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(54) Title: COMBINATION COMPRISING EVEROLIMUS AND AMCENESTRANT

(57) Abstract: Herein are provided a combination of everolimus and of amcenestrant or a pharmaceutically acceptable salt thereof, a pharmaceutical composition containing such a combination, and the therapeutic uses thereof, in particular for the treatment of cancer, including breast cancer.



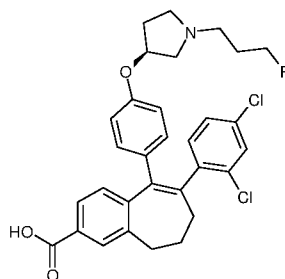
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## COMBINATION COMPRISING EVEROLIMUS AND AMCENESTRANT

Herein are provided a combination of everolimus and amcenenstrant, a pharmaceutical composition containing such combination, and the therapeutic uses of such combination and pharmaceutical composition, in particular for the treatment of cancer.

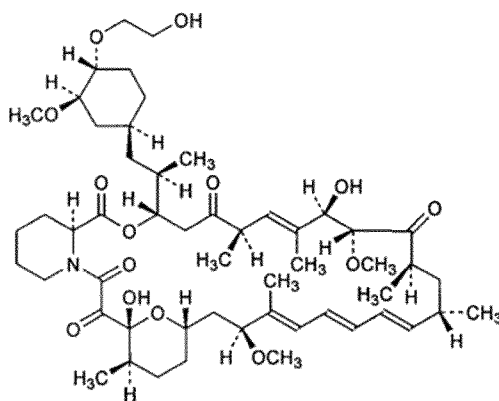
The estrogen receptor  $\alpha$  (ESR1) is expressed in the majority of breast tumors, enabling them to respond to the mitogenic actions of estrogens.

Amcenenstrant, INN name for the compound 6-(2,4-dichlorophenyl)-5-[4-[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxyphenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (also known by its laboratory code SAR439859), is a selective estrogen receptor degrader (SERD) which is an estrogen receptor antagonist and accelerates the proteasomal degradation of the estrogen receptor. This compound is disclosed in the patent application WO 2017/140669:



15

Everolimus (INN name) is an inhibitor of mammalian target of rapamycin (mTOR). It has the following formula:



20

Everolimus is a marketed drug, with AFINITOR<sup>®</sup> as one of its tradenames. It is indicated in several oncology settings. In breast cancer, everolimus is indicated for the treatment of postmenopausal women with advanced hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole (FDA label).

There is always a need to find new antitumoral treatments. Now, it is shown herein that a combination of amcenestrant with everolimus demonstrates significant anti-tumor efficacy, and induces tumor regression, with a synergistic effect compared to each of the active  
5 ingredient alone.

Herein is provided a combination comprising amcenestrant and everolimus.

In the combination provided herein, amcenestrant may exist not only in the form of a  
10 zwitterion (i.e., a globally neutral molecule having an acid group and a basic group), but also in the form of addition salts with acids or bases. Such addition salts may be used in the above combination. Hence, herein is provided a combination comprising amcenestrant, or a pharmaceutically acceptable salt thereof, and everolimus.

In an embodiment, the combination of amcenestrant, or a pharmaceutically acceptable  
15 salt thereof, with everolimus shows therapeutic synergy. A combination demonstrates therapeutic synergy if its therapeutic effect is superior compared to the cumulative effect of either active agent of the combination alone.

In another embodiment, amcenestrant, or a pharmaceutically acceptable salt thereof,  
20 and everolimus are administered orally.

Provided herein is also a combination of amcenestrant, or a pharmaceutically  
acceptable salt thereof, and everolimus for its use as a medicament.

25

Provided herein is also a pharmaceutical composition comprising amcenestrant, or a  
pharmaceutically acceptable salt thereof, and everolimus, as well as at least one  
pharmaceutically acceptable excipient.

The excipients are selected from the customary excipients which are known to a person  
30 skilled in the art. More particularly, the excipients are selected from those useful for oral administration in whatever form (liquid solution, dispersion or suspension, tablets, capsules, or the like).

In another embodiment, amcenestrant, or a pharmaceutically acceptable salt thereof,  
35 and everolimus may be administered simultaneously, separately, or spaced out over a period

of time (sequential administration). Therefore, the combination and pharmaceutical composition provided herein are not exclusively limited to the ones which are obtained by physical association of the constituents in a single unit dosage, but also to those which allow a separate administration, which can be simultaneous or sequential (also called “spaced out” or “spread out”) over a period of time.

Herein is also provided a pharmaceutical kit which comprises:

- (i) a first pharmaceutical composition comprising amcnestrant, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient;
- (ii) a second pharmaceutical composition comprising everolimus, and at least one pharmaceutically acceptable excipient;

wherein the first pharmaceutical composition and the second pharmaceutical composition are in separate compartments and are intended to be independently administered, each administration with regards to the other one being simultaneous or spaced out (sequential) over time.

In the combinations, pharmaceutical compositions and pharmaceutical kit described above, amcnestrant, or a pharmaceutically acceptable salt thereof, and everolimus are advantageously present at effective doses, adapted considering the treated pathology and the condition of the patient to which the combination is administered. In particular, for everolimus the recommended dose for adult patients is 10 mg once daily, taken orally.

Herein is also provided a combination comprising amcnestrant, or a pharmaceutically acceptable salt thereof, and everolimus, as well as a pharmaceutical composition and kit as described above, for use in the treatment of cancer.

Herein is also provided amcnestrant or a pharmaceutically acceptable salt thereof for use in the treatment of cancer by co-administration with everolimus.

Herein is also provided everolimus for use in the treatment of cancer by co-administration with amcnestrant or a pharmaceutically acceptable salt thereof.

Co-administration is understood herein as an administration of the active ingredients to a patient in need thereof, which is separated, simultaneous or spaced out (sequential) over time, with respect to each of the active ingredients.

In some embodiments, amcnestrant, or a pharmaceutically acceptable salt thereof, and everolimus are administered in a therapeutically effective amount. A "therapeutically effective amount" means the amount of an active ingredient or combination of active ingredients that, when administered to a patient for treating a disease, is sufficient to affect such treatment for the disease. The "therapeutically effective amount" will vary depending on the disease and its severity and the age, weight, etc., of the subject to be treated.

In some embodiments, amcnestrant, or a pharmaceutically acceptable salt thereof, and everolimus are administered in an amount to show therapeutic synergy.

In another embodiment, the cancer is a hormone dependent cancer.

In another embodiment, the cancer is an estrogen receptor dependent cancer, particularly the cancer is an estrogen receptor  $\alpha$  dependent cancer.

Herein is also provided a method of treating the pathological conditions indicated above, particularly breast cancer, comprising administering to a subject in need thereof a therapeutically effective amount of amcnestrant, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of everolimus.

Herein is also provided a method of treating the pathological conditions indicated above, particularly breast cancer, comprising administering to a subject in need thereof a pharmaceutical composition or a pharmaceutical kit as described above.

Herein is also provided a method of treating the pathological conditions indicated above, particularly breast cancer, comprising administering to a subject in need thereof a combination as described above.

Herein is also provided a method of treating the pathological conditions indicated above, particularly breast cancer, comprising co-administering to a subject in need thereof amcnestrant or a pharmaceutically acceptable salt thereof and everolimus. In said method, amcnestrant, or a pharmaceutically acceptable salt thereof, is administered with everolimus either separately, simultaneously or spaced out over time.

Herein is also provided a method of treating the pathological conditions indicated above, particularly breast cancer, comprising co-administering to a subject in need thereof everolimus and amcenestrant, or a pharmaceutically acceptable salt thereof. In said method, everolimus is administered with amcenestrant, or a pharmaceutically acceptable salt thereof, either separately, simultaneously or spaced out over time.

Herein is also provided a method of treating cancer comprising administering to a patient in need thereof a therapeutically effective amount of amcenestrant or a pharmaceutically acceptable salt thereof in combination with a therapeutically effective amount of everolimus.

Herein is also provided a method of treating cancer in a patient who is on therapy with compound amcenestrant, or a pharmaceutically acceptable salt thereof, comprising administering to said patient an effective amount of everolimus.

Herein is also provided a method of treating cancer in a patient on stable treatment with compound amcenestrant, or a pharmaceutically acceptable salt thereof, comprising administering to said patient a therapeutically effective amount of everolimus.

Herein is also provided a method of treating cancer comprising administering to a patient in need thereof a therapeutically effective amount of compound everolimus, wherein said patient is also on therapy with amcenestrant or a pharmaceutically acceptable salt thereof.

In an embodiment of the methods described above, the subject is a mammal. In another embodiment, the subject is a human.

Herein is also provided a combination comprising amcenestrant, or a pharmaceutically acceptable salt thereof, and everolimus for the manufacture of a medicament useful in treating the pathological conditions indicated above, particularly breast cancer.

Herein is also provided the use of amcenestrant, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament useful in treating the pathological conditions indicated above, particularly breast cancer, by co-administration with everolimus.

Herein is also provided the use of everolimus in the manufacture of a medicament useful in treating the pathological conditions indicated above, particularly breast cancer, by co-administration with amcenestrant or a pharmaceutically acceptable salt thereof.

- 5           Herein is also provided an article of manufacture, a packaging, or an administration unit, comprising:
- a packaging material;
  - the above defined combination, pharmaceutical composition, or pharmaceutical kit;
- and
- 10           - a label or package insert contained within said packaging material, indicating that said combination, pharmaceutical composition or pharmaceutical kit is administered to a patient for the treatment of cancer.

The examples below show the pharmacological results obtained with amcenestrant, everolimus and their combination against a breast cancer cell line xenograft in NOD/SCID (nonobese diabetic/severe combined immunodeficiency) mice.

**Evaluation of the efficacy of amcenestrant combined with everolimus against a subcutaneous breast cancer cell line xenograft in female NOD/SCID mice**

20           In the present study, the anti-tumor efficacy of amcenestrant combined with everolimus was investigated after 28 days treatment against an orthotopic MCF7 human breast cancer cell line xenograft in female NOD/SCID mice.

The treated groups included amcenestrant at 10 mg/kg alone, everolimus at 10 mg/kg alone, and the combination of amcenestrant and everolimus at the same dose and regime.

For 28 days, amcenestrant was orally dosed twice a day (BID), and everolimus was orally dosed twice a week (BIW). Anti-tumor efficacy was evaluated by tumor volume measurement.

30

**1: Experimental procedure**

1-1: Animals, cell line, compounds

Female NOD/SCID mice were obtained from GemPharmatech Co.,Ltd (Nanjing University National Resource Center for Mutant Mice, Model Animal Research Center) (Nanjing, CHINA). Animals were allowed to acclimate for at least four days before the study

enrollment. Mice were 7 to 8 weeks old and weighed between 22.5 and 28.4 grams at the beginning of the treatments. These animals were housed under conditions outlined in the guidelines approved by the Institutional Animal Care and Use Committee (IACUC) of CrownBio following the guidance of the Association for Assessment and Accreditation of Laboratory  
5 Animal Care (AAALAC).

MCF7 cells were obtained from the American Type Culture Collection (ATCC® HTB-22™). The MCF7 tumor cells were maintained in vitro with MEM medium supplemented with 10% fetal bovine serum, 0.01mM non-essential amino acid, 0.01 mg/ml bovine insulin,  
10 and 2 mM L-glutamine at 37°C in an atmosphere of 5% CO<sub>2</sub> in air. The cells in exponential growth phase were harvested and quantitated by cell counter before tumor inoculation.

The mouse was subcutaneously implanted with estrogen pellets (0.18 mg/pellet, 17β-estradiol, Innovative Research of America, Sarasota, Florida, USA), hereafter referred to as  
15 “E2 supplement”, at the right flank one day before the tumor inoculation. Each mouse was inoculated with MCF-7 tumor cells (2 x 10<sup>7</sup>) in 0.25 ml of PBS/Matrigel (1:1) mixture at the right mammary fat pad for tumor development.

Everolimus (Manufacturer: Selleck; Lot number: S1120) was formulated in 30%  
20 propylene glycol (dissolve first): 5% Tween 80: 65% ddH<sub>2</sub>O (double distilled water).

Dose volume for amcenestrant and everolimus for oral administration: 10 ml/kg.

Doses: amcenestrant at 10 mg/kg and everolimus at 10 mg/kg in the above volume.

#### 25 1-2: Study design, end points

The animals required for experiment (plus extra) were pooled and implanted with MCF7 cells. On day 0 (12 days post implantation), the mice were pooled and randomly distributed to the treatment and control groups (10 mice per group), where median tumor volumes for each  
30 group was 119 mm<sup>3</sup>. Treatments of amcenestrant and everolimus were initiated on day 1. For 28 days, amcenestrant was orally administered at 10 mg/kg BID (8 hours apart), and everolimus was orally administered at 10 mg/kg BIW. Animal body weight was assessed daily.

The dosages are expressed in mg/kg and based on daily body weight per animal.  
35 Vehicle treated animals were used as controls. Mice were checked daily for adverse clinical reactions. Individual mice were weighed daily until the end of the experiment. Mice were

5 euthanized when morbid or weight loss  $\geq 20\%$  was observed. Tumors were measured with a caliper twice weekly until final sacrifice. When a tumor size reached approximately  $3000 \text{ mm}^3$  or when there were animal health issues (40% area of a tumor ulcerated), animals were euthanized, and date of death recorded. Solid tumor volumes were estimated from two-dimensional tumor measurements and calculated according to the following equation:

$$Tumor\ volume\ (mm^3) = \frac{length\ (mm) \times width^2\ (mm^2)}{2}$$

Toxicity end points:

10 A dosage producing either 15% body weight loss during 3 consecutive days for an individual mouse, 20% body weight loss during 1 day, or 10% or more drug related deaths were considered an excessively toxic dosage, unless under certain circumstances bodyweight loss or animal death could be considered non-drug related. Examples include E2 supplement related body weight loss and urine scalding, animal handling issues such as misgavage, tumor model related issues such as tumor induced cachexia leading to body weight loss that can be  
15 observed in control, or vehicle treated groups and excessive tumor ulceration. Mice that had non-drug related death or significant bodyweight loss were not considered toxic and were excluded from statistical analysis. Animal body weight included the tumor weight.

Efficacy end points:

20 The primary efficacy end points include tumor volume changes from baseline summarized by the ratio of medians of tumor volume changes from baseline between the treated and control groups ( $\Delta T/\Delta C$ ). Changes in tumor volume for each treated (T) and control (C) group were calculated for each animal on each day by subtracting the tumor volume on the day of first treatment (staging day) from the tumor volume on the specified observation  
25 day. The median  $\Delta T$  was calculated for the treated group and the median  $\Delta C$  was calculated for the control group. The ratio  $\Delta T/\Delta C$  was calculated and expressed as percentage:

$$\Delta T / \Delta C = \left( \frac{Median\ \Delta T}{Median\ \Delta C} \right) \times 100$$

30  $\Delta T/\Delta C \leq 40\%$  is considered as therapeutically active,  $\Delta T/\Delta C = 0\%$  is considered as tumor stasis, and  $\Delta T/\Delta C < 0\%$  is considered as tumor regression (very active).  $\Delta T/\Delta C > 40\%$  is considered as therapeutically inactive.

Percent tumor regression is defined as % (percentage) of tumor volume decrease in the treated group on a specified observation day compared to its volume when the study was initiated. At a specific time point (t) and for each animal, the regression percentage was calculated using the following formula:

$$5 \quad \% \text{ regression (at } t) = \left( \frac{\text{volume}_{t_0} - \text{volume}_t}{\text{volume}_{t_0}} \right) \times 100$$

The median percent regression for a group on a given day was then calculated by taking the median of individual % regression values calculated for each animal in the group. The day of calculation was determined by the day when  $\Delta T/\Delta C$  is calculated, except if median percent regression was not representative of the activity of the group. In this case, the day was determined by the first day when the median percent regression was maximal.

### 1-3: Statistical analysis

A two-way analysis of variance (ANOVA) with factors treatment and day (repeated) was performed on tumor volume changes from baseline. It was followed by contrast analyses with Bonferroni-Holm correction for multiplicity to compare all treated groups to the control group and to compare the combination *versus* each single agent at the dose involved in the combination at each day from day 4 to 28.

In the figures, the medians and Median Absolute Deviation (MAD) of each group are represented for each day of measurement.

In the tables, the medians and Normalized MAD ( $nMAD = 1.4826 * MAD$ ) of each group are reported for each day of measurement.

Tumor volume changes from baseline were calculated for each animal and each day by subtracting the tumor volume on the day of first treatment (day 0) from the tumor volume on the specified observation day.

All statistical analyses were performed using SAS version 9.2 software. A probability of less than 5% ( $p < 0.05$ ) was considered as significant.

## 2: Results

Amcenestrant at 10 mg/kg BID, everolimus 10 mg/kg BIW and the combination of amcenestrant and everolimus at the doses and regime for 28 days were tolerated, and no

drug-related body weight loss/animal death was observed in the study. But we observed E2 supplement-related significant body weight loss or death, which was excluded from data statistical analysis.

5 Amcenestrant at a dose of 10 mg/kg BID for 28 days had statistically significant anti-tumor efficacy with  $\Delta T/\Delta C$  value of -13% ( $p < 0.0001$ ) on day 28. Everolimus at a dose of 10 mg/kg BIW for 28 days induced statistically significant anti-tumor efficacy with  $\Delta T/\Delta C$  value of -17% ( $p < 0.0001$ ) on day 28. When amcenestrant at 10 mg/kg combined with everolimus 10 mg/kg with the same dose regime as BID for amcenestrant and BIW for everolimus, the  
10 combination treatment demonstrated statistically significant anti-tumor efficacy (tumor regression) with  $\Delta T/\Delta C$  value of -31% ( $p < 0.0001$ ) on day 28. The statistical analysis indicated that the combination effect was significantly different when compared to either amcenestrant alone or everolimus alone on day 28 ( $p < 0.0001$ ).

15 Detailed results are shown in Tables 1 to 3 below, as well as in Figures 1 and 2.

Brief description of the drawings:

- Figure 1: Antitumor activity of amcenestrant combined with everolimus against orthotopic human breast cancer cell line MCF7 xenograft in NOD/SCID mice: tumor volume  
20 evolution. The curves represent medians + or - MAD (Median Absolute Deviation) at each day for each group.

- Figure 2: Antitumor activity of amcenestrant combined with everolimus against orthotopic human breast cancer cell line MCF7 xenograft in NOD/SCID mice: tumor volume  
25 changes from baseline on day 28. Points represent individual tumor volume changes from baseline on day 28, bars correspond to medians.

From this experiment, it was concluded that amcenestrant at 10 mg/kg twice a day combined with the mTOR inhibitor everolimus at 10 mg/kg twice a week in MCF7 human breast  
30 cancer cell line xenograft model in NOD/SCID mice induced significant anti-tumor efficacy that was superior to single agents alone, and induced tumor growth inhibition and tumor regression.

**Table 1:** Efficacy of amcnestrant (SAR439859) combined with everolimus against orthotopic MCF7 human breast cancer xenograft in NOD/SCID mice. PO: per os

Agent	Route/ Dosage (in mL/kg per injection)	Dosage in mg/kg per injection	Schedule in days (total of 28 days)	*Unscheduled death (Day of death)	$\Delta T/\Delta C$ in % at day 28	Median % of regressions on day 28	Regressions		p-value on day 28	Biological Interpretation
							Partial	Complete		
Vehicle	PO, BID (10)	-	-	0/7	100	-	0/7	0/7	-	-
SAR439859	PO, BID (10)	10	0 to 28	0/9	-13	-13	8/9	0/9	p < 0.0001	Very active
Everolimus	PO, BIW (10)	10	0 to 28	0/6	-17	-17	5/6	0/6	p < 0.0001	Very active
SAR439859 + Everolimus	PO, BID (10)  PO, BIW (10)	10 + 10	0 to 28	0/7	-31	-31	6/7	1/7	p < 0.0001	Very active

**Table 2:** Efficacy of amcenenstrant (SAR439859) combined with everolimus against orthotopic human breast cancer cell line MCF7 xenograft model in NOD/SCID mice. Comparison of each group to the control group at each day.

Tumor volume changes from baseline mm <sup>3</sup> : Median (nMAD), n and p-value									
Treatment Group	Global	Day 4	Day 7	Day 11	Day 14	Day 18	Day 21	Day 25	Day 28
Control	-	54.0 (29.65) n=10	91.0 (19.27) n=9	170.0 (16.31) n=9	195.0 (26.69) n=9	216.0 (35.58) n=7	258.0 (29.65) n=7	292.0 (40.03) n=7	312.0 (47.44) n=7
Everolimus 10 mg/kg BIW	-	28.5 (12.60) n=10	48.0 (14.83) n=9	65.0 (26.69) n=9	81.5 (87.47) n=8	10.0 (60.79) n=7	-48.0 (13.34) n=7	-47.0 (51.89) n=7	-53.0 (20.76) n=6
	<b>&lt;.0001</b>	0.0756	<b>0.0026</b>	<b>0.0035</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>
Amcenenstrant 10 mg/kg BID	-	22.0 (14.83) n=10	32.5 (14.83) n=10	60.0 (10.38) n=10	76.5 (37.81) n=10	40.0 (23.72) n=9	-2.0 (19.27) n=9	-38.0 (16.31) n=9	-42.0 (16.31) n=9
	<b>&lt;.0001</b>	<b>0.0238</b>	<b>&lt;.0001</b>	<b>0.0008</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>
Everolimus 10 mg/kg BIW + amcenenstrant 10 mg/kg BID	-	10.0 (2.22) n=10	18.5 (5.93) n=10	-53.5 (9.64) n=8	-70.0 (16.31) n=8	-86.5 (11.86) n=8	-92.5 (8.15) n=8	-94.0 (2.97) n=7	-97.0 (4.45) n=7
	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>
# p-values obtained with a contrast analysis versus control at each day with Bonferroni-Holm adjustment for multiplicity after a two-way Anova-Type on tumor volume changes from baseline. MAD= Median Absolute Deviation; nMAD= normalized MAD ; nMAD= 1.4826*MAD									

**Table 3:** Efficacy of amcnestrant (SAR439859) combined with everolimus against orthotopic human breast cancer cell line MCF7 xenograft model in NOD/SCID mice. Comparison of amcnestrant 10 mg/kg and everolimus 10 mg/kg as single agents *versus* the combination at each day.

Tumor volume changes from baseline mm <sup>3</sup> : Median (nMAD), n and p-value									
Treatment Group	Global	Day 4	Day 7	Day 11	Day 14	Day 18	Day 21	Day 25	Day 28
Everolimus 10 mg/kg BIW + amcnestrant 10 mg/kg BID	-	10.0 (2.22) n=10	18.5 (5.93) n=10	-53.5 (9.64) n=8	-70.0 (16.31) n=8	-86.5 (11.86) n=8	-92.5 (8.15) n=8	-94.0 (2.97) n=7	-97.0 (4.45) n=7
Amcnestrant 10 mg/kg BID	-	22.0 (14.83) n=10	32.5 (14.83) n=10	60.0 (10.38) n=10	76.5 (37.81) n=10	40.0 (23.72) n=9	-2.0 (19.27) n=9	-38.0 (16.31) n=9	-42.0 (16.31) n=9
	<b>&lt;.0001</b>	<b>0.0339</b>	<b>0.0282</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>0.0003</b>	<b>0.0007</b>
Everolimus 10 mg/kg BIW	-	28.5 (12.60) n=10	48.0 (14.83) n=9	65.0 (26.69) n=9	81.5 (87.47) n=8	10.0 (60.79) n=7	-48.0 (13.34) n=7	-47.0 (51.89) n=7	-53.0 (20.76) n=6
	<b>&lt;.0001</b>	<b>0.0085</b>	<b>0.0014</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>	<b>&lt;.0001</b>
# p-values obtained with a contrast analysis to compare the combinations of everolimus and amcnestrant versus each single agent at the dose involved in the combination at each day with Bonferroni-Holm adjustment for multiplicity after a two-way Anova-Type on tumor volume changes from baseline. MAD= Median Absolute Deviation; nMAD= normalized MAD ; nMAD= 1.4826*MAD									

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**CLAIMS**

1. A combination comprising amcenenstrant, or a pharmaceutically acceptable salt thereof, and everolimus.

5

2. The combination according to claim 1, showing therapeutic synergy.

3. The combination according to claim 1 or claim 2, for use in the treatment of cancer.

10

4. The combination according to claim 3, wherein the cancer is breast cancer.

5. The combination according to any of claims 1 to 4, wherein amcenenstrant, or a pharmaceutically acceptable salt thereof, and everolimus are administered separately, simultaneously or spaced out over a period of time.

15

6. A pharmaceutical composition comprising amcenenstrant, or a pharmaceutically acceptable salt thereof, and everolimus, and at least one pharmaceutically acceptable excipient.

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7. The pharmaceutical composition according to claim 6, for use in the treatment of cancer.

8. The pharmaceutical composition according to claim 7, wherein the cancer is breast cancer.

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9. Amcenenstrant or a pharmaceutically acceptable salt thereof for use in the treatment of cancer by co-administration with everolimus.

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10. The compound for use in the treatment of cancer according to claim 9, which is administered separately, simultaneously, or spaced out over time, with everolimus.

11. Everolimus for use in the treatment of cancer by co-administration with amcenenstrant or a pharmaceutically acceptable salt thereof.

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12. Everolimus for use in the treatment of cancer according to claim 11, which is administered separately, simultaneously, or spaced out over time, with amcenenstrant or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical kit comprising:

- (i) a first pharmaceutical composition comprising amcenestrant, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient;
- 5 (ii) a second pharmaceutical composition comprising everolimus, and at least one pharmaceutically acceptable excipient;

wherein the first pharmaceutical composition and the second pharmaceutical composition are in separate compartments and are intended to be independently administered, each administration with regards to the other one being simultaneous or spaced out over time.

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14. A method of treating cancer comprising administering to a patient in need thereof a therapeutically effective amount of amcenestrant or a pharmaceutically acceptable salt thereof in combination with a therapeutically effective amount of everolimus.

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15. A method of treating cancer in a patient who is on therapy with compound amcenestrant, or a pharmaceutically acceptable salt thereof, comprising administering to said patient an effective amount of everolimus.

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16. A method of treating cancer in a patient on stable treatment with compound amcenestrant, or a pharmaceutically acceptable salt thereof, comprising administering to said patient a therapeutically effective amount of everolimus.

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17. A method of treating cancer comprising administering to a patient in need thereof a therapeutically effective amount of compound everolimus, wherein said patient is also on therapy with amcenestrant or a pharmaceutically acceptable salt thereof.

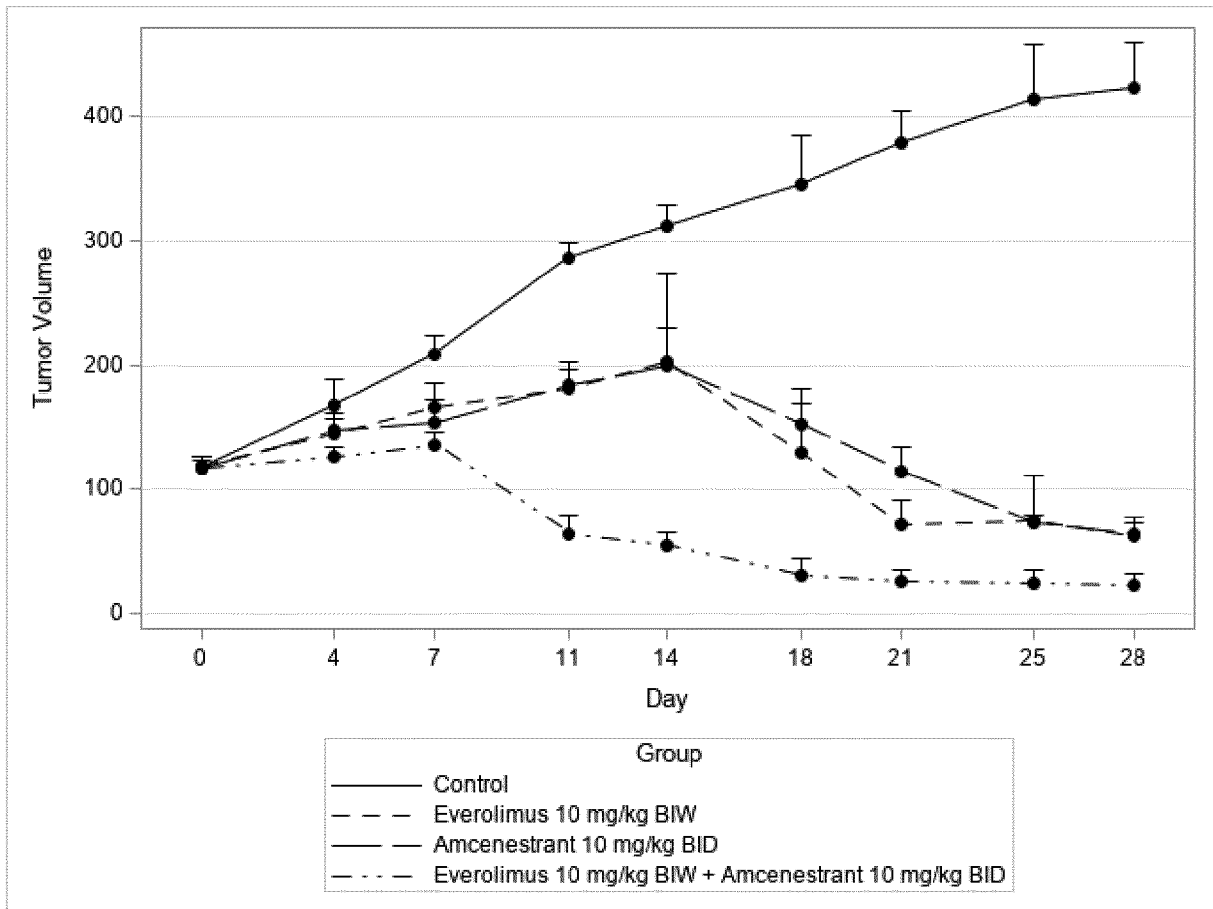


Figure 1

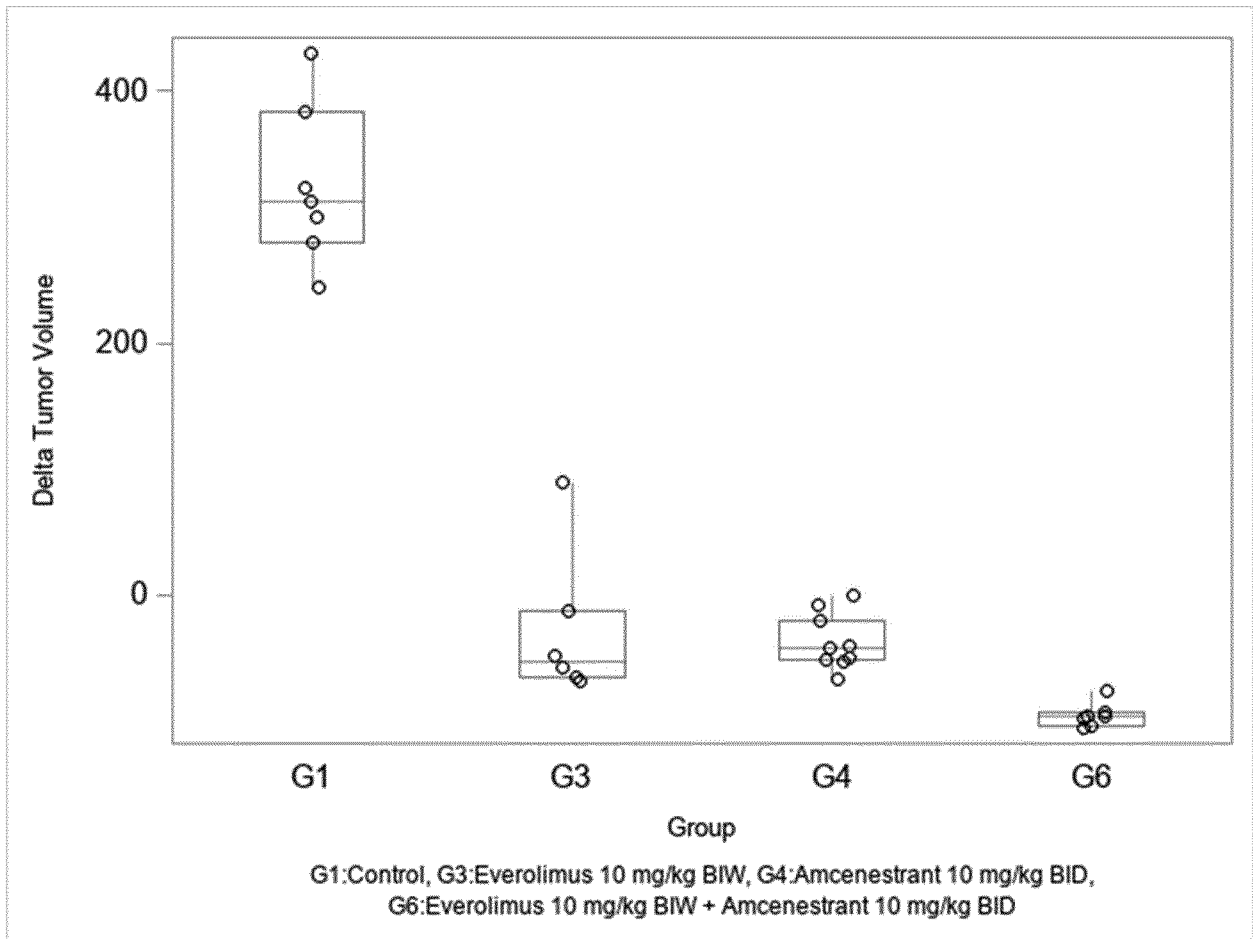


Figure 2

# INTERNATIONAL SEARCH REPORT

International application No  
**PCT/EP2022/059704**

**A. CLASSIFICATION OF SUBJECT MATTER**  
**INV. A61K31/4015 A61K31/436 A61P35/04**  
**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, WPI Data**

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
<b>X, P</b>	<b>WO 2021/178846 A1 (OLEMA PHARMACEUTICALS INC [US]) 10 September 2021 (2021-09-10) paragraph [0116]; claims 3, 49</b> -----	<b>1-13</b>
<b>Y</b>	<b>WO 2017/140669 A1 (SANOFI SA [FR]) 24 August 2017 (2017-08-24) cited in the application page 57; claim 13; compound 51</b> -----	<b>1-3, 5-7, 9-17</b>
<b>Y</b>	<b>US 2016/184311 A1 (CHEN YAN [US] ET AL) 30 June 2016 (2016-06-30) paragraph [0001]; claims 13, 21</b> -----	<b>1-3, 5-7, 9-17</b>
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Further documents are listed in the continuation of Box C.       See patent family annex.

\* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&amp;" document member of the same patent family</p>
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Date of the actual completion of the international search  <b>11 July 2022</b>	Date of mailing of the international search report  <b>21/07/2022</b>
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  <b>Bergkemper, Victoria</b>
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## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2022/059704

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p><b>Anonymous: "Phase 1 / 2 Study of Amcenestrant (SAR439859) Single Agent and in Combination With Other Anti-cancer Therapies in Postmenopausal Women With Estrogen Receptor Positive Advanced Breast Cancer",</b></p> <p>, 15 September 2017 (2017-09-15), XP055919472, Retrieved from the Internet: URL:<a href="https://www.clinicaltrials.gov/ct2/show/NCT03284957">https://www.clinicaltrials.gov/ct2/show/NCT03284957</a> [retrieved on 2022-05-10] the whole document</p> <p style="text-align: center;">-----</p>	1, 2, 6, 13

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International application No

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