Antitumor combination combining AVE8062 and docetaxel

The present invention relates to an antitumor combination combining **AVE8062** or a salt of **AVE8062** and docetaxel in the treatment of solid tumors.

[Prior Art]

Clinical Cancer Research **2004**, *10*, 415-427 compares vascular targeting agents (or VTAs) in the treatment of solid tumors. Among these, **AVE8062A** (**AVE8062** hydrochloride) is administered alone at a weekly dose of 4.3-30 mg/m^2.

Proc. Am. Soc. Clin. Oncol. **2003**, *22*, 834, abstract 834 describes the administration of **AVE8062A** alone at weekly doses of 4.5, 6.0, 8.0, 11.5, 15.5, 22 and 30 mg/m^2. When **AVE8062A** is administered at too high a dose, cardiotoxicity was observed.

J. Clin. Onc. **2006**, ASCO meeting, **2006**:13074, Vol.24, No.18S describes, in abstract form, the combination of **AVE8062A** with oxaliplatin. This combination is also described in *Jpn. J Cancer Res.* **1999**, 90, 1016-1025.

WO 02/056692 describes combinations of a combretastatin A-4 and of two anticancer agents. Among the examples given, combretastatin A-4 at a dose of 1-100 mg/m^2 is combined with paclitaxel at a dose of 40-250 mg/m^2. **WO 2006/078422** also describes a combination of a combretastatin at a dose of 1-100 mg/m^2 and of paclitaxel at a dose of 40-250 mg/m^2.

WO 02/074229 describes the combination of **AVE8062** and of an anticancer agent chosen from taxanes, especially taxol or docetaxel, vinca alkaloids, alkylating agents and antimetabolites. The combination may consist in administering the two compounds at the same time or sequentially. The order of administration is not specified. The compounds may be administered orally, intravenously, subcutaneously or intramuscularly.

In the case of a taxane, this is administered by intraperitoneal injection at a dose between 1 and 10 mg/kg or intraveneous injection at a dose between 1 and 3 mg/kg. Examples are given of a combination, in mice, of **AVE8062** at a dose of 150 mg/kg and of docetaxel at a dose of 109.6 mg/kg (**AVE8062A**/docetaxel ratio: 1.37). By

taking a mouse⇨man conversion factor of 3 in the case of mice (see Freireich, EJ "Quantitative comparison of toxicity of anticancer agents in mouse, rat, dog, monkey and man", *Cancer Chemother Rep.* **1966**, *50(4)*, 219-244), this results in a dose, in man, of 450 mg/m^2 of **AVE8062** and 330 mg/m^2 of docetaxel.

Cancer Res. **2007**, *67*(19), 9337-9345 describes the combination of **AVE8062A** and of docetaxel in the treatment, in mice, of tumor cells of SKOV3ip1, HeyA8 or HeyA8-MDR type (ovarian cancer cells). The **AVE8062A** was administered, in mice, at a dose of 10, 30, 50 and 100 mg/kg (30-300 mg/m^2) and the docetaxel at a dose of 2 or 1.4 mg/kg (6 or 4.2 mg/m^2). The dose of 30 mg/kg is that recommended for **AVE8062**.

On the site **www.clinicaltrials.gov**, a phase I study (code NCT00719524) of an **AVE8062**+cisplatin (D1)/docetaxel (D2) combination in the treatment of patients having an advanced solid tumor is presented. No dose is specified.

Proc. Amer. Assoc. Cancer Res. **2005**, Vol.46, abstract#3425 (*In vivo* synergy between docetaxel and **AVE8062A**, a tumor vasculature targeting agent) describes the combination of **AVE8062A** and of docetaxel administered to mice bearing an MA13/C mammary tumor. The highest non-toxic dose (HNTD) which was found for this combination is 37.5 mg/kg/injection of **AVE8062A** and 54.8 mg/kg/injection of docetaxel (i.e. a docetaxel/AVE8062A ratio of 1.461). The present invention describes a combination intended to be administered to human patients.

[Brief description of the invention]

The invention relates to an antitumor and sequential combination of **AVE8062** or of an **AVE8062** salt and of docetaxel, characterized in that the **AVE8062** is administered to a patient at a dose between 10 and 50 mg/m^2, then on a different day of the week, preferably after an interval of 24 hours, the docetaxel is administered at a dose between 50 and 120 mg/m^2.

The dose of **AVE8062** or of the **AVE8062** salt is rather 20-40 mg/m^2, rather 30-40 mg/m^2. The dose of docetaxel is rather 50-100 mg/m^2, rather 60-80 mg/m^2. The dose of **AVE8062** or of the **AVE8062** salt may be 35 mg/m^2 and that of docetaxel 75 mg/m^2.

The **AVE8062** or the **AVE8062** salt and the docetaxel may be administered by

perfusion.

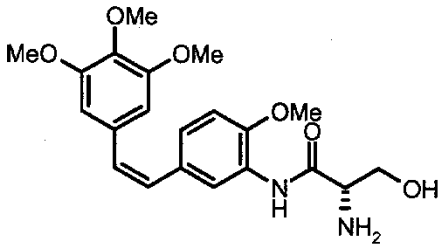
The invention also relates to a combination intended to be administered to a patient during a cycle comprising an administration of **AVE8062** or of an **AVE8062** salt that marks the start of the cycle, then an administration of docetaxel, characterized in that the **AVE8062** or the **AVE8062** salt is administered first, then on a different day of the week, preferably after an interval of 24 hours, the docetaxel is administered, the doses of **AVE8062** and of docetaxel being as defined in one of claims 1 to 4. The cycle may be repeated, the interval between two administrations of **AVE8062** or of the **AVE8062** salt ranges from 1 to 4 weeks, preferably 3 weeks.

The invention also relates to the use of **AVE8062** or of an **AVE8062** salt and of docetaxel for the preparation of an antitumor combination as defined in one of claims 1 to 10. The invention also relates to the use of **AVE8062** or of an **AVE8062** salt for the preparation of an antitumor combination as defined in one of claims 1 to 10.

The combination makes it possible to treat a solid tumor. It makes it possible to treat breast cancer, ovarian cancer, esophageal cancer, pancreatic cancer, cancer of the muscle tissue or of the soft tissue, head/neck cancer, bladder cancer, liver cancer, prostate cancer, ovarian cancer or skin cancer.

[Detailed description of the invention]

Regarding AVE8062, this has the formula:

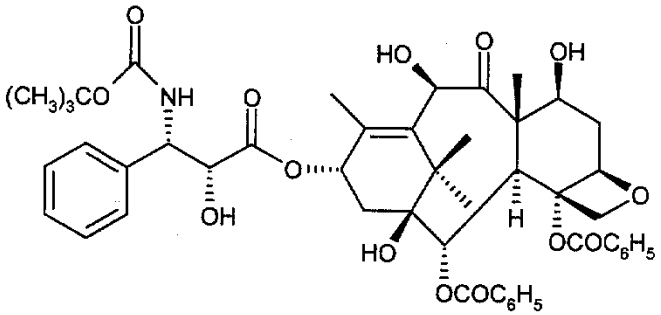


and has the chemical name (Z)-N-[2-methoxy-5-[2-(3,4,5 trimethoxyphenyl)vinyl]phenyl]-L-serinamide. **AVE8062A** denotes the hydrochloride of **AVE8062**.

AVE8062 may be prepared according to the process described in **WO 03/084919.** In the context of the protocol used, **AVE8062A** was used; this compound is packaged in the form of a vial containing an aqueous solution of the active principle. An amount of 25 mg of **AVE8062A** approximately is withdrawn from the vial, then diluted in a

perfusion bag before being administered to the patient. The concentration of **AVE8062A** in the bag is between 0.012 mg/ml and 1.62 mg/ml. The perfusion volume administered to each patient depends on the patient.

Regarding docetaxel, this is sold under the trademark Taxotere® by Sanofi-Aventis. It has the chemical formula:



It may be in a form having the CAS No. **114977-28-5** or **148408-66-6** (trihydrate). The preparation of docetaxel is described, for example, in **EP 0253738**, **EP 0253739** and **WO 92/09589**.

In the context of the protocol used, the docetaxel was packaged in the form of a vial containing anhydrous docetaxel in polysorbate 80 at a concentration of 40 mg/ml. It is possible to use a vial containing 20 mg of docetaxel (0.5 ml) that is then diluted with the contents of a vial (1.98 ml) of an aqueous solution of ethanol at 13% w/w so as to obtain a premix solution having a final docetaxel concentration of 10 mg/ml. It is also possible to use a vial containing 80 mg of docetaxel (2 ml) that is then diluted with the contents of a vial (7.33 ml) of an aqueous solution of ethanol at 13% w/w so as to obtain a premix solution having a final docetaxel concentration of 10 mg/ml.

The premix solution is itself then rediluted in a perfusion bag containing glucose or sodium chloride. The perfusion volume administered to each patient depends on the patient.

Regarding the antitumor combination, this consists in sequentially administering, preferably by perfusion, the **AVE8062** or an **AVE8062** salt, at a dose between 10 and 50 mg/m^2, then on a different day of the week, preferably after an interval of 24 hours, the docetaxel at a dose between 50 and 120 mg/m^2. It is preferable to sequentially combine the two compounds in this order, namely first the **AVE8062** or the **AVE8062** salt, then the docetaxel.

Prefably, the dose of **AVE8062** or of the **AVE8062** salt is 20-40 mg/m^2, rather 30-40 mg/m^2 and/or the dose of docetaxel is 50-100 mg/m^2, rather 60-80 mg/m^2. One combination may be, for example, 35 mg/m^2 of **AVE8062** or of the **AVE8062** salt and 75 mg/m^2 of docetaxel.

[Results]

The protocol consisted in administering a combination of **AVE8062A** and of docetaxel to patients having an advanced solid tumor. The **AVE8062A** is administered by perfusion over a period of 30 min approximately and the next day, the docetaxel is administered by perfusion over a period of one hour approximately. This **AVE8062A**/docetaxel cycle is then repeated every three weeks.

Patients: median age: 53 years old (range 28-71 years old); 39 patients, 14 men/25 women; main tumor: breast (12 patients) and esophagus (8 patients).

Table I

Number of patients treated		39
Sex	Male	14 (35.9%)
	Female	25 (64.1%)
median age (years) [range]		53 [28-71]
ECOG PS	0	15 (38.5%)
	1	24 (61.5%)
Type of tumor	breast	12 (30.8%)
	esophagus	8 (20.5%)
	muscle/soft tissue	5 (12.8%)
	pancreas	5 (12.8%)
	other[a]	9 (23.1%)
Prior chemotherapy	Prior chemotherapy (CT)	36 (92.3%)
	Median number of CT regimens for an advanced tumor [range]	1 [0-7]
	Prior treatment with taxanes for an advanced tumor and a refractory tumor[b]	18 (46.1%) 3 (7.7%)

[a] includes head/neck cancer or cancer of unknown origin (2 patients each), and bladder, liver, prostate, ovarian and skin cancers (1 patient each).
[b] tumor in progression during taxane treatment

Table II

dose[1]	AVE8062A [mg/m²]	docetaxel [mg/m²]	$N_{patients}$	Number of patients with DLT at the 1st cycle	Number of patients with DLT at a subsequent cycle
I	11.5	75	3	none	none
II	15.5	75	5	none	1 gr 4 > 5 days (C2) neutropenia
III	20	75	3	none	neutropenic sepsis with gr 3 respiratory failure (C4)
IV	25	75	6	1 neutropenic infection	1 gr 3 (C10, 11, 12) nail toxicity 1 gr 3 (C6) fistula
V	30	75	3	none	
V	35	75	13	none	1 gr 3 (C2) ALAT
VI	42	75	6	- grade 3 headaches - 1 grade 3 fatigue	1 gr 3 (C2) fatigue

1. median cycle number: 3 (1-14)

These combinations did not lead to any severe cardiotoxic effect.

Table III

dose AVE8062A [mg/m²]	11.5 N=3	15.5 N=5	20 N=3	25 N=6	30 N=3	35 N=13	42 N=6	total N=39
Evaluable number (N)	3	5	3	6	2	11	6	36 (92.3%)
Partial response	0	1[a]	0	2[a]	0	0	0	3 (7.7%)
Stable disease	1	1	3	2	2	7[b]	2	18 (50%)
Tumor progression	2	3	0	2	0	4	4	15 (46.2%)

Regarding the tumor, this may be a solid tumor, especially a solid tumor in an adult or in a child. The combination makes it possible to treat breast cancer, ovarian

cancer, esophageal cancer, pancreatic cancer, cancer of the muscle tissue or of the soft tissue, head/neck cancer, bladder cancer, liver cancer, prostate cancer, ovarian cancer or skin cancer.

CLAIMS

1. An antitumor and sequential combination of **AVE8062** or of an **AVE8062** salt and of docetaxel, characterized in that the **AVE8062** is administered to a patient at a dose between 10 and 50 mg/m^2, then on a different day of the week, preferably after an interval of 24 hours, the docetaxel is administered at a dose between 50 and 120 mg/m^2.

2. The combination as claimed in claim 1, in which the dose of **AVE8062** or of the **AVE8062** salt is 20-40 mg/m^2, rather 30-40 mg/m^2.

3. The combination as claimed in claim 1 or 2, in which the dose of docetaxel is 50-100 mg/m^2, rather 60-80 mg/m^2.

4. The combination as claimed in claim 1, in which the dose of **AVE8062** or of the **AVE8062** salt is 35 mg/m^2 and that of docetaxel is 75 mg/m^2.

5. The combination as claimed in one of claims 1 to 4, in which the **AVE8062** or the **AVE8062** salt and the docetaxel are administered by perfusion.

6. A combination intended to be administered to a patient during a cycle comprising an administration of **AVE8062** or of an **AVE8062** salt that marks the start of the cycle, then an administration of docetaxel, characterized in that the **AVE8062** or the **AVE8062** salt is administered first, then on a different day of the week, preferably after an interval of 24 hours, the docetaxel is administered, the doses of **AVE8062** and of docetaxel being as defined in one of claims 1 to 4.

7. The combination as claimed in claim 6, characterized in that the cycle is repeated, the interval between two administrations of **AVE8062** or of the **AVE8062** salt ranges from 1 to 4 weeks, preferably 3 weeks.

8. The combination as claimed in one of claims 1 to 7, for treating a solid tumor.

9. The combination as claimed in claim 8, in which the solid tumor is not a solid breast tumor.

10. The combination as claimed in claims 1 to 7, for treating breast cancer, ovarian cancer, esophageal cancer, pancreatic cancer, cancer of the muscle tissue or of the soft tissue, head/neck cancer, bladder cancer, liver cancer, prostate cancer, ovarian cancer or skin cancer.

11. The use of **AVE8062** or of an **AVE8062** salt and of docetaxel for the preparation of an antitumor combination as defined in one of claims 1 to 10.

12. The use of **AVE8062** or of an **AVE8062** salt for the preparation of an antitumor combination as defined in one of claims 1 to 10.