Inventors/Applicants (for US only): LOPEZ MARTIN, Jose, Antonio [ES/ES]; Hospital Universitario 12 de Octubre, Avda de Cordoba s/n, E-28041 Madrid (ES).

Inventors/Applicants (for GB only): Mina, Antonio [ES/ES]; Colmenar Viejo, Madrid (ES).
COMBINATION OF APLIDINE AND CARBOPLATIN IN ANTICANCER TREATMENTS

The present invention relates to the treatment of cancers and, in particular, to the effective treatment of human cancers using Aplidine in combination with another drug, specifically Carboplatin.

BACKGROUND OF THE INVENTION

Cancer develops when cells in a part of the body begin to grow out of control. Although there are many kinds of cancer, they all start because of out-of-control growth of abnormal cells. Cancer cells can invade nearby tissues and can spread through the bloodstream and lymphatic system to other parts of the body. There are several main types of cancer. Carcinoma is cancer that begins in the skin or in tissues that line or cover internal organs. Epithelial cells, which cover internal and external surfaces of the body, including organs and lining of vessels, may give rise to a carcinoma. Sarcoma is cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is cancer that starts in blood-forming tissue such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream. Lymphoma and multiple myeloma are cancers that begin in the cells of the immune system.

In addition, cancer is invasive and tends to metastasise to new sites. It spreads directly into surrounding tissues and also may be disseminated through the lymphatic and circulatory systems.

Many treatments are available for cancer, including surgery and radiation for localised disease, and chemotherapy. However, the efficacy of available treatments for many cancer types is limited, and new, improved forms of treatment showing clinical benefit are needed. This is especially true
for those patients presenting with advanced and/or metastatic disease and for patients relapsing with progressive disease after having been previously treated with established therapies which become ineffective or intolerable due to acquisition of resistance or to limitations in administration of the therapies due to associated toxicities.

Since the 1950s, significant advances have been made in the chemotherapeutic management of cancer. Unfortunately, more than 50% of all cancer patients either do not respond to initial therapy or experience relapse after an initial response to treatment and ultimately die from progressive metastatic disease. Thus, the ongoing commitment to the design and discovery of new anticancer agents is critically important. Chemotherapy, in its classic form, has been focused primarily on killing rapidly proliferating cancer cells by targeting general cellular metabolic processes, including DNA, RNA, and protein biosynthesis.

Chemotherapy drugs are divided into several groups based on how they affect specific chemical substances within cancer cells, which cellular activities or processes the drug interferes with, and which specific phases of the cell cycle the drug affects. The most commonly used types of chemotherapy drugs include: DNA-alkylating drugs (such as cyclophosphamide, ifosfamide, cisplatin, carboplatin, dacarbazine), antimetabolites (5-fluorouracil, capecitabine, 6-mercaptopurine, methotrexate, gemcitabine, cytarabine, fludarabine), mitotic inhibitors (such as paclitaxel, docetaxel, vinblastine, vincristine), anthracyclines (such as daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone), topoisomerase II inhibitors (such as topotecan, irinotecan, etoposide, teniposide), and hormone therapy (such as tamoxifen, flutamide). The ideal antitumor drug would kill cancer cells selectively, with a wide index relative to its toxicity towards non-cancer cells and it would also retain its efficacy against cancer cells, even after prolonged exposure to the drug.
Unfortunately, none of the current chemotherapies with these agents possess an ideal profile. Most possess very narrow therapeutic indexes and, in addition, cancerous cells exposed to slightly sublethal concentrations of a chemotherapeutic agent may develop resistance to such an agent, and quite often cross-resistance to several other antitumor agents.

Aplidine (Dehydrodidemnin B) is a cyclic depsipeptide that was isolated from a Mediterranean marine tunicate, *Aplidium albicans*, and it is the subject of WO 91/04985. It is related to compounds known as didemnins, and has the following structure:

![Aplidine Structure](image)

More information on Aplidine, aplidine analogues, its uses, formulations and synthesis can be found in patent applications WO 99/42125, WO 01/35974, WO 01/76616, WO 02/30441, WO 02/02596, WO 03/33013 and WO 2004/080477. We incorporate by specific reference the content of each of these PCT texts.

In both animal preclinical studies and human clinical Phase I studies Aplidine has been shown to have cytotoxic potential against a broad spectrum of tumor types including leukemia and lymphoma. See for example:


Mechanistic studies indicate that Aplidine can block VEGF secretion in ALL-MOLT4 cells and in vitro cytotoxic activity at low concentrations (5nM) has been observed in AML and ALL samples from pediatric patients with de novo or relapsed ALL and AML. Aplidine appears to induce both a G1 and a G2 arrest in drug treated leukemia cells in vitro. Apart from down regulation of the VEGF receptor, little else is known about the mode(s) of action of Aplidine.

In phase I clinical studies with Aplidine, L-carnitine was given as a 24 hour pretreatment or co-administered to prevent myelotoxicity, see for example WO 02/30441. Co-administration of L-carnitine was proven to be able to improve the recovery of the drug induced muscular toxicity and has allowed for dose escalation of Aplidine.

Previously, in vitro and in vivo assays conducted with Aplidine in combination with other anticancer agents showed that the assayed drug combinations were useful in combination therapy for the treatment of leukemia and lymphoma. In WO 2004/080421, Aplidine was specifically evaluated in combination with methotrexate, cytosine arabinoside, mitoxantrone, vinblastine, methylprednisolone and doxorubicin for the treatment of leukemia and lymphoma. On the other hand, in PCT/US07/62936, Aplidine was specifically evaluated in combination with paclitaxel (Taxol®), doxorubicin, cisplatin, arsenic trioxide, 5-fluorouracil (5-
FU), cytosine arabinoside (AraC), carboplatin, 7-ethyl-10-hydroxycamptothecin (SN38), etoposide (VP16), melphalan, dexamethasone, cyclophosphamide, bortezomib, erlotinib, trastuzumab, lenalidomide (Revlimid®), interleukin-2 (IL-2), interferon-α 2 (INF-α), dacarbazine (DTIC), bevacizumab (Avastin®), idarubicin, thalidomide, and rituximab for the treatment of lung cancer, breast cancer, colon cancer, prostate cancer, renal cancer, melanoma, multiple myeloma, leukemia and lymphoma.

Carboplatin is a chemotherapy drug that belongs to the same family as cisplatin, specifically to the family of DNA alkylating agents. This compound is a platinum coordination complex with the following structural formula:

\[
\text{H}_2\text{N} \quad \begin{array}{c}
\text{O} \\
\text{Pt} \\
\text{O} \\
\text{H}_2\text{N}
\end{array} \\
\text{O} \\
\text{O}
\]

The treatment of cancer patients with platinum coordination complex, such as cisplatin or carboplatin, has increased substantially in the last decade. Carboplatin has proved to be useful in the treatment of some types of cancer, mainly brain tumors, endometrial cancer, germ cell tumors, head and neck cancer, and ovarian cancer.

Cancer patients eventually become resistant to treatment with platinum coordination complexes, such as carboplatin. The mechanism of resistance to these compounds is unclear but may be related to decreased drug accumulation, elevation of intracellular concentrations of metallothioneines or glutathione which bind and inactivate the drug, or to decreased drug-DNA adduct formation or repair. Therefore there is a need to develop effective therapies that overcome this resistance.

In PCT/US07/62936, preclinical assays combining Aplidine with Carboplatin were reported. According to the *in vitro* studies conducted a synergistic interaction of the combination was observed in prostate adenocarcinoma, colon adenocarcinoma and melanoma cells. Additionally, *in vivo* assays showed that a clear statistically significant potentiation of antitumor activity was obtained using this combination in two melanoma models.

It is an object of the present invention to provide an efficacious treatment of cancer in humans based on the combination of Aplidine with Carboplatin. In particular, it is an object of the invention to provide efficacious methods and products for preventing resistance, overcoming or mitigating established resistance to Carboplatin in human patients.

It is another object of the present invention to provide an effective method and products for potentiating the cytotoxic effects of Carboplatin in the clinical setting.
SUMMARY OF THE INVENTION

Unexpectedly, we found that when Aplidine and Carboplatin are given in combination, the maximum dosage of Carboplatin can be given without an increase or addition of the toxicity. This has been confirmed in clinical trials, in which full dose of Carboplatin has been given successfully with escalating doses of Aplidine.

Thus, the present invention provides a new method for treating a human patient afflicted with cancer, comprising administering to said patient Carboplatin in combination with Aplidine.

The invention further provides a method for treating a human patient afflicted with cancer, which involves administering Carboplatin and Aplidine, in which the amount of Carboplatin is at least 50%, at least 75%, at least 85%, at least 90%, at least 95% or at least 100% of the Recommended Dose for Carboplatin given as monotherapy, that is in the absence of Aplidine.

In a related aspect, the invention provides a method of treating a human patient afflicted with cancer, which involves administering Carboplatin and wherein Aplidine is administered as a combination therapy without a compensating drop in the dose of Carboplatin.

In another aspect, the present invention is directed to a method for treating a human patient afflicted with cancer which involves administering Aplidine in combination with Carboplatin, characterised in that the combination overcomes resistance to Carboplatin without increasing the toxicity of the therapy.

In a related aspect, the present invention provides a method of reducing resistance to Carboplatin in an individual having cancer.
comprising administering to the individual Aplidine and Carboplatin in a dose range for Carboplatin which is the same as the dosage given if Carboplatin was administered alone.

In another aspect, the present invention provides a combination therapy for the treatment of cancer in humans which comprises administering Aplidine and Carboplatin, using a cyclical protocol. Typical dosing protocols for the combination therapy are provided. The administration of Aplidine in combination with Carboplatin in humans in accordance with the methods and compositions of this invention is tolerable and provides antitumor activity at the dosage and regimens given.

In addition, this invention provides a method of treating cancer in humans, which method comprises administering Aplidine and Carboplatin in a specific sequence and with a predetermined cycle.

In another aspect, the present invention also provides a pharmaceutical composition comprising an effective therapeutic amount of Aplidine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, for use in the procedures and methods of this invention.

In a further aspect, the present invention also provides a pharmaceutical composition comprising an effective therapeutic amount of Carboplatin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, for use in the procedures and methods of this invention.

In addition, the present invention also provides a pharmaceutical composition comprising an effective therapeutic amount of Aplidine, or a pharmaceutically acceptable salt thereof, an effective therapeutic amount of Carboplatin, or a pharmaceutically acceptable salt thereof, and a
pharmaceutically acceptable carrier, for use in the procedures and methods of this invention.

The invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, in the preparation of a composition for use in the procedures and methods of this invention. Additionally, the invention also provides for the use of Carboplatin, or a pharmaceutically acceptable salt thereof, in the preparation of a composition for use in the procedures and methods of this invention.

In a further aspect of the present invention, a medical kit for administering Aplidine in combination with Carboplatin is provided, comprising printed instructions for administering Aplidine according to the procedures and methods of treatment set forth herein, and a supply of Aplidine in dosage units for at least one cycle, wherein each dosage unit comprises the appropriate amount of Aplidine for the treatments as defined above and a pharmaceutically acceptable carrier.

In a related aspect, a medical kit for administering Carboplatin in combination with Aplidine is also provided, comprising printed instructions for administering Carboplatin according to the procedures and methods of treatment set forth herein, and a supply of Carboplatin in dosage units for at least one cycle, wherein each dosage unit comprises the appropriate amount of Carboplatin for the treatments as defined above and a pharmaceutically acceptable carrier.
EMBODIMENTS OF THE INVENTION

Aplidine is a cyclic depsipeptide with the following structure:

\[
\begin{array}{c}
\text{\includegraphics[width=0.5\textwidth]{aplidine_structure.png}}
\end{array}
\]

The term "Aplidine" is intended here to cover any pharmaceutically acceptable salt, ester, solvate, hydrate or any other compound which, upon administration to the patient is capable of providing (directly or indirectly) the compound as described herein. However, it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the invention since these may be useful in the preparation of pharmaceutically acceptable salts. The preparation of salts and prodrugs and derivatives can be carried out by methods known in the art.

Pharmaceutical compositions of Aplidine that can be used include solutions, suspensions, emulsions, lyophilised compositions, etc., with suitable excipients for intravenous administration. Preferably, Aplidine may be supplied and stored as a sterile lyophilized product, comprising Aplidine and excipients in a formulation adequate for therapeutic use. In particular a formulation comprising mannitol is preferred. Further guidance on Aplidine formulations is given in WO 99/42125 which is incorporated herein by reference in its entirety.
The present invention is directed to provide an efficacious treatment of cancer in humans based on the combination of Aplidine with Carboplatin. The term "combination" as used throughout the specification, is meant to encompass the administration of the therapeutic agents in the same or separate pharmaceutical formulations, and at the same time or at different times.

Thus, Aplidine and Carboplatin may be provided as separate medicaments for administration at the same time or at different times. Preferably, Aplidine and Carboplatin are provided as separate medicaments for administration at different times. When administered separately and at different times, either Aplidine or Carboplatin may be administered first; however, it is preferable to administer Aplidine followed by Carboplatin. In addition, both drugs can be administered in the same day or at different days, and they can be administered using the same schedule or at different schedules during the treatment cycle.

Administration of the compounds or compositions of the present invention is by intravenous infusion. When Aplidine and Carboplatin are provided as separate medicaments for administration at different times, the infusion times for each may differ. Infusion times of up to 6 hours can be used, more preferably between 1 and 3 hours, with about 1 hour most preferred.

The administration of the combination is performed in cycles in accordance with the method of the invention. Intravenous infusion of Aplidine to the patient is typically repeated weekly on a cyclic basis. In this case the cyclic basis comprises a phase of weekly infusing and a phase of not infusing wherein patients are allowed to recover. Preferably Aplidine is administered weekly during 3 weeks and the phase of not infusing consists in 1-2 additional weeks, being 1 week the most preferred. The preferred
duration of each cycle for Aplidine is typically of 4-5 weeks, being 4 weeks the most preferred. Intravenous infusion of Carboplatin is given to the patients typically the first day of each cycle and then the patients are allowed to recover for the remainder of the cycle. The preferred duration of each cycle for Carboplatin is typically of 3-4 weeks, being 4 weeks the most preferred. Multiple cycles for both drugs can be given as needed. Thus, in a particularly preferred embodiment of the invention, a treatment cycle consists in the drug administration of Aplidine on day 1, 8, and 15, followed by Carboplatin on day 1, and treatment cycles are repeated every 4 weeks.

Dose delays and/or dose reductions and schedule adjustments are performed as needed depending on individual patient tolerance to treatments.

Therefore, in one aspect the invention provides a method for treating a human patient afflicted with cancer, comprising administering to said patient a therapeutically effective amount of Aplidine, or a pharmaceutical composition thereof, and a therapeutically effective amount of Carboplatin, or a pharmaceutical composition thereof, wherein Aplidine is administered by intravenous infusion and its administration is repeated weekly, preferably during 3 weeks out of 4, and wherein Carboplatin is preferably administered once every 4 weeks. On the first day of the treatment both drugs are administered by intravenous infusion with infusion times of up to 6 hours, preferably about 1 hour, and Aplidine is preferable first administered followed by Carboplatin.

On the other hand, in the present method of the invention, Aplidine is administered at a dose below 3.0 mg/m², preferably about 2.4 mg/m². Suitably the dose is at least about 2.4 mg/m². Preferably the dose is in the range of 2.4-3.0 mg/m². Preferably the dose is 2.4 mg/m², 2.5 mg/m², 2.6 mg/m², 2.7 mg/m², 2.8 mg/m², 2.9 mg/m², or 3.0 mg/m². Particularly preferably, the dose is 2.4 mg/m².
The dosage amount of Carboplatin is the full dosage range used in monotherapy according to the type of schedule given. This dose of Carboplatin is calculated using Calvert's formula (Calvert A.H. et al. J. Clin. Oncol. 1989, 7(11), 1748-1756): Dose of Carboplatin = Target AUC x (GFR + 25), wherein creatinine clearance is determined using $^{51}$Cr-EDTA method. This dosage formula was derived from a retrospective analysis of Carboplatin pharmacokinetics in 18 subjects with pretreatment glomerular filtration rate (GFR) in the range of 33 to 136 mL/min. Carboplatin plasma clearance was linearly related to GFR ($r = 0.85$, $P$ less than 0.00001) and rearrangements of the equation describing the correlation gave the dosage formula dose (mg) = target area under the free carboplatin plasma concentration versus time curve (AUC) x (1.2 x GFR + 20). In a prospective clinical and pharmacokinetic study the formula was used to determine the dose required to treat 31 subjects (GFR range, 33 to 135 mL/min) with 40 courses of carboplatin. The target AUC was escalated from 3 to 8 mg carboplatin /mL/min. Over this AUC range the formula accurately predicted the observed AUC (observed/ predicted ratio 1.24 +/- 0.11, $r = 0.886$) and using these additional data, the formula was refined.

Dose (mg) = target AUC x (GFR + 25) is now the recommended formula. AUC values of 4 to 6 and 6 to 8 mg/mL/min gave rise to manageable haematological toxicity in previously treated and untreated subjects, respectively, and hence target. AUC values of 5 and 7 mg/mL/min are recommended for single-agent carboplatin in these patient groups. Pharmacokinetic modeling demonstrated that the formula was reasonably accurate regardless of whether a one- or two-compartment model most accurately described carboplatin pharmacokinetics, assuming that body size did not influence non-renal clearance. The validity of this assumption was demonstrated in 13 subjects where no correlation between surface area and non-renal clearance was found ($r = 0.31$, $P = 0.30$). Therefore, the formula provides a simple and consistent method of determining carboplatin dose in
adults. Since the measure of carboplatin exposure in the formula is AUC, and not toxicity, it will not be influenced by previous or concurrent myelosuppressive therapy or supportive measures. The formula is therefore applicable to combination and high-dose studies as well as conventional single-agent therapy, although the target AUC for carboplatin will need to be redefined for combination chemotherapy.

Accordingly, in the present method of the invention, the dose of Carboplatin preferably targets an AUC of about 4-8 mg/mL/min, more preferably an AUC of about 4-6 mg/mL/min, and even more preferably an AUC of about 5 mg/mL/min.

Therefore according to a preferred embodiment of this aspect the invention provides a method for treating a human patient afflicted with cancer, comprising administering to said patient Aplidine, or a pharmaceutical composition thereof, at a dose below 3.0 mg/m\(^2\), preferably about 2.4 mg/m\(^2\), followed by the administration of Carboplatin, or a pharmaceutical composition thereof, at a dose targeting an AUC of about 5 mg/mL/min. Preferably both drugs are administered by intravenous infusion in infusion times of about 1 hour. The administration of Aplidine is repeated weekly, preferably during 3 weeks out of 4, and Carboplatin is preferably administered once every 4 weeks.

In another aspect, the present invention is directed to a medical kit for administering Aplidine in combination with Carboplatin, comprising printed instructions for administering Aplidine according to the dosages and schedules set forth above, and a supply of Aplidine in dosage units for at least one cycle, wherein each dosage unit comprises the appropriate amount of Aplidine for the treatments as defined above and a pharmaceutically acceptable carrier.
In a related aspect, the present invention is directed to a medical kit for administering Carboplatin in combination with Aplidine, comprising printed instructions for administering Carboplatin according to the dosages and schedules set forth above, and a supply of Carboplatin in dosage units for at least one cycle, wherein each dosage unit comprises the appropriate amount of Carboplatin for the treatments as defined above and a pharmaceutically acceptable carrier.

In another aspect, the present invention also provides a pharmaceutical composition comprising an effective therapeutic amount of Aplidine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, for use in the procedures and methods as defined herein.

In a further aspect, the present invention also provides a pharmaceutical composition comprising an effective therapeutic amount of Carboplatin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, for use in the procedures and methods as defined herein.

In addition, the present invention also provides a pharmaceutical composition comprising an effective therapeutic amount of Aplidine, or a pharmaceutically acceptable salt thereof, an effective therapeutic amount of Carboplatin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, for use in the procedures and methods as defined herein.

In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, in the preparation of a composition for use in the procedures and methods as defined herein.
In a related aspect, the invention further provides for the use of Carboplatin, or a pharmaceutically acceptable salt thereof, in the preparation of a composition for use in the procedures and methods as defined herein.

And in a further aspect, the invention also provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, and Carboplatin, or a pharmaceutically acceptable salt thereof, in the preparation of a composition for use in the procedures and methods as defined herein.

In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer, in combination therapy with Carboplatin.

In a related aspect, the invention further provides for the use of Carboplatin, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer, in combination therapy with Aplidine.

In a related aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof in combination with Carboplatin, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer.

In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, for the treatment of cancer, in combination therapy with Carboplatin.

In a related aspect, the invention further provides for the use of Carboplatin, or a pharmaceutically acceptable salt thereof, for the treatment of cancer, in combination therapy with Aplidine.
In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof in combination with Carboplatin, or a pharmaceutically acceptable salt thereof, for the treatment of cancer.

In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, as a medicament, in combination therapy with Carboplatin.

In a related aspect, the invention further provides for the use of Carboplatin, or a pharmaceutically acceptable salt thereof, as a medicament, in combination therapy with Aplidine.

In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof in combination with Carboplatin, or a pharmaceutically acceptable salt thereof, as a medicament.

In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, as a medicament for the treatment of cancer, in combination therapy with Carboplatin.

In a related aspect, the invention further provides for the use of Carboplatin, or a pharmaceutically acceptable salt thereof, as a medicament for the treatment of cancer, in combination therapy with Aplidine.

In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof in combination with Carboplatin, or a pharmaceutically acceptable salt thereof, as a medicament for the treatment of cancer.

In another aspect, the invention further provides for the use of
Aplidine, or a pharmaceutically acceptable salt thereof, as a medicament formulated to be provided in a dosage and/or schedule as defined herein for the treatment of cancer, in combination therapy with Carboplatin.

In a related aspect, the invention further provides for the use of Carboplatin, or a pharmaceutically acceptable salt thereof, as a medicament formulated to be provided in a dosage and/or schedule as defined herein for the treatment of cancer, in combination therapy with Aplidine.

In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, as a medicament formulated to be provided/suitable to administered at a dosage and/or schedule as defined herein in combination with Carboplatin, or a pharmaceutically acceptable salt thereof, as a medicament formulated to be provided in a dosage and/or schedule as defined herein for the treatment of cancer.

In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament formulated to be provided/suitable to administered at a dosage and/or schedule as defined herein for the treatment of cancer, in combination therapy with Carboplatin.

In a related aspect, the invention further provides for the use of Carboplatin, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament formulated to be provided/suitable to administered at a dosage and/or schedule as defined herein for the treatment of cancer, in combination therapy with Aplidine.

In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof and Carboplatin, or a pharmaceutically acceptable salt thereof, for the manufacture of a
medicament formulated to be provided/ suitable to administered at a dosage and/ or schedule as defined herein for the treatment of cancer.

In another aspect, the invention further provides for the formulation of one or more dosage units of Aplidine, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, said dosage units formulated to be provided in a dosage and/ or schedule as defined herein for the treatment of cancer, in combination therapy with Carboplatin.

In a related aspect, the invention further provides for the formulation of one or more dosage units of Carboplatin, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, said dosage units formulated to be provided in a dosage and/ or schedule as defined herein for the treatment of cancer, in combination therapy with Aplidine.

In another aspect, the invention further provides for the formulation of one or more dosage units of Aplidine, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, and one or more dosage units of Carboplatin, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, said dosage units formulated to be provided in a dosage and/ or schedule as defined herein for the treatment of cancer.

In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, in the preparation of a composition, formulated to be provided in a dosage and/ or schedule as defined herein for use in the procedures and methods as defined herein, in combination therapy with Carboplatin.

In a related aspect, the invention further provides for the use of Carboplatin, or a pharmaceutically acceptable salt thereof, in the preparation of a composition, formulated to be provided in a dosage and/ or
schedule as defined herein for use in the procedures and methods as defined herein, in combination therapy with Aplidine.

In another aspect, the invention further provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, in the preparation of a composition, and Carboplatin, or a pharmaceutically acceptable salt thereof, in the preparation of a composition, both formulated to be provided in a dosage and/or schedule as defined herein for use in the procedures and methods as defined herein.

In another aspect, the invention further provides a medicament, dosage unit(s), formulation or composition of Aplidine, or a pharmaceutically acceptable salt thereof, specifically configured to the dosages and/or schedules given herein, the Aplidine being given in combination therapy with Carboplatin. This specific configuration is carried out during the preparation process of the final medicament, and is not part of the actions carried out by the doctor when treating the patient.

In a related aspect, the invention further provides a medicament, dosage unit(s), formulation or composition of Carboplatin, or a pharmaceutically acceptable salt thereof, specifically configured to the dosages and/or schedules given herein, the Carboplatin being given in combination therapy with Aplidine. This specific configuration is carried out during the preparation process of the final medicament, and is not part of the actions carried out by the doctor when treating the patient.

In another aspect, the invention further provides a medicament, dosage unit(s), formulation or composition of Aplidine, or a pharmaceutically acceptable salt thereof, specifically configured to the dosages and/or schedules given herein, together with a medicament, dosage unit(s), formulation or composition of Carboplatin, or a pharmaceutically acceptable salt thereof, specifically configured to the dosages and/or schedules given
herein. This specific configuration is carried out during the preparation process of the final medicament, and is not part of the actions carried out by the doctor when treating the patient.

In a further aspect, the invention provides a dosage unit(s), medicament, formulation or composition comprising Aplidine, or a pharmaceutically acceptable salt thereof, specifically adapted to be administered in the dosages and/or schedules given herein, the Aplidine being given in combination therapy with Carboplatin.

In a related aspect, the invention provides a dosage unit(s), medicament, formulation or composition comprising Carboplatin, or a pharmaceutically acceptable salt thereof, specifically adapted to be administered in the dosages and/or schedules given herein, the Carboplatin being given in combination therapy with Aplidine.

In a further aspect, the invention provides a dosage unit(s), medicament, formulation or composition comprising Aplidine, or a pharmaceutically acceptable salt thereof, and a dosage unit(s), medicament, formulation or composition comprising Carboplatin, or a pharmaceutically acceptable salt thereof, specifically adapted to be administered in the dosages and/or schedules given herein.

In a further aspect, the invention provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, in a medicament for the treatment of cancer wherein the medicament is configured for administration at the dosages and/or schedules given herein, the Aplidine being given in combination therapy with Carboplatin.

In a related aspect, the invention provides for the use of Carboplatin, or a pharmaceutically acceptable salt thereof, in a medicament for the treatment of cancer wherein the medicament is configured for administration
at the dosages and/or schedules given herein, the Carboplatin being given in combination therapy with Aplidine.

In a further aspect, the invention provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, and Carboplatin, or a pharmaceutically acceptable salt thereof, in a medicament for the treatment of cancer wherein the medicament is configured for administration at the dosages and/or schedules given herein.

In a further aspect, the invention provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer wherein the medicament is configured for administration at the dosages and/or schedules given herein, the Aplidine being given in combination therapy with Carboplatin.

In a related aspect, the invention provides for the use of Carboplatin, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer wherein the medicament is configured for administration at the dosages and/or schedules given herein, the Carboplatin being given in combination therapy with Aplidine.

In a further aspect, the invention provides for the use of Aplidine, or a pharmaceutically acceptable salt thereof, and Carboplatin, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer wherein the medicament is configured for administration at the dosages and/or schedules given herein.

In a further aspect, the invention provides Aplidine or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein Aplidine is administered in combination therapy with Carboplatin or a pharmaceutically acceptable salt thereof.
In a further aspect, the invention provides Carboplatin or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein Carboplatin is administered in combination therapy with Aplidine or a pharmaceutically acceptable salt thereof.

In one of the preferred embodiments, Example 1, it is showed the results of a phase I clinical trial wherein Aplidine is administered intravenously as a 1-hour infusion on days 1, 8, and 15 every 4 weeks, followed by the intravenous administration of Carboplatin, at a dose targeting an AUC of about 5 mg/mL/min, as 1-hour infusion on day 1 every 4 weeks. According to said study the maximum tolerated dose (MTD) of Aplidine was determined as 3.0 mg/m² in the course of treatments, and the recommended dose (RD) was determined as 2.4 mg/m².

By using a dosing regimen in accordance with that used in this preferred embodiment, it has been found that the combination is well tolerated when Carboplatin is administered at full therapeutic dose for prolonged periods of time.

Premedication and supportive medication can be given. As disclosed in Example 1, a premedication using Glucocorticoids (dexamethasone or equivalent), 5-HT3-receptor antagonists (ondansetron, granisetron, tropisetron, or equivalent), Hi-receptor antagonist (difenhydramine hydrochloride or equivalent), and H2-receptor antagonist (ranitidine or equivalent) can be useful to avoid the side effects due to the administration of the chemotherapeutic agents. If necessary, in addition to the above premedication, metoclopramide can be also administered.

Depending on the type of tumor and the development stage of the disease, the treatments of the invention are useful in promoting tumor regression, in stopping tumor growth and/or in preventing metastasis. In
particular, the method of the invention is suited for human patients, especially those who are relapsing or refractory to previous chemotherapy. First line therapy is also envisaged.

Preferably, the method of the invention is used according to the above schedules and dosages for the treatment of colorectal cancer, malignant melanoma, ovarian cancer, cholangiocarcinoma, liver cancer (hepatocarcinoma), hepatobiliary cancer, esophageal carcinoma (esophagus carcinoma), carcinoma of esophagogastric junction, adenocarcinoma of stomach, bladder cancer, neuroendocrine gallbladder carcinoma and pancreas cancer.

The following example further illustrates the invention. It should not be interpreted as a limitation of the scope of the invention.

To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about". It is understood that, whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value.

EXAMPLES OF THE INVENTION

Example 1
A phase I trial combining Aplidine with Carboplatin was conducted. The main objective of this study was to determine the safety, tolerability and to identify the maximum tolerated dose (MTD) and the recommended dose
of Aplidine administered in combination with Carboplatin to subjects with advanced malignant solid tumours or lymphoma, for whom no standard therapy is left. Other secondary objectives of the trial were to study drug-drug pharmacokinetic interactions between Aplidine and Carboplatin, and to evaluate the preliminary antitumor activity of Aplidine when administered in combination with Carboplatin. Aplidine was administered intravenously (IV) over 1 hour, on days 1, 8, and 15, every 4 weeks, and Carboplatin was administered intravenously (IV) over 1 hour at a fixed dose targeting an AUC of about 5 mg/mL/min, immediately after the infusion of Aplidine, once every 4 weeks (on day 1).

The maximum tolerated dose (MTD) relates to the highest dose at which at least 2 out of 3-6 subjects experience a dose limiting toxicity (DLT) at any given dose level, being this dose level considered the MTD. On the other hand, the recommended dose (RD) is intended to relate to the highest dose at which less than 2 of 6 subjects experience DLT during the cycles 1 or 2.

We designed a dose finding trial wherein cohorts of 3-6 patients were treated at increasing Aplidine doses (1.8, 2.4 and 3.0 mg/m²) administered intravenously over 1 hour on days 1, 8, 15, every 4 weeks. As mentioned before, Carboplatin was administered intravenously over 1 hour at a fixed dose targeting an AUC of about 5 mg/mL/min, immediately after the infusion of Aplidine, once every 4 weeks (on day 1).

All subjects received the following premedication, 20-30 minutes before the administration of Aplidine: Glucocorticoids (dexamethasone 8 mg IV or equivalent), 5-HT3-receptor antagonists (ondansetron 8 mg IV, granisetron 3 mg IV, tropisetron 5 mg IV, or equivalent), Hi-receptor antagonist (difenhydramine hydrochloride 25 mg IV or equivalent), and H2-receptor antagonist (ranitidine 50 mg IV or equivalent). If necessary, in addition to the above premedication, 10 mg of metoclopramide every 8 hours
were administered after infusion, and the duration of treatment with 5-HT3-receptor antagonists and/or dexamethasone was extended, if needed.

Aplidine drug product was provided as a lyophilized powder containing Aplidine and mannitol, and it was reconstituted with a reconstitution solution containing Cremophor EL/Ethanol/Water for injection (15%/15%/70%). Carboplatin was provided in the form of Carboplatin Solution for Injection and supplied in individually packed clear glass containing sterile solutions of Carboplatin 10 mg/ml.

Subjects enrolled in this clinical trial were adult patients with confirmed malignant solid tumor or lymphoma for which no standard therapy would reasonable be expected to result in cure or palliation. Inclusion criteria included recovery from any drug-related adverse event derived from previous therapies excluding alopecia and NCI-CTCAE grade < 2 symptomatic peripheral neuropathy, life expectancy of at least 3 months, adequate cardiac function (Left ventricular ejection fraction (LVEF) within normal limits), adequate renal, liver and bone marrow functions, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0, 1 or 2, no evidence of progressive central nervous system metastasis or any symptomatic brain or leptomeningeal metastases, no active infection or serious intercurrent illness, and no active cardiac disease, no chemotherapy, radiotherapy, hormonal therapy or biological therapy within four weeks prior to entry (8 weeks in case of extensive radiotherapy and 6 weeks in case of previous nitrosourea, mitomycin C or high dose chemotherapy), and measurable or non measurable disease using the RECIST criteria. Subjects whose disease progressed while on a prior carboplatin-based chemotherapy and never responded to such regime were excluded.

Dose limiting toxicities (DLT) were defined as follows:
- Haematological drug-related adverse events:
- Grade 4 neutropenia (absolute neutrophil count (ANC) < 0.5 x 10^9/L) lasting more than 5 days
- Grade 4 neutropenia concomitant with fever (i.e. body temperature \( \geq 38.5^\circ C \)), and fever should not be disease-related
- Grade 4 neutropenia and sepsis or other severe infection
- Platelets (thrombocytopenia) < 25 x 10^9/L

- Any other grade 3-4 non-hematological adverse event suspected to be related to study drugs, except nausea/vomiting (unless the patient was receiving an optimal anti-emetic regimen), reversible diarrhoea, hypersensitivity reactions, and non-clinically relevant biochemical abnormalities (i.e. isolated increase in GGT)

- Grade 3-4 increases in AST/ALT were individually discussed, and was not considered DLT if:
  - They were disease-related
  - They were not associated with clinically relevant drug-related clinical symptoms
  - They were the only abnormality in liver function tests besides eventual increases in GGT (including drug-related direct hyperbilirubinemia of any grade, drug-related increase of alkaline phosphatase > grade 1, > grade 1 drug-related decreases in albumin or phothrombin), and there were no other relevant drug-related biochemistry abnormalities
  - They were rapidly reversible (i.e. recover to \( \leq 2.5 \times ULN \) by day 29) and did not compromise the administration of Aplidine on days 8 and 15

- Delay in the administration of a subsequent dose of Aplidine and/ or Carboplatin exceeding 2 weeks, due to adverse event suspected to be related to study drug(s).

Nineteen patients were included in the clinical trial. These patients were suffering of different types of cancers, such as colorectal cancer (6), malignant melanoma (4), ovarian cancer (2), cholangiocarcinoma (1), liver
cancer (hepatocarcinoma) (1), neuroendocrine gallbladder carcinoma (1), pancreas cancer (1), esophageal carcinoma (esophagus carcinoma) (1), carcinoma of esophagogastric junction (gastroesophageal junction carcinoma) (1) and adenocarcinoma of stomach (1).

In Table I it is summarised the dose cohorts, patients and adverse events (DLTs) observed during the study.

Table I

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>No. Patients</th>
<th>Carboplatin (Target AUC)</th>
<th>Aplidine</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>4**</td>
<td>5</td>
<td>1.8 mg/m²</td>
<td>-</td>
</tr>
<tr>
<td>Level 2</td>
<td>10</td>
<td>5</td>
<td>2.4 mg/m²</td>
<td>-</td>
</tr>
<tr>
<td>Level 3</td>
<td>5</td>
<td>5</td>
<td>3.0 mg/m²</td>
<td>2*</td>
</tr>
</tbody>
</table>

* 1 patient experienced a delay of 2nd cycle > 2 weeks due to G3 transaminitis (ALT increase) and G3 thrombocytopenia, and another patient experienced an omission of 2nd infusion in first cycle due to G3 ALT increase.

** 3 patients evaluable for DLT.

In Table II, III, and IV, it is summarised the drug-related hematological toxicity, biochemical alterations, and adverse events observed per patient during the study.

Table H: Drug-related Hematological Toxicity per patient (n=19)

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose Level Aplidine (N)</th>
<th>Grade all No. of patients</th>
<th>Grade 3 and 4 No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>1.8 (4) 2.4 (10) 3.0 (5)</td>
<td>2 1 2</td>
<td>0 0 2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.8 (4) 2.4 (10) 3.0 (5)</td>
<td>4 6 5</td>
<td>0 0 2</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.8 (4) 2.4 (10) 3.0 (5)</td>
<td>3 9 5</td>
<td>0 1 0</td>
</tr>
</tbody>
</table>
Table HI: Drug-related Biochemical alterations per patient (n=19)

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose Level Aplidine (N)</th>
<th>Grade all No. of patients</th>
<th>Grade 3 and 4 No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/GPT increase</td>
<td>1.8 (4)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2.4 (10)</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3.0 (5)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>AST/GOT increase</td>
<td>1.8 (4)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2.4 (10)</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3.0 (5)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>1.8 (4)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2.4 (10)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3.0 (5)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>1.8 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2.4 (10)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3.0 (5)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CPK increase</td>
<td>1.8 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2.4 (10)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3.0 (5)</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Table IV: Drug related adverse events per patient (n=19)

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose Level Aplidine (N)</th>
<th>Grade all No. of patients</th>
<th>Grade 3 and 4 No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>1.8 (4)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2.4 (10)</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3.0 (5)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.8 (4)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2.4 (10)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3.0 (5)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.8 (4)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2.4 (10)</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3.0 (5)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>1.8 (4)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2.4 (10)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3.0 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1.8 (4)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2.4 (10)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3.0 (5)</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
Therefore, the most common drug-related adverse events were fatigue, mild to moderate nausea and vomiting, transient muscular weakness, and asymptomatic, reversible increase of transaminases.

On the other hand, regarding the antitumor activity observed during the study, four patients suffering of different types of cancers had stable disease (SD). Table V summarises the antitumor activity observed assessed by RECIST criteria.

Table V

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Primary tumor type</th>
<th>Dose level Aplidine</th>
<th>No. of prior chemotherapy lines</th>
<th>TTP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD ≥ 3 months</td>
<td>Hepatocarcinoma</td>
<td>2.4</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Esophagogastric junction</td>
<td>2.4</td>
<td>1</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>Neuroendocrine gallbladder</td>
<td>3</td>
<td>1</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Colorectal</td>
<td>2.4</td>
<td>2</td>
<td>3.5</td>
</tr>
</tbody>
</table>

From this study it was concluded that administration of Aplidine in combination with Carboplatin was safe and well tolerated. In addition, the MTD of Aplidine was determined at 3.0 mg/m² (at level 3), and its RD was established at 2.4 mg/m² (at level 2), when is administered in combination with Carboplatin at a fixed dose targeting an AUC of about 5 mg/mL/min. Additionally, it has been demonstrated that the maximum dosage of Carboplatin can be given in combination with Aplidine without an increase or addition of the toxicity. Finally, prolonged stabilizations of disease were observed in patients with different gastrointestinal tumors.
Claims:

1. A method for treating a human patient afflicted with cancer, which comprises administering to the patient Carboplatin, or a pharmaceutically acceptable salt thereof, and Aplidine, or a pharmaceutically acceptable salt thereof.

2. A method for preventing resistance, overcoming or mitigating established resistance to Carboplatin in a human patient afflicted with cancer which comprises administering to the patient Carboplatin, or a pharmaceutically acceptable salt thereof, and Aplidine, or a pharmaceutically acceptable salt thereof.

3. A method for potentiating the cytotoxic effects of Carboplatin in a human patient afflicted with cancer which comprises administering to the patient Carboplatin, or a pharmaceutically acceptable salt thereof, and Aplidine, or a pharmaceutically acceptable salt thereof.

4. The method according to any preceding claim, wherein Aplidine is administered as a combination therapy with Carboplatin without a compensating drop in the dose of Carboplatin.

5. The method according to claim 4, wherein the amount of Carboplatin is at least 90% of the Recommended Dose for Carboplatin given as monotherapy.

6. The method according to any preceding claim, wherein Carboplatin and Aplidine are administered sequentially.

7. The method according to claim 6, wherein Aplidine is first administered followed by Carboplatin.
8. The method according to any one of claims 6 or 7, wherein Carboplatin and Aplidine are administered by intravenous infusion and the infusion time for each drug is up to 6 hours.

9. The method according to claim 8, wherein the infusion time for each drug is about 1 hour.

10. The method according to any one of claims 6 to 9, wherein Aplidine is administered weekly during 3 weeks out of 4-5 weeks, and Carboplatin is administered once every 3-4 weeks.

11. The method according to claim 10, wherein Aplidine is administered weekly during 3 weeks out of 4 weeks, and Carboplatin is administered once every 4 weeks.

12. The method according to claim 11, wherein Aplidine is administered on day 1, 8 and 15, followed by Carboplatin on day 1, and treatment cycles are repeated every 4 weeks.

13. The method according to any preceding claim, wherein Aplidine is administered at a dose between about 2.4 and about 3.0 mg/m² and Carboplatin is administered at a dose targeting an AUC of between about 4 and about 6 mg/mL/min.

14. The method according to any preceding claim, wherein Aplidine is administered at a dose about 2.4 mg/m² over an infusion time of about 1 hour followed by the administration of Carboplatin at a dose targeting an AUC of about 5 mg/mL/min over an infusion time of about 1 hour.

15. The method according to any preceding claim, in which the patient is relapsing or refractory to previous chemotherapy.
16. The method according to any preceding claim, in which the patient has a cancer selected from colorectal cancer, malignant melanoma, ovarian cancer, cholangiocarcinoma, liver cancer, hepatobiliary cancer, esophageal carcinoma, adenocarcinoma of stomach, bladder cancer and pancreas cancer.

17. The method according to any of claims 1 to 15, in which the patient has a cancer selected from neuroendocrine gallbladder carcinoma, esophagus carcinoma, and carcinoma of esophagogastric junction.

18. The use of Aplidine, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for a method according to any of claims 1 to 17.

19. The use of Carboplatin, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for a method according to any of claims 1 to 17.

20. A formulation of one or more dosage units of Aplidine, or a pharmaceutically acceptable salt thereof, wherein said dosage units are formulated to be provided for a method according to any of claims 1 to 17.

21. A formulation of one or more dosage units of Carboplatin, or a pharmaceutically acceptable salt thereof, wherein said dosage units are formulated to be provided for a method according to any of claims 1 to 17.

22. A medical kit for administering Aplidine in combination with Carboplatin, comprising printed instructions for administering Aplidine in a method according to any of claims 1 to 17, and a supply of Aplidine in dosage units for at least one cycle, wherein each dosage unit comprises the appropriate amount of Aplidine for a method according to any of claims 1 to 16 and a pharmaceutically acceptable carrier.
23. A medical kit for administering Carboplatin in combination with Aplidine, comprising printed instructions for administering Carboplatin in a method according to any of claims 1 to 17, and a supply of Carboplatin in dosage units for at least one cycle, wherein each dosage unit comprises the appropriate amount of Carboplatin for a method according to any of claims 1 to 17 and a pharmaceutically acceptable carrier.

24. Aplidine or a pharmaceutically acceptable salt thereof for use in a method according to any of claims 1 to 17.

25. Carboplatin or a pharmaceutically acceptable salt thereof for use in a method according to any of claims 1 to 17.
## INTERNATIONAL SEARCH REPORT

### A. CLASSIFICATION OF SUBJECT-MATTER

<table>
<thead>
<tr>
<th>INV.</th>
<th>A61K31/555</th>
<th>A61K38/15</th>
<th>A61P35/00</th>
</tr>
</thead>
</table>

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 practical, search terms used)

- EPO-Internal
- EMBASE
- BIOSIS
- PHARMAPROJECTS

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>x,P</td>
<td>WO 2007/101235 A (PHARMA MAR S A U [ES]; FAIRCLOTH GLYNN THOMAS [US]; AVILES MARIN PABLO) 7 September 2007 (2007-09-07) cited in the application pages 63-6.5</td>
<td>1-25</td>
</tr>
</tbody>
</table>

* Special categories of cited documents:

- **A**: document defining the general state of the art which is not considered to be of particular relevance
- **E**: earlier document but published on or after the International filing date
- **I**: document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **O**: document referring to an oral disclosure, use, exhibition or other means
- **P**: document published prior to the international filing date but later than the priority date claimed
- **T**: document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- **X**: document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- **Y**: document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- **S**: document member of the same patent family

Date of the actual completion of the International search: 9 June 2008

Date of mailing of the international search report: 17/06/2008

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31651 epo M, Fax: (+31-70) 340-3016

Authorized officer:

Trifl | jeff-Riolo, S

Form PCT/02/4210 (second sheet) (April 2002)
<table>
<thead>
<tr>
<th>Patent document <em>cited</em> in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 2004080421 A</td>
<td>23-09-2004</td>
<td>AU 2004220451 A1</td>
<td>23-09-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2516572 A1</td>
<td>23-09-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1753684 A</td>
<td>29-03-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1761480 A</td>
<td>19-04-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1620117 A2</td>
<td>01-02-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2006519848 T</td>
<td>31-08-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20060002778 A</td>
<td>09-01-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MX PA05009741 A</td>
<td>16-11-2005</td>
</tr>
<tr>
<td>WO 2007101235 A</td>
<td>07-09-2007</td>
<td>NONE</td>
<td></td>
</tr>
</tbody>
</table>