved water and irradiated food (5058-ms Pico Lab mouse chow, Purina

Mills, Richmond, Ind.) were provided ad libitum, and the animals were maintained on a 12 hour light and dark cycle. Cages, bedding and water bottles were autoclaved before use and changed weekly. All animal experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals, local regulations, and protocols approved by the Roche Animal Care and Use Committee in an AAALAC accredited facility.

Tumors

[0030] SJSA cells (ATCC) were maintained in RPMI 1640+10% (v/v) heat-inactivated FBS+1% (v/v) 200 nM L-glutamine. Each mouse received 5×10^6 cells in a 1:1 mixture of phosphate buffered saline and Matrigel in a total volume of 0.2 ml. Cells were implanted subcutaneously in the right flank using a 1 cc syringe and a 26 gauge needle.

Study Design

[0031] The doses selected for Compound A and schedules utilized in this study are shown in Table 1 below.

TABLE 1

Study Design	
Tumor Model	Treatment Groups
SJSA	1. Vehicle qd po 2. Compound A 7.5 mg/kg qd po 3. Compound A 15 mg/kg qd po 4. Compound A 30 mg/kg qd po 5. Compound A 20 mg/kg 20 days qd po, 8 days off 6. Compound A 50 mg/kg 1x/week po 7. Compound A 100 mg/kg 1x/week po 8. Compound A 200 mg/kg (given as two 100 mg/kg doses 8 hours apart (bid)), 1x/week po 9. Compound A 50 mg/kg 4 days qd po, 10 days off x 2 cycles 10. Compound A 50 mg/kg 2 days qd po, 5 days off x 4 cycles 11. Compound A 100 mg/kg 2 days qd po, 5 days off x 4 cycles 12. Compound A 80 mg/kg 5 days qd po, 23 days off 13. Compound A 100 mg/kg 2 days qd po, 12 days off x 2 cycles

Treatment

[0032] Compound A was administered orally (po) using a 1 cc syringe and 18-gauge gavage needle (0.2 ml/animal). Treatment duration was 2-4 weeks. Dates of tumor implant, treatment initiation (study start date), and termination of treatment (study end date) can be found in Table 6 below. The starting tumor volume for this study was about 220 mm^3. Tumor volumes and animal body weights were measured three times per week and animals were monitored for clinical signs daily.

[0033] The results of this experiment are summarized Tables 1-3 below and FIGS. **1** and **2**. As can be seen, the 5 day treatment schedule yielded the greatest per cent increase in life span (% ILS) as well as high per cent tumor growth inhibition (% TGI) with reasonable toxicity. FIG. **1** also shows good growth inhibitory activity of the 5 day on/23 day off treatment schedule.

TABLE 2

Toxicity Summary						
Group	Frequency	% Change in Body Weight at end of Study Day 29	Maximum % Weight loss	Maximum % Weight gain	# of animals ≥20% BWL	Mortality
Vehicle	QD	13.0	−1.2	13.0	0	0
Compound A 100 mg/kg	1×/wk	9.1	4.2	9.1	0	0
Compound A 200 mg/kg (Two 100 mg/kg doses, 8 hr apart	1×/wk	6.3	1.9	6.3	0	0
Compound A 50 mg/kg	2 on/5 off × 4, QD	7.1	−0.8	7.1	0	0
Compound A 80 mg/kg	5 on/23 off, QD	8.0	0.3	8.0	0	0
Compound A 20 mg/kg	20 on/8 off, QD	1.2	−3.9	1.2	0	0
Compound A 100 mg/kg	2 on/ 12 off × 2, QD	0.9	−0.6	1.8	0	0
Compound A 50 mg/kg	4 on/10 off × 2, QD	1.2	−1.1	1.2	0	0
Compound A 15 mg/kg	QD	5.9	−2.2	5.9	0	0
Compound A 100 mg/kg	2 on/5 off × 4, QD	1.3	−2.8	1.3	0	0

TABLE 2-continued

Toxicity Summary						
Group	Frequency	% Change in Body Weight at end of Study Day 29	Maximum % Weight loss	Maximum % Weight gain	# of animals ≥20% BWL	Mortality
Compound A 30 mg/kg	QD	1.3	−0.2	1.3	0	0
Compound A 50 mg/kg	1×/wk	6.6	−0.3	6.6	0	0
Compound A 7.5 mg/kg	QD	9.0	−0.3	9.0	0	0

TABLE 3

Efficacy Summary (left side)								
Group Vehicle or Compound A	Frequency	Mean Tumor (mm3) Start Study Day: 11	SEM	SD	Mean Tumor Volume (mm3) End Study Day: 32	SD	SEM
Vehicle	QD	215.03	±19.00	±60.08	4696.49	±785.28	±296.91
50 mg/kg	1×/week	275.41	±22.66	±71.65	22.66	±1103.00	±348.80
−7.5 mg/kg	QD	240.88	±18.01	±56.95	18.01	±956.45	±302.46
100 mg/kg	1×/week	193.61	±9.67	±30.57	474.73	±273.78	±86.58
15 mg/kg	QD	232.37	±16.42	±51.93	16.42	±872.83	±276.01
50 mg/kg	2 on/5 off × 4, QD	203.43	±18.78	±59.39	257.29	±102.12	±32.29
80 mg/kg	5 on/23 off, QD	197.38	±12.80	±40.48	128.05	±84.89	±26.84
20 mg/kg	20 on/8 off, QD	207.20	±16.97	±53.67	315.19	±277.51	±87.76
100 mg/kg	2 on/12 off × 2, QD	201.40	±9.86	±31.18	179.88	±154.02	±48.71
50 mg/kg	4 on/10 off x 2, QD	213.61	±12.09	±38.23	244.70	±240.07	±75.92
100 mg/kg	2 on/5 off × 4, QD	190.78	±25.68	±81.22	25.68	±15.82	±5.00
30 mg/kg	QD	250.86	±19.35	±61.19	19.35	±159.01	±50.28
100 mg/kg	200 mg/kg (Two 100 mg/kg doses, 8 hr apart) × 1×	224.88	±12.02	±38.02	158.95	±68.86	±21.78

Efficacy Summary Continued (right side)								
% T/C End of Study Day: 32	% Inhibition end of study Day: 32	p value end of study Day: 32	Average % Regression per Group	Partial Regression	Full Regression	Animal per Group	% Increased Life Span	p Value versus Vehicle
—	—	—	—	0	0	7	—	—
43	57	<0.001	—	0	0	10	23	0.0036
34	66	<0.001	—	0	0	10	23	0.0012
6	94	<0.001	—	1	0	10	77	<0.0001
21	79	<0.001	—	0	0	10	62	<0.0001
1	99	<0.001	—	3	0	10	119	<0.0001
−2	regression	<0.001	35	6	2	10	127	<0.0001
2	98	<0.001	—	5	0	10	77	<0.0001
0	regression	<0.001	11	7	0	10	119	<0.0001
1	99	<0.001	—	6	0	10	112	<0.0001
−2	regression	<0.001	47	9	0	10	188	<0.0001
−1	regression	<0.001	13	7	0	10	127	<0.0001
−1	regression	<0.001	29	7	0	10	162	<0.0001

TABLE 4

Survival Summary

Group		50% Treatment Days	50% Vehicle days	% ILS	p value
Vehicle	QD	—	—	—	—
Compound A 100 mg/kg	1 x/wk	46	26	77	<0.0001
Compound A 200 mg/kg	Two 100 mg/kg doses, 8 hr apart 1 x/wk	68	26	162	<0.0001
Compound A 50 mg/kg	2 on/5 off x 4, QD	57	26	119	<0.0001
Compound A 80 mg/kg	5 on/23 off, QD	59	26	127	<0.0001
Compound A 20 mg/kg	20 on/8 off, QD	46	26	77	<0.0001
Compound A 100 mg/kg	2 on/12 off x 2, QD	57	26	119	<0.0001
Compound A 50 mg/kg	4 on/10 off x 2, QD	55	26	112	<0.0001
Compound A 15 mg/kg	QD	42	26	62	<0.0001
Compound A 100 mg/kg	2 on/5 off x 4, QD	75	26	188	<0.0001
Compound A 30 mg/kg	QD	59	26	127	<0.0001
Compound A 50 mg/kg	1 x/wk	32	26	23	0.0036
Compound A 7.5 mg/kg	QD	32	26	23	0.0012

[0034] Overall, the 5 days on and 23 days off (5+/23−) schedule is predicted to reduce MDM2 inhibitor-induced thrombocytopenia in humans undergoing treatment for solid tumors, while still maintaining antitumor efficacy, as compared to other regimens considered.

What is claimed:

1. A method of treating a patient suffering from cancer, comprising administering to said patient a pharmaceutical composition containing as an active ingredient Compound A in an amount from about 800 mg/day to about 3000 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.

2. A method of treating a patient suffering from cancer, comprising administering to said patient a pharmaceutical composition containing as an active ingredient Compound A in an amount from about 800 mg/day to about 3000 mg/day, daily, for up to about 5 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.

3. The method of claim **2** wherein Compound A is administered in an amount from about 1000 mg/day to about 2500 mg/day.

4. The method of claim **3** wherein Compound A is administered in an amount of from about 1250 mg/day to about 1800 mg/day.

5. The method of claim **1** wherein the treatment cycle being repeated every 28 days for up to about 12 cycles.

6. The method of claim **1** wherein Compound A is administered twice daily in equal doses.

7. The method of claim **1** wherein the cancer is colorectal cancer.

8. The method of claim **1** wherein the cancer is prostate cancer.

9. The method of claim **1** wherein the cancer is lung cancer.

10. The method of claim **1** wherein the cancer is kidney cancer.

11. The method of claim **1** wherein the cancer is breast cancer.

* * * * *