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(54) **Title**: ANTITUMOUR COMBINATION COMPRISING OMBRABULIN AND CETUXIMAB, ASSOCIATED WITH RADIOTHERAPY

(57) **Abstract**: The invention relates to an antitumour pharmaceutical combination comprising ombrabulin or AVE8062, which may be in the form of a base or in the form of a pharmaceutically acceptable salt, and cisplatin, for use thereof as an antitumour agent intended for patients who are also treated with radiotherapy, in particular suffering from cancers and even more particularly suffering from solid tumours.

ANTITUMOUR COMBINATION COMPRISING OMBRABULIN AND CETUXIMAB, ASSOCIATED WITH RADIOTHERAPY

The present invention relates to a combination therapy for treating cancer, in particular involving solid tumours, implementing a coadministration of ombrabulin, of cetuximab and of radiotherapy.

[Prior art]

Combinations including ombrabulin or AVE8062 are described in the patent documents below:

- WO 2007/077309 describes the combination of AVE8062 and VEGF Trap (or aflibercept), an agent which prevents tumour angiogenesis.

- WO 99/51246 describes the combination of AVE8062 and platinum salts.

- WO 2004/037258 describes the combination of AVE8062 and various antitumour agents chosen from taxanes, including taxol and taxotere, alkylating agents such as cyclophosphamide, or ifosfamide, antimetabolites such as 5-FU or cytarabine, epidophyllotoxin, antibiotics, including doxorubicin, and also vinca alkaloids.

- EP 1407784 describes the combination of AVE8062 with dexamethasone.

- WO 2010/128259 describes an antitumour combination comprising AVE8062 and sorafenib.

- WO 2009/103076 describes a combination comprising a tumour vascular disrupting agent (VDA) and a small molecule which inhibits receptor tyrosine kinases (RTKs).

Moreover, the document Katsuyoshi Hori *et al. "Tumor blood flow interruption after radiotherapy strongly inhibits tumor regrowth"*, Japanese Cancer Association July 2008, describes the combination of ombrabulin with radiotherapy, the ombrabulin possibly being advantageously administered after the irradiation.

On the EMEA website, the Summary of Product Characteristics for the product cetuximab, sold under the brand Erbitux® (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000558/WC500029119.pdf) indicates that cetuximab can be

combined with other anticancer treatments such as radiotherapy and platinum-salt-based chemotherapy.

[Brief description of the invention]

The invention relates to a combination therapy for treating cancer, in particular involving solid tumours.

The invention relates more particularly to a pharmaceutical combination comprising ombrabulin or AVE8062 in the form of a base or in the form of a pharmaceutically acceptable salt, and cetuximab, for use thereof as an antitumour agent intended for patients who are also treated with radiotherapy, in particular suffering from cancers and even more particularly suffering from solid tumours.

The administration of ombrabulin, of cetuximab and of radiotherapy can be separate, simultaneous or spread out over time.

The invention also relates to the use of ombrabulin or AVE8062 and of cetuximab for preparing an antitumour combination intended for treating patients who are also treated with radiotherapy, in particular patients suffering from cancers and even more particularly suffering from solid tumours.

It also relates to the use of ombrabulin or AVE8062 and of cetuximab for preparing an antitumour combination intended to be administered in association, simultaneously, separately or spread out over time, with radiotherapy.

It also relates to the use of ombrabulin or AVE8062 and of cetuximab for preparing a medicament intended to be used simultaneously, separately or spread out over time, with radiotherapy, for treating cancer and more particularly solid tumours.

According to another aspect, the present invention relates to a pharmaceutical combination comprising ombrabulin or AVE8062 in the form of a base or in the form of a pharmaceutically acceptable salt, and cetuximab, for separate administration, administration spread out over time or simultaneous administration to patients who are also treated with radiotherapy, in particular patients suffering from cancers and even more particularly suffering from solid tumours.

According to yet another aspect, the present invention relates to a pharmaceutical combination comprising ombrabulin or AVE8062 in the form of a base or

in the form of a pharmaceutically acceptable salt, and cetuximab, for use thereof as an antitumour agent, said combination being administered in association with radiotherapy.

The combination, which, in the context of the present invention, means the combination of ombrabulin or AVE8062 in the form of a base or in the form of a pharmaceutically acceptable salt and of cetuximab, comprises an effective amount of ombrabulin or AVE8062 and an effective amount of cetuximab. The radiotherapy is also administered at an effective dose.

[Description of the invention]

Definitions

- pharmaceutically acceptable acid: organic or inorganic acid exhibiting low toxicity (see "Pharmaceutical salts" J.Pharm.Sci. 1977, 66, 1-19);
- effective amount: amount of a pharmaceutical compound which produces an effect on the tumour treated;
- effective dose: dose of radiotherapy which produces an effect on the tumour treated;
- the separate administration, simultaneous administration or administration spread out over time of a medicinal combination means that the elementary constituents of the combination, and in the present case, including the ionizing radiations, can be administered at the same time, each in one go at distinct moments, or repeatedly, or else at different moments, in particular during cycles. The elementary constituents can, in order to do this, be formulated as mixtures, only if they are administered simultaneously, or else formulated separately for the other administration schemes.

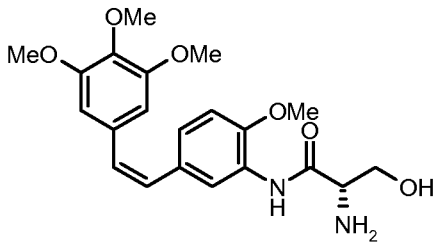
The inventors have in fact noted that the triple administration of ombrabulin, of cetuximab and of radiotherapy produces antitumour effects which are enhanced in comparison with those obtained by means of monotherapy with ombrabulin alone, or else by means of bitherapy with ombrabulin and cetuximab, ombrabulin and radiotherapy or cetuximab and radiotherapy, as attested to by the results discussed in the experimental section.

Ombrabulin

Ombrabulin or AVE8062 can be in the form of a base or in the form of a pharmaceutically acceptable acid salt.

Among the salts, mention may be made of the hydrochloride, acetate, phosphate or methanesulfonate.

Ombrabulin or AVE8062 has the formula:

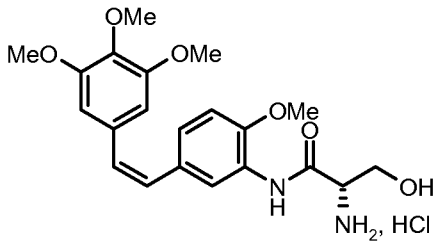


(Z isomer)

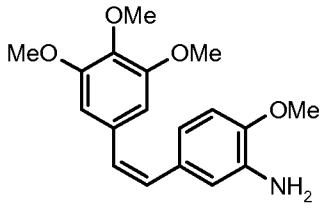
It is a tumour vascular disrupting agent (or VDA).

Its chemical name is: (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide. This compound, which is described in EP 31085 B1, can be prepared according to the process described in WO 03/084919.

More particularly, ombrabulin or AVE8062 can be administered in the form of a base (cf. formula above) or in the form of a pharmaceutically acceptable acid salt, for example in the form of the hydrochloride, represented below:



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



Cetuximab

Cetuximab is sold under the brand Erbitux®. It is a chimeric monoclonal antibody which binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). It is composed of the Fv region of a murine anti-EGFR antibody and of the human IgG1 constant regions (heavy and kappa chains). It is produced by cell culture of a murine myeloma.

The EGFR signalling pathways are involved in the control of cell survival, of cell cycle progression, of angiogenesis, of migration, of cell invasion and of the metastatic potential of cells. Cetuximab blocks the binding of the endogenous ligands of the EGFR, resulting in an inhibition of the function of the receptor.

Combination and administration scheme

As regards the combination, according to one particular embodiment, said combination can be in the form of a unit pharmaceutical preparation.

Alternatively, according to another particular embodiment, said combination can consist in combining ombrabulin or AVE8062 and cetuximab in the form of two pharmaceutical preparations. In other words, the combination can be in the form of a combination kit or product.

The pharmaceutical combination of ombrabulin and cetuximab can in particular take the form of a kit comprising:

(i) ombrabulin or AVE8062 in the form of a base or of a pharmaceutically acceptable salt in a first galenical formulation, and

(ii) cetuximab in a second galenical formulation.

The combination can be administered repeatedly over the course of several cycles according to a protocol which 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.). The protocol can be determined by any practitioner specializing in oncology.

According to one particular embodiment, the present invention relates to a pharmaceutical kit, in particular intended for treating cancer and more particularly solid tumours, comprising:

(i) a first galenical formulation comprising ombrabulin or AVE8062 in the form of a base or of a pharmaceutically acceptable salt,

(ii) a second galenical formulation comprising cetuximab,

the two galenical formulations (i) and (ii) being intended to be administered separately, simultaneously or spread out over time with respect to one another, of use for a joint administration of radiotherapy, the two galenical formulations (i) and (ii) being intended to be administered independently of one another, separately, simultaneously or spread out over time with respect to said administration of radiotherapy.

According to another of its aspects, the present invention relates to a pharmaceutical kit, in particular intended for treating cancer and more particularly solid tumours, comprising:

(i) a first galenical formulation comprising ombrabulin or AVE8062 in the form of a base or of a pharmaceutically acceptable salt,

(ii) a second galenical formulation comprising cetuximab,

the two galenical formulations (i) and (ii) being intended to be administered separately, simultaneously or spread out over time with respect to one another, said kit being administered in association with radiotherapy, the radiotherapy being itself intended to be administered separately, simultaneously or spread out over time with said kit.

Radiotherapy is a method of locoregional treatment of cancers, using radiation to destroy the cancer cells by blocking their ability to multiply.

Radiotherapy, in the context of the present invention, consists in particular of the therapeutic use of ionizing radiation. Said radiotherapy and the associated ionizing radiation are those commonly used and known to those skilled in the art.

Radiotherapy includes in particular the use of ionizing radiation, for example γ-rays, X-rays and/or radiation emanating from radioisotopes. In the context of the present invention, it is more particularly X-ray radiation.

Thus, the combination may be intended to be administered to a patient over the course of a cycle that can range from 1 to 4 weeks, more particularly 3 weeks. The cycle defines the interval between the beginning and the end of an administration scheme for the combination in accordance with the present invention. For example, this cycle comprises an administration of ombrabulin or AVE8062, and three administrations of

cetuximab. The administration of the ombrabulin and of the first dose of cetuximab may be simultaneous or at different times. For example, the first dose of cetuximab may be delayed by one or two days after the administration of ombrabulin, the taking of which starts the duration of the cycle. When the cycle takes three weeks, cetuximab can be administered in three intakes, with one week between intakes.

The radiotherapy may, for its part, be administered in fractionated form during one or more cycles such as defined above.

The radiotherapy may in particular be administered at a rate of one daily irradiation, 5 days out of 7, for 7 weeks.

The administration mode may be the parenteral route and/or the oral route and depends on the galenical form used for the antitumour agent.

Via the parenteral route, the antitumour agent may be administered intravenously, as a bolus or prepared in an intravenous drip bag, with pharmaceutically acceptable vectors by means of various methods known to those skilled in the art.

According to one particular embodiment, the ombrabulin or AVE8062 is administered parenterally, such as by intravenous administration, as a bolus or by drip, and the cetuximab is administered parenterally, such as the intravenous route.

One galenical form of ombrabulin or AVE8062 which is suitable for the parenteral route is that in which the ombrabulin or AVE8062 is in solution in water. One galenical form of cetuximab which is suitable for the intravenous route is, for example, that sold under the brand Erbitux® in the form of a drip solution.

Thus, according to one of its aspects, the invention relates to a combination as defined previously, suitable for parenteral administration, and more particularly suitable for administration of the ombrabulin or AVE8062 intravenously, as a bolus or by drip and for administration of the cetuximab intravenously.

The doses of AVE8062 and of cetuximab administered each time to a patient depend on various parameters, such as the nature and stage of the cancer to be treated, and also on the patient to be treated (age, weight, previous treatment(s), etc.). The AVE8062 can be administered once every 3 weeks at a tolerated dose of between 5 and 60 mg/m^2 of

body surface (dose defined for each administration). The cetuximab can be administered, for its part, at a tolerated dose of between 250 and 400 mg/m^2 of body surface (dose defined for each administration).

The radiotherapy doses depend on the type of tumour and can range from 45 to more than 75 gray (Gy), more specifically from 50 to 60 Gy, over the total duration of the treatment. The doses may, for example, be 10 Gy per week at a rate of five sessions of 2 Gy per day.

The combination can be effective in the treatment of cancers, more particularly of solid tumours in general, preferentially in the treatment of head and neck cancer, lung cancer, cervical cancer or stomach cancer.

The present application also relates to a method for prevention or therapeutic treatment of cancers and more particularly solid tumours, consisting in administering to patients, in need thereof, an effective amount of ombrabulin or AVE8062, an effective amount of cetuximab and an effective dose of radiotherapy, it being possible for their administration to be carried out separately, simultaneously or spread out over time.

The example hereinafter illustrates the invention without limiting the scope thereof.

Example

The efficacy of a combination in coadministration with radiotherapy can be demonstrated in preclinical animal models.

In these trials on mice, the antitumour activity can be determined in accordance with various parameters, such as the dose (in mg/kg), the administration mode, the administration time, the toxicity, the change in tumour weight in the treated group compared with the control group on a given day (%△T/△C), the median percentage of tumour regression on a given day, the median delay in reaching (T-C) a target tumour weight in the treated group (T) compared with the control group (C), and the number of partial tumour regressions (PR = regression of 50% of the initial tumour size) and complete tumour regressions (CR = regression below the palpation threshold). In the

experimental trials described hereinafter, an antitumour activity is declared for $\triangle T/\triangle C < 40\%$.

The antitumour activity on solid tumours is determined experimentally in the following way: the animals subjected to the experiment are NMRI female mice which are subcutaneously inoculated unilaterally with 3 million cells of the FaDu tumour line originating from a human hypopharyngeal tumour, on day 0. This tumour, representative of head and neck squamous cell carcinomas, is sensitive to cetuximab and to irradiation. The animals, bearing tumours having reached a tumour size previously defined and greater than 100 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.

Generally, the chemotherapy begins from 3 to 22 days after the graft, depending on the type of tumour and the tumour size desired. The animals are observed and weighed every day. A dose which induces a weight loss of 20% or more on the day the weight loss is at a maximum (nadir - mean of the group) or a mortality of 10% or more is considered to be toxic. The tumours are measured two or three times per week until they reach approximately 2 g or until the animal dies if that occurs before the tumour reaches 2 g. The animals are autopsied when they are sacrificed.

In the context of the studies which follow, the ombrabulin or AVE8062 in hydrochloride form is formulated in water with 0.9% NaCl. The cetuximab is formulated in a calcium- and magnesium-free phosphate buffer, at pH 7.4. The locoregional radiotherapy is carried out at a dose rate of 0.35 Gy/min.

In this study, in which the tumours are treated at an advanced stage, the ombrabulin or AVE8062 was administered intravenously, at a sub-optimal dose, on days 15 and 19 following tumour implantation. The cetuximab was administered intraperitoneally, at a sub-optimal dose, on the same days. The animals were irradiated at a sub-optimal dose on days 15 and 19. In the combination groups, the same schemes and doses as those used for the agents alone were repeated, with treatment of the animals on days 15 and 19. The combination of the two chemotherapy agents is performed 5 hours apart (cetuximab administered first). In the groups treated with cetuximab and irradiated, the radiotherapy is performed 4 hours after the administration of the cetuximab. In the groups treated with ombrabulin or AVE8062 and irradiated, the animals receive the ombrabulin or AVE8062 one hour after irradiation.

The loss of body weight is reported for each group on the day it reaches its nadir. The change in tumour weight in the treated group compared with the control group and also the median regression percentage are reported 7 days after the final treatment (D26) and the delay in reaching a target tumour weight of 1000 mg is calculated. The statistical studies compare the tumour volumes in the treated groups compared with the control group (for the irradiation alone), compared with the chemotherapy agents alone (for the combinations in doublet) or compared with the doublets (for the triple combination). The benefit of the combinations is evaluated over a period of 21 days after the end of the treatment (up to D40).

Table I gives the experimental results of the study. The tumour doubling time was approximately 8 days. The median tumour weight at the beginning of the treatments was from 308 to 456 mg, the control having reached a tumour weight of 1000 mg 23.2 days after the tumour graft.

Agents alone:

The dose tested for AVE8062 is 36 mg/kg per injection, i.e. a total dose of 72 mg/kg. At this dose, AVE8062 is marginally active with a median %△T/△C of 37% and one partial regression (14% PR). The delay in growth compared with the control group is 4.8 days.

Cetuximab is tested at the dose of 20 mg/kg per administration, i.e. a total dose of 40 mg/kg. At this dose, cetuximab is active with a median %△T/△C of 23.8%, no tumour regression (0% PR) and a delay in growth of 12.2 days.

The irradiation at the dose of 3 Gy per session, i.e. a total dose of 6 Gy, exhibits a marginal antitumour activity with a median %△T/△C of 36.8%, no tumour regression (0% PR) and a delay in growth of 7.0 days.

Combinations of the agents in pairs at the same doses:

AVE8062 combined with radiotherapy is highly active with a negative median %△T/△C, a median tumour regression of 16%, and two partial tumour regressions (29% PR). The delay in tumour growth in this group is 13.8 days.

Cetuximab combined with radiotherapy is also highly active with a negative median %△T/△C of 0.1%, but no partial tumour regression (0% PR). The delay in tumour growth in this group is 13.3 days.

Finally, AVE8062 combined with cetuximab is highly active with a negative median at %△T/△C and a median tumour regression of 42%. Five animals out of eight exhibit a partial regression (62% PR), none exhibiting complete tumour regression (0% CR). The delay in tumour growth in this group reaches 18.2 days.

Combinations of the three agents at the same doses:

The triple combination of AVE8062, cetuximab and irradiation shows the maximum antitumour activity in this study. The treatment is highly active with a negative median %△T/△C and a median tumour regression of 50%. Four animals out of seven exhibit a partial tumour regression (57% PR) and one animal exhibits complete tumour regression (14% CR). The delay in tumour growth in this group reaches 23.3 days.

All the treatments are well tolerated, with a maximum weight loss of 7.1% for the group receiving AVE8062 combined with radiotherapy.

Table II shows the statistical analysis of the results of the study. The statistical analysis relating to the tumour volumes, shows that:

the irradiated group differs significantly from the control group ($p<0.0001$),

the double combinations of chemotherapy with radiotherapy are significantly different from the chemotherapies with agent alone ($p<0.0001$),

the combination of the two chemotherapies is statistically different from each of the chemotherapies with agent alone ($p<0.0001$),

the triple combination is statistically different from the three double combinations tested (from $p<0.0003$ to $p=0.0208$), making it possible to conclude that there is therapeutic synergy.

In conclusion, the combination of AVE8062 with cetuximab and radiotherapy induces partial tumour regressions, also observed in the double combinations containing AVE8062, and a complete tumour regression, only observed in this treatment group. The delay in growth for the triple combination is greater than that observed in the double combinations, making the triple combination the best arm of treatment in this study. The combination of AVE8062 with cetuximab and radiotherapy therefore confers a statistically significant therapeutic advantage in an experimental model of head and neck tumour.

Table I. Evaluation of AVE8062 in combination with cetuximab and radiotherapy on NMRI female mice bearing the FaDu head and neck squamous cell carcinoma: experimental results

Agent	Route / injection volume in ml/kg	Dose in mg/kg per injection (total dose)	Scheme in days	Treatment-related mortality	%bwc at the nadir (day of the nadir)	Median %△T/△C at day 26	Median % regression at day 26	Median day for reaching 1000 mg	T-C in days	Tumour regression		Comments
										Partial	Complete	
AVE8062	IV 11ml/kg	36.0 (72.0)	15, 19	0/7	1.7 (22)	37.0	-	28.0	4.8	1/7	0/7	Marginal activity
Cetuximab	IP 4ml/kg	20.0 (40.0)	15, 19	0/7	1.9 (22)	23.8	-	35.4	12.2	0/7	0/7	Active
IR		3 Gy (6 Gy)	15, 19	0/8	4.8 (22)	36.8	-	30.2	7.0	0/8	0/8	Marginal activity
Cetuximab	IP 4ml/kg	20.0 (40.0)	15, 19	0/8	2.0 (22)	<0	42	41.4	18.2	5/8	0/8	Highly active
AVE8062	IV 11ml/kg	36.0 (72.0)	15, 19									
Cetuximab	IP 4ml/kg	20.0 (40.0)	15, 19	0/7	1.1 (22)	0.1	-	36.5	13.3	0/7	0/7	Highly active
IR		3 Gy (6 Gy)	15, 19									
IR		3 Gy (6 Gy)	15, 19	0/7	7.1 (22)	<0	16	37.0	13.8	2/7	0/7	Highly active
AVE8062	IV 11ml/kg	36.0 (72.0)	15, 19									
Cetuximab	IP 4ml/kg	20.0 (40.0)	15, 19	0/7	4.7 (22)	<0	50	46.5	23.3	4/7	1/7	Highly active
IR		3 Gy (6 Gy)	15, 19									
AVE8062	IV 11ml/kg	36.0 (72.0)	15, 19									
Control					2.5 (26)			23.2		0/7	0/7	

Tumour doubling time ~ 8 days. Median tumour weight at the beginning of treatments = 308 - 456 mg. Treatment duration: cetuximab = 5 days, AVE8062 = 5 days.
Formulation: AVE8062 in water with 0.9% NaCl; cetuximab in a calcium- and magnesium-free phosphate buffer at pH 7.4
Abbreviations: bwc = body weight change, △T/△C = change in tumour weight in the treated group compared with the control group, T-C = delay in reaching the target tumour weight in the treated group compared with the control group, IV = intravenous route, IP = intraperitoneal route

Table II. Evaluation of AVE8062 in combination with cetuximab and radiotherapy on NMRI female mice bearing the FaDu head and neck squamous cell carcinoma: statistical analysis

Agents	Median %△T/△C (median % regression) at day 26	Statistics on tumour volumes [(a)]					
		control	AVE8062	Cetuximab	Cetuximab + AVE8062	Cetuximab + IR	IR + AVE8062
AVE8062	37.0 (-)						
Cetuximab	23.8 (-)						
IR	36.8 (-)	<0.0001					
Cetuximab + AVE8062	<0 (42)		<0.0001	<0.0001			
Cetuximab + IR	0.1 (-)			<0.0001			
IR + AVE8062	<0 (16)		<0.0001				
Cetuximab + IR + AVE8062	<0 (50)				0.0208	0.0010	0.0003

(a) Three-way analysis of variance followed by contrast analysis with Bonferroni-Holm correction, related back to the group specified in the title of the column. A probability of less than 5% (p-value<0.05) is considered to be statistically significant.

CLAIMS

1. Pharmaceutical combination comprising ombrabulin or AVE8062 in the form of a base or in the form of a pharmaceutically acceptable salt, and cetuximab, for use thereof as an antitumour agent intended for patients who are also treated with radiotherapy.

2. Combination according to Claim 1, in which the ombrabulin or AVE8062 is in hydrochloride, acetate, phosphate or methanesulfonate form.

3. Combination according to either one of Claims 1 and 2, in which the administration of ombrabulin or AVE8062, of cetuximab and of radiotherapy is simultaneous, separate or spread out over time.

4. Combination according to either of Claims 1 and 2, intended to be administered to a patient over the course of a cycle comprising an administration of ombrabulin, three administrations of cetuximab and a cycle of radiotherapy, characterized in that the combination is administered at different times or concomitantly.

5. Combination according to Claim 4, in which the cycle is repeated, the interval between two administrations of ombrabulin ranging from 1 to 4 weeks.

6. Combination according to any one of Claims 1 to 5, in which the ombrabulin or AVE8062 and cetuximab are administered parenterally.

7. Combination according to Claim 6, in which the ombrabulin or AVE8062 is administered intravenously, as a bolus or by drip, and the cetuximab is administered intravenously.

8. Combination according to any one of Claims 1 to 7, intended for the treatment of patients suffering from solid tumours.

9. Combination according to any one of Claims 1 to 8, intended for the treatment of patients suffering from head and neck cancer, lung cancer, cervical cancer or stomach cancer.

10. Pharmaceutical combination comprising ombrabulin or AVE8062 in the form of a base or in the form of a pharmaceutically acceptable salt, and cetuximab, for separate administration, administration spread out over time or simultaneous

administration to patients who are also treated with radiotherapy, in particular patients suffering from cancers and even more particularly suffering from solid tumours.

11. Pharmaceutical kit, in particular intended for treating cancer and more particularly solid tumours, comprising:

(i) a first galenical formulation comprising ombrabulin or AVE8062 in the form of a base or of a pharmaceutically acceptable salt,

(ii) a second galenical formulation comprising cetuximab,

the two galenical formulations (i) and (ii) being intended to be administered separately, simultaneously or spread out over time with respect to one another, of use for a joint administration of radiotherapy, the two galenical formulations (i) and (ii) being intended to be administered independently of one another, separately, simultaneously or spread out over time with respect to said administration of radiotherapy.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/053881

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/167 A61K39/395 A61K9/00 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, WPI Data, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/209496 A1 (CHAPLIN DAVID [GB] ET AL) 20 August 2009 (2009-08-20) cited in the application page 1, paragraphs 5, 7, 9, 21 - page 2 page 6, paragraph 71 page 8, paragraphs 98, 100 page 11, paragraph 123 page 12, paragraphs 129, 138 ----- -/--	1-11

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 October 2012	25/10/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Houyvet-Landriscina

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BONNER JAMES A ET AL: "Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.", THE NEW ENGLAND JOURNAL OF MEDICINE 9 FEB 2006 LNKD- PUBMED:16467544, vol. 354, no. 6, 9 February 2006 (2006-02-09), pages 567-578, XP002680334, ISSN: 1533-4406 the whole document	1-11

Y	SHIBUYA ET AL: "Targeted Therapy Against VEGFR and EGFR With ZD6474 Enhances the Therapeutic Efficacy of Irradiation in an Orthotopic Model of Human Non-Small-Cell Lung Cancer", INTERNATIONAL JOURNAL OF RADIATION: ONCOLOGY BIOLOGY PHYSICS, PERGAMON PRESS, USA, vol. 69, no. 5, 20 November 2007 (2007-11-20), pages 1534-1543, XP022354203, ISSN: 0360-3016, DOI: 10.1016/J.IJROBP.2007.07.2350 abstract	1-11

Y	MAGNE ET AL: "Donnees actuelles des associations chimioradiotherapeutiques et place potentielle des therapies ciblees dans les cancers du col uterin", CANCER RADIOTHERAPIE, ELSEVIER, PARIS, FR, vol. 12, no. 1, 15 January 2008 (2008-01-15), pages 31-36, XP022510158, ISSN: 1278-3218, DOI: 10.1016/J.CANRAD.2007.11.008 abstract page 33, column 2	1-11

Y	CHARGARI C ET AL: "Etat des lieux des associations chimioradiotherapeutiques et place potentielle des therapies ciblees dans les cancers bronchiques non a petites cellules", CANCER RADIOTHERAPIE, ELSEVIER, PARIS, FR, vol. 13, no. 2, 1 April 2009 (2009-04-01), pages 114-122, XP025977246, ISSN: 1278-3218, DOI: 10.1016/J.CANRAD.2008.08.273 [retrieved on 2009-01-20] the whole document page 117, column 2	1-11

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/053881

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATTERSON ET AL: "Vascular Damaging Agents", CLINICAL ONCOLOGY, W.B. SAUNDERS, AMSTERDAM, NL, vol. 19, no. 6, 2 July 2007 (2007-07-02), pages 443-456, XP022137687, ISSN: 0936-6555, DOI: 10.1016/J.CLON.2007.03.014 abstract page 447 - page 449 -----	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/053881

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009209496 A1	20-08-2009	US 2009209496 A1	20-08-2009
		WO 2009103076 A1	20-08-2009