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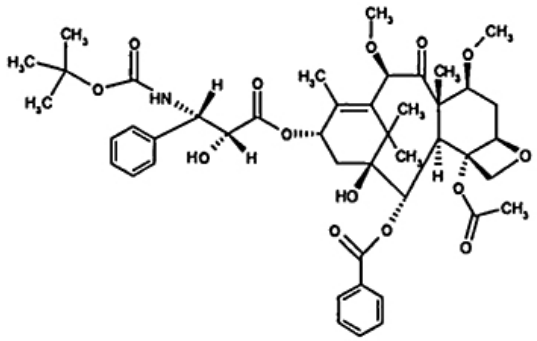
(54) **Titre : New pediatric uses of cabazitaxel.**

(57) **Abrégé :**

The present invention relates to the compound of formula (I)



which may be in the form of an anhydrous base, a hydrate or a solvate, for its use for the treatment of pediatric cancers.

Fig. 1

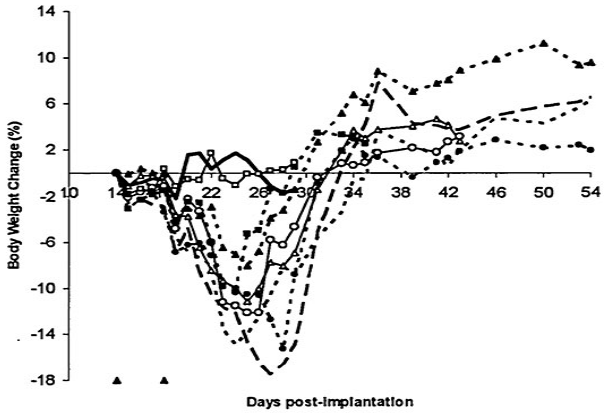


FIG.1

NEW PEDIATRIC USES OF CABAZITAXEL

The present invention concerns new pediatric uses of cabazitaxel. It also concerns a new method for treating children and young adults.

Over the past 20 years, there has been some increase in the incidence of children diagnosed with all forms of invasive cancer. Long-term trends in incidence for leukemias and brain tumors, the most common childhood cancers, show patterns that are somewhat different from the others. Incidence of childhood leukemias appeared to rise in the early 1980s. Rates in the succeeding years have shown no consistent upward or downward trend.

While leukemia is the most common pediatric malignancy, brain tumors are the most common solid tumors, representing 21% of all cancers in children, followed by neuroblastoma (8.3%), nephroblastoma (5.9%), bone tumors (4.6%) such as Osteosarcoma, Ewing's, and soft tissue sarcoma (3.7%) [K.Pritchard-Jones et al. *Eur. J. Cancer* **42**: 2183-2190 (2006)].

Although chemotherapy improves disease-free survival of patients with osteosarcomas the long-term overall survival benefit remains unproven. Chemotherapy is not efficient in chondrosarcoma and its role is currently more limited for patients with soft-tissue sarcomas. Medulloblastoma is the most common malignant brain tumour occurring in children, adolescents and young adults, with a response rate of ~40% to temozolomide. Nevertheless, the improvement in the treatment of childhood brain tumors is particularly critical in tumor types for which outcome remains poor (such as high-grade gliomas).

There is thus an urgent and unmet need to find new antitumoral treatments in the pediatric indication.

Among the taxoid derivatives with antitumoral activity, one may cite cabazitaxel.

In particular, WO96/30355 discloses taxoids derivatives, including cabazitaxel, useful as antitumoral agents. This document also discloses a long list of other drugs that may be used as co-treatments with such taxoids.

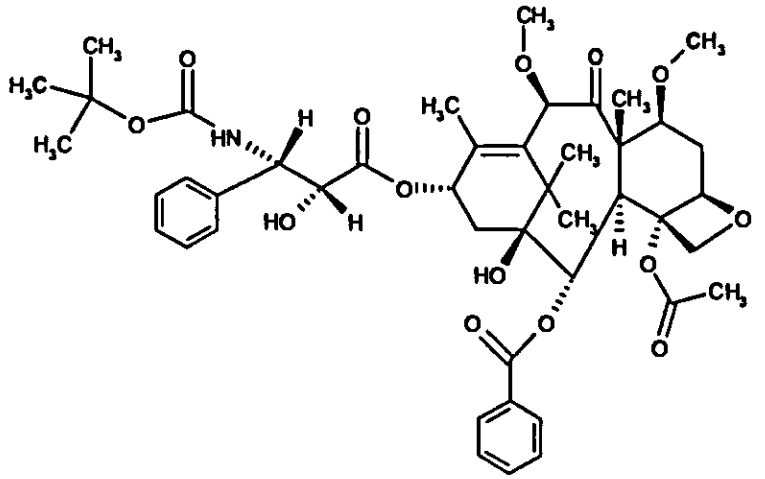
WO2010/128258 discloses an antitumoral combination comprising cabazitaxel and capecitabine in the treatment of metastatic breast cancer for patients progressing after a previous treatment by anthracyclines and taxanes.

WO2011/051894 discloses the use of cabazitaxel in combination with prednisone or prednisolone in the treatment of prostate cancer.

The aim of the present invention is thus to provide with a new therapeutic option for treating pediatric cancers.

The aim of the present invention is to provide evidence of activity of cabazitaxel in pediatric sarcomas, using tumor models directly obtained from fresh tumors of pediatric patients (J.J. Tentler, A. Choon Tan, C.D. Weekes, A. Jimeno, S. Leong, T.M. Pitts, J.J. Arcaroli, W.A. Messersmith and S.G. Eckhardt. Patient-derived tumour xenografts as models for oncology drug development. Nature Reviews Clinical Oncology 2012, 9: 338-350).

The present invention relates to a compound of formula (I):



(I)

which may be in the form of an anhydrous base, a hydrate or a solvate,

for its use for the treatment of pediatric cancers.

The present invention is based on an improved antitumoral activity of cabazitaxel, which may be in the form of an anhydrous base, a hydrate or a solvate, in comparison with docetaxel in preclinical pediatric models.

Indeed the present inventors have now demonstrated that the efficacy of cabazitaxel is better than that of docetaxel in this pediatric indication.

In the present invention, the term "pediatric cancers" refers to cancers or tumors occurring in children and young adults.

The present invention also relates to the above-mentioned compound for its use for the treatment of pediatric solid tumors.

In the present invention, the term "pediatric solid tumors" refers to solid tumors occurring in children and young adults.

The present invention also relates to the above-mentioned compound for its use for the treatment of high grade gliomas, such as glioblastomas.

The term "high-grade glioma" (or malignant glioma) refers to tumors that are classified as Grade III (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ependymoma) or Grade IV (glioblastoma).

According to an embodiment, the pediatric solid tumors are chosen from the group consisting of anaplastic astrocytomas, glioblastomas, anaplastic oligodendrogliomas, oligoastrocytomas, anaplastic ependymomas, nephroblastoma, medulloblastomas, neuroblastomas, Wilm's tumors, rhabdomyosarcomas, chondrosarcomas, Ewing's sarcomas and osteosarcomas.

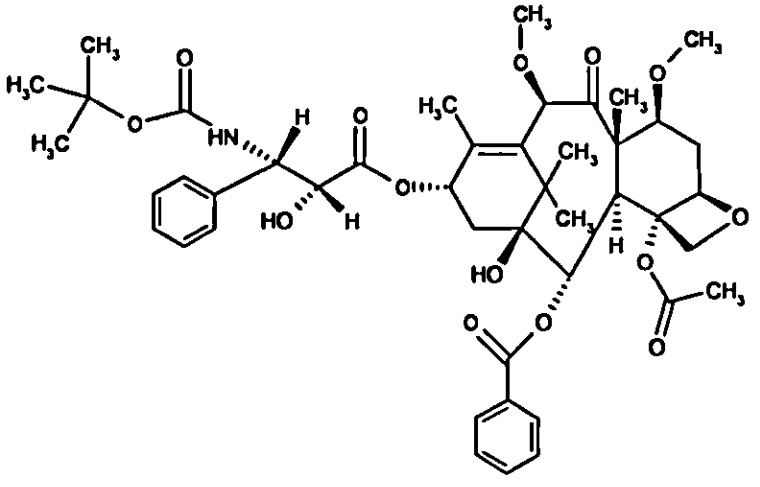
According to an embodiment, the present invention relates to the above-mentioned compound for its use for the treatment of rhabdomyosarcoma (such as Human Rhabdomysarcoma RH-30).

According to an embodiment, the present invention relates to the above-mentioned compound for its use for the treatment of Ewing's tumor (such as Human Ewing's sarcoma TC71, and Human Ewing's sarcoma SK-ES-1 or Human Ewing's sarcoma DM101).

According to an embodiment, the present invention relates to the above-mentioned compound for its use for the treatment of osteosarcomas (such as human osteosarcoma DM77 or human osteosarcoma DM113).

The present invention also relates to a method for treating pediatric cancers comprising the administration of a therapeutically efficient amount of the above-mentioned compound to a patient in need thereof.

Cabazitaxel is an antitumoral agent of the taxoid family and has the following formula:



It may be in the form of anhydrous base, a hydrate or a solvate.

The chemical name of cabazitaxel is 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-*tert*-butoxycarbonylamino-2-hydroxy-3-phenylpropionate. Cabazitaxel is synonymously known as (2α,5β,7β,10β,13α)-4-acetoxy-13-(((2R,3S)-3-[(tertbutoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate.

This compound and a preparative method thereof are described in WO96/30355, EP0817779 and US5847170.

Cabazitaxel may be administered in base form (cf. above formula), or in the form of a hydrate. It may also be a solvate, i.e. a molecular complex characterized by the incorporation of a crystallization solvent into the crystal of the molecule of the active principle (see in this respect page 1276 of *J. Pharm. Sci.* **1975**, *64*(8), 1269-1288).

In the present invention, the above-mentioned compound may be in the form of an acetone solvate.

According to an embodiment, the acetone solvate comprises from 5% to 8% by weight of acetone.

In particular, the above-mentioned compound may be the acetone solvate described in WO2005/02846.

It may be an acetone solvate of cabazitaxel containing from 5% to 8% and preferably from 5% to 7% by weight of acetone (% means content of acetone/content of acetone+cabazitaxel × 100). An average value of the acetone content is 7%, which approximately represents the acetone stoichiometry, which is 6.5% for a solvate containing one molecule of acetone.

The procedure described below allows the preparation of an acetone solvate of cabazitaxel: 940 ml of purified water are added at 20 ± 5°C (room temperature) to a solution of 207 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-*tert*-butoxycarbonylamino-2-hydroxy-3-phenylpropionate at about 92% by weight in about 2 litres of acetone, followed by seeding with a suspension of 2 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-*tert*-butoxycarbonylamino-2-hydroxy-3-phenylpro-pionate isolated from acetone/water in a mixture of 20 ml of water and 20 ml of acetone. The resulting mixture is stirred for about 10 to 22 hours, and 1.5 litres of purified water are added over 4 to 5 hours. This mixture is stirred for 60 to 90 minutes, and the suspension is then filtered under reduced

pressure. The cake is washed on the filter with a solution prepared from 450 ml of acetone and 550 ml of purified water, and then oven-dried at 55°C under reduced pressure (0.7 kPa) for 4 hours. 197 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-*tert*-butoxycarbonyl-amino-2-hydroxy-3-phenylpropionate acetone containing 0.1% water and 7.2% acetone (theoretical amount: 6.5% for a stoichiometric solvate) are obtained.

In the present invention, the above-mentioned compound may be administered by parenteral route.

According to an embodiment, the compound of formula (I) is administered by intravenous route.

Cabazitaxel may be administered parenterally, such as via intravenous administration. A galenical form of cabazitaxel suitable for administration by intravenous infusion is that in which the cabazitaxel is dissolved in water in the presence of excipients chosen from surfactants, cosolvents, glucose or sodium chloride, etc. For example, a galenical form of cabazitaxel may be prepared by diluting a premix solution of cabazitaxel contained in a sterile vial (80 mg of cabazitaxel + 2 ml of solvent + Polysorbate 80) with a sterile vial containing a solution of 6 ml of water and ethanol (13% by weight of 95% ethanol) in order to obtain 8 ml of a solution ready to be rediluted in a perfusion bag. The concentration of cabazitaxel in this ready-to-redilute solution is about 10 mg/ml. The perfusion is then prepared by injecting the appropriate amount of this ready-to-redilute solution into the perfusion bag containing water and glucose (about 5%) or sodium chloride (about 0.9%).

Antitumor activity

The better antitumor activity of cabazitaxel as compared to docetaxel according to the invention is demonstrated by the head to head evaluation at same dosages and/or at equi-toxic dosages in low passage patient-derived pediatric cancer xenografts or in pediatric cancer models.

In the reported examples supporting this invention, vials of the clinical formulation of cabazitaxel and docetaxel were used. Docetaxel was diluted into 0.9% sodium chloride. Each vial of cabazitaxel, 60 mg/1.5 mL was first mixed with the entire contents of supplied diluent [13% (w/w) aqueous solution of ethanol]. The resultant solution contains 10 mg/mL of cabazitaxel. Stock solution of cabazitaxel was then diluted in 0.9% sodium chloride.

This efficacy may be quantified, for example, as changes in tumor volume for each treated (T) and control (C) group, which are calculated for each animal and each day by subtracting the tumor volume on the day of first treatment (staging day) from the tumor volume on the specified observation day. This allows calculating the tumor growth inhibition: $\Delta T/\Delta C$ = (median delta T/ median delta C) x 100. Individual tumor volume changes from baseline are thereafter analyzed by a non-parametric two-way ANOVA-TYPE (with factors: group and repeated days) followed by a post-hoc contrasts analysis, with Bonferroni-Holm adjustment for multiplicity, comparing all treated groups to the control group. Additionally, a non parametric two-way ANOVA-TYPE (with factors: treated group and repeated days) was performed and followed by a contrast analysis, with Bonferroni-Holm adjustment for multiplicity, to compare at each day the effects of docetaxel and cabazitaxel when administered at the same dose or at equi-toxic doses. A probability less than 5% ($p<0.05$) was considered as significant.

Based on the National Cancer Institute (NCI) standards, a $\Delta T/\Delta C \leq 40\%$ is the minimal level required to declare activity.

The tumor doubling time (in days; Td) was estimated from the plot of the log linear growth of the control group tumors in exponential growth (100 to 1000 mm^3 range) [T.H. Corbett et al., *Cancer*, **40**: 2660-2680 (1977); F.M. Schabel et al., *Cancer Drug Development*, Part B, Methods in Cancer Research, **17**: 3-51, New York, Academic Press Inc. (1979)].

This efficacy may also be quantified by the number of tumor regressions observed after therapy. Individual mice reporting a tumor volume ≤50% of the Day 0 measurement for two consecutive measurements over a seven day period were considered partial responders (PR). Individual mice lacking palpable tumors (< 4x4 mm^2 for two consecutive measurements over a seven day period) were classified as complete responders (CR); a CR that persisted until study completion was considered a tumor-free survivor (TFS).

Efficacy could also be determined at study completion, using tumor growth delay (T-C) in days, which is calculated using the median time to endpoint (MTTE) value for each treatment (T) group versus control (C). A Log Rank multiple comparison test with Bonferroni-Holm adjustment for multiplicity was applied on individual TTE to compare the treated groups to the control group.

The efficacy of cabazitaxel in comparison with docetaxel on pediatric patient-derived tumor xenografts was determined experimentally in the following manner:

The animals subjected to the experiment are subcutaneously grafted unilaterally with approximately 30 mg of a tumor fragment from low passage pediatric patient-derived tumor xenografts. The animals are implanted with a human patient-derived pediatric tumor xenografted in immuno-compromised mice (Harlan; *nu/nu*). Several days post tumor implantation, mice are randomized according to their tumor burden to the different groups of treatments and controls. The agents are dosed intravenously at 5.8, 9.3, 15 or 24.2 mg/kg every 4 days for a total of 3 doses (q4dx3) to mice bearing a tumor burden at start of therapy (day 0) ranged from 125 to 250 mm^3.

Beginning Day 0, animals were observed daily and weighed twice weekly using a digital scale; data including individual and mean gram weights (Mean We ± SD), mean percent weight change versus Day 0 were recorded for each group. Animal deaths were recorded daily and designated as drug-related (D), technical (T), tumor related (B), or unknown (U) based on weight loss and gross observation; single agent or combination groups reporting a mean >20% for a period of 7 days and/or >10% mortality were considered above the maximum tolerated dose (MTD) for that treatment on the evaluated regimen.

The efficacy of cabazitaxel in comparison with docetaxel on pediatric solid tumors was determined experimentally in the following manner:

The animals subjected to the experiment are subcutaneously grafted unilaterally with approximately 30 mg of a tumor fragment on day 0. The animals are implanted with a human tumor xenografted in immunocompromized mice. Several days post tumor implantation, mice are randomized according to their body weight to the different groups of treatments and controls. The animals are observed every day. The different animal groups are weighed daily during treatment until the maximum weight loss is reached and subsequent full weight recovery has occurred. The groups are then weighed once or twice a week until the end of the trial.

The tumors are measured 1 to 5 times a week, depending on the tumor doubling time, until the tumor reaches approximately 1,000 mm^3, or until the animal dies (if this occurs before the tumor reaches 1,000 mm^3). The animals are necropsied immediately after euthanasia or death.

The antitumor activity is determined in accordance with the different parameters recorded.

DESCRIPTION OF THE FIGURES

Figure 1 represents the body weight change during the evaluation of the antitumor activity of cabazitaxel and docetaxel against human RH-30 bearing SCID female mice (example 1). Curves represent means at each day for each group.

It represents the body weight change (%) over time (days post-implantation).

The curve with continuous line corresponds to control; the curve with dotted line (— —) corresponds to docetaxel at 14.5 mg/kg; the curve with continuous line and a white triangle (Δ) corresponds to docetaxel at 9 mg/kg; the curve with continuous line and a white circle (o) corresponds to docetaxel at 5.6 mg/kg; the curve with continuous line and a white square (□) corresponds to docetaxel at 3.5 mg/kg; the curve with dotted line (- - -) corresponds to cabazitaxel at 14.5 mg/kg; the curve with dotted line and a black triangle (▲) corresponds to cabazitaxel at 9 mg/kg; the curve with dotted line and a black circle (●) corresponds to cabazitaxel at 5.6 mg/kg; the curve with dotted line and a black square (■) corresponds to cabazitaxel at 3.5 mg/kg; and the black triangles indicate the treatment IV.

Figure 2 represents the antitumor activity of cabazitaxel and docetaxel against human RH-30 bearing SCID female mice (example 1). Curves represent medians at each day for each group.

It represents the tumor volume (mm^3) over time (days post-implantation).

The curve with continuous line corresponds to control; the curve with dotted line (— —) corresponds to docetaxel at 14.5 mg/kg; the curve with continuous line and a white triangle (Δ) corresponds to docetaxel at 9 mg/kg; the curve with continuous line and a white circle (o) corresponds to docetaxel at 5.6 mg/kg; the curve with continuous line and a white square (□) corresponds to docetaxel at 3.5 mg/kg; the curve with dotted line (- - -) corresponds to cabazitaxel at 14.5 mg/kg; the curve with dotted line and a black triangle (▲) corresponds to cabazitaxel at 9 mg/kg; the curve with dotted line and a black circle (●) corresponds to cabazitaxel at 5.6 mg/kg; the curve with dotted line and a black square (■) corresponds to cabazitaxel at 3.5 mg/kg; and the black triangles indicate the treatment IV.

Figure 3 represents the body weight change during the evaluation of the antitumor activity of cabazitaxel and docetaxel against human TC-71 bearing SCID female mice (example 2). Curves represent means at each day for each group.

It represents the body weight change (%) over time (days post-implantation).

The curve with continuous line corresponds to control; the curve with dotted line (— —) corresponds to docetaxel at 14.5 mg/kg; the curve with continuous line and a white triangle (Δ) corresponds to docetaxel at 9 mg/kg; the curve with continuous line and a white circle (o) corresponds to docetaxel at 5.6 mg/kg; the curve with continuous line and a white square (□) corresponds to docetaxel at 3.5 mg/kg; the curve with dotted line (- - -) corresponds to cabazitaxel at 14.5 mg/kg; the curve with dotted line and a black triangle (▲) corresponds to cabazitaxel at 9 mg/kg; the curve with dotted line and a black circle (●) corresponds to cabazitaxel at 5.6 mg/kg; the curve with dotted line and a black square (■) corresponds to cabazitaxel at 3.5 mg/kg; and the black triangles indicate the treatment IV.

Figure 4 represents the antitumor activity of cabazitaxel and docetaxel against human TC-71 bearing SCID female mice (example 2). Curves represent medians at each day for each group.

It represents the tumor volume (mm^3) over time (days post-implantation).

The curve with continuous line corresponds to control; the curve with dotted line (— —) corresponds to docetaxel at 14.5 mg/kg; the curve with continuous line and a white triangle (Δ) corresponds to docetaxel at 9 mg/kg; the curve with continuous line and a white circle (o) corresponds to docetaxel at 5.6 mg/kg; the curve with continuous line and a white square (□) corresponds to docetaxel at 3.5 mg/kg; the curve with dotted line (- - -) corresponds to cabazitaxel at 14.5 mg/kg; the curve with dotted line and a black triangle (▲) corresponds to cabazitaxel at 9 mg/kg; the curve with dotted line and a black circle (●) corresponds to cabazitaxel at 5.6 mg/kg; the curve with dotted line and a black square (■) corresponds to cabazitaxel at 3.5 mg/kg; and the black triangles indicate the treatment IV.

Figure 5 represents the body weight change during the evaluation of the antitumor activity of cabazitaxel and docetaxel against human SK-ES-1 bearing SCID female mice (example 3). Curves represent means at each day for each group.

It represents the body weight change (%) over time (days post-implantation).

The curve with continuous line corresponds to control; the curve with dotted line (— —) corresponds to docetaxel at 14.5 mg/kg; the curve with continuous line and a white triangle (Δ) corresponds to docetaxel at 9 mg/kg; the curve with continuous line and a white circle (o) corresponds to docetaxel at 5.6 mg/kg; the

curve with continuous line and a white square (□) corresponds to docetaxel at 3.5 mg/kg; the curve with dotted line (- - -) corresponds to cabazitaxel at 14.5 mg/kg; the curve with dotted line and a black triangle (▲) corresponds to cabazitaxel at 9 mg/kg; the curve with dotted line and a black circle (●) corresponds to cabazitaxel at 5.6 mg/kg; the curve with dotted line and a black square (■) corresponds to cabazitaxel at 3.5 mg/kg; and the black triangles indicate the treatment IV.

Figure 6 represents the antitumor activity of cabazitaxel and docetaxel against human SK-ES-1 bearing SCID female mice (example 3). Curves represent medians at each day for each group.

It represents the tumor volume (mm^3) over time (days post-implantation).

The curve with continuous line corresponds to control; the curve with dotted line (— —) corresponds to docetaxel at 14.5 mg/kg; the curve with continuous line and a white triangle (Δ) corresponds to docetaxel at 9 mg/kg; the curve with continuous line and a white circle (o) corresponds to docetaxel at 5.6 mg/kg; the curve with continuous line and a white square (□) corresponds to docetaxel at 3.5 mg/kg; the curve with dotted line (- - -) corresponds to cabazitaxel at 14.5 mg/kg; the curve with dotted line and a black triangle (▲) corresponds to cabazitaxel at 9 mg/kg; the curve with dotted line and a black circle (●) corresponds to cabazitaxel at 5.6 mg/kg; the curve with dotted line and a black square (■) corresponds to cabazitaxel at 3.5 mg/kg; and the black triangles indicate the treatment IV.

Figure 7 represents the antitumor activity of cabazitaxel and docetaxel against human DM77 osteosarcoma in nude female mice (example 4). Curves represent medians at each day for each group.

It represents the tumor volume (mm^3) over time (days post first treatment).

The curve with continuous line corresponds to control; the curve with dotted line (— —) corresponds to docetaxel at 24.2 mg/kg; the curve with continuous line and a white triangle (Δ) corresponds to docetaxel at 15 mg/kg; the curve with continuous line and a white circle (o) corresponds to docetaxel at 9.3 mg/kg; the curve with continuous line and a white square (□) corresponds to docetaxel at 5.8 mg/kg; the curve with dotted line (- - -) corresponds to cabazitaxel at 24.2 mg/kg; the curve with dotted line and a black triangle (▲) corresponds to cabazitaxel at 15 mg/kg; the curve with dotted line and a black circle (●) corresponds to cabazitaxel at 9.3 mg/kg; the curve with dotted line and a black square (■) corresponds to cabazitaxel at 5.8 mg/kg; and the black triangles indicate the IV treatment.

Figure 8 represents the antitumor activity of cabazitaxel and docetaxel against human DM113 osteosarcoma in nude female mice (example 5). Curves represent medians at each day for each group.

It represents the tumor volume (mm^3) over time (days post first treatment).

The curve with continuous line corresponds to control; the curve with dotted line (— —) corresponds to docetaxel at 24.2 mg/kg; the curve with continuous line and a white triangle (Δ) corresponds to docetaxel at 15 mg/kg; the curve with continuous line and a white circle (o) corresponds to docetaxel at 9.3 mg/kg; the curve with continuous line and a white square (□) corresponds to docetaxel at 5.8 mg/kg; the curve with dotted line (- - -) corresponds to cabazitaxel at 24.2 mg/kg; the curve with dotted line and a black triangle (▲) corresponds to cabazitaxel at 15 mg/kg; the curve with dotted line and a black circle (●) corresponds to cabazitaxel at 9.3 mg/kg; the curve with dotted line and a black square (■) corresponds to cabazitaxel at 5.8 mg/kg; and the black triangles indicate the IV treatment.

Figure 9 represents the antitumor activity of cabazitaxel and docetaxel against human DM101 Ewing's sarcoma in nude female mice (example 6). Curves represent medians at each day for each group.

It represents the tumor volume (mm^3) over time (days post first treatment).

The curve with continuous line corresponds to control; the curve with dotted line (— —) corresponds to docetaxel at 24.2 mg/kg; the curve with continuous line and a white triangle (Δ) corresponds to docetaxel at 15 mg/kg; the curve with continuous line and a white circle (o) corresponds to docetaxel at 9.3 mg/kg; the curve with continuous line and a white square (□) corresponds to docetaxel at 5.8 mg/kg; the curve with dotted line (- - -) corresponds to cabazitaxel at 24.2 mg/kg; the curve with dotted line and a black triangle (▲) corresponds to cabazitaxel at 15 mg/kg; the curve with dotted line and a black circle (●) corresponds to cabazitaxel at 9.3 mg/kg; the curve with dotted line and a black square (■) corresponds to cabazitaxel at 5.8 mg/kg; and the black triangles indicate the IV treatment.

The better antitumor activity of cabazitaxel as compared to docetaxel, according to the invention, is demonstrated as illustrated in the 6 following examples.

Example 1: ANTITUMOR ACTIVITY OF CABAZITAXEL AND DOCETAXEL AGAINST HUMAN RHABDOMYOSARCOMA RH-30 IN SCID FEMALE MICE.

In this example, the better antitumor activity of cabazitaxel as compared to docetaxel for tumor growth inhibition was demonstrated *in vivo*.

The selected tumor model was a human rhabdomyosarcoma RH-30, xenografted in SCID mice [Douglass EC, et al. Cytogenet Cell Genet. 1987; 45(3-4):14855.].

Cabazitaxel and docetaxel were weighed for each treatment and dissolved in ethanol. Treatment solutions were prepared first by mixing 1 volume of ethanolic stock solution and 1 volume of polysorbate 80, then by adding 18 volumes of glucose 5% in water.

Cabazitaxel and docetaxel were administered intravenously on days 14 and 18 after tumor implantation.

The results of the experiments are reported below in Tables 1, 2 & 3 and in Figures 1 & 2.

The tumor doubling time (in days; Td) was estimated from the plot of the log linear growth of the control group tumors in exponential growth (100 to 1,000 mm^3 range) and the number of tumor regressions observed after therapy. Tumor doubling time was 3.2 days.

The following end points were used:

- Toxicity was declared at dosages inducing ≥ 20% body weight loss or ≥ 10 % drug death;
- Relative tumor growth inhibition was determined on day 27 post tumor implantation when the median tumor size in the control group was 1148 mm^3;
- Antitumor efficacy was determined by calculating the $\Delta T/\Delta C$ value in percent, according to the above mentioned formula;
- Tumor regressions (as explained above);
- Statistical analysis performed as explained above.

Table 1 Evaluation of the efficacy of docetaxel and cabazitaxel in SCID female mice bearing human rhabdomyosarcoma RH-30.

Agent	Route/ Dosage in mL/kg per injection	Dosage in mg/kg per injection (total dose)	Schedule in days	Drug death (Day of death)	Average body weight change in % per mouse at nadir (day of nadir)	ΔT/ΔC in % (day 27)	Regressions		Tumor free survivors at day 120	P value (Day 27)[a]	Biological interpretation
							Partial	Complete			
CABAZITAXEL	IV (16)	14.5 (29)	14;18	0/6	-15.0 (24)	<0	6/6	6/6	6/6	p<0.0001	Highly active
		9.0 (18)		0/6	-8 0 (25)	7	6/6	6/6	5/6	p<0.0001	Very active
		5 6 (11.2)		0/6	-15 3 (28)	0	5/6	2/6	0/6	p<0.0001	Highly active
		3 5 (7.0)		0/6	-10.1 (24)	24	0/6	0/6	0/6	p<0.0001	Active
DOCETAXEL	IV (18)	14.5 (29)	14;18	0/6	-17.6 (27)	1	5/6	3/6	0/6	p<0.0001	Very active
		9.0 (18)		0/6	-11.2 (25)	<0	2/6	0/6	0/6	p<0.0001	Highly active
		5 8 (11.2)		0/6	-12.1 (25)	<0	4/6	0/6	0/6	p<0.0001	Highly active
		3.5 (7.0)		0/6	-1 8 (15)	77	0/6	0/6	0/6	p=0.5534	Inactive
Control	-	-	-	0/8	-2.2 (19)	-	0/8	0/8	0/8		

Tumor doubling time = 3.2 days. Tumor size at start of therapy was 108-392mm^3, with a median tumor burden per group of 188-198 mm^3.

Mice average weight: Due to body weight heterogeneity (range: DOCETAXEL= 19.73-24 51 g; CAZABITAXEL =20 54-24.72 g) dosages were adjusted to the individual body weights.

Abbreviations used, ΔT/ΔC= ratio of median tumor volume changes from baseline between treated and control groups.

[a] Statistical analysis: p-value obtained with a contrast analysis versus control with Bonferroni-Holm adjustment for multiplicity after Anova-Type on tumor volume changes from baseline.

The median tumor burden at start of therapy was 188 to 198 mm^3. Cabazitaxel and docetaxel were administered as single agents by IV tail vein injection on day 14 and day 18 post tumor at the following doses: 14.5, 9.0, 5.6 and 3.5 mg/kg per injection (Table 1).

Cabazitaxel and docetaxel were well tolerated, with a maximum 15.3% bwl on day 28 for cabazitaxel and 17.6% bwl on day 27 for docetaxel (Table 1 and Figure 1).

Cabazitaxel and docetaxel were both highly active, $\Delta T/\Delta C \leq 0\%$ on day 27 ($p<0.0001$) at 14.5 and 5.6 mg/kg per injection for cabazitaxel and 9.0 and 5.6 mg/kg per injection for docetaxel.

Cabazitaxel at 9.0 mg/kg per injection was very active ($\Delta T/\Delta C = 7\%$ on day 27, $p<0.0001$) and docetaxel at 14.5 mg/kg per injection were also very active ($\Delta T/\Delta C = 1\%$ on day 27, $p<0.0001$).

At 3.5 mg/kg per injection, cabazitaxel was still active ($\Delta T/\Delta C = 24\%$ on day 27, $p<0.0001$), while docetaxel was inactive ($\Delta T/\Delta C > 40\%$ on day 27, NS) (Table 1).

The effect of cabazitaxel was significant in comparison with control on days 19, 22, 25 and 27 at 14.5 mg/kg per injection, from day 18 to day 27 at 9 mg/kg per injection, at days 18, 19, 22, 25 and 27 at 5.6 mg/kg per injection, on days 25 and 27 at 3.5 mg/kg per injection.

Global p values were $p<0.0001$, $p<0.0001$, $p<0.0001$ & $p=0.0473$ respectively for each dose (Table 2 and Figure 2).

In this study, docetaxel had a significant effect in comparison with control on days 19, 22, 25 and 27 at 14.5 and 9 mg/kg per injection, on days 25 and 27 at 5.6 mg/kg per injection. Global p values were $p<0.0001$, $p<0.0001$ & $p=0.0005$, respective for each dose (Table 2 and Figure 2).

Table 2 Antitumor activity of cabazitaxel and docetaxel against human rhabdomyosarcoma RH-30 bearing SCID mice: Comparison of each agent versus control group.

Group	Tumor volume changes from baseline: Median (nMad) and Anova-Type followed by a contrast analysis versus control on tumor volume changes from baseline						
		Day					
	Global	18	19	20	22	25	27
Control	-	327 (83) n=8	437 (149.7) n=8	403 (106.7) n=8	852.5 (418 8) n=8	757.5 (281.7) n=8	956 5 (588 6) n=8
	-	-	-	-	-	-	-
Cabazitaxel 14.5 mg/kg	-	217.5 (87.5) n=6	146 (138 6) n=6	359 (285 4) n=6	272 (180.1) n=6	86 5 (318) n=6	-13.5 (281) n=6
	p<.0001	p=0 0996	p=0 0012	p=0 5335	p=0 0071	p<.0001	p<.0001
Cabazitaxel 9 mg/kg	-	138 5 (34 8) n=6	139 5 (48 2) n=6	215 5 (88 2) n=6	129 5 (45.2) n=6	78.5 (174.9) n=6	82.5 (102.3) n=6
	p< 0001	p=0 0047	p<.0001	p=0 0042	p< 0001	p<.0001	p<.0001
Cabazitaxel 5.6 mg/kg	-	164 (30 4) n=6	203 (80.1) n=6	302 5 (220 2) n=6	192 5 (196 4) n=6	22 (147.5) n=6	0 (130 5) n=6
	p<.0001	p=0 0076	p=0.0003	p=0.1708	p=0 0016	p<.0001	p<.0001
Cabazitaxel 3.5 mg/kg	-	307 (35 6) n=6	433.5 (232) n=6	601 (114.2) n=6	418 (258) n=6	280 (168 3) n=6	229 (78 6) n=6
	p=0 0473	p=0 8325	p=1.0000	p=1.0000	p=0.2529	p=0 0043	p< 0001
Docetaxel 14.5 mg/kg	-	166 5 (87.5) n=6	195 (83) n=6	247 (126) n=6	172 (64 5) n=6	154.5 (54 9) n=6	13 (67.5) n=6
	p<.0001	p=0.0828	p=0 0042	p=0.1178	p=0 0009	p<.0001	p<.0001
Docetaxel 9 mg/kg	-	202 (98 6) n=6	202 (71.9) n=6	325 (181.6) n=6	290.5 (139.4) n=6	115 5 (120 8) n=6	-50 5 (60) n=6
	p<.0001	p=0.3352	p=0 0293	p=0 8168	p=0 027	p<.0001	p< 0001
Docetaxel 5.6 mg/kg	-	218 (84 5) n=6	289 (57.1) n=6	409 5 (109 7) n=6	405 5 (226 8) n=6	-30 5 (68 2) n=6	-73 (51.1) n=6
	p=0 0005	p=0.604	p=0 6497	p=1 0000	p=0 2529	p<.0001	p< 0001
Docetaxel 3.6 mg/kg	-	236 5 (125.3) n=6	477 (157.9) n=6	475 (198.7) n=6	495 5 (276 5) n=6	621.5 (318) n=6	736 (288.4) n=6
	p=0 0473	p=0 8325	p=1.0000	p=1 0000	p=0.2529	p=0.0043	p<.0001

p-value: obtained with a contrast analysis versus control with Bonferroni-Holm adjustment for multiplicity after Anova-Type on tumor volume changes from baseline

Table 3 Antitumor activity of cabazitaxel and docetaxel against human rhabdomyosarcoma RH-30 bearing SCID mice: Comparison of the agents at the same dose

Tumor volume changes from baseline: Median (nMad) and Anova-Type followed by a contrast analysis on tumor volume changes from baseline											
Day	Cabazitaxel 3.5 mg/kg	Docetaxel 3.5 mg/kg	P value	Cabazitaxel 5.6 mg/kg	Docetaxel 5.6 mg/kg	P value	Cabazitaxel 9 mg/kg	Docetaxel 9 mg/kg	P value	Cabazitaxel 14.5 mg/kg	Docetaxel 14.5 mg/kg	P value
18	307 (35 6) n=6	236 5 (125.3) n=6	0.4525	164 (30.4) n=6	218 (64.5) n=6	0.0294	138 5 (34 8) n=6	202 (98 6) n=6	0 0891	217.5 (87.5) n=6	168.5 (87.5) n=6	0 9728
19	433.5 (232) n=6	477 (157.9) n=6	0 5377	203 (80.1) n=6	289 (57.1) n=6	0 0086	139 5 (48 2) n=6	202 (71 9) n=6	0 0167	146 (138 6) n=6	195 (83) n=6	0 6549
20	601 (114.2) n=6	475 (198.7) n=6	0 5365	302 5 (220.2) n=6	409 5 (109 7) n=6	0 0993	215 5 (88.2) n=6	325 (181.6) n=6	0 0495	359 (285 4) n=6	247 (126) n=6	0 8251
22	418 (258) n=6	495 5 (278.5) n=6	0 5872	192.5 (196.4) n=6	405.5 (226 8) n=6	0.1388	129 5 (45 2) n=8	290 5 (139 4) n=6	0 0672	272 (180.1) n=6	172 (64 5) n=6	0.7155
25	280 (168.3) n=6	621.5 (318) n=6	0.1899	22 (147.5) n=6	-30 5 (68.2) n=6	0 9608	78 5 (174.9) n=6	115 5 (120 8) n=6	0 5782	86 5 (318) n=6	154 5 (54.9) n=6	0.4871
27	229 (78 6) n=6	736 (288 4) n=6	< 0001	0 (130 5) n=6	-73 (51.1) n=6	0 4408	82.5 (102.3) n=6	-50 5 (80) n=6	0 8153	-13 5 (281) n=6	13 (67.5) n=6	0 7016
29	356 5 (362 5) n=6	905.5 (41.5) n=6	0 0022	106 (147.5) n=6	-47 (89.7) n=6	0 6123	62.5 (91.9) n=6	119 5 (164 6) n=6	0.1300	-107 (150 5) n=6	87 (100 8) n=6	0 0712
33				-85 (117.1) n=6	67 (262.4) n=8	0 0469	-129 (142.3) n=6	272 (328 9) n=6	0 0002	-180 (68) n=6	17 (111.2) n=6	< 0001
35				-120 (98 6) n=6	129 (281.7) n=6	0 0030	-180 (94 9) n=6	253 5 (210 5) n=6	< 0001	-194 (74.1) n=6	-80 (63 8) n=6	0 0034
39				-139 (113.4) n=6	454 5 (348.4) n=6	< 0001	-189 5 (66.7) n=6	676 (499 6) n=6	< 0001	-194 (74.1) n=6	-112 (57.8) n=6	0 0275
41				-157 (113.4) n=6	712 (361 8) n=6	<.0001	-189 5 (86 7) n=6	904.5 (636) n=6	< 0001	-194 (74.1) n=6	-96 (78 6) n=6	0 0264
43				-104 5 (114 2) n=6	1039 5 (526 3) n=6	<.0001	-189 5 (68.7) n=6	909 (523 4) n=6	<.0001	-194 (74.1) n=6	-72 5 (146) n=6	0 0191
46										-194 (74.1) n=6	18.5 (270 6) n=6	0 0048
50										-194 (74.1) n=6	485 (487.8) n=6	<.0001

p-value: obtained with a contrast analysis to compare the compounds at the same tested dose after 2-way Anova-Type on tumor volume changes from baseline on the two corresponding groups

Upon comparison between cabazitaxel and docetaxel treatment at the equivalent doses, a significant difference was observed with regards to improved antitumor activity for cabazitaxel.

- At 14.5 mg/kg per injection a significant difference was observed between docetaxel and cabazitaxel from day 33 to day 50.
- At 9.0 mg/kg per injection a significant difference was observed on days 19, 20 and from day 33 to 43.
- At 5.6 mg/kg per injection a significant difference was observed on days 18, 19 and from day 33 to 43.
- At 3.5 mg/kg per injection a significant difference was observed on days 27 and 29 (Table 3; $p < 0.05$).

Tumor regressions were seen in 3 cabazitaxel groups 14.5 mg/kg per injection (6/6 CR), 9 mg/kg per injection (6/6 CR), and 5.6 mg/kg per injection (2/6 CR, 5/6 PR), and TFS (Tumor Free Survivors) on day 120 were only obtained post treatment with cabazitaxel at 14.5 mg/kg per injection (6/6), and at 9 mg/kg per injection (5/6).

In comparison, 3/6 mice displayed CR and 5/6 PR at 14.5 mg/kg per injection of docetaxel without TFS, docetaxel achieving only PR at 9 (2/6) and 5.6 mg/kg per injection (4/6) (Table 1 and Figure 2).

In conclusion, cabazitaxel is more active than docetaxel against the human pediatric tumor, rhabdomyosarcoma RH-30.

Cabazitaxel achieves 100% CR at 2 dose levels, leading to TFS, tumor regressions being also observed at the third dose level.

In comparison, docetaxel only induces CR at the highest dose tested.

Example 2: ANTITUMOR ACTIVITY OF CABAZITAXEL AND DOCETAXEL AGAINST HUMAN EWING'S SARCOMA TC-71 IN SCID FEMALE MICE.

In this example, the better antitumor activity of cabazitaxel as compared to docetaxel for tumor growth Inhibition was demonstrated *in vivo*.

The selected tumor model was a human Ewing's sarcoma TC-71, xenografted in SCID mice [Whang-Peng J, et al. Cancer Genet Cytogenet. 1986 Apr 1;21(3):185208].

Cabazitaxel and docetaxel were weighed for each treatment and dissolved in ethanol. Treatment solutions were prepared first by mixing 1 volume of ethanolic stock solution and 1 volume of polysorbate 80, then by adding 18 volumes of glucose 5% in water.

Cabazitaxel and docetaxel were administered intravenously on days 12 and 16 after tumor implantation.

The results of the experiments are reported in Tables 4, 5 & 6 and in Figures 3 & 4.

The Td in days was estimated from the plot of the log linear growth of the control group tumors in exponential growth (100 to 1,000 mm^3 range) and the number of tumor regressions observed after therapy. Tumor doubling time was 2.5 days.

The following end points were used:

- Toxicity was declared at dosages inducing ≥ 20% body weight loss or ≥ 10 % drug death
- Relative tumor growth inhibition was determined on day 21 post tumor implantation when the median tumor size in the control group was 1588.5 mm^3.
- Antitumor efficacy was determined by calculating the $\Delta T/\Delta C$ value in percent, according to the above-mentioned formula;
- Tumor regressions (as explained above);
- Statistical analysis performed (as explained above).

Table 4 Evaluation of the efficacy of cabazitaxel and docetaxel in SCID female mice bearing human Ewing's sarcoma TC-71.

Agent	Route/ Dosage in mL/kg per injection	Dosage in mg/kg per injection (total dose)	Schedule in days	Drug death	Average body weight change in % per mouse at nadir (day of nadir)	ΔT/ΔC in % (day 21)	Regressions		Tumor free survivors at day 120	P value (Day 21)[a]	Biological Interpretation
							Partial	Complete			
CABAZITAXEL	IV (16)	14 5 (29)	12; 16	0/7	-9 0 (23)	<0	7/7	7/7	6/7	p<0.0001	Highly Active
		9 0 (18)		0/7	-7.0 (18)	<0	7/7	6/7	6/7	p<0.0001	Highly Active
		5 8 (11.2)		0/7	-7.0 (18)	<0	6/7	0/7	0/7	p<0.0001	Highly Active
		3 5 (7.0)		0/7	-2.3 (21)	27	0/7	0/7	0/7	p=0.0047	Active
DOCETAXEL	IV (18)	14 5 (29)	12; 16	0/7	-12 4 (23)	<0	6/7	2/7	1/7	p<0.0001	Highly Active
		9 0 (18)		0/7	-10 8 (23)	<0	2/7	0/7	0/7	p<0.0001	Highly Active
		5 6 (11.2)		0/7	-13.7 (22)	31	0/7	0/7	0/7	p=0.0400	Active
		3.5 (7.0)		0/7	-1.8 (13)	77	0/7	0/7	0/7	p=0.9778	Inactive
Control	-	-	-	0/10	-0 8 (13)	-	0/10	0/10	0/10		

Tumor doubling time = 2 5 days. Tumor size at start of therapy was 126 – 294 mm^3, with a median tumor burden per group of 172 -198 mm^3.

Mice average weight: Due to body weight heterogeneity (range: docetaxel = 19 70 - 24.15 g; cabazitaxel = 19 25 – 25 07 g) dosages were adjusted to individual body weight.

Abbreviations used ΔT/ΔC= ratio of median tumor volume changes from baseline between treated and control groups.

a) Statistical analysis: p-value obtained with a contrast analysis versus control with Bonferroni-Holm adjustment for multiplicity after Anova-Type on tumor volume changes from baseline.

The median tumor burden at start of therapy was 172 to 198 mm^3.

Cabazitaxel and docetaxel were administered as single agents by IV tail vein injection on day 12 and day 16 post tumor at the following doses, 14.5, 9, 5.6 and 3.5 mg/kg per injection (Table 4).

Cabazitaxel and docetaxel were well tolerated with a maximum 9% bwl on day 23 for cabazitaxel and 13.7% bwl on day 22 for docetaxel (Table 4 and Figure 3).

Cabazitaxel and docetaxel were both highly active, $\Delta T/\Delta C < 0\%$ on day 21 ($p<0.0001$) at 14.5, 9.0 and 5.6 mg/kg per injection for cabazitaxel and at 14.5 and 9.0 mg/kg per injection for docetaxel.

Cabazitaxel at 3.5mg/kg per injection was considered active ($\Delta T/\Delta C = 27\%$ on day 21, $p=0.0047$), while docetaxel at 5.6 mg/kg per injection was considered active ($\Delta T/\Delta C = 31\%$ on day 21, $p=0.0400$), but inactive at 3.5 mg/kg per injection, $\Delta T/\Delta C > 40\%$ on day 21, NS (Table 4).

Table 5 Antitumor activity of cabazitaxel and docetaxel against human Ewing's sarcoma TC-71 bearing SCID mice: Comparison of each agent versus control group.

Tumor volume changes from baseline: Median (nMad) and Anova-Type followed by a contrast analysis versus control on tumor volume changes from baseline					
Group	Day				
	Global	14	16	19	21
Control	-	157 (86) n=10	399 (205.3) n=10	917.5 (396 6) n=10	1354.5 (583 4) n=10
	-	-	-	-	-
Cabazitaxel 14.5 mg/kg	-	36 (53 4) n=7	32 (47.4) n=7	-140 (44.5) n=7	-166 (32 6) n=7
	p<.0001	p=0 0029	p<.0001	p< 0001	p<.0001
Cabazitaxel 9 mg/kg	-	54 (43) n=7	52 (91 9) n=7	-105 (26.7) n=7	-166 (57.8) n=7
	p<.0001	p=0 012	p<.0001	p<.0001	p<.0001
Cabazitaxel 5.6 mg/kg	-	88 (29 7) n=7	150 (80.1) n=7	-16 (46) n=7	-81 (28 2) n=7
	p<.0001	p=0.2155	p=0 0004	p< 0001	p<.0001
Cabazitaxel 3.5 mg/kg	-	78 (43) n=7	194 (32 6) n=7	355 (112.7) n=7	369 (93 4) n=7
	p=0 0229	p=0.1702	p=0.0676	p=0 2377	p=0 0047
Docetaxel 14.5 mg/kg	-	96 (86) n=7	154 (140 8) n=7	-72 (115 6) n=7	-130 (112 7) n=7
	p<.0001	p=0.2155	p< 0001	p<.0001	p< 0001
Docetaxel 9 mg/kg	-	108 (19 3) n=7	222 (29 7) n=7	139 (151.2) n=7	-36 (118 6) n=7
	p<.0001	p=0.4719	p=0 0393	p< 0001	p<.0001
Docetaxel 5.6 mg/kg	-	116 (4 4) n=7	268 (17 8) n=7	371 (150.5) n=6	415 (146 6) n=6
	p=0 2527	p=0 6391	p=0.7707	p=0 3631	p=0 0400
Docetaxel 3.5 mg/kg	-	101 (26.7) n=7	320 (90 4) n=7	629 (200 2) n=7	1044 (243.1) n=7
	p=0 6691	p=0 6391	p=0 8453	p=0 864	p=0 9778

p-value: obtained with a contrast analysis versus control with Bonferroni-Holm adjustment for multiplicity after Anova-Type on tumor volume changes from baseline

The effect of cabazitaxel was significant in comparison with control from days 14 to 21 at 14.5 and 9.0 mg/kg per injection, for days 16, 19 and 21 at 5.6 mg/kg per injection, and on day 21 at 3.5 mg/kg per injection (Table 5 and Figure 4).

In this study, docetaxel had a significant effect in comparison with control on days 16, 19 and 21 at 14.5 and 9 mg/kg per injection (global p values of p<0.0001; Table 5 and Figure 4).

A significant effect was also seen on day 21 for docetaxel at 5.6 mg/kg per injection (p=0.04). Docetaxel at 3.5 mg/kg per injection had no significant effect on tumor volume changes as compared to the control group (Table 5 and Figure 4).

Table 6 Antitumor activity of cabazitaxel and docetaxel against human Ewing's sarcoma TC-71 bearing SCID mice: Comparison of the agents at the same dose.

Tumor volume changes from baseline: Median (nMad) and Anova-Type followed by a contrast analysis on tumor volume changes from baseline											
Day	Cabazitaxel 3.5 mg/kg	Docetaxel 3.5 mg/kg	P value	Cabazitaxel 5.6 mg/kg	Docetaxel 5.6 mg/kg	P value	Cabazitaxel 9 mg/kg	Docetaxel 9 mg/kg	P value	Cabazitaxel 14.5 mg/kg	Docetaxel 14.5 mg/kg	P value
14	78 (43) n=7	101 (26 7) n=7	0 1681	88 (29.7) n=7	116 (4 4) n=7	0.2209	54 (43) n=7	108 (19 3) n=7	0 0755	36 (53 4) n=7	96 (86) n=7	0.3339
16	194 (32 6) n=7	320 (90 4) n=7	<.0001	150 (80.1) n=7	268 (17 8) n=7	0 0096	52 (91.9) n=7	222 (29 7) n=7	0.0006	32 (47.4) n=7	154 (140 8) n=7	0 0404
19	355 (112.7) n=7	629 (200 2) n=7	0 0031	-18 (46) n=7	371 (150 5) n=6	<.0001	-105 (26 7) n=7	139 (151.2) n=7	< 0001	-140 (44.5) n=7	-72 (115 6) n=7	0.1164
21	369 (93 4) n=7	1044 (243.1) n=7	<.0001	-81 (28.2) n=7	416 (148 8) n=6	< 0001	-166 (57.8) n=7	-36 (118 6) n=7	0 0019	-166 (32 6) n=7	-130 (112.7) n=7	0 2719
26				-182 (65 2) n=7	1022.5 (493) n=6	<.0001	-196 (51 9) n=7	158 (173 5) n=7	< 0001	-184 (43) n=7	-130 (80.1) n=7	0.1633
26							-196 (50.4) n=7	243 (244 6) n=7	<.0001	-194 (47.4) n=7	-144 (56.3) n=7	0 0608
30							-196 (50.4) n=7	406 (252) n=7	<.0001	-198 (53 4) n=7	-126 (80 1) n=7	0 0112
34							-196 (72.8) n=7	867 (209) n=5	<.0001	-198 (53 4) n=7	-49 (260 9) n=7	0 0048
36										-180 (53 4) n=7	75 (330.6) n=7	0.0055
40										-180 (53 4) n=7	763 (775 4) n=7	0 0259
p-value: obtained with a contrast analysis to compare the compounds at the same tested dose after 2-way Anova-Type on tumor volume changes from baseline on the two corresponding groups												

Upon comparison between cabazitaxel and docetaxel at equivalent doses, a significant difference was observed with regards to improved antitumor activity for cabazitaxel.

- At 14.5 mg/kg per injection, a significant difference was observed between cabazitaxel and docetaxel on day 16, and from day 30 to day 40.
- At 9.0 mg/kg per injection, a significant difference was observed from day 16 to 34.
- At 5.6 mg/kg per injection, a significant difference was observed from day 16 to 26.
- At 3.5 mg/kg per injection, a significant difference was observed from days 16 to 21 (Table 6; $p<0.05$).

Tumor regressions and TFS were observed at the 2 highest doses of cabazitaxel, 14.5mg/kg per injection (7/7 CR, 6/7 TFS) and 9 mg/kg per injection (6/7 CR, 7/7 PR, 6/7 TFS), 6/7 PR being achieved at 5.6 mg/kg per injection.

In comparison, CR and TFS were only obtained at the highest dose of docetaxel, 14.5 mg/kg per injection (2/7 CR, 6/7 PR, 1/7 TFS), 5/7 PR being observed at 9 mg/kg per injection (Table 4 and Figure 4).

In conclusion, cabazitaxel is also more active than docetaxel against this second human pediatric tumor, Ewing's sarcoma TC-71.

Cabazitaxel achieves 6/7 TFS at 2 dose levels, 6/7 PR being also observed at the third dose level. In comparison, docetaxel only induces CR at the highest dose tested.

Example 3: ANTITUMOR ACTIVITY OF CABAZITAXEL AND DOCETAXEL AGAINST HUMAN EWING'S SARCOMA SK-ES-1 IN SCID FEMALE MICE.

In this example, the better antitumor activity of cabazitaxel as compared to docetaxel for tumor growth inhibition was demonstrated *in vivo*.

The selected tumor model was a human Ewing's sarcoma SK-ES-1, xenografted in SCID mice [Fogh J. New York: Plenum Press, 1975].

Cabazitaxel and docetaxel were weighed for each treatment and dissolved in ethanol. Treatment solutions were prepared first by mixing 1 volume of ethanolic stock solution and 1 volume of polysorbate 80, then by adding 18 volumes of glucose 5% in water.

Cabazitaxel and docetaxel were administered intravenously on days 15 and 19 after tumor implantation.

The results of the experiments are reported in Tables 7, 8 & 9 and in Figures 5 & 6.

The Td in days was estimated from the plot of the log linear growth of the control group tumors in exponential growth (100 to 1,000 mm^3 range) and the number of tumor regressions observed after therapy.

Tumor doubling time was 6.1 days.

The following end points have been used:

- Toxicity was declared at dosages inducing ≥ 20% body weight loss or ≥ 10 % drug death;
- Relative tumor growth inhibition was determined on day 22 post tumor implantation when the median tumor size in the control group was 456 mm^3;
- Antitumor efficacy was determined by calculating the $\Delta T/\Delta C$ value in percent, according to the above-mentioned formula;
- Tumor regressions (as explained above);
- Statistical analysis performed (as explained above).

Table 7 Evaluation of the efficacy of cabazitaxel and docetaxel in SCID female mice bearing a model of human Ewing's sarcoma SK-ES-1.

Agent	Route/ Dosage in mL/kg per injection	Dosage in mg/kg per injection (total dose)	Schedule in days	Drug death	Average body weight change in % per mouse at nadir (day of nadir)	ΔT/ΔC in % (day 22)	Regressions		Tumor free survivors at day 120	P value (Day 22)[a]	Biological interpretation
							Partial	Complete			
CABAZITAXEL	IV (16)	14.5 (29)	1,5,9	0/7	-7.1 (20)	<0	7/7	6/7	3/7	p<0.0001	Highly Active
		9 0 (18)		0/7	-6 3. (16)	<0	7/7	0/7	0/7	p<0.0001	Highly Active
		5 6 (11.2)		0/7	-4.2 (16)	<0	7/7	0/7	0/7	p<0.0001	Highly Active
		3.5 (7 0)		0/7	-4 4 (16)	22	0/7	0/7	0/7	p=0.0422	Active
DOCETAXEL	IV (16)	14 5 (29)	1,5,9	0/7	-10 5 (27)	<0	7/7	3/7	0/7	p<0.0001	Highly Active
		9 0 (18)		0/7	-6 8 (23)	<0	6/7	0/7	0/7	p<0.0001	Highly Active
		5 6 (11.2)		0/7	-5 4 (16)	<0	1/7	0/7	0/7	p=0.0001	Highly Active
		3.5 (7 0)		0/7	-2.1 (16)	72	0/7	0/7	0/7	p=0.0978	Inactive
Control	-	-	-	0/10	-1 4 (16)	-	0/10	0/10	0/10		

Tumor doubling time = 6 1 days. Tumor size at start of therapy was 126-384mm^3, with a median tumor burden per group of 221-245mm^3.

Mice average weight: Due to body weight heterogeneity (range: DOCETAXEL= 19 09 - 26 69g; CAZABITAXEL =19.13 - 25.19g) dosages were adjusted to individual body weight.

Abbreviations used ΔT/ΔC= ratio of median tumor volume changes from baseline between treated and control groups.

a) Statistical analysis: p-value obtained with a contrast analysis versus control with Bonferroni-Holm adjustment for multiplicity after Anova-Type on tumor volume changes from baseline.

The median tumor burden at start of therapy was 221 to 245 mm^3.

Cabazitaxel and docetaxel were administered as single agents by IV tail vein injection on day 15 and day 19 post tumor at the following doses, 14.5, 9.0, 5.6 and 3.5 mg/kg per injection (Table 7).

Cabazitaxel and docetaxel were well tolerated with a maximum 7.1% bwl on day 20 for cabazitaxel and 10.5% bwl on day 27 for docetaxel (Table 7 and Figure 5).

Cabazitaxel and docetaxel were both highly active at 14.5, 9.0 and 5.6 mg/kg per injection, $\Delta T/\Delta C < 0\%$ on day 22 ($p<0.0001$ for all doses).

Cabazitaxel at 3.5mg/kg per injection was considered active ($\Delta T/\Delta C = 22\%$ on day 22, $p=0.0422$), while docetaxel at 3.5 mg/kg per injection was inactive, $\Delta T/\Delta C > 40\%$ on day 22, NS (Table 7).

Table 8 Antitumor activity of cabazitaxel and docetaxel against human Ewing's sarcoma SK-ES-1 bearing SCID mice: Comparison of each agent versus control group.

Tumor volume changes from baseline: Median (nMad) and Anova-Type followed by a contrast analysis versus control on tumor volume changes from baseline					
Group	Day				
	Global	19	22	25	28
Control	-	32 (81.5) n=10	188.5 (149) n=10	341.5 (123.1) n=10	648.5 (196.4) n=10
	-	-	-	-	-
Cabazitaxel 14.5 mg/kg	-	-108 (91 9) n=7	-203 (87.5) n=7	-221 (81.5) n=7	-221 (81.5) n=7
	p<.0001	p=0.0053	p<.0001	p<.0001	p<.0001
Cabazitaxel 9 mg/kg	-	25 (37.1) n=7	-137 (60 8) n=7	-227 (100 8) n=7	-227 (100 8) n=7
	p< 0001	p=1.0000	p< 0001	p< 0001	p< 0001
Cabazitaxel 5.6 mg/kg	-	-31 (87.5) n=7	-126 (86) n=7	-157 (81.5) n=7	-157 (81.5) n=7
	p<.0001	p=0 7871	p<.0001	p<.0001	p< 0001
Cabazitaxel 3.5 mg/kg	-	32 (207.6) n=7	41 (108 2) n=7	180 (100.8) n=7	499 (324.7) n=7
	p=0 6074	p=1 0000	p=0.0422	p=0 5810	p=0 9384
Docetaxel 14.5 mg/kg	-	-18 (77.1) n=7	-156 (56.3) n=7	-173 (69 7) n=7	-164 (56 3) n=7
	p<.0001	p=0 5639	p< 0001	p<.0001	p<.0001
Docetaxel 9 mg/kg	-	0 (37.1) n=7	-101 (62.3) n=7	-126 (32 6) n=7	-126 (46) n=7
	p<.0001	p=1.0000	p<.0001	p<.0001	p<.0001
Docetaxel 5.6 mg/kg	-	0 (106 7) n=7	-36 (60.8) n=7	168 (80.1) n=7	342 (89) n=7
	p=0.0194	p=1 0000	p=0 0001	p=0 0359	p=0.1047
Docetaxel 3.5 mg/kg	-	52 (89) n=7	136 (266.9) n=7	712 (29 7) n=7	900 (373 6) n=7
	p=0.7742	p=1 0000	p=0 0978	p=0.5810	p=0.9384

p-value: obtained with a contrast analysis versus control with Bonferroni-Holm adjustment for multiplicity after Anova-Type on tumor volume changes from baseline

The effect of cabazitaxel was significant in comparison with control from days 19 to 28 at 14.5 mg/kg per injection, on days 22 to 28 at 9.0 and 5.6 mg/kg per injection. Global p values were $p<0.0001$ for each dose.

A significant effect was also seen on day 22 only for cabazitaxel at 3.5mg/kg per injection ($p=0.0422$) (Table 8 and Figure 6).

In this study, docetaxel had a significant effect in comparison with control on days 22 to 28 at 14.5 and 9 mg/kg per injection and on day 22 and 25 at 5.6 mg/kg per injection. Global p values were $p<0.0001$, $p<0.001$ & $p=0.0194$ respective for each dose (Table 8 and Figure 6).

Docetaxel at 3.5 mg/kg per injection had no significant effect on tumor volume changes as compared to the control group.

Table 9 Antitumor activity of cabazitaxel and docetaxel against human Ewing's sarcoma SK-ES-1 bearing SCID mice: Comparison of the agents at the same dose.

Tumor volume changes from baseline: Median (nMad) and Anova-Type followed by a contrast analysis on tumor volume changes from baseline												
Day	Cabazitaxel 3.5 mg/kg	Docetaxel 3.5 mg/kg	P value	Cabazitaxel 5.6 mg/kg	Docetaxel 5.6 mg/kg	P value	Cabazitaxel 9 mg/kg	Docetaxel 9 mg/kg	P value	Cabazitaxel 14.5 mg/kg	Docetaxel 14.5 mg/kg	P value
19	32 (207.6) n=7	52 (89) n=7	0 7323	-31 (87 5) n=7	0 (106.7) n=7	0 3683	25 (37.1) n=7	0 (37.1) n=7	0 5214	-108 (91 9) n=7	-18 (77.1) n=7	0 4035
22	41 (108.2) n=7	136 (266 9) n=7	0.3594	-126 (86) n=7	-36 (60 8) n=7	0 0466	-137 (80 8) n=7	-101 (62.3) n=7	0.1647	-203 (87.5) n=7	-156 (56 3) n=7	0 2939
25	180 (100 8) n=7	712 (29 7) n=7	0 0057	-157 (81.5) n=7	168 (80.1) n=7	<.0001	-227 (100 8) n=7	-126 (32.6) n=7	0 0031	-221 (81.5) n=7	-173 (69.7) n=7	0 6869
28	499 (324.7) n=7	900 (373 6) n=7	0.1065	-157 (81.5) n=7	342 (89) n=7	<.0001	-227 (100 8) n=7	-126 (46) n=7	0 0005	-221 (81.5) n=7	-164 (56 3) n=7	0 6382
32				-128 (112 7) n=7	480 (204 6) n=7	<.0001	-231 (78 6) n=7	-49 (100.8) n=7	<.0001	-221 (87.5) n=7	-162 (60 8) n=7	0.25
35				-157 (112.7) n=7	2005 (1055 6) n=7	<.0001	-231 (78 6) n=7	201 (256 5) n=7	< 0001	-221 (87.5) n=7	-162 (60 8) n=7	0.257
39										-221 (108.2) n=7	290 (468 5) n=7	0 0002
41										-221 (140 8) n=7	274 (299 5) n=6	0 0011
43										-221 (140 8) n=7	427.5 (428 5) n=6	0.0002
45										-144 (222 4) n=7	574 (566 4) n=5	0 0014
p-value: obtained with a contrast analysis to compare the compounds at the same tested dose after 2-way Anova-Type on tumor volume changes from baseline on the two corresponding groups												

Upon comparison between cabazitaxel and docetaxel at equivalent doses, a significant difference was observed with regards to improved antitumor activity for cabazitaxel.

- At 14.5 mg/kg per injection, a significant difference was observed between docetaxel and cabazitaxel from day 39 to day 45.
- At 9.0 mg/kg per injection, a significant difference was observed from day 25 to 35.
- At 5.6 mg/kg per injection, a significant difference was observed from day 22 to 35.
- At 3.5 mg/kg per injection, a significant difference was observed on day 25 only (Table 9; $p<0.05$).

CR and TFS were observed at the highest dose of cabazitaxel, 14.5 mg/kg per injection (6/7 CR, 7/7 PR, 3/7 TFS), 100 % PR being achieved at 9 and 5.6 mg/kg per injection.

In comparison only 3/7 mice displayed CR at 14.5 mg/kg per injection of docetaxel, with 7/7 PR and no TFS on day 120. At 9 and 5.6 mg/kg per injection, docetaxel induced 6/7 and 1/7 PR, respectively (Table 7 and Figure 6).

In conclusion, cabazitaxel is more also active than docetaxel against this third human pediatric tumor, Ewing's sarcoma SK-ES-1.

Cabazitaxel achieves 100% PR at a 3 dose levels, with 6/7 CR leading to 3/7 TFS at the highest doses tested. In comparison, docetaxel induced 3/7 CR at the highest dose tested and no TFS.

Example 4: ANTITUMOR ACTIVITY OF CABAZITAXEL AND DOCETAXEL AGAINST HUMAN OSTEOSARCOMA DM77 IN NUDE FEMALE MICE.

In this example, the better antitumor activity of cabazitaxel as compared to docetaxel for tumor growth inhibition was demonstrated *in vivo*.

The selected tumor model, DM77, was a low passage patient-derived tumor xenograft derived from an osteosarcoma taken from the lung of a 19 year old male patient.

The results of the experiments are reported below in Tables 10, 11 & 12 and in Figure 7.

The tumor doubling time (in days; Td) was 6.6 days.

The following end points were used:

- Toxicity was declared at dosages inducing ≥ 20% body weight loss or ≥ 10 % drug death;

- Antitumor efficacy was determined by calculating the $\Delta T/\Delta C$ value in percent on day 21 post treatment initiation, according to the above mentioned formula;

- Individual tumor volume changes from baseline were analyzed by a non-parametric two-way ANOVA-TYPE (with factors: group and repeated day from 3 to 21) followed by a post-hoc contrasts analysis, with Bonferroni-Holm adjustment for multiplicity, comparing all treated groups to the control group on day 21. Additionally, a non parametric two-way ANOVA-TYPE (with factors: treated group and repeated day from 3 to 56) was performed and followed by a contrast analysis, with Bonferroni-Holm adjustment for multiplicity, to compare at each day the effects of docetaxel and cabazitaxel when administered at the same dose or at equi-toxic doses.

- At study completion, tumor growth delay (T-C) in days is calculated using the median time to endpoint (MTTE) value for each treatment (T) group versus control (C). The volume endpoint for T-C calculations was chosen to be 1400 mm^3. A Log Rank multiple comparison test with Bonferroni-Holm adjustment for multiplicity was applied on individual TTE to compare the treated groups to the control group.

- Tumor regressions (as explained above).

Results:

Cabazitaxel and docetaxel demonstrate anti-tumor effects compared to the control (Figure 7 and Table 11). At day 21, a ΔT/ΔC of 14.1% or 18.5% was reported for animals treated with 5.8 mg/kg of cabazitaxel or docetaxel, respectively and 0% or 9.6% ΔT/ΔC was reported for animals treated with 9.3 mg/kg of cabazitaxel or docetaxel, respectively. Animals dosed with 15 or 24.2 mg/kg had a ΔT/ΔC lower than 0% for both test agents.

Comparison of tumor volume changes demonstrated that cabazitaxel at 9.3 mg/kg was more efficacious than docetaxel from day 25 to day 56 (Table 12). Similar results are observed when comparing the numbers of PR between treatment groups at 9.3 mg/kg (2/9 versus 0/9 PR, respectively) (Table 11).

Using weight loss as a gross indicator of toxicity, docetaxel appears to more toxic than cabazitaxel (Table 10). Docetaxel at 24.2 mg/kg was inducing an excessive body weight loss of 17% on day 14. At 15 mg/kg, docetaxel is inducing 14% body weight loss on day 11, which is comparable to the 15% body weight loss observed for cabazitaxel at 24.2 mg/kg on day 14. Alternative analysis, adjusting for the higher level of toxicity was performed (Table 12). The tumor volume changes from baseline for docetaxel at 5.8, 9.3, or 15 mg/kg were compared along time to cabazitaxel at 9.3, 15, or 24.2 mg/kg, respectively. Docetaxel was significantly different from cabazitaxel: 5.8 mg/kg docetaxel to 9.3 mg/kg cabazitaxel (from day 18) and 9.3 mg/kg docetaxel to 15 mg/kg cabazitaxel (from day 11). The comparison of tumor volume changes did not show any significant differences at the highest dosages, the study being terminated before the regrowth of the tumors.

Table 10 - Cabazitaxel and docetaxel toxicity in nude mice bearing DM77 osteosarcoma

Treatment	Dose (mg/kg)	Route/Schedule	Weight Change at Nadir		Drug Deaths	
			%	Day	Total	Day (#)
Control	--	i.v./ q4dx3	--	--	--	--
Cabazitaxel	5.8	i.v./ q4dx3	-5%	11	0	--
	9.3	i.v./ q4dx3	-8%	11	0	--
	15	i.v./ q4dx3	-9%	11	0	--
	24.2	i.v./ q4dx3	-15%	14	0	--
Docetaxel	5.8	i.v./ q4dx3	-6%	11	0	--
	9.3	i.v./ q4dx3	-7%	14	0	--
	15	i.v./ q4dx3	-14%	11	0	--
	24.2	i.v./ q4dx3	-17%	14	0	--

Table 11 - Cabazitaxel and docetaxel antitumor activity in nude mice bearing DM77 osteosarcoma

Treatment	Dose (mg/kg)	Route/Schedule	Tumor Volume Data (Day 21)			MTTE (days)	pvalue**	T-C (days)	n	#PR/CR/TFS
			Median (mm^3)	ΔT/ΔC %	pvalue*					
Control	--	i.v./ q4dx3	1102.5			25	--	--	10	--
Cabazitaxel	5 8	i.v./ q4dx3	333	14.1	p=0.0006	49	p=0.0132	24	9	0/0/0
	9.3	i.v./ q4dx3	131	0	p<0.0001	>60	p<.0001	>35	9	2/0/0
	15	i.v./ q4dx3	78	-9.3	p<0.0001	>60	p<.0001	>35	9	6/0/0
	24.2	i.v./ q4dx3	101.5	-6.9	p<0.0001	>60	p<.0001	>35	10	5/1/1
Docetaxel	5.8	i.v./ q4dx3	300	18.5	p=0.0056	53	p=0.0023	28	9	0/0/0
	9.3	i.v./ q4dx3	266	9 6	p<0.0001	>60	p=0.0014	>35	9	0/0/0
	15	i.v./ q4dx3	78	-5.9	p<0.0001	>60	p<.0001	>35	9	3/0/0
	24.2	i.v./ q4dx3	71.5	-6.1	p<0.0001	>60	p<.0001	>35	10	6/1/1

*: Contrasts analysis versus control with Bonferroni-Holm adjustment for multiplicity following a non parametric two-way Anova-Type on tumor volume changes from baseline

**: Log-Rank multiple comparisons test versus control on individuals time to event

Table 12 - Comparison of the tumor volumes of the groups treated with cabazitaxel and docetaxel at the same dose and at equi-toxic doses in nude mice bearing DM77 osteosarcoma

	Median +/- nMAD (number of subject) and pvalue*							
	Cabazitaxel 5.8 mg/kg	Cabazitaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	Docetaxel 5.8 mg/kg	Docetaxel 9.3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24.2 mg/kg
DAY 4	47 +/- 47 (n=9)	54 +/- 54 (n=9)	0 +/- 0 (n=9)	22 +/- 22 (n=10)	47 +/- 47 (n=9)	57 +/- 40 (n=9)	66 +/- 66 (n=9)	0 +/- 0 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 8 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p=1 0000	p=1 0000	p=1 0000	p=1 0000	p=1 0000	p=1 0000	
DAY 7	121 +/- 80 (n=9)	73 +/- 73 (n=9)	0 +/- 25 (n=9)	0 +/- 9 5 (n=10)	73 +/- 23 (n=9)	87 +/- 42 (n=9)	73 +/- 73 (n=9)	0 +/- 0 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p=1 0000	p=1 0000	p=1 0000	p=1 0000	p=0 5271	p=1 0000	
DAY 11	162 +/- 89 (n=9)	19 +/- 35 (n=9)	-53 +/- 19 (n=9)	-26 5 +/- 26 5 (n=10)	122 +/- 56 (n=9)	96 +/- 77 (n=9)	-41 +/- 41 (n=9)	-50 +/- 24 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p=1 0000	p=1 0000	p=1 0000	p=1 0000	p=0.0008	p=1 0000	
DAY 14	182 +/- 97 (n=9)	19 +/- 35 (n=9)	-53 +/- 27 (n=9)	-29 5 +/- 29 5 (n=10)	129 +/- 83 (n=9)	96 +/- 89 (n=9)	-41 +/- 41 (n=9)	-55 5 +/- 20 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p=1 0000	p=1 0000	p=1 0000	p=1 0000	p<0.0001	p=1 0000	
DAY 18	195 +/- 122 (n=9)	0 +/- 33 (n=9)	-73 +/- 20 (n=9)	-61 5 +/- 27 (n=10)	189 +/- 118 (n=9)	96 +/- 89 (n=9)	-53 +/- 17 (n=9)	-55 5 +/- 20 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p=0 1171	p=1 0000	p=1 0000	p=0.8302	p<0.0001	p=1 0000	
DAY 21	129 +/- 129 (n=9)	0 +/- 34 (n=9)	-85 +/- 13 (n=9)	-63 +/- 25 5 (n=10)	189 +/- 103 (n=9)	66 +/- 74 (n=9)	-54 +/- 12 (n=9)	-55 5 +/- 10 5 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p=0 1509	p=1 0000	p=1 0000	p=0.0175	p<0.0001	p=1 0000	
DAY 25	96 +/- 115 (n=9)	-19 +/- 26 (n=9)	-85 +/- 13 (n=9)	-69 5 +/- 24 5 (n=10)	217 +/- 151 (n=9)	124 +/- 93 (n=9)	-66 +/- 17 (n=9)	-55 5 +/- 10 5 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p=0.0028	p=1 0000	p=1 0000	p=0.0002	p<0.0001	p=1 0000	
DAY 28	96 +/- 115 (n=9)	-45 +/- 26 (n=9)	-85 +/- 13 (n=9)	-60 +/- 28 5 (n=10)	290 +/- 198 (n=9)	124 +/- 171 (n=9)	-66 +/- 17 (n=9)	-53 5 +/- 13 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p=0 0002	p=1 0000	p=1 0000	p<0.0001	p<0.0001	p=1 0000	
DAY 32	96 +/- 109 (n=9)	-45 +/- 26 (n=9)	-85 +/- 19 (n=9)	-60 +/- 28 5 (n=10)	332 +/- 268 (n=9)	154 +/- 201 (n=9)	-66 +/- 17 (n=9)	-53 5 +/- 33 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p<0.0001	p=1 0000	p=1 0000	p<0.0001	p<0.0001	p=1 0000	
DAY 35	169 +/- 182 (n=9)	-66 +/- 7 (n=9)	-85 +/- 19 (n=9)	-60 +/- 35 (n=10)	342 +/- 250 (n=9)	169 +/- 235 (n=9)	-66 +/- 13 (n=9)	-57 5 +/- 45 5 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p<0.0001	p=1 0000	p=1 0000	p<0.0001	p<0.0001	p=1 0000	

	Median +/- nMAD (number of subject) and pvalue*							
	Cabazitaxel 5.8 mg/kg	Cabazitaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	Docetaxel 5.8 mg/kg	Docetaxel 9.3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24.2 mg/kg
DAY 39	239 +/- 172 5 (n=8)	-66 +/- 7 (n=9)	-85 +/- 38 (n=9)	-60 +/- 35 (n=10)	342 +/- 121 (n=9)	202 +/- 268 (n=9)	-66 +/- 13 (n=9)	-57 5 +/- 45 5 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p<0.0001	p=1 0000	p=1 0000	p<0.0001	p<0.0001	p=1 0000	
DAY 42	240 +/- 182 (n=8)	-66 +/- 7 (n=9)	-85 +/- 38 (n=9)	-71 +/- 46 5 (n=10)	401 +/- 169 5 (n=8)	309 +/- 375 (n=9)	-66 +/- 13 (n=9)	-57.5 +/- 45 5 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p<0.0001	p=1 0000	p=0 9613	p<0.0001	p<0.0001	p=1 0000	
DAY 46	364 5 +/- 226 (n=8)	-66 +/- 7 (n=9)	-85 +/- 38 (n=9)	-71 +/- 46 5 (n=10)	548 +/- 165 5 (n=8)	309 +/- 375 (n=9)	-58 +/- 11 (n=9)	-57 5 +/- 45 5 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=1 0000	p<0.0001	p=1 0000	p=0 7558	p<0.0001	p<0.0001	p=1 0000	
DAY 49	402 +/- 254 (n=8)	-66 +/- 7 (n=9)	-85 +/- 38 (n=9)	-71 +/- 43 (n=10)	512 +/- 142 (n=7)	424 5 +/- 394 5 (n=8)	-58 +/- 11 (n=9)	-46 +/- 45 5 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=0 9989	p<0.0001	p=0 9989	p=0 4781	p<0.0001	p<0.0001	p=0 9989	
DAY 53	706 +/- 516 (n=8)	-47 +/- 25 (n=9)	-85 +/- 38 (n=9)	-64 5 +/- 45 5 (n=10)	657 5 +/- 211 5 (n=8)	542 +/- 447 5 (n=8)	-58 +/- 11 (n=9)	-46 +/- 69 5 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=0 7526	p<0.0001	p=0 7526	p=0 4742	p<0.0001	p<0.0001	p=0 7526	
DAY 56	878 +/- 602 5 (n=8)	-47 +/- 26 (n=9)	-85 +/- 38 (n=9)	-64 5 +/- 46 5 (n=10)	875 5 +/- 358 5 (n=8)	493 +/- 236 (n=7)	-58 +/- 11 (n=9)	-48 +/- 69 5 (n=10)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9 3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24 2 mg/kg	
	p=0 7397	p<0.0001	p=0 7397	p=0 8100	p<0.0001	p<0.0001	p=0 7397	

*. Contrasts analysis with Bonferroni-Holm adjustment for multiplicity following a two-way ANOVA-TYPE on tumor volume changes from baseline to compare, at each day, the groups treated with Cabazitaxel or Docetaxel at the same dose or at equi-toxic doses

Conclusion: Cabazitaxel and docetaxel demonstrated robust dose-dependent anti-tumor activity. Overall, dosing with 15 mg/kg and 9.3 mg/ kg of cabazitaxel induces higher antitumor activity than docetaxel at an equivalent dose or a toxicity adjusted dose. Overall cabazitaxel is more efficacious than docetaxel at both mid doses, on a dose equivalent basis.

Example 5: ANTITUMOR ACTIVITY OF CABAZITAXEL AND DOCETAXEL AGAINST HUMAN OSTEOSARCOMA DM113 IN NUDE FEMALE MICE.

In this second example, the better antitumor activity of cabazitaxel as compared to docetaxel for tumor growth inhibition was demonstrated *in vivo*.

The selected tumor model, DM113, was a low passage patient-derived tumor xenograft derived from an osteosarcoma taken from the lung of a 3 year old female patient.

The results of the experiments are reported below in Tables 13, 14 & 15 and in Figure 8.

The tumor doubling time (in days; Td) was 7.9 days.

The following end points were used:

- Toxicity was declared at dosages inducing ≥ 20% body weight loss or ≥ 10 % drug death;

- Antitumor efficacy was determined by calculating the $\Delta T/\Delta C$ value in percent on day 28 post treatment initiation, according to the above mentioned formula;

- Individual tumor volume changes from baseline were analyzed by a non-parametric two-way ANOVA-TYPE (with factors: group and repeated day from 3 to 28) followed by a post-hoc contrasts analysis, with Bonferroni-Holm adjustment for multiplicity, comparing all treated groups to the control group on day 28. Additionally, a non parametric two-way ANOVA-TYPE (with factors: treated group and repeated day from 3 to 46) was performed and followed by a contrast analysis, with Bonferroni-Holm adjustment for multiplicity, to compare at each day the effects of docetaxel and cabazitaxel when administered at the same doses.

- At study completion, tumor growth delay (T-C) in days is calculated using the median time to endpoint (MTTE) value for each treatment (T) group versus control (C). The volume endpoint for T-C calculations was chosen to be 1600 mm^3. A Log Rank multiple comparison test with Bonferroni-Holm adjustment for multiplicity was applied on individual TTE to compare the treated groups to the control group.

- Tumor regressions (as explained above).

Results:

Treatment with cabazitaxel and docetaxel had minor impacts for the health status of the animals though weight losses were noted at the higher doses of 24.2 (11% versus 13 %, respectively) and 15 mg/kg (9% and 8 %, respectively) (Table 13).

Both Cabazitaxel and docetaxel demonstrate anti-tumor effects compared to the control via either tumor volume changes from baseline or T-C analysis ($p<0.05$ for both end-points), except at the 5.8 mg/kg dose level of docetaxel ($\Delta T/\Delta C$ = 42.9%, $p = 0.3938$; T-C = 9 days, $p = 0.1771$) (Figure 8 and Table 14).

As shown in Table 15, comparison of tumor volume changes from baseline at equivalent dose levels demonstrated significantly greater activity for cabazitaxel compared to docetaxel at 9.3 mg/kg (on days 14 to 38), 15 mg/kg (on days 11 to 46), and 24.2 mg/kg (on days 11, 24 and 31 to 46).

Additionally, as reported in Table 14, when comparing the numbers of PR between treatment groups, a greater activity of cabazitaxel compared to docetaxel has been observed at 15 mg/kg (4/10 PR versus 0/10 PR, respectively) and at 24.2 mg/kg (5/10 PR versus 1/10 PR, respectively).

Table 13 - Cabazitaxel and docetaxel toxicity in nude mice bearing DM113 osteosarcoma

Treatment	Dose (mg/kg)	Route/Schedule	Weight Nadir		Drug Deaths	
			%	Day	Total	Day (#)
Control	--	i.v./ q4dx3	-1%	3	--	--
Cabazitaxel	5.8	i.v./ q4dx3	--	--	0	--
	9.3	i.v./ q4dx3	-3%	3	0	--
	15	i.v./ q4dx3	-9%	14	0	--
	24.2	i.v./ q4dx3	-11%	11	0	--
Docetaxel	5.8	i.v./ q4dx3	-2%	3	0	--
	9.3	i.v./ q4dx3	-3%	17	0*	--
	15	i.v./ q4dx3	-8%	17	0	--
	24.2	i.v./ q4dx3	-13%	17	0	--

*one animal died on day 35 with no known cause of death following necropsy

Table 14 - Cabazitaxel and docetaxel antitumor activity in nude mice bearing DM113 osteosarcoma

Treatment	Dose (mg/kg)	Route/ Schedule	Tumor Volume Data (Day 28)			MTTE (days)	pvalue**	T-C (days)	n	#PR/CR/TFS
			Median (mm^3)	ΔT/ΔC %	pvalue*					
Control	–	i.v./ q4dx3	1258			31	–	–	10	–
Cabazitaxel	5.8	i.v./ q4dx3	512.5	29.4	p=0.0442	47	p=0.0206	16	10	0/0/0
	9.3	i.v./ q4dx3	204	1.8	p<.0001	>59	p=0 0003	>28	10	0/0/0
	15	i.v./ q4dx3	131	-4.4	p<.0001	>59	p<.0001	>28	10	4/0/0
	24.2	i.v./ q4dx3	112	-3.6	p<.0001	>59	p<.0001	>28	10	5/0/0
Docetaxel	5.8	i.v./ q4dx3	598	42.9	p=0.3938	41	p=0.1771	9	10	0/0/0
	9.3	i.v./ q4dx3	442	27.4	p=0.0235	49	p=0.0206	17	9	1/0/0
	15	i.v./ q4dx3	178	3.2	p<.0001	>59	p<.0001	>28	10	0/0/0
	24.2	i.v./ q4dx3	131	0	p<.0001	>59	p<.0001	>28	10	1/0/0

*: Contrasts analysis versus control with Bonferroni-Holm adjustment for multiplicity following a non parametric two-way Anova-Type on tumor volume changes from baseline

**: Log-Rank multiple comparisons test versus control on individuals time to event

Table 15 - Comparison of the tumor volumes of the groups treated with cabazitaxel and docetaxel at the same equi-toxic doses in nude mice bearing DM113 osteosarcoma

	Median +/- MAD (number of subject) and pvalue*							
	Cabazitaxel 5.8 mg/kg	Docetaxel 5.8 mg/kg	Cabazitaxel 9.3 mg/kg	Docetaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Docetaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	Docetaxel 24.2 mg/kg
DAY 3	58 +/- 21 5 (n=10)	22 5 +/- 22 5 (n=10)	29 5 +/- 27 (n=10)	56 5 +/- 26 5 (n=10)	13 +/- 13 (n=10)	26 +/- 26 (n=10)	9 5 +/- 9 5 (n=10)	29 5 +/- 13 5 (n=10)
comparison	p=1 0000		p=1 0000		p=1 0000		p=1 0000	
DAY 8	63 5 +/- 37 (n=10)	95 +/- 22 5 (n=10)	29 5 +/- 29 5 (n=10)	85 5 +/- 27 (n=10)	0 +/- 0 (n=10)	26 +/- 26 (n=10)	0 +/- 26 5 (n=10)	22 5 +/- 22 5 (n=10)
comparison	p=0 5005		p=0 3795		p=0 5005		p=0 1597	
DAY 11	63 5 +/- 21 5 (n=10)	117 5 +/- 45 (n=10)	29 5 +/- 29 5 (n=10)	73 +/- 42 5 (n=10)	-23 5 +/- 23 5 (n=10)	13 +/- 16 5 (n=10)	-40 5 +/- 34 (n=10)	0 +/- 22 (n=10)
comparison	p=0 3121		p=0 3121		p=0 0056		p=0 0240	
DAY 14	95 +/- 41 5 (n=10)	189 +/- 60 5 (n=10)	9 +/- 9 (n=10)	85 5 +/- 34 5 (n=10)	-40 5 +/- 30 (n=10)	13 +/- 18 5 (n=10)	-43 5 +/- 28 5 (n=10)	-9 5 +/- 35 (n=10)
comparison	p=0 1492		p=0 0253		p=0 0011		p=0 1105	
DAY 17	95 +/- 59 (n=10)	242 5 +/- 110 (n=10)	0 +/- 0 (n=10)	117 5 +/- 51 5 (n=10)	-40 5 +/- 30 (n=10)	13 +/- 18 5 (n=10)	-40 5 +/- 24 5 (n=10)	-9 5 +/- 26 (n=10)
comparison	p=0 1026		p=0 0057		p=0 0011		p=0 1026	
DAY 21	158 5 +/- 39 5 (n=10)	278 5 +/- 142 (n=10)	0 +/- 9 (n=10)	140 5 +/- 52 (n=10)	-40 5 +/- 30 (n=10)	0 +/- 19 (n=10)	-40 5 +/- 24 5 (n=10)	-9 5 +/- 26 (n=10)
comparison	p=0 1026		p=0 0005		p=0 0129		p=0 1026	
DAY 24	234 +/- 63 5 (n=10)	435 +/- 159 (n=10)	0 +/- 31 (n=10)	239 +/- 94 5 (n=10)	-50 +/- 36 5 (n=10)	22 5 +/- 23 5 (n=10)	-40 5 +/- 40 5 (n=10)	0 +/- 0 (n=10)
comparison	p=0 1050		p=0 0001		p=0 0018		p=0 0282	
DAY 28	334 5 +/- 96 (n=10)	487 +/- 231 5 (n=10)	20 +/- 39 5 (n=10)	311 +/- 75 5 (n=10)	-50 +/- 36 5 (n=10)	36 5 +/- 35 5 (n=10)	-40 5 +/- 40 5 (n=10)	0 +/- 9 5 (n=10)
comparison	p=0 1591		p=0 0002		p=0 0008		p=0 0704	
DAY 31	459 5 +/- 123 (n=10)	598 +/- 204 (n=9)	69 +/- 69 (n=10)	390 +/- 90 5 (n=10)	-53 +/- 36 5 (n=10)	42 5 +/- 29 5 (n=10)	-40 5 +/- 34 (n=10)	0 +/- 9 5 (n=10)
comparison	p=0 2301		p=0 0011		p=0 0004		p=0 0332	
DAY 35	579 5 +/- 228 (n=10)	813 +/- 367 (n=9)	67 5 +/- 70 5 (n=10)	545 +/- 52 (n=9)	-59 5 +/- 29 (n=10)	81 +/- 61 (n=10)	-51 +/- 41 5 (n=10)	0 +/- 9 5 (n=10)
comparison	p=0 2378		p=0 0132		p<0 0001		p=0 0118	
DAY 38	634 5 +/- 245 (n=10)	960 +/- 388 (n=8)	182 +/- 155 5 (n=10)	677 +/- 118 (n=9)	-59 5 +/- 39 5 (n=10)	81 +/- 61 (n=10)	-51 +/- 41 5 (n=10)	0 +/- 9 5 (n=10)
comparison	p=0 3251		p=0 0401		p<0 0001		p=0 0089	
DAY 42	1097 +/- 248 (n=10)	1032 +/- 326 (n=7)	311 +/- 248 (n=10)	627 5 +/- 293 5 (n=8)	-59 5 +/- 39 5 (n=10)	107 +/- 90 (n=10)	-51 +/- 41 5 (n=10)	0 +/- 9 5 (n=10)
comparison	p=0 4213		p=0 2684		p<0 0001		p=0 0057	
DAY 46	1548 5 +/- 438 5 (n=10)	1340 +/- 384 (n=6)	576 +/- 317 5 (n=10)	1187 +/- 347 5 (n=8)	-59 5 +/- 42 5 (n=10)	155 +/- 153 (n=10)	-51 +/- 41 5 (n=10)	50 5 +/- 47 5 (n=10)
comparison	p=0 8530		p=0 8530		p<0 0001		p<0 0001	

*: Contrasts analysis with Bonferroni-Holm adjustment for multiplicity following a two-way ANOVA-TYPE on tumor volume changes from baseline to compare, at each day, the groups treated with Cabazitaxel or Docetaxel at the same dose or at equi-toxic doses

Conclusion: These results demonstrate that both cabazitaxel and docetaxel demonstrate robust anti-tumor activity in this model. Furthermore, cabazitaxel demonstrates higher efficacy than docetaxel at the 9.3, 15, and 24.2 mg/kg dose levels.

Example 6: ANTITUMOR ACTIVITY OF CABAZITAXEL AND DOCETAXEL AGAINST HUMAN EWING'S SARCOMA DM101 IN NUDE FEMALE MICE.

In this third example, the better antitumor activity of cabazitaxel as compared to docetaxel for tumor growth inhibition was demonstrated *in vivo*.

The selected tumor model, DM101, was a low passage patient-derived tumor xenograft derived from an Ewing's sarcoma taken from the bone of a 17 year old male patient.

The results of the experiments are reported below in Tables 16, 17 & 18 and in Figure 9.

The tumor doubling time (in days; Td) was 4 days.

The following end points were used:

- Toxicity was declared at dosages inducing ≥ 20% body weight loss or ≥ 10 % drug death;

- Antitumor efficacy was determined by calculating the $\Delta T/\Delta C$ value in percent on day 11 post treatment initiation, according to the above mentioned formula;

- Individual tumor volume changes from baseline were analyzed by a non-parametric two-way ANOVA-TYPE (with factors: group and repeated day from 4 to 14) followed by a post-hoc contrasts analysis, with Bonferroni-Holm adjustment for multiplicity, comparing all treated groups to the control group on day 11. Additionally, a non parametric two-way ANOVA-TYPE (with factors: treated group and repeated day from 4 to 32) was performed and followed by a contrast analysis, with Bonferroni-Holm adjustment for multiplicity, to compare at each day the effects of docetaxel and cabazitaxel when administered at the same doses or at equi-toxic doses.

- At study completion, tumor growth delay (T-C) in days is calculated using the median time to endpoint (MTTE) value for each T group versus C. The volume endpoint for T-C calculations was chosen to be 2000 mm^3. A Log Rank multiple

comparison test with Bonferroni-Holm adjustment for multiplicity was applied on individual TTE to compare the treated groups to the control group.

- Tumor regressions (as explained above).

Results:

Both cabazitaxel and docetaxel demonstrate significant anti-tumor effects compared to the control via ΔT/ΔC on day 11 (Figure 6 and Table 17).

Using weight loss as a gross indicator of toxicity (Table 16), docetaxel is more toxic than cabazitaxel at 24.2 mg/kg (17% versus 5 % body weight loss).

At equivalent dose levels, the comparison of tumor volume changes from baseline shows no significant difference between the groups treated with cabazitaxel or docetaxel at dose 5.8 and 9.3 mg/kg. However, as shown in Table 18, starting from day 7, the groups treated with cabazitaxel at the 15 or 24.2 mg/kg doses were significantly different from the groups treated with docetaxel at the same dose (15 or 24.2 mg/kg, respectively) or at the equi-toxic dose (9.3 or 15mg/kg, respectively).

In addition, animals treated with 15 or 24.2 mg/kg of cabazitaxel induced more CR and TFS as compared to docetaxel (9/9 CR and 7/9 TFS for cabazitaxel *versus* 4/9 CR and 1/9 TFS for docetaxel at 15 mg/kg; 9/9 CR and 8/9 TFS for cabazitaxel *versus* 3/9 CR and 2/9 TFS for docetaxel at 24.2 mg/kg).

Table 16 - Cabazitaxel and docetaxel toxicity in nude mice bearing DM101 Ewing's sarcoma

Treatment	Dose (mg/kg)	Route/Schedule	Weight Nadir		Drug Deaths	
			%	Day	Total	Day (#)
Control	--	i.v./ q4dx3	--	--	--	--
Cabazitaxel	5.8	i.v./ q4dx3	--	--	0	--
	9.3	i.v./ q4dx3	-2%	7	0	--
	15	i.v./ q4dx3	-3%	7	0	--
	24.2	i.v./ q4dx3	-5%	11	0	--
Docetaxel	5.8	i.v./ q4dx3	-1%	4	0	--
	9.3	i.v./ q4dx3	-4%	7	0	--
	15	i.v./ q4dx3	-6%	14	0	--
	24.2	i.v./ q4dx3	-17%	14	0	--

Table 17 - Cabazitaxel and docetaxel antitumor activity in nude mice bearing DM101 Ewing's sarcoma

Treatment	Dose (mg/kg)	Route/Schedule	Tumor Volume Data (Day 11)			MTTE (days)	pvalue**	T-C (days)	n	#PR/CR/TFS
			Median (mm^3)	ΔT/ΔC %	pvalue*					
Control	–	i.v./ q4dx3	940			16.9	–	–	10	–
Cabazitaxel	5.8	i v./ q4dx3	204	8.9	p=0.0044	34.8	p=0.0576	17.9	9	0/0/0
	9.3	i.v./ q4dx3	255	9.4	p=0.0004	23.9	p=0.1185	7	9	1/1/1
	15	i.v./ q4dx3	0	-16	p<0.0001	>61	p=0.0002	>44.1	9	9/9/7
	24.2	i.v./ q4dx3	0	-18.3	p<0.0001	>61	p<0.0001	>44.1	9	9/9/8
Docetaxel	5.8	i.v./ q4dx3	366	24.7	p=0.0397	35	p=0.1185	18.1	9	0/0/0
	9.3	i.v./ q4dx3	505	36 8	p=0.0004	30.5	p=0.0576	13.6	9	4/4/1
	15	i.v./ q4dx3	204	8.9	p=0.0002	50.9	p=0.0562	34	9	4/4/1
	24.2	i.v./ q4dx3	300	14.9	p=0.0001	32.3	p=0.0576	15.4	9	4/3/2

*: Contrasts analysis versus control with Bonferroni-Holm adjustment for multiplicity following a non parametric two-way Anova-Type on tumor volume changes from baseline

**: Log-Rank multiple comparisons test versus control on individual time to event

Table 18 - Comparison of the tumor volumes of cabazitaxel and docetaxel at the same equi-toxic doses in nude mice bearing DM101 Ewing's sarcoma

	Median +/- MAD (number of subject) and pvalue*							
	Cabazitaxel 5.8 mg/kg	Cabazitaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	Docetaxel 5.8 mg/kg	Docetaxel 9.3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24.2 mg/kg
DAY 4	0 +/- 0 (n=9)	0 +/- 33 (n=9)	0 +/- 0 (n=9)	-19 +/- 19 (n=9)	51 +/- 38 (n=9)	25 +/- 25 (n=9)	26 +/- 25 (n=9)	26 +/- 40 (n=9)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9.3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	
	p=1 0000	p=1 0000	p=1.0000	p=1 0000	p=1 0000	p=1 0000	p=1 0000	
DAY 7	34 +/- 34 (n=9)	13 +/- 41 (n=9)	-113 +/- 32 (n=9)	-150 +/- 52 (n=9)	98 +/- 79 (n=9)	96 +/- 172 (n=9)	73 +/- 109 (n=9)	122 +/- 184 (n=9)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9 3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	
	p=1.0000	p=1 0000	p=0.0159	p=0.0042	p=0 6555	p=0.0174	p=0.0043	
DAY 11	73 +/- 73 (n=9)	77 +/- 118 (n=9)	-131 +/- 47 (n=9)	-150 +/- 38 (n=9)	202 +/- 183 (n=9)	301 +/- 223 (n=9)	73 +/- 186 (n=9)	122 +/- 184 (n=9)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9.3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24.2 mg/kg	Cabazitaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	
	p=1 0000	p=1 0000	p=0.0019	p=0.0019	p=0 5726	p=0.0015	p=0.0019	
DAY 14	155 +/- 136 (n=9)	188 +/- 241 (n=9)	-131 +/- 47 (n=9)	-150 +/- 38 (n=9)	446 +/- 393 (n=9)	472 +/- 550 (n=9)	73 +/- 251 (n=9)	122 +/- 215 (n=9)
Comparison versus	Docetaxel 5.8 mg/kg	Docetaxel 9.3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	
	p=1.0000	p=1.0000	p=0.0008	p=0.0012	p=0.4725	p=0.0003	p=0.0008	
DAY 17	306 +/- 152 (n=9)	498 +/- 485 (n=9)	-131 +/- 47 (n=9)	-150 +/- 38 (n=9)	640 +/- 621 (n=9)	750 +/- 828 (n=9)	169 +/- 347 (n=9)	122 +/- 234 (n=9)
Comparison versus	Docetaxel 5.8 mg/kg	Docetaxel 9.3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	
	p=1 0000	p=1.0000	p=0.0002	p=0.0003	p=0 6650	p<0.0001	p=0.0002	
DAY 20	489 +/- 199 (n=9)	766 +/- 713 (n=9)	-131 +/- 47 (n=9)	-150 +/- 38 (n=9)	813 +/- 756 (n=9)	813 +/- 891 (n=9)	290 +/- 468 (n=9)	394 +/- 407 (n=9)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9.3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	
	p=1 0000	p=1 0000	p<0.0001	p<0.0001	p=0.7250	p<0.0001	p<0.0001	
DAY 25	696.5 +/- 295 5 (n=8)	1095 +/- 1023 (n=9)	-131 +/- 47 (n=9)	-150 +/- 38 (n=9)	766 +/- 478 (n=7)	-78 +/- 110 (n=7)	-78 +/- 100 (n=7)	351.5 +/- 463.5 (n=8)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9.3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24 2 mg/kg	Cabazitaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	
	p=0 9784	p=0 6388	p=0.0001	p<0.0001	p=0.7289	p<0.0001	p=0.0001	
DAY 28	1097 +/- 117 (n=8)	182.5 +/- 248 (n=6)	-131 +/- 47 (n=9)	-150 +/- 38 (n=9)	1140 +/- 564 (n=7)	-78 +/- 36 (n=6)	-84 5 +/- 70 (n=6)	681 +/- 793 (n=8)
Comparison versus	Docetaxel 5 8 mg/kg	Docetaxel 9.3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24.2 mg/kg	Cabazitaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	
	p=0 9886	p=0.5325	p=0.0003	p<0.0001	p=0.5169	p<0.0001	p=0.0003	

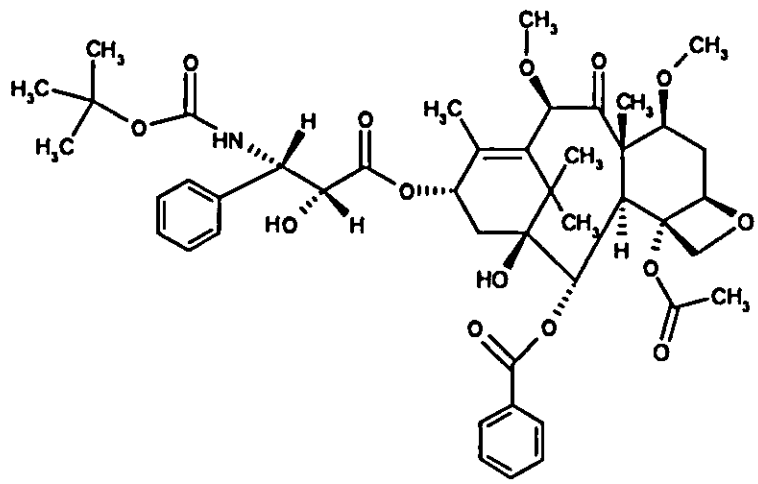
DAY 32	1396 +/- 182.5 (n=8)	385 +/- 414 (n=6)	-131 +/- 40 (n=9)	-150 +/- 38 (n=9)	1694 +/- 281 (n=7)	-78 +/- 34 (n=5)	-91 +/- 40 (n=5)	254 +/- 366 (n=5)
Comparison versus	Docetaxel 5.8 mg/kg	Docetaxel 9.3 mg/kg	Docetaxel 15 mg/kg	Docetaxel 24.2 mg/kg	Cabazitaxel 9.3 mg/kg	Cabazitaxel 15 mg/kg	Cabazitaxel 24.2 mg/kg	
	p=0 8900	p=0.5900	**p=0.0018**	**p<0.0001**	p=0 5900	**p<0.0001**	**p=0.0016**	

*: Contrasts analysis with Bonferroni-Holm adjustment for multiplicity following a two-way ANOVA-TYPE on tumor volume changes from baseline to compare, at each day, the groups treated with Cabazitaxel or Docetaxel at the same dose or at equi-toxic doses.

Conclusion: Both cabazitaxel and docetaxel demonstrate robust anti-tumor activity in this model. Cabazitaxel at the 15 or 24.2 mg/kg doses was significantly more active than docetaxel at the same dose (15 or 24.2 mg/kg, respectively) or at the equi-toxic dose (9.3 or 15 mg/kg, respectively).

CLAIMS

1. The compound of formula (I):



(I)

which may be in the form of an anhydrous base, a hydrate or a solvate, for its use for the treatment of pediatric cancers.

2. The compound for the use of claim 1, for the treatment of pediatric solid tumors.

3. The compound for the use of claim 2, wherein the pediatric solid tumors are chosen from the group consisting of: anaplastic astrocytomas, glioblastomas, anaplastic oligodendrogliomas, oligoastrocytomas, anaplastic ependymomas, nephroblastoma, medulloblastomas, neuroblastomas, Wilm's tumors, rhabdomyosarcomas, chondrosarcomas, Ewing's sarcomas and osteosarcomas.

4. The compound for the use of any one of claims 1 to 3, for the treatment of rhabdomyosarcoma.

5. The compound for the use of any one of claims 1 to 3, for the treatment of Ewing's tumor.

6. The compound for the use of any one of claims 1 to 3, for the treatment of osteosarcoma.

7. The compound for the use of claim 1, for the treatment of high grade gliomas.

8. The compound for the use of any one of claims 1 to 7, wherein said compound is in the form of an acetone solvate.

9. The compound for the use of claim 8, wherein the acetone solvate comprises from 5% to 8% by weight of acetone.

10. The compound for the use of any one of claims 1 to 9, wherein said compound is administered by parenteral route.

11. The compound for the use of claim 10, wherein said compound is administered by intravenous route.

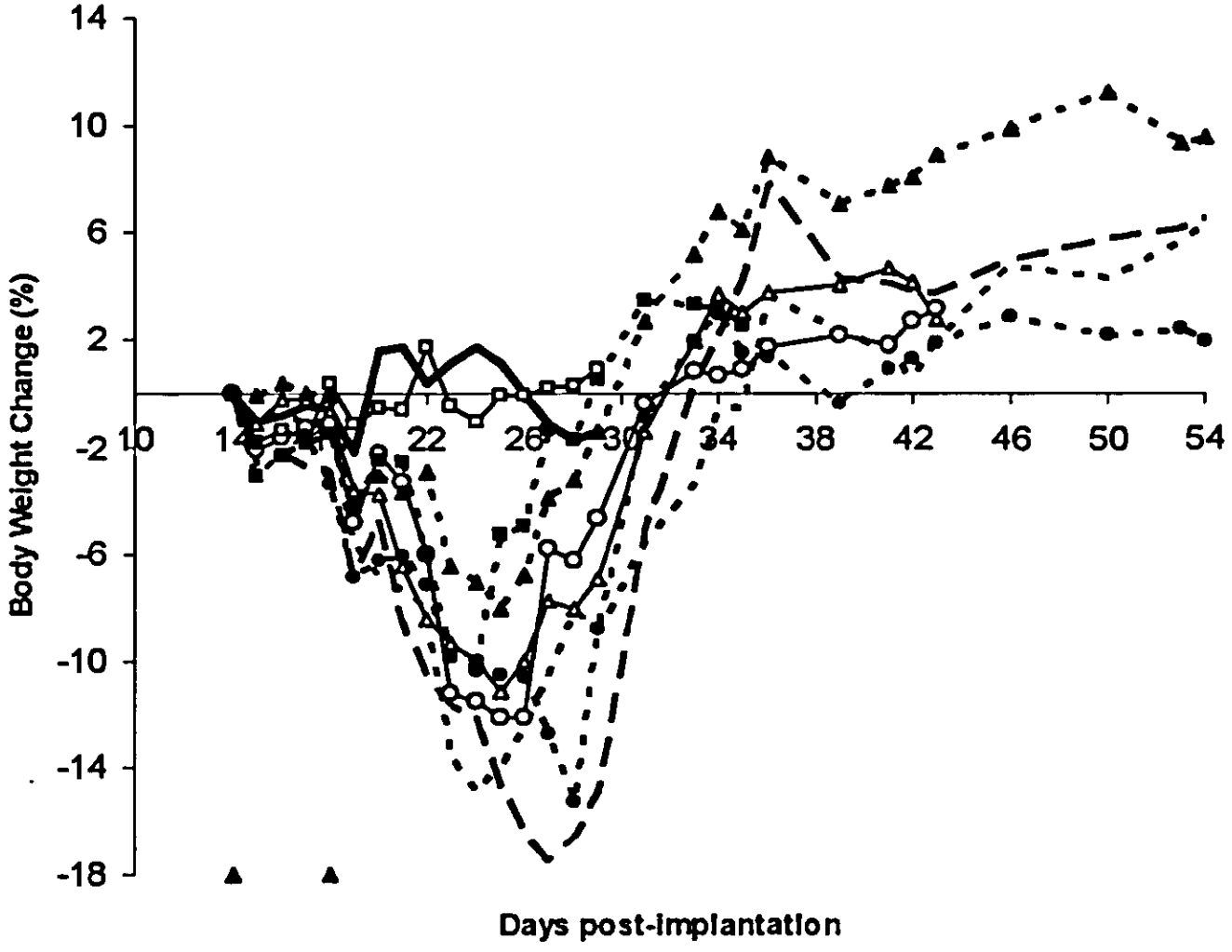

14
10
6
2
-2
-6
-10
-14
-18
10
14
18
22
26
30
34
38
42
46
50
54
Body Weight Change (%)
Days post-implantation

FIG.1

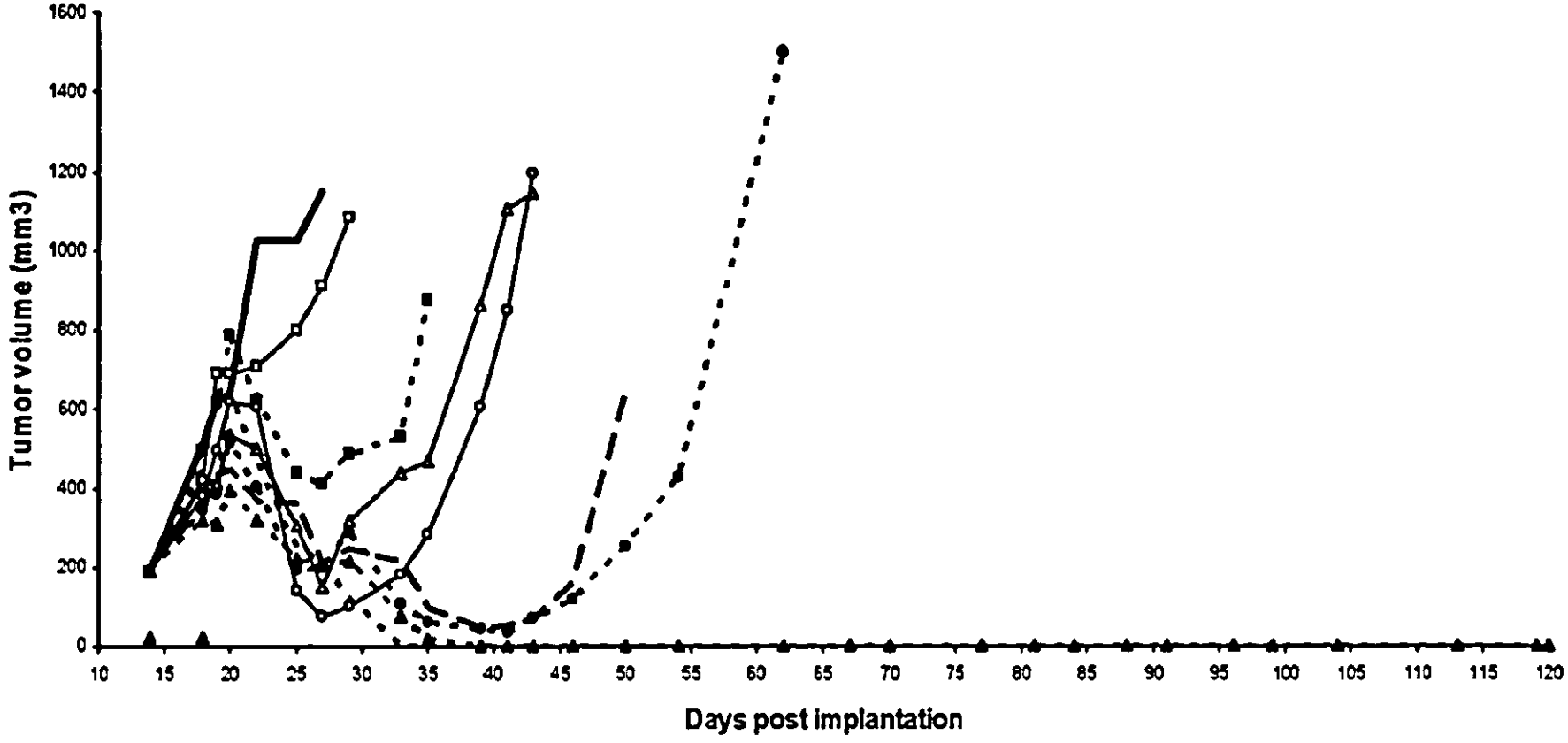

Tumor volume (mm3)
1600
1400
1200
1000
800
600
400
200
0
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
Days post implantation

FIG.2

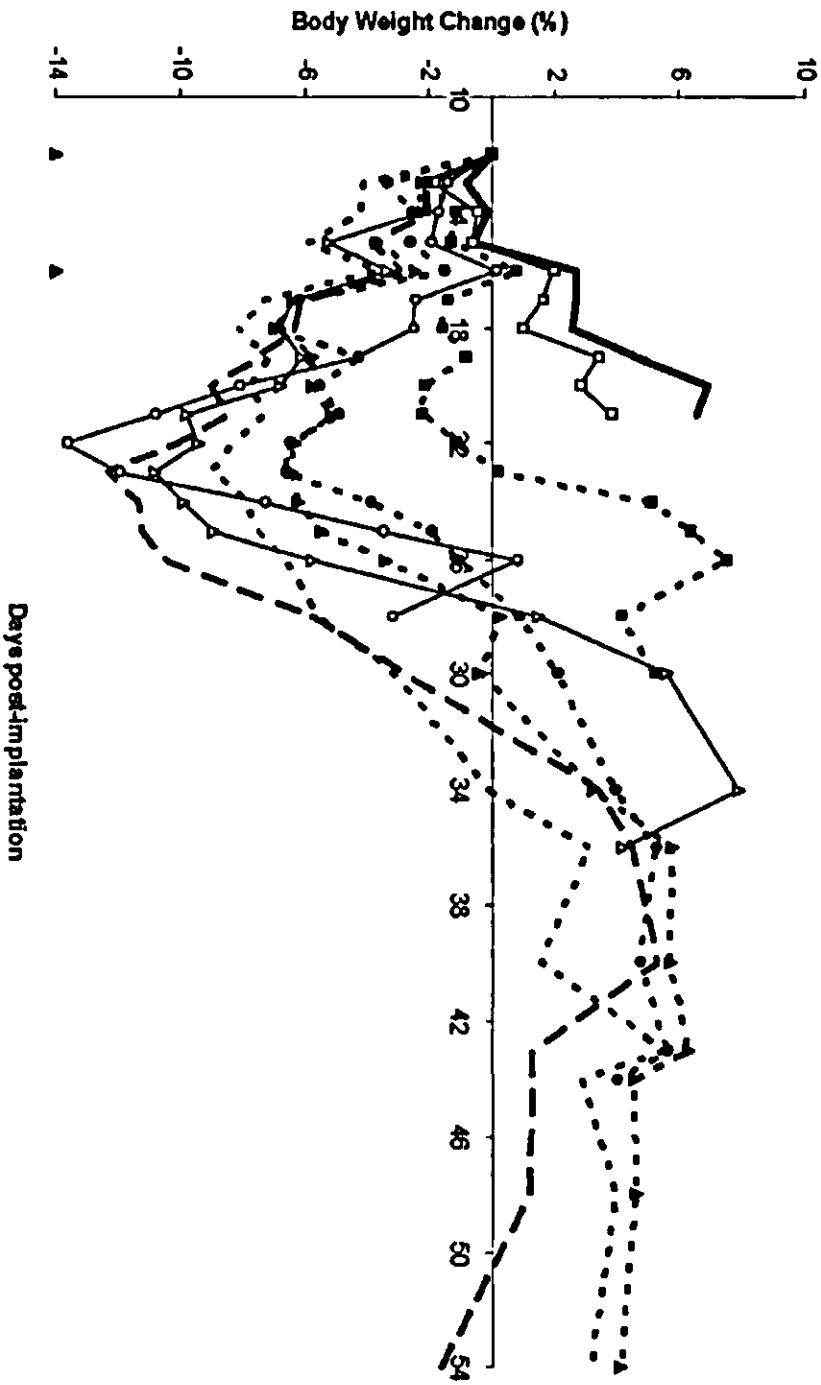

Body Weight Change (%)
-14
-10
-6
-2
2
6
10
Days post-implantation
10
18
26
30
34
38
42
46
50
54

FIG.3

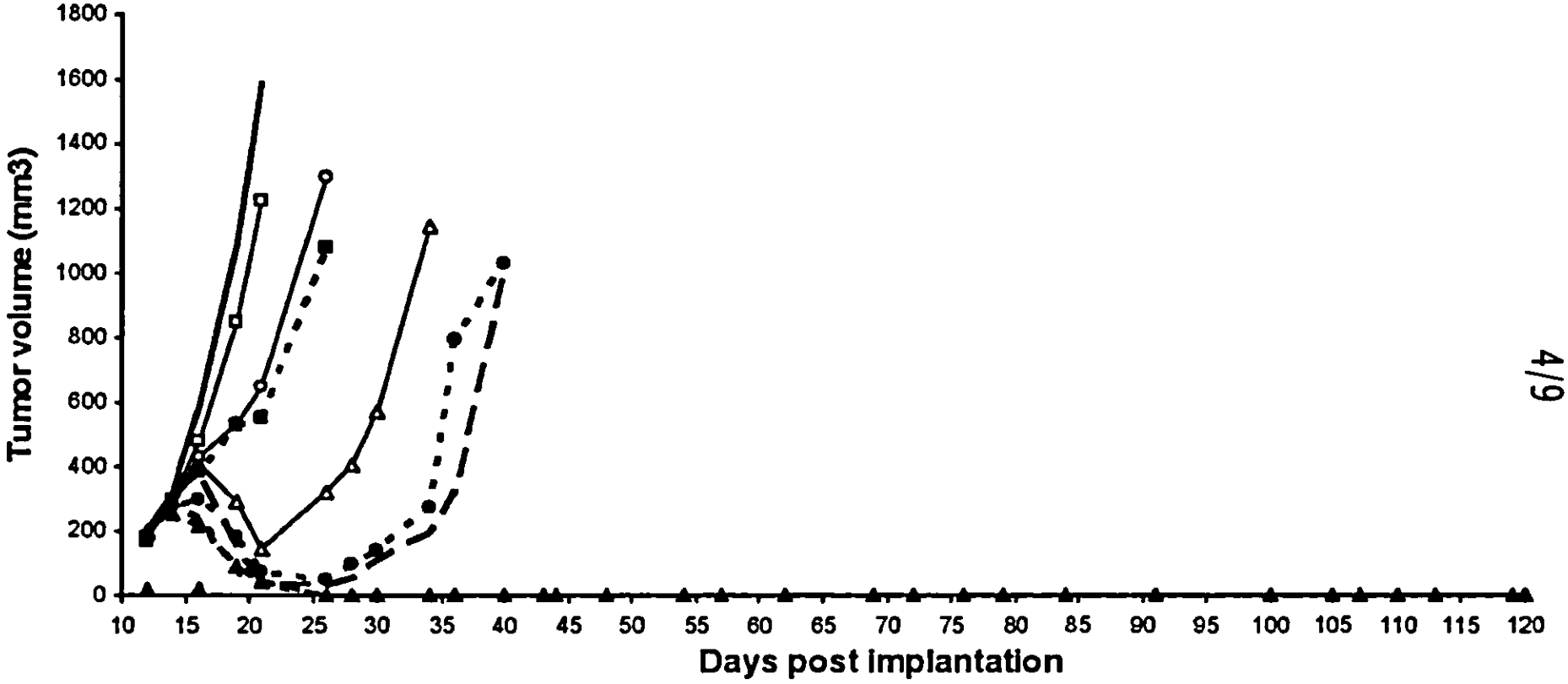

Tumor volume (mm3)
1800
1600
1400
1200
1000
800
600
400
200
0
10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120
Days post implantation

FIG.4

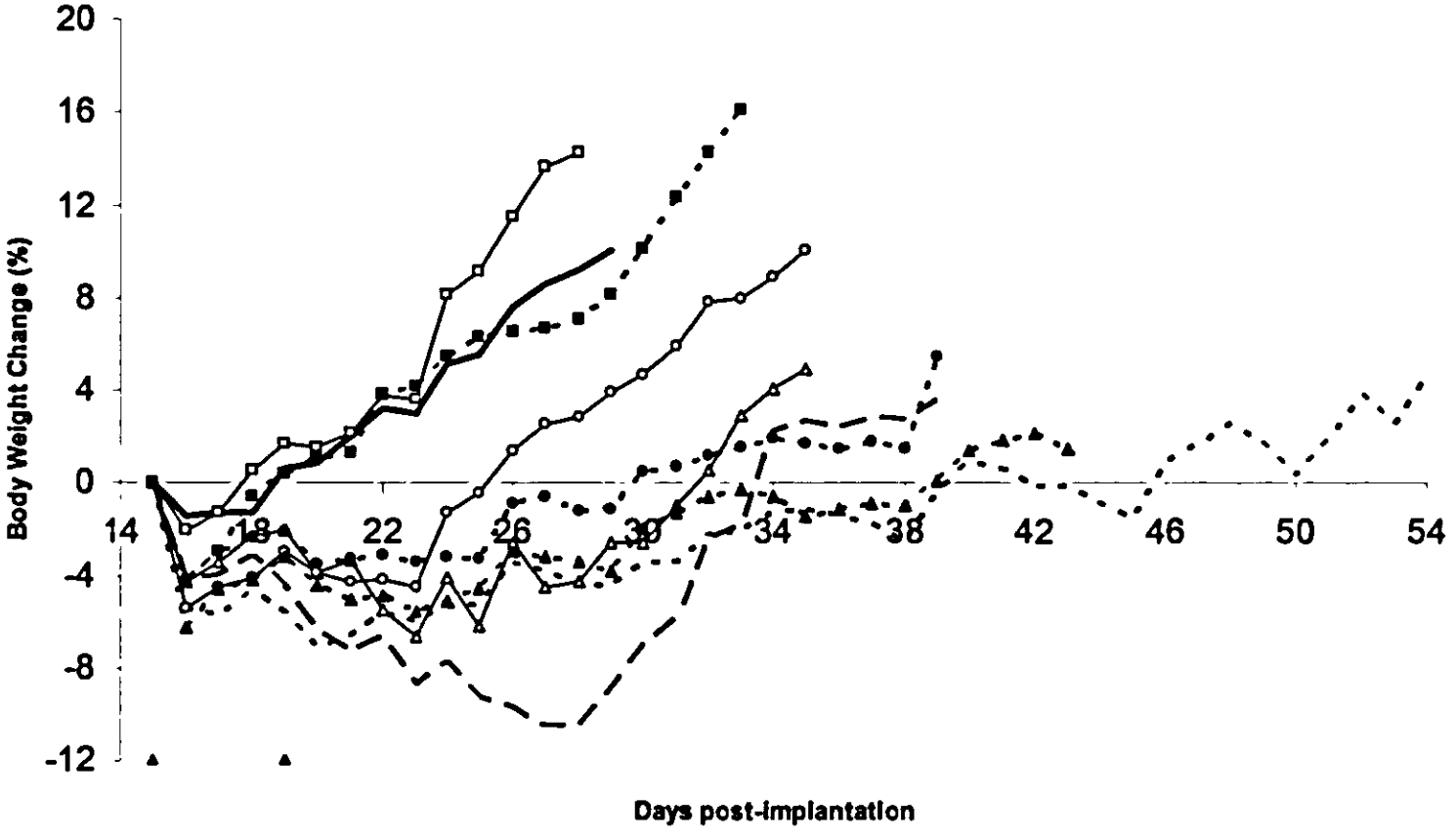

20
16
12
8
4
0
-4
-8
-12
Body Weight Change (%)
14
18
22
26
30
34
38
42
46
50
54
Days post-implantation

FIG.5

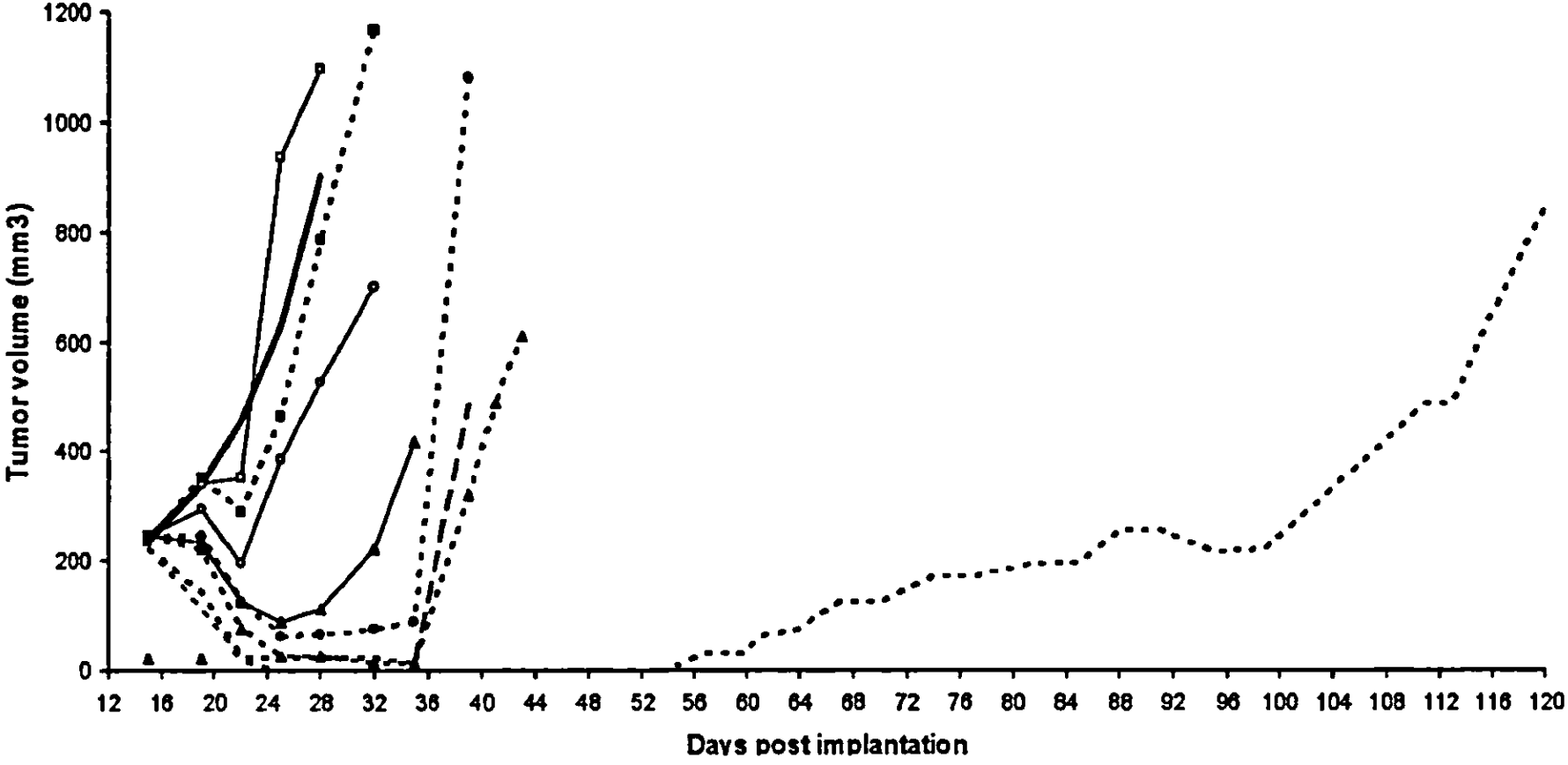

Tumor volume (mm3)
1200
1000
800
600
400
200
0
12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100 104 108 112 116 120
Days post implantation

FIG.6

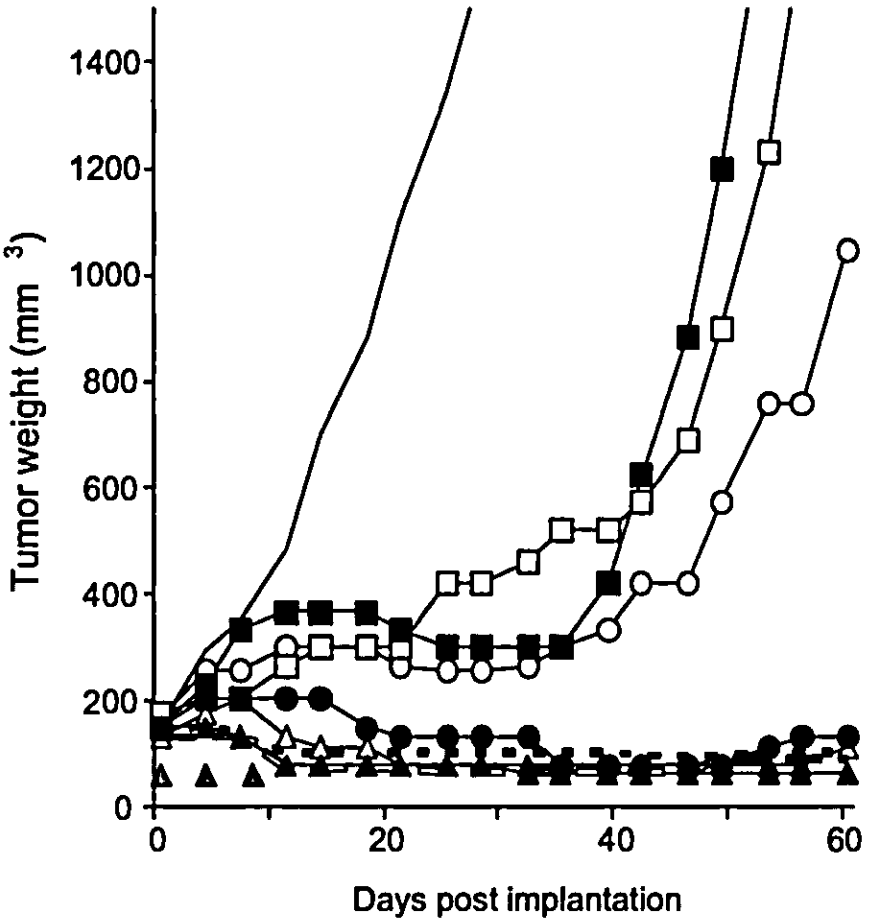

Tumor weight (mm 3)
1400
1200
1000
800
600
400
200
0
0
20
40
60
Days post implantation

FIG.7

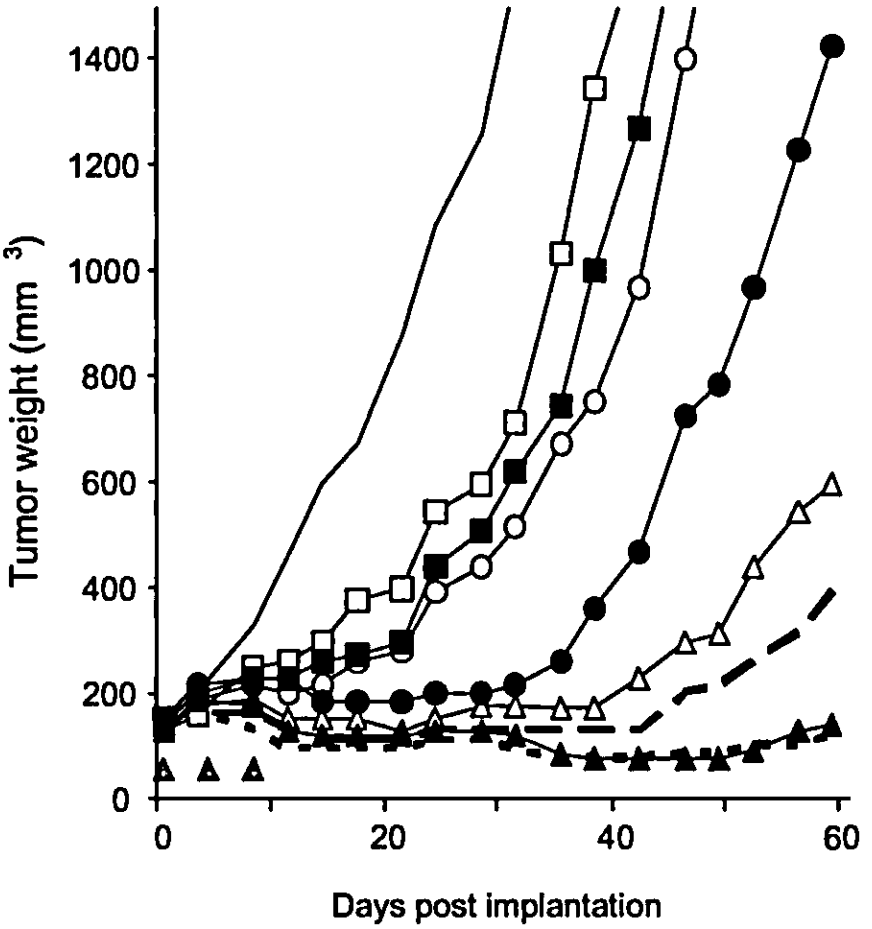

1400
1200
1000
800
600
400
200
0
Tumor weight (mm 3)
0
20
40
60
Days post implantation

FIG.8

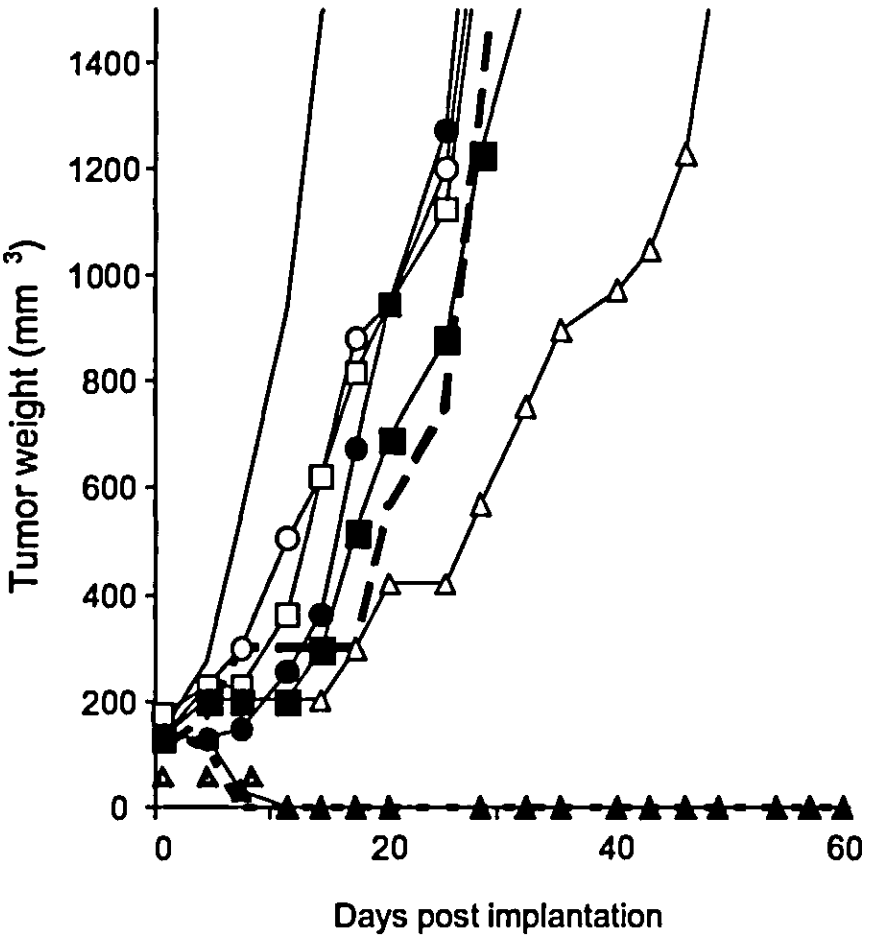

1400
1200
1000
800
600
400
200
0
Tumor weight (mm 3)
0
20
40
60
Days post implantation

FIG.9