ANTITUMOR COMBINATION INCLUDING AVE8062 AND SORAFENIB

The present invention relates to an antitumour combination that combines **AVE8062** and sorafenib that is effective in the treatment of cancers, more particularly of solid tumours.

[Prior art]

WO 2007/077309 describes the combination between the antivascular agent **AVE8062** (or VDA, Vascular Disrupting Agent) and the antiangiogenic agent VEGF Trap.

WO 99910779 describes the **AVE8062** / platinum salt combination.

WO 2004/037258 describes the combination of **AVE8062** with various antitumour agents chosen from taxanes (taxol, taxotere), alkylating agents (cyclophosphamide, isosfamide, etc.), antimetabolites (5-FU, cytarabine, etc.), epidophylloptoxin, antibiotics (doxorubicin, etc.), and vinca alkaloids.

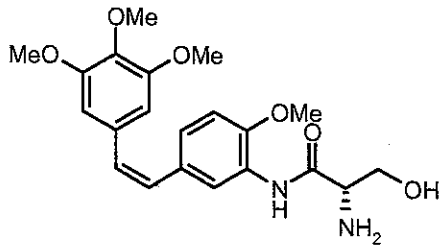
EP 1407784 describes the **AVE8062** / dexamethasone combination.

On the website www.clinicaltrials.gov, the patient recruitment phase for the Phase I study of the combretastatin CA4P / Avastin combination ("Safety study of increasing doses of combretastatin in combination with Bevacizumab (Avastin) in patients with advanced solid tumours") is described. It is specified that the patients excluded are those who have already undergone a treatment based on a VEGF or VEGFR inhibitor such as sorafenib or sutent ("exclusion criteria: prior therapy with CA4P or bevacizumab, or other agents which target vascular endothelial growth factor (VEGF) or VEGFR signaling such as Sorafenib and Sutent").

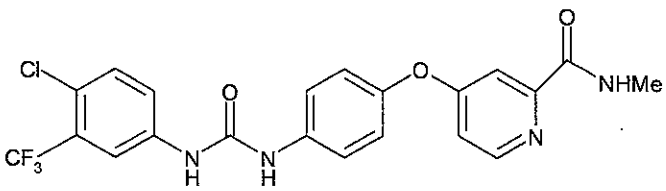
In the file on Nexavar available on the website of the EMEA (http://www.emea.europa.eu/humandocs/PDFs/EPAR/nexavar/H-690-PI-fr.pdf), it is indicated that Nexavar® (sorafenib tosylate) may be combined with various anticancer agents such as gemcitabine, oxaliplatin, doxorubicin, irinotecan or docetaxel.

[Brief description of the invention]

The invention relates to an antitumour pharmaceutical combination comprising **AVE8062** of formula:



and sorafenib of formula:



, these two antitumour agents possibly being in the base form or in the form of a salt of a pharmaceutically acceptable acid. The combination comprises an effective amount of **AVE8062** and an effective amount of sorafenib.

The combination is intended to be administered to a patient during a cycle comprising an administration of **AVE8062** that marks the beginning of said cycle and several administrations of sorafenib, the combination being staggered over time and not concomitant, the **AVE8062** being administered before the very first administration of sorafenib. The **AVE8062** may be administered the same day as the sorafenib with a time delay of 1 to 4 hours before the very first administration of sorafenib. The **AVE8062** may also be administered the day before the very first administration of sorafenib, more particularly with a time delay of at least 24 hours. The cycle is repeated, the interval between two administrations of **AVE8062** ranging from 1 to 4 weeks.

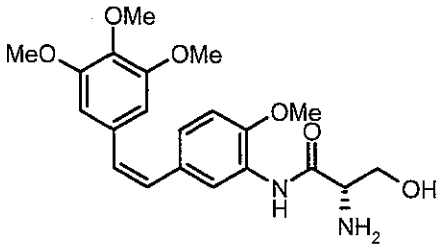
The invention also relates to the use of **AVE8062** and sorafenib for the preparation of the antitumour combination described above.

[Description of the invention]

definitions

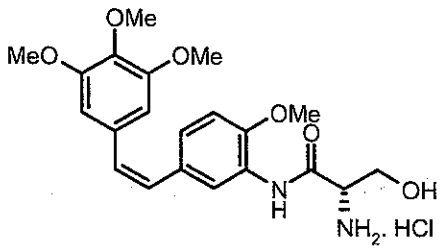
- pharmaceutically acceptable acid: organic or inorganic acid having a low toxicity (see "Pharmaceutical salts" *J.Pharm.Sci.* **1977**, *66*, 1-19);
- effective amount: amount of a pharmaceutical compound that produces an effect on the treated tumour.

Regarding AVE8062, this belongs to the family of combretastatins and has the formula:

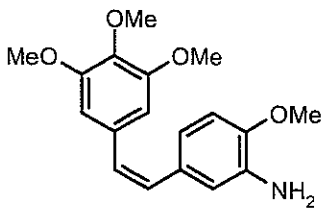


(it is the Z isomer)

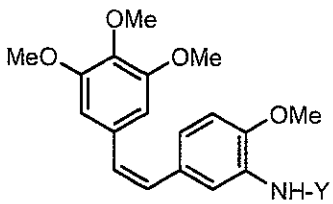
It is an antivascular agent (or VDA, Vascular Disrupting Agent). It has the chemical name: (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide. This compound, which is described in **EP 731085 B1,** may be prepared according to the method described in **WO 03/084919**. **AVE8062** may be administered in base form (cf. above formula) or in the form of a salt of a pharmaceutically acceptable acid, for example in the form of the hydrochloride, represented below:



Once administered, **AVE8062** releases *in vivo* the active metabolite (Z)-1-(3-amino-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene, which has the formula:

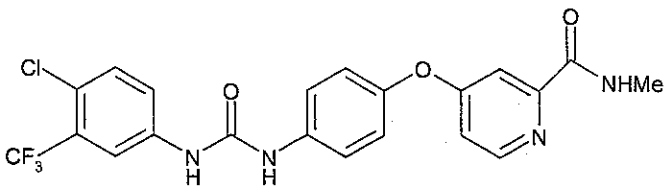


It is therefore also possible to substitute, for **AVE8062,** another combretastatin of formula:



in base form or in the form of a salt of a pharmaceutically acceptable acid, in which Y represents an amino acid, which releases *in vivo* this metabolite.

Regarding sorafenib, this is sold by Bayer HealthCare under the trademark Nexavar®. Sorafenib is a multikinase inhibitor that targets VEGF and BRAF receptors which has the chemical formula:



and has the chemical name: 4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino] phenoxy]-N-methylpyridine-2-carboxamide. It is an antiangiogenic agent. This compound is described in **WO 00/42012** and **WO 00/41698**. Sorafenib may be administered in base form (cf. formula above) or in the form of a salt of a pharmaceutically acceptable acid, for example in tosylate form.

Regarding the combination, this consists in combining, in the form of two separate pharmaceutical preparations, **AVE8062** and sorafenib.

The combination is administered repeatedly in a course of several cycles according to a protocol that depends on the nature and on the stage of the cancer to be treated and also on the patient to be treated (age, weight, previous treatment(s), etc.). Each cycle begins with the administration of **AVE8062** and comprises, in addition to this, several administrations of sorafenib (one cycle is therefore characterized by an administration of **AVE8062** that marks the beginning of said cycle and several administrations of sorafenib). The **AVE8062** is administered to a patient in an intermittent pattern with an interval between two administrations (duration of one cycle) which may range from 1 to 4 weeks, for example 3 weeks (comment: in the case of tests on mice, the administration interval of **AVE8062** was 4 or 5 days). Sorafenib may itself be administered to a patient in a daily pattern over a certain duration of the cycle. Sorafenib may optionally be administered up to the end of one cycle.

The mode of administration may be the parenteral route and/or oral route and depends on the galenic form use for the antitumour agent. By the parenteral route, the antitumour agent may be administered intravenously as a bolus or prepared in an intravenous infusion bag, with pharmaceutically acceptable vectors, by various methods known to a person skilled in the art. According to one particular mode, the **AVE8062** is administered parenterally, such as via intravenous administration, as a bolus or via infusion, and the sorafenib is administered orally.

One galenic form of **AVE8062** suitable for parenteral administration is that where the **AVE8062** is in solution in water. One galenic form of sorafenib suitable for oral administration is, for example, that sold under the trademark Nexavar® in the form of tablets containing 274 mg of sorafenib in sorafenib tosylate form (equivalent to 200 mg of active principle).

The doses of **AVE8062** and of sorafenib administered each time to a patient depend on various parameters such as the nature and the stage of the cancer to be treated and also on the patient to be treated (age, weight, previous treatment(s), etc.). The **AVE8062** may be administered at a tolerated dose between 5 and 100, 5 and 60, 10 and 50, 20 and 42 or 20 and 40 mg/m² (weight/body surface area, dose defined for each administration). The sorafenib may itself be administered at a tolerated dose between 200 and 600 mg, or 300 and 500 mg (dose defined for each administration). The sorafenib may be taken two times a day at a dose of active principle of 200 mg, which corresponds to a daily dose of 400 mg. Furthermore, according to the product instructions, it is recommended to take this product at least one hour before or two hours after a meal.

The combination is effective in the treatment of cancers, more particularly of solid tumours in general, more particularly of a sarcoma, lung, ovarian, kidney or liver cancers.

It has been observed that a better efficacy in the treatment of the tumour is obtained when, in the course of one cycle, the administration of the two antitumour agents is staggered over time and is not concomitant, the **AVE8062** being administered before the very first administration of the sorafenib.

According to one particular mode, the **AVE8062** is administered the same day and with a time delay of 1 to 4 hours before the very first administration of sorafenib. A cycle example: day D1: infusion of AVE8062 and, 1 to 4 hours after the infusion, sorafenib is taken orally (e.g. in the form of two doses of sorafenib); day D2 to D14: sorafenib is taken orally (e.g. in the form of two doses of sorafenib), then the cycle is repeated at D1 + 3 weeks.

According to another particular mode, the **AVE8062** is administered the day before the very first administration of sorafenib. More particularly, the time delay between the administration of the AVE8062 and the very first administration of sorafenib is at least 24 hours. Cycle example: day D1: infusion of AVE8062; day D2 after a time delay of at least 24 hours: sorafenib is taken orally (e.g. in the form of two doses of sorafenib); day D3 to D14: sorafenib is taken orally (e.g. in the form of two doses of sorafenib), then the cycle is repeated at D1 + 3 weeks.

The efficacy of a combination can be demonstrated by determining its therapeutic synergy. A combination manifests therapeutic synergy if it is therapeutically superior to the best agent used alone at its optimum dose (T.H. Corbett et al., Cancer Treatment Reports **1982**, *66*, 1187). The

efficacy of a combination can also be demonstrated by comparing the maximum tolerated dose of the combination with the maximum tolerated dose of each of the separate constituents in the study in question. This efficacy can be quantified by the $\log_{10}$ cell kill, which is determined by the following formula:

$$\log_{10} \text{ cell kill} = \text{T-C (days)}/3.32 \times T_d$$

in which T-C represents the tumour growth delay, which is the mean time, in days, required by the treatment-group tumours (T) to reach a predetermined value (1 g for example) and for the control-group tumours (C) to reach the same value, and T_d represents the time, in days, necessary for the volume of the control-group tumours to double during the exponential phase of tumour growth (T.H. Corbett et al. Cancer, **1977**, *40*, 2660-2680; F.M. Schabel et al., Cancer Drug Development, Part B, Methods in Cancer Research **1979**, *17*, 3-51, New York, Academic Press Inc.). A product is considered to be active if the $\log_{10}$ cell kill is greater than or equal to 0.7. A product is considered to be highly active if the $\log_{10}$ is greater than 2.8. When the treatment time is at least equal to 10 days, and/or is different between the two agents evaluated in the combination, it is possible to calculate the net log cell kill:

$$\text{net } \log_{10} \text{ cell kill} = \text{(T-C in days)} - \text{(treatment time in days)}/3.32 \times T_d.$$

The activity in this case is acknowledged for a net log cell kill that is positive (>0). A cytostatic activity corresponds to a net log cell kill of 0, that is to say that the treatment time is equal to the duration of the antitumour effect.

The combination, used at its own maximum tolerated dose, in which each of the constituents is present at a dose that generally does not exceed its maximum tolerated dose, will show therapeutic synergy when the $\log_{10}$ cell kill is at least 1 $\log_{10}$ greater than the value of the $\log_{10}$ cell kill of the best constituent when the latter is administered alone.

[Examples]

Antitumor effect and tests

The efficacy of the combinations on solid tumours can be determined experimentally in the following way: the animals subjected to the experiment are female SCID mice which are bilaterally grafted subcutaneously with 30 to 60 mg of a fragment of NCI-H460 (ATCC#HTB-177) human non-small cell lung tumour at day 0. In the case of an early tumour treatment, the implanted animals are distributed randomly in various groups which are, or are not (controls), intended to receive the treatment(s). Where it is a question of treatment of advanced tumours, the animals bearing tumours that have reached a predefined tumour size greater than 150 mg are distributed in the various treatment and control groups in such a way that the tumour size range is

comparable from one group to the other. The animals which do not bear tumours can also be subjected to the same treatments as the animals bearing tumours, so that it is possible to dissociate the toxic effect from the specific effect on the tumour. Generally, the chemotherapy begins from 3 to 22 days after the graft, depending on the type of tumour and the desired tumour size. The animals are observed and weighed every day. A dose which induces a weight loss of 20% or more at the lowest point (average of the group) or a mortality of 10% or more is considered to be toxic. The tumour activity is evaluated at the highest non-toxic dose, or at the highest dose tested, within the context of a non-cytotoxic agent.

The tumours are measured 2 or 3 times a week until the tumour reaches approximately 2 g or until the animal dies, if this occurs before the tumour reaches 2 g. The animals are autopsied when they are sacrificed.

The antitumor activity is determined in accordance with various recorded parameters, such as the dose (mg/kg), the method of administration, the administration time, the toxicity and the $\log_{10}$ cell kill, which depends on the tumour growth delay and also on the tumour doubling time.

Within the context of the following studies, the **AVE8062**, in hydrochloride form, is formulated in water with 0.9% NaCl. The sorafenib is formulated with 12.5% of ethanol, 12.5% of polysorbate 80 and 75% of 5% glucose in water.

Study 1: Sorafenib administered simultaneously with AVE8062 (Table I)

The AVE8062 was administered intravenously on days 9 and 13 post tumour implantation. The sorafenib was administered orally from day 9 to day 24. When the two agents were administered in combination, the same schedules were used as for the agents alone, the combination of the two agents having been carried out simultaneously on days 9 and 13.

The tumour doubling time was two days.

The median tumour weight at the start of the treatments was 219 to 234 mg, the control having reached a tumour weight of 1000 mg, 12.8 days after the tumour grafting.

The highest evaluated dose (HED) of **AVE8062** is 58 mg/kg per injection, i.e. a total dose of 116 mg/kg. At this dose, **AVE8062** is active with 0.9 $\log_{10}$ cell kill (log cell kill), 1/6 partial regression (PR = 50% regression of the initial tumour size) being obtained at this dose.

The sorafenib, at its highest dose tested (HDT) of 62 mg/kg per administration, i.e. a total dose of 992 mg/kg, is also active with 2.3 log cell kill. However, the sorafenib did not have a cytostatic activity at this dose (-0.1 net log cell kill), the tumour having escaped treatment.

The highest non-toxic dose (HNTD) of the combination was determined at the dose of 36 mg/kg per administration of **AVE8062** combined with that of 62 mg/kg per administration of sorafenib, higher doses of the combination having been found to be toxic. At this HNTD, the combination is active with 2.4 log cell kill, and 0.0 net log cell kill. However, no partial regression was observed at this dose. Lower doses of the combination are also active (2.2 to 2.5 log cell kill), without inducing tumour regression either.

In conclusion, the concomitant administration of **AVE8062** and of sorafenib is active, maintaining at least the therapeutic gain of each of the two agents alone. Furthermore, it has been possible to observe that this activity is maintained at several dose levels only for the combination.

Study 2: Sorafenib adminisered 1 h after AVE8062 in the combination (Table II)

The AVE8062 was administered intravenously on days 10 and 14 post tumour implantantion. The sorafenib was administered orally from day 10 to day 14. The two agents were administered in combination, according to the same schedules as those used for the agents alone, but the administration of sorafenib having been staggered one hour after the administration of the AVE8062.

The tumour doubling time was 1.6 days.

The median tumour weight at the start of the treatments was 431 to 458 mg, the control having reached a tumour weight of 1500 mg, 13.2 days after tumour grafting.

The 2 highest doses of AVE8062 were toxic and the highest non-toxic dose (HNTD) is 22.3 mg/kg per injection, i.e. a total dose of 44.6 mg/kg. At this dose, AVE8062 is active with 1.1 $\log_{10}$ cell kill (log cell kill), without inducing tumour regression.

Sorafenib, at its highest dose tested (HDT) of 100 mg/kg per administration, i.e. a total dose of 447.4 mg/kg, is also active with 1.1 log cell kill.

The HNTD of the combination was determined at the dose of 58 mg/kg per administration of AVE8062 combined with that of 38.4 mg/kg per administration of sorafenib, the higher doses of the combination having been found to be toxic. At this HNTD, the combination is active with 2.1

log cell kill, i.e. 1 log cell kill more than the agents alone, 1.1 log cell kill for each). Furthermore, 50% (3/6) of partial regressions (PR = 50% regression of the initial tumour size) was obtained at this dose. Five lower doses of the combination are also active, with a log cell kill of 1.9 to 1.5, and inducing PR at 4 dose levels.

In conclusion, the combination of AVE8062 with sorafenib administered 1 h later, induces more tumour regressions than each of the agents alone, a therapeutic synergy being observed at the HNTD.

Study 3: Sorafenib administered 24 h after AVE8062 in the combination (Table III)

The AVE8062 was administered intravenously on days 9 and 14 post implantation of the NCI-H460 pulmonary tumour in female SCID mice. The sorafenib was administered orally from day 9 to day 20. When the 2 agents were administered in combination, the same schedules were used as for the agents alone, but the administrations of sorafenib were started 24 hours after that of AVE8062.

The tumour doubling time was 1.5 days.
The median tumour weight at the start of the treatments was 217 to 235 mg, the control having reached a tumour weight of 1000 mg, 13.6 jours after tumour grafting.

The highest non-toxic dose (HNTD) of the AVE8062 is 36 mg/kg per injection, i.e. a total dose of 72 mg/kg. At this dose, AVE8062 is active with 1.7 $\log_{10}$ cell kill (log cell kill) without inducing tumour regression.

Sorafenib, at its highest dose tested (HDT) of 100 mg/kg per administration, i.e. a total dose of 1213.3 mg/kg, is also active with 2.4 log cell kill. However, sorafenib did not have a cytostatic activity at this dose (-0.4 net log cell kill), the tumour having escaped treatment.

The HNTD of the combination was determined at the dose of 36 mg/kg per administration of AVE8062 combined with that of 100 mg/kg per administration of sorafenib, the higher doses of the combination having been found to be toxic. At this HNTD, the combination is highly active with 3.1 log cell kill, and 0.3 net log cell kill. Furthermore, 50% (3/6) of partial regressions (PR = 50% regression of the initial tumour size) and 16% (1/6) of complete regression (CR = regression below the palpable limit of 63 mg) were obtained at this dose. Lower doses of the combination are also active (2.6 to 3 log cell kill), and induce PR at 5 dose levels and CR at 2 dose levels.

In conclusion, this combination, which uses a sequence during which sorafenib is administered after AVE8062, induces complete and/or partial tumour regressions, which is not observed for the agents alone. These regressions, in combination, are observed at several dose levels. The log_{10} cell kill in combination is systematically higher than that observed in monotherapy.

In conclusion, for these 3 studies, staggering the administration of sorafenib by at least 1 hour after the administration of AVE8062, gives a therapeutic gain compared to the administration of the two antitumour agents when they are administered alone. Expanding this interval up to at least 24 hours increases this therapeutic advantage.

Table I. Evaluation of AVE8062 in combination with sorafenib (simultaneously) on female SCID mice bearing the NCI-H460 human tumour.

Agent (schedule)	Dosage in mg/kg per injection	Total dose in mg/kg	log cell kill	net log cell kill	PR	CR	Observations
AVE8062	58.0	116.0	0.9	0.1	1/6	0/6	HED – active
(9, 13)	36.0	72.0	0.8	0.0	1/6	0/6	Active
	22.3	44.6	0.6	-0.1	0/6	0/6	Inactive
Sorafenib	62.0	992.0	2.3	- 0.1	0/6	0/6	HDT – no cytostatic activity
(9-24)	38.4	614.4	1.5	- 0.9	0/6	0/6	No cytostatic activity
AVE8062 / sorafenib	36.0 / 62.0	72.0 / 992.0	2.4	0.0	0/6	0/6	HNTD - active
(9, 13) (9-24)	22.3 / 62.0	44.6 / 992.0	2.4	0.0	0/6	0/6	Active
	36.0 / 38.4	72.0 / 614.4	2.4	0.0	0/6	0/6	Active
	13.8 / 62.0	27.6 / 992.0	2.4	0.0	0/6	0/6	Active
	8.6 / 62.0	17.2 / 992.0	2.4	0.0	0/6	0/6	Active
	22.3 / 38.4	44.6 / 614.4	2.5	0.0	0/6	0/6	Active
	13.8 / 38.4	27.6 / 614.4	2.5	0.0	0/6	0/6	Active
	8.6 / 38.4	8.6 / 614.4	2.2	- 0.3	0/6	0/6	No cytostatic activity

Tumour doubling time = 2 days. Median tumour weight at the start of the treatments = 219 - 234 mg. Median time to reach 1000 mg in the control = 12.8 days. Treatment time: sorafenib = 16 days, AVE8062 = 5 days.

Formulation: AVE8062 in water with 0.9% NaCl; sorafenib = 12.5% ethanol, 12.5% PS80, 75% of 5% glucose in water.

Abbreviations: HED = highest evaluated dose, HNTD = highest non-toxic dose, HDT = highest dose tested, PR = partial regressions, CR = complete regressions.

Table II. Evaluation of AVE8062 in combination with sorafenib (1 h after AVE8062) on female SCID mice bearing the NCI-H460 human tumour.

Agent, route Dose in mg/kg/adm in mg/kg)		Schedule in days	Mortality (day of death)	% BWC (day of lowest point)	T-C in days	log cell kill	Regressions		Observations
							partial	complete	
AVE8062. i.v.	sorafenib. p.o.								
58.0 (58.0)		10	3/5 (2d12,13)	-6.9 (11)	-	-	-	-	Toxic
36.0 (36.0)			1/5 (12)	-3.9 (11)	-	-	-	-	Toxic
22.3 (44.6)		10,14	0/5	-3.2 (21)	5.8	1.1	0/5	0/5	HNTD - active
	100.0 (447.4)	10-14	0/6	-4.8 (17)	6.1	1.1	0/6	0/6	HDT - Active
	62.0 (277.6)		0/6	-7.1 (16)	4.4	0.8	0/6	0/6	Modest activity
	38.4 (171.9)		0/6	-4.2 (15)	4.5	0.8	0/6	0/6	Active
58.0 (116.0)	100.0 (447.4)	10,14 / 10-14	1/6 (15)	-13.6 (16)	-	-	-	-	Toxic
	62.0 (277.6)		1/6 (15)	-15.9 (15)	-	-	-	-	Toxic
	38.4 (171.9)		0/6	-10.3 (15)	10.9	2.1	3/6	0/6	HNTD – active
36.0 (72.0)	100.0 (447.4)		1/6 (16)	-12.9 (15)	-	-	-	-	Toxic
	62.0 (277.6)		0/6	-9.5 (15)	10.2	1.9	1/6	0/6	Active
	38.4 (171.9)		0/6	-8.7 (15)	9.5	1.8	2/6	0/6	Active
22.3 (44.6)	100.0 (447.4)		0/6	-7.7 (15)	9.4	1.8	1/6	0/6	Active
	62.0 (277.6)		0/6	-5.6 (15)	8.0	1.5	1/6	0/6	Active
	38.4 (171.9)		0/6	-6.2 (15)	8.1	1.5	0/6	0/6	Active

Tumour doubling time = 1.6 days. Median tumour weight at the start of the treatments = 431 - 458 mg. Median time to reach 1500 mg in the control = 13.2 days.

Formulation: AVE8062 with 0.9% NaCl; sorafenib = 12.5% ethanol, 12.5% PS80, 75% of 5% glucose in water.

Abbreviations: HNTD = highest non-toxic dose, HDT = highest dose tested, BWC = body weight change.

Table III. Evaluation of AVE8062 in combination with sorafenib (24 h after AVE8062) on female SCID mice bearing the NCI-H460 human tumour.

Agent	Dosage in mg/kg per injection	Toatl dose in mg/kg	gross log cell kill	net log cell kill	PR	CR	Observations
AVE8062	36.0	72.0	1.7	0.3	0/6	0/5	HNTD – active
(9, 14)	22.3	44.6	1.7	0.3	0/6	0/6	Active
Sorafenib	100.0	1213.3	2.4	- 0.4	0/6	0/6	HDT – no cytostasis
(9-20)	62.0	752.2	2.3	- 0.5	0/6	0/6	No cytostasis
AVE8062 / sorafenib	58.0 / 100.0	116.0 / 1101.3	3.3	0.5	5/6	3/6	HED – highly active
(9, 14) (9-20)	36.0 / 100.0	72.0 / 1101.3	3.1	0.3	3/6	1/6	HNTD – highly active
	36.0 / 62.0	72.0 / 682.8	3.0	0.2	4/6	2/6	Highly active
	22.3 / 100.0	44.6 / 1101.3	2.7	-0.1	2/6	0/6	No cytostasis
	13.8 / 100.0	27.6 / 1101.3	2.6	-0.2	0/6	0/6	No cytostasis
	22.3 / 62.0	44.6 / 682.8	3.0	0.2	5/6	2/6	Highly active
	8.6 / 100.0	17.2 / 1101.3	2.8	0.0	0/6	0/6	Active
	13.8 / 62.0	27.6 / 682.8	2.9	0.1	1/6	0/6	Highly active
	8.6 / 62.0	8.6 / 682.8	2.8	0.0	2/6	1/6	Active

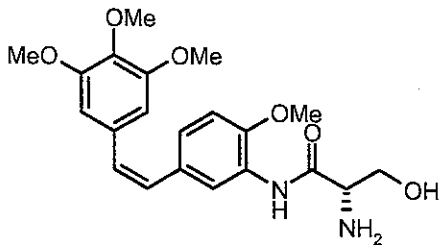
Tumour doubling time = 1.5 days. Median tumour weight at the start of the treatments = 217 - 235 mg. Median time to reach 1000 mg in the control = 13.6 days. Treatment time: Combination and sorafenib alone = 12 days, AVE8062 alone = 5 days.

Formulation: AVE8062 with 0.9% NaCl; sorafenib = 12.5% ethanol, 12.5% PS80, 75% of 5% glucose in water.

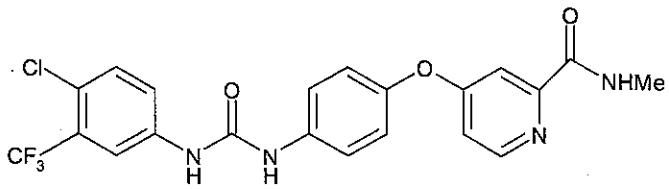
Abbreviations: HNTD = highest non-toxic dose, HDT = highest dose tested, PR = partial regressions, CR = complete regressions.

CLAIMS

1. Antitumour pharmaceutical combination comprising **AVE8062** of formula:



and sorafenib of formula:



, these two antitumour agents possibly being in the base form or in the form of a salt of a pharmaceutically acceptable acid.

2. Combination according to Claim 1, comprising an effective amount of **AVE8062** and an effective amount of sorafenib.

3. Combination according to Claim 1 or 2, in which the **AVE8062** is in hydrochloride form and/or the sorafenib is in tosylate form.

4. Combination according to Claims 1 to 3, intended to be administered to a patient during a cycle comprising an administration of **AVE8062** that marks the beginning of said cycle and several administrations of sorafenib, characterized in that the combination is staggered over time and is not concomitant, the **AVE8062** being administered before the very first administration of sorafenib.

5. Combination according to Claim 4, in which the **AVE8062** is administered the same day as the sorafenib with a time delay of 1 to 4 hours before the very first administration of sorafenib.

6. Combination according to Claim 4, in which the **AVE8062** is administered the day before the very first administration of sorafenib.

7. Combination according to Claim 6, in which the time delay between the administration of the **AVE8062** and the very 1st administration of sorafenib is at least 24 hours.

8. Combination according to one of Claims 4 to 7, in which the cycle is repeated, the interval between two administrations of **AVE8062** ranging from 1 to 4 weeks.

9. Combination according to one of Claims 1 to 8, in which the **AVE8062** is administered parenterally and/or the sorafenib orally.

10. Combination according to one of Claims 1 to 9, intended for the treatment of a solid tumour, more particularly a sarcoma, lung, ovarian, kidney or liver cancers.

11. Use of **AVE8062** and of sorafenib for the preparation of an antitumour combination as described in one of Claims 1 to 10.