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(54) Title: KIT FOR INHALED CHEMOTHERAPY, AND TREATMENT OF LUNG CANCER WITH SAID KIT

(57) Abstract: Kit for an inhaled chemotherapy comprising a series of single hermetically packaged therapeutic doses of a dry powder for inhalation containing at least one anti-neoplastic agent chosen in the group consisting of platinum drugs with a lipid matrix and a PEGylated excipient and a series of disposable dry powder inhaler devices, its use and method of treatment of cancer lungs with said kit.



**KIT FOR INHALED CHEMOTHERAPY, AND TREATMENT OF LUNG CANCER
WITH SAID KIT**

5 The present invention relates to a kit for an inhaled chemotherapy, the use of the kit for an inhaled chemotherapy in a polytherapy and a therapeutic treatment against lung cancer.

 Lung cancer is the cancer with the highest prevalence and mortality in the world. In most cases, lung cancer is diagnosed at advanced
10 stages. Therefore, the patients often present already metastases in the lungs or in other organs, i.e. extrapulmonary metastases. Treatment modalities are mostly used in combination and consist in surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy.

 Chemotherapy is used in up to 60% of lung cancer patients,
15 mainly in advanced stages of the disease. Chemotherapy is currently administered through intravenous injection or per os, i.e. systemic routes of administration, i.e. systemic chemotherapy. Chemotherapy is responsible for severe systemic toxicities due to (i) the broad distribution of the chemotherapeutic in the organism and (ii) the lack of selectivity for cancer cells.
20 Oncologists are consequently in great need for new more efficient and better-tolerated treatment approaches.

 Chemotherapy is indeed a matter of finding the highest amount of anti-neoplastic agent to be administered by reducing at a maximum level the non-reversible toxicity side effects and disagreeable side effects generated by
25 the chemotherapy.

 Accordingly, very complex therapeutic scheme are foreseen combining very often different therapeutic modalities and acts, such as for example, surgery, with a first cycle of radiotherapy, followed by complex cycles of anti-neoplastic agent injections or intravenous infusion, which can be the

same or different for each cycle and adapted depending on response to said therapeutic scheme and the side effect identified on the body of the patient.

Each anti-neoplastic agent or molecule has a dose limiting toxicity (DLT) such as nephrotoxicity, neurotoxicity, ... which require to
5 introduce in the therapeutic scheme rest period allowing the patient body to recover from the adverse side effects, when not non-reversible.

Further, anti-neoplastic agent has a half-life time period which directly determine the duration of action of a drug. The half-life time period is the period of time required for the concentration or amount of drug in the body
10 to be reduced by one-half. The half-time period of anti-neoplastic agent is typically comprised between 12 hours and 36 hours, which can be short as representing the exposition time of the human body to the beneficial effect of the anti-neoplastic agent.

However, due to the dose limiting toxicity (DLT) of anti-
15 neoplastic agent, the amount of administered doses during several administering periods (i.e., a cycle) remains limited and should be separated one to each other, as said previously, by off-period.

The combination of the half-life period together with the dose limiting toxicities, together with the fact that when the anti-neoplastic agent is
20 administered by injection or intravenous infusion, the concentration of the anti-neoplastic agent which reach efficiently the solid tumor site is low, with limited effect on the tumor itself and high systemic toxicity for the patient body.

Further another constrain of anti-neoplastic agent is the cumulative dose which is the total dose resulting from repeated exposures to
25 the anti-neoplastic agent of the same part of the body or of the whole body.

For cisplatin, administered through intravenous route, the cumulative dose is 300 mg/m² (m² of the human body) within 4 to 6 cycles.

Those considerations yielded researchers to develop more targeted therapies and on-site injection/infusions.

30 One approach is to deliver chemotherapy by means of the pulmonary route, i.e. by inhalation. Inhalation allows the administration of high

drug doses directly to lung tumors without prior distribution in the organism. The severe systemic toxicities are consequently reduced.

However, local adverse effects linked to the pulmonary route can also occur depending on the drug candidate, its formulation and the related inhalation device. Moreover, the higher financial costs (due to particular hospital facilities and inhalation procedure to limit environmental contamination), in addition to the lack of drastic improvement in the benefit/risk ratio in both preclinical and clinical evaluations, make that pulmonary route has been underexploited in lung tumor therapy.

While chemotherapy delivered through the pulmonary route may offer strong perspectives, there is a need to provide candidate which can improve the benefit/risk ratio in both preclinical and clinical evaluation and are susceptible to provide a candidate where the benefits of chemotherapy will outweigh the adverse effect together with improving the life quality.

Inhaled therapy is of different kind and one can distinguish nebulizers form inhalers as distinct manner to deliver active substances to the respiratory tract. Inhalers can also be of different type and dry powder inhalers (DPI) are one of them.

Compared to nebulizers, dry powder inhalers (DPI) are well-adapted to chemotherapy. They allow high doses of active substances, but also poorly water-soluble compounds (i.e. most chemotherapeutics in cancer) to be administered directly into the lungs. Moreover, DPI limit environmental contamination by the aerosol due to (i) their activation and drive by the patient's inspiratory flow only and (ii) negligible exhaled drug doses. Finally, DPI can be designed as single-use disposable devices.

However, conventional immediate-release DPI formulations might nevertheless lead to too short residence in the lungs and to poor local tolerance. These may result from the fast dissolution of drug particles and high peak concentrations of the anticancer drug in lung fluids after lung deposition.

There is therefore a need to develop pulmonary route for chemotherapy and to adapt deeply current inhalation devices and formulations

used in clinical trials to deliver effective anticancer therapies to tumor-bearing lungs

In that context, controlled-release cisplatin-based DPI formulations were developed with high drug loading and high fine particle fraction (Levet et al, Int J Pharm 2016). The formulations presented controlled-release and prolonged lung retention abilities leading to low systemic distribution (Levet et al, Int J Pharm 2017). According to this document, in a lung cancer mice model, this approach led to comparable tumor response in vivo than the intravenous regimen at half dose [dose (1.0 mg/kg vs 0.5 mg/kg, respectively)]. The intravenous regimen gives good results for extrapulmonary metastases while inhaled cisplatin seemed more active against primary lung tumors.

DPI formulations composed of paclitaxel-based nanocarriers were also developed with increased residence time in the lungs, limited systemic distribution and aimed specifically at lung cancer cells by targeting the folate receptor (FR) (Rosière et al, Int J Pharm 2016; Rosière et al, Mol Pharm, 2018). FR, especially FR- α , is overexpressed on the cancer cell surfaces in many lung tumors (i.e. more than 70% of adenocarcinomas) and is a promising membrane receptor to target in lung cancer. Significantly longer survival rates were observed for the FR-targeted inhaled treatments in combination with intravenous Taxol® (the commercial form of paclitaxel), than for intravenous Taxol® alone in a lung cancer mice model.

To resume, although the use of DPI chemotherapy led to encouraging preclinical results in terms of pharmacokinetic profiles and safety, efficacy is still rather limited.

The present invention encounters to solve at least a part of these drawbacks by providing a kit, for example to be used in a polytherapy, for an inhaled chemotherapy.

The kit according to the present invention is characterized in that it comprises:

- a) a series of single hermetically packaged therapeutic doses of a dry powder for inhalation containing at least one anti-neoplastic agent

chosen in the group consisting of Platinum drugs such as cisplatin, carboplatin, oxaliplatin and nedaplatin with a lipid matrix and optionally a PEGylated excipient and

b) a series of disposable dry powder inhaler devices,

5 wherein

- i) each single hermetically packaged therapeutic dose having a close state and an open state,
- ii) each disposable dry powder inhaler device having an open position and a close position,
- 10 iii) each single hermetically packaged therapeutic dose being provided for being accommodated in said close state in one disposable dry powder inhaler device of said series of disposable dry powder inhaler devices in said open position, and
- iv) each single hermetically packaged therapeutic dose being also
15 provided for being in said open state only when said one disposable dry powder inhaler device is in said close position.

By the terms "single hermetically packaged doses", it is meant within the meaning of the present invention that the single hermetically packaged doses of the neoplastic agent under the form of a dry powder for
20 inhalation is filled in a capsule (e.g. HPMC or gelatin capsule) sealed in a blister (e.g. aluminium-aluminium blister) or is directly filled in a blister, which is the sealed dose, i.e. the single hermetically packaged dose.

Within the meaning of the present invention, the said one disposable dry powder inhaler device is a capsule-based or a blister-based
25 device that is sealed after use, i.e. after the single hermetically packaged dose has been in the open state, such as after the administration of a single dose by the patient, preferably assisted by a nurse or the medical staff.

The device can be sealed by avoiding re-opening, capping the drug exit, blocking any air exit through one-way valves, or simply introducing it
30 into a hermetic bag after use.

The said one disposable dry powder inhaler device has a specific use procedure to limit the contamination during its use and is hermetically

packaged after the use (for instance contained in a hermetic bag) in order to be eliminated as a waste using an appropriate procedure.

Preferably, the disposable dry powder device of the present invention is a disposable single dose blister-based device which is hermetically
5 packaged device (for instance, contained in a hermetic bag) in close position and already containing the single drug dose filled in in a blister in said close state. The single hermetically packaged dose having its open state just before its use (for instance by piercing or opening the blister), so the patient can inhale the dose contained inside the blister before being eliminated as explained
10 before. The hermetic bag in which the device can be packaged before and/or after use can be the same or different.

In another preferred variant according to the present invention, the single hermetically packaged dose under the form of the blister containing the single dose and the disposable dry power blister-based device are both
15 tightly (sealedly) packaged separately and the blister is inserted in the device just before the administration of the dose.

In a further preferred variant according to the present invention, preferably, the disposable dry powder device of the present invention is a disposable single dose capsule-based device which is hermetically packaged
20 device (i.e. contained in a hermetic bag) in close position and already containing the single drug dose filled in a capsule in said close state. The single hermetically packaged dose having its open state just before its use (e.g. by piercing or opening the capsule), so the patient can inhale the dose contained inside the capsule before being eliminated as explained before. The hermetic bag in which
25 the device can be packaged before and/or after use can be the same or different.

In yet another preferred variant according to the present invention, the single hermetically packaged dose under the form of the capsule containing the single dose and the disposable and tight dry power capsule-
30 based device are both tightly (sealedly) packaged separately and the capsule is inserted in the device just before the administration of the dose.

According to the present invention, the capsule-based device can be in a partially open/close position when the single hermetically package dose is in the close state. However, once the capsule-based device is closed by the patient/nurse after the insertion of the capsule, the device is definitely
5 closed (i.e. a re-opening of the device is not possible) and the capsule is open for having the single hermetically packaged dose in open state), so the patient can inhale the dose contained inside the capsule before being eliminated together with the capsule-based device as explained before.

This is again to allow to limit the contamination by the anticancer
10 drug to patient, nurse and environment during the use (i.e. re-open the device to remove the pierced/opened capsule, re-use several times the same device containing a fine powder, etc.).

In still another alternative according to the present invention, the single hermetically packaged dose, i.e. the capsule containing the single
15 therapeutic dose in said close state and the capsule-based disposable dry powder inhaler device are tightly (sealedly) packaged separately. The capsule is inserted in the device just before the administration of the dose. The device can be opened by the patient/nurse to allow the capsules filling. Once the capsule is adequately placed in the device capsule loading chamber in the close
20 state, the capsule-based device is closed, and the opening of the capsule provokes the definitive closure of the device. Again, the device should be disposable and be packaged after a single-use, preferably after setting the cap on the device (cap sealing position) in a specific tight bag in order to be eliminated as a waste.

25 Whatever the type of the disposable device and the single hermetically packaged dose used according to the present invention, when the device is activated (e.g. by piercing/opening the capsule or the blister), the inhalation procedure by the patient can be performed one time or repeated sequentially one or two times to ensure that the whole dose contained in the
30 device is inhaled.

The present invention, through providing a kit for inhaled chemotherapy comprising a series of single hermetically packaged therapeutic

doses of at least one anti-neoplastic agent and a series of disposable dry powder inhaler devices allow to dispose of a fully secured chemotherapy in terms of environmental contamination of cytotoxic agent in the surrounding atmosphere, thereby drastically increasing the comfort of the patient and offering many possibilities for an ambulatory treatment and/or a home therapy.

It has been indeed foreseen according to the present invention a kit comprising a series of single hermetically packaged therapeutic doses of at least one anti-neoplastic agent together with a series of disposable dry powder inhaler devices, where each single hermetically packaged therapeutic doses of at least one anti-neoplastic agent will be used in a new and clean disposable dry powder inhaler device, thereby preventing the escape of cytotoxic substance in the surrounding environment as a new disposable dry powder inhaler device will be used for each single hermetically packaged therapeutic doses of at least one anti-neoplastic agent. This means that after its use, the disposable dry powder inhaler devices will be properly and immediately discarded to be then isolated in a container for cytotoxic waste to be incinerated and that for the next use, when manipulation has to be foreseen to introduce the new single hermetically packaged therapeutic doses of at least one anti-neoplastic agent in the disposable dry powder inhaler devices, the disposable dry powder inhaler devices has never been in contact with cytotoxic agent and the manipulation will never cause any contamination of the surrounding atmosphere. This allows the patient to take their therapy at home since the risk of having cytotoxic anti-neoplastic agent in the atmosphere during the manipulation of the dry powder inhaler is drastically reduced.

It is contemplated according to the present invention that this will help drastically patient suffering from lung cancer as it has been recognized that long term and/or repetitive stay(s) in hospital environment is impacting negatively the ability to recover of the patient.

To ensure no dispersion of cytotoxic substance in the surrounding atmosphere occurs, the disposable dry powder inhaler devices has

an open position and a close position and each single hermetically packaged therapeutic dose has a close state and an open state.

In the kit for inhaled chemotherapy according to the present invention, each single hermetically packaged therapeutic dose is provided for
5 being accommodated in said close state in one disposable dry powder inhaler device of said series of disposable dry powder inhaler devices in said open position and each single hermetically packaged therapeutic dose being also provided for being in said open state only when said one disposable said tight dry powder inhaler device is in said close position.

10 This allows to make sure the single hermetically packaged therapeutic doses of at least one anti-neoplastic agent is not to be open if not fully accommodated in the disposable dry powder inhaler device and isolated from the surrounding environment.

Preferably, in the kit according to the present invention, said
15 single hermetically packaged therapeutic dose is a capsule or a blister.

In a preferred embodiment of the kit according to the present invention, the lipid matrix is a pure or a mixture of triglycerides, such as for example tristearin, hydrogenated vegetal oil (e.g. hydrogenated castor oil) or any hydrophobic glyceride derivative having values of Log P higher than 5,
20 preferably comprised between 14 and 25, more particularly between 18 and 25 and preferably around 20, as measured using the shake-flask method.

According to the present invention, said lipid matrix comprises a pure or a mixture of triglycerides having a melting point temperature higher than or equal to 60°C, preferably higher than or equal to 75°C.

25 In another preferred embodiment of the present invention, the PEGylated excipient is derived from vitamin E or from phospholipids, such as tocopheryl polyethylene glycol succinate (TPGS) or distearoyl phosphoethanolamine polyethylene glycol 2000 (DSPE-mPEG-2000).

Advantageously, in the kit for a inhaled chemotherapy according
30 to the present invention, said disposable dry powder inhaler device comprises a dispersion chamber in fluid connection with an inhalation channel and connected to an entry by means of a channel for accommodating said single

hermetically packaged therapeutic dose in a loading chamber inside said disposable dry powder inhaler device, said entry comprising locking means provided to isolate tightly the outside environment from the inside of the disposable dry powder inhaler device, said disposable dry powder inhaler device comprising opening means provided to open the single hermetically packaged therapeutic dose only when the locking means are activated and isolating tightly the outside environment from the inside of the disposable dry powder inhaler device.

In a particular embodiment of the present invention, said single hermetically packaged therapeutic dose comprises a therapeutic dose in the form of a dry and fine powder having a granulometric distribution PSD d_{50} lower than or equal to 15 μm , preferably lower than or equal to 10 μm , preferably lower than or equal to 5 μm , and a d_{90} lower than or equal to 30 μm , preferably lower than or equal to 15 μm , preferably lower than or equal to 10 μm and more preferably lower than or equal to 7 μm , and optionally a volume mean diameter $D[4,3]$ lower than or equal to 20 μm , preferably lower than or equal to 15 μm , preferably lower than or equal to 10 μm , preferably lower than or equal to 6 μm .

In yet a preferred embodiment according to the present invention, each single hermetically packaged therapeutic dose has a weight comprised between 1 and 100 mg, preferably between 5 and 75 mg, more preferably between 10 and 50 mg.

In a further preferred embodiment according to the present invention, each single hermetically packaged therapeutic dose comprises between 0.1 and 90 mg, preferably between 1 mg and 40 mg of said anti-neoplastic agent.

According to the present invention, each single hermetically packaged therapeutic dose comprises from 10 to 99.9 mg, preferably between 10 and 49 mg of said lipid matrix.

Advantageously, in the present invention, each single hermetically packaged therapeutic dose comprises from 0.01 to 5 mg, preferably between 0.05 mg and 1 mg of PEGylated excipient.

Other embodiments of the kit for an inhaled chemotherapy according to the present invention are mentioned in the appended claims

The present invention also relates the use of a kit for inhaled chemotherapy in a polytherapy.

5 Advantageously, said polytherapy comprises one primary therapy chosen in the group consisting of systemic chemotherapy (including intravenous infusion and oral per os), hormonotherapy, targeted therapy, immunotherapy, tumor ablative surgery, ablative surgery for removing a part of or a full organ bearing a tumor, a curative surgery, a radiotherapy and their
10 combination and one chemotherapy by inhalation as additional therapy.

Intravenous infusion chemotherapy can be composed of two anti-neoplastic agents (e.g. platinum doublets) or more.

Cumulative dose of cisplatin can be safely increased with inhaled chemotherapy. The current IV cumulative dose is 300 mg/m² within 4 to 6
15 cycles.

Preferably, in the use of the kit according to the present invention, said primary therapy comprises at least intravenous infusion or oral chemotherapy or an immunotherapy provided to be administered for a series of cycles, each cycle comprising an administration period and an off-period,
20 said chemotherapy by inhalation being provided to be administered during said off-period of the therapy.

According to the present invention, it is preferred that said administration period extends over less than one day, preferably over a period of time between 3 to 6 hours, and where said off- period extends over a period
25 of time from 1 to 5 weeks, preferably from 2 to 4 weeks, more preferably between 2,5 and 3,5 weeks and particularly over about 3 weeks $\pm$ 2 days.

According to the present invention, it is preferred that chemotherapy by inhalation is provided to be administered at a rate of at least 1 single hermetically packaged therapeutic dose/week of off-period, preferably
30 of at least 3 single hermetically packaged therapeutic doses/week of off-period, preferably of at least 5 single hermetically packaged therapeutic doses/week of off-period, possibly 7 single packaged therapeutic doses/week of off-period for

a daily dosage regimen, optionally in an equally spread manner over said off-period.

According to the present invention, it is preferred that chemotherapy by inhalation is provided to be administered at a rate of one or more single hermetically packaged therapeutic dose(s) during the same administration event. When more than one single hermetically packaged therapeutic doses are administered for one administration event, the single hermetically packaged doses can be administered sequentially (together) or spaced by a predetermined period of time, such as one single hermetically packaged dose each 2 hours, 3 singles hermetically packaged doses forming one administration event.

According to the present invention, it is foreseen that chemotherapy by inhalation is provided to be administered at a rate of at least 1 administration event/week of off-period, preferably of at least 3 administration event/week of off-period, preferably of at least 5 administration event/week of off-period, possibly 7 administration event/week of off-period for a daily dosage regimen, optionally in an equally spread manner over said off-period.

If said off-period is one week, the chemotherapy by inhalation can be administered at a rate of 1, 2, 3 or even 5 single hermetically packaged therapeutic dose. Preferably, the chemotherapy by inhalation can be administered at a rate of 2 or 3 single hermetically packaged therapeutic doses by said week off-period.

If said off-period is three weeks, the chemotherapy by inhalation can be administered at a rate of one single hermetically packaged therapeutic dose each day, meaning between 15 and 21 doses for the off-period of about 3 weeks. Optionally, the chemotherapy by inhalation can be administered at a rate of one single hermetically packaged therapeutic dose each two days, meaning between 9 and 12 doses for the off-period of about 3 weeks. Alternatively, the chemotherapy by inhalation can be administered at a rate of one single hermetically packaged therapeutic dose each three days, meaning between 6 and 9 doses for the off-period of about 3 weeks.

If said off-period is four weeks, the chemotherapy by inhalation can be administered at a rate of one single hermetically packaged therapeutic dose each day, meaning between 20 and 28 doses for the off-period of about 4 weeks. Optionally, the chemotherapy by inhalation can be administered at a
5 rate of one single hermetically packaged therapeutic dose each two days, meaning between 12 and 16 doses for the off-period of about 4 weeks. Alternatively, the chemotherapy by inhalation can be administered at a rate of one single hermetically packaged therapeutic dose each three days, meaning between 8 and 12 doses for the off-period of about 4 weeks.

10 According to the present invention, in one particular embodiment of the use of the kit for a inhaled chemotherapy, said polytherapy comprises at least tumor ablative surgery, ablative surgery for removing a part of or a full organ bearing a tumor, a curative surgery, or a radiotherapy followed by a recovery period, said chemotherapy by inhalation being provided to be
15 administered after or before said recovery period of the therapy.

Advantageously, in the use of the kit according to the present invention, said chemotherapy by inhalation is provided to be administered at a rate of at least 1 single hermetically packaged therapeutic dose/week of off-period, preferably of at least 3 single hermetically packaged therapeutic
20 doses/week of off-period, preferably of at least 5 single hermetically packaged therapeutic doses/week of off-period, possibly 7 single packaged therapeutic doses/week of off-period for a daily dosage regimen, optionally in an equally spread manner over said off-period.

Other embodiments of the use according to the present
25 invention are mentioned in the appended claims.

The present invention further relates to a therapeutic treatment against lung cancer comprising the steps of administering a inhaled chemotherapy in a polytherapy comprising at least one therapy chosen in the group consisting of intravenous infusion or oral chemotherapy,
30 hormonotherapy, targeted therapy, immunotherapy, tumor ablative surgery, ablative surgery for removing a part of or a full organ bearing a tumor, a

curative surgery, a radiotherapy and their combination said inhaled chemotherapy being an additional therapy.

Advantageously, in the therapeutic treatment according to the present invention, said therapy comprises at least intravenous infusion or oral
5 chemotherapy or an immunotherapy provided to be administered for a series of cycles, each cycle comprising an administration period and an off-period, said chemotherapy by inhalation being provided to be administered before said therapy or during said off-period of the primary therapy.

Preferably, in the therapeutic treatment according to the
10 present invention, said administration period extends over less than one day, preferably over a period of time between 3 to 6 hours, and where said off-period extends over a period of time from 2 to 5 weeks, preferably from 2 to 4 weeks, more preferably between 2,5 and 3,5 weeks and particularly over about 3 weeks $\pm$ 2 days.

15 More particularly, in the present invention, the chemotherapy by inhalation is provided to be administered at a rate of at least 1 single hermetically packaged therapeutic dose/week of off-period, preferably of at least 3 single hermetically packaged therapeutic doses/week of off-period, preferably of at least 5 single hermetically packaged therapeutic doses/week of
20 off-period, possibly 7 single packaged therapeutic doses/week of off-period for a daily dosage regimen, optionally in an equally spread manner over said off-period.

In a variant according to the present invention, said polytherapy comprises at least tumor ablative surgery, ablative surgery for removing a part
25 of or a full organ bearing a tumor, a curative surgery, or a radiotherapy followed by a recovery period, said chemotherapy by inhalation being provided to be administered before said therapy or after said recovery period of the therapy.

In this variant, according to the present invention, said inhaled chemotherapy is administered at a rate of at least 1 single hermetically
30 packaged therapeutic dose/week of off-period, preferably of at least 3 single hermetically packaged therapeutic doses/week of off-period, preferably of at least 5 single hermetically packaged therapeutic doses/week of off-period,

possibly 7 single packaged therapeutic doses/week of off-period for a daily dosage regimen, optionally in an equally spread manner over said off-period, after said recovery period.

In particular, according to the present invention, said lung cancer
5 is a small cell lung cancer or a non-small cell lung cancer.

Other embodiments of the therapeutic treatment according to the present invention are mentioned in the appended claims.

Other characteristics and advantages of the present invention will be derived from the non-limitative following description, and by making
10 reference to the drawings and the examples.

In the drawings, figure 1 shows the tumor growth for the two cisplatin-treated groups, compared with the untreated control group of example 3. Data are presented as the mean ratio of bioluminescence signals related to day 3 post graft $\pm$ SEM.

15 Figure 2 shows the survival rates ($p < 0.05$, Log-rank Test) for the two cisplatin-treated groups, compared with the untreated control group of example 3.

Figure 3 shows the tumor growth in the chest and in the lungs for cisplatin IV compared with cisplatin DPI from example 3. Data are presented
20 as mean bioluminescence signal $\pm$ SEM.

Figure 4 shows the tumor growth for the two cisplatin-treated groups, compared with the untreated control group of example 4. Data are presented as the mean ratio of bioluminescence signals related to day 3 post graft $\pm$ SEM.

25 Figure 5 shows the survival rates ($p < 0.05$, Log-rank Test) for the two cisplatin-treated groups, compared with untreated the untreated control group of example 4.

In the drawings, the same reference numbers have been allocated to the same or analog element

30 **Examples.-**

Example 1.- preparation of cisplatin dry powder formulation

n°1

Briefly, raw cisplatin microcrystals from bulk powder (Shanghai Jinhe Bio-technology Co., Ltd., Shanghai, PRC) were first suspended in 50 mL isopropanol to reach a 5% w/v suspension and reduced in size by high-speed (10 min at 24 000 rpm) (X620 motor and a T10 dispersing shaft, Ingenieurbüro CAT M. Zipperer GmbH, Staufen, Germany) and high-pressure homogenization (EmulsiFlex-C5 high-pressure homogenizer, Avestin Inc., Ottawa, Canada) at 5 000 psi then 10 000 psi over 10 pre-milling cycles each, then at 20 000 psi over 20 milling cycles. A heat exchanger was connected to the homogenizing valve and maintained at -15°C using an F32-MA cooling circulator (Julabo GmbH, Seelbach, Germany). An aliquot was removed from the suspension at the end of the process to measure the particle size distribution (PSD) of cisplatin microcrystals by laser diffraction (see below).

Then, tristearin (Tokyo Chemical Company, Tokyo, Japan) and TPGS (Sigma-Aldrich, St-Louis, USA) solubilized in heated isopropanol were added to the microcrystal suspension to obtain a final concentration of 1.0% w/v of cisplatin and 1.0% w/v of tristearin/TPGS (99:1 w/w) mixture and spray dried with a Mini-Spray Dryer B-290 (Büchi Labortechnik AG, Flawil, Switzerland) to obtain a DPI formulation for human use.

The geometrical PSD of bulk cisplatin, cisplatin microparticles from the size-reduction process, and cisplatin dry powder formulation, was measured as suspended and individualized particles. This was done using a Mastersizer 3000 laser diffractometer (Malvern Instruments Ltd., Worcestershire, UK) connected to a Hydro MV dispenser equipped with a 40 W ultrasonic probe (Malvern Instruments Ltd.). Measurements of bulk cisplatin and aliquots of cisplatin microparticles from the size-reduction process were performed in cisplatin-saturated isopropanol. The cisplatin dry powder formulation was previously dispersed, vortexed and measured in cisplatin-saturated NaCl 0.9% aqueous solution containing 0.1% w/v Poloxamer 407 (BASF, Ludwigshafen, Germany). The PSD was expressed as the volume median diameter d_{50} (for which 50% of particles lie under the expressed diameter), the volume mean diameter $D[4,3]$ and the percentage of fine particles determined

from the cumulative undersize curves (% of particles below 5 μm). The results are presented in table 1.

Table 1. Volume median diameter d_{50} (for which 50% of particles lie under the expressed diameter), the volume mean diameter $D[4,3]$ and the percentage of fine particles determined from the cumulative undersize curves (% of particles below 5 μm) of raw cisplatin, cisplatin microparticles from the size-reduction process, and cisplatin dry powder formulation. Data are expressed as the mean $\pm$ SD, $n = 3$.

	D_{50} (μm)	$D[4,3]$ (μm)	Undersize (% below 5 μm)
Raw cisplatin	16.5 ± 3.6	18.9 ± 4.3	10.2 ± 4.0
Cisplatin microparticles	0.89 ± 0.01	1.0 ± 0.1	97.9 ± 1.0
Cisplatin dry powder formulation	4.2 ± 0.2	4.4 ± 0.1	63.4 ± 3.3

10 **Example 2.- Preparation of cisplatin dry powder formulation** **n°2**

First, cisplatin microparticles were produced as described in Example 1.

Then, castor oil hydrogenated (BASF, Ludwigshafen, Germany) and TPGS (Sigma-Aldrich) solubilized in heated isopropanol were added to the cisplatin microparticle suspension to obtain a final concentration of 1.0% w/v of cisplatin and 1.0% w/v of castor oil hydrogenated /TPGS (99:1 w/w) mixture and spray dried with a Mini-Spray Dryer B-290 (Büchi Labortechnik AG, Flawil, Switzerland) to obtain a DPI formulation for human use.

20 The operating parameters used during spray-drying were as follows: feed rate 3.0 g/min, inlet temperature 70°C, 0.7 mm nozzle, 1.5 mm nozzle-cap, compressed air at 800 L/min and drying air flow 35 m^3/h . The

apparatus was equipped with a B-296 dehumidifier (Büchi Labortechnik AG) to maintain the relative humidity at 50% HR during spray-drying.

Example 3.- Cisplatin administration to mice model

1. Cisplatin as a monotherapy

5 All the animal studies were approved by ULB's ethical committee from the Faculty of Medicine (protocol 424N and 585N) and Center for Microscopy and Molecular Imaging (protocol CMMI 2017 01).

Lung cancer mice model.

The orthotopic intrapulmonary implantation procedure was
10 performed using an adaption of the protocol described previously (Wauthoz et al., Nanomedicine 2015). Briefly, under anesthesia, 6 to 7-week-old BALB/c mice were grafted with 1.4 million M109-HiFR-*LUC2* cells in 20 µL of a 50:50 v/v mix of folate-free RPMI/Matrigel® injected intercostally after incision of the skin and dissection of subcutaneous muscles. The different tissue incisions were
15 stitched with a 3-0 silk (Ethicon®, St-Stevens-Woluwe, Belgium). The mice were closely observed until complete recovery. The therapeutic response of the M109 model to cisplatin was evaluated by *in vivo* optical imaging (bioluminescence) and survival analysis. Bioluminescence is directly proportional to the number of living M109-HiFR-*LUC2* tumor cells.
20 Bioluminescence was performed up to day 19 post tumor cell engraftment using a PhotonImager RT (Biospace Lab, France) using the conventional supplier's protocol. Mice were weighted three times a week and sacrificed if their weight loss exceeded 20% from the beginning of the experiment or 15% from the last measurement or if they were suffocating. In these cases, the
25 mouse death was notified as occurred the day after.

Three groups of 6-8 mice were compared: (i) untreated negative control, (ii) mice injected intravenously (IV) with 1.5 mg/kg cisplatin in a three-week cycle (one administration in weeks 1 and 3, week 2 is a week-off) , (iii) mice treated with cisplatin DPI prepared in example 2 at a dose of 0.5 mg/kg
30 cisplatin in a three-week cycle (three administrations in weeks 1 and 3, week 2 is a week-off) using an endotracheal device adapted to mice (Dry Powder Insufflator™ model DP4-M®, Penn-Century, Philadelphia, USA) and using the

protocol described by Levet et al (Levet et al., Int J Pharm 2017). Treatments were administered from day 3 post tumor cell engraftment.

As it can be seen in figure 1, a decrease in tumor growth for the two cisplatin-treated groups, compared with the untreated control group was observed, but not statistically significant ($p > 0.05$, 1-way ANOVA). Data are presented as the mean ratio of bioluminescence signals related to day 3 post graft $\pm$ SEM.

As it can be seen on figure 2, a significant increase in survival rates ($p < 0.05$, Log-rank Test) for the two cisplatin-treated groups, compared with the untreated control group was observed. No significant differences between cisplatin DPI and cisplatin IV is observed ($p > 0.05$, Log-rank Test).

An additional experiment was performed evaluating cisplatin DPI according to example 2 vs cisplatin IV on the same lung cancer mice model.

The mice were euthanized on day 19 post tumor cell engraftment to perform an *ex vivo* bioluminescence analysis to analyze tumor localization in the resected lungs (as considered as the primary lung tumors) vs in the chest cavity (as considered as loco-regional metastases).

As it can be seen in figure 3, a decrease of tumor growth in the chest for cisplatin IV compared with cisplatin DPI was observed but the tumor growth in the lungs was similar. Data are presented as mean bioluminescence signal $\pm$ SEM.

Example 4.- Combination of cisplatin DPI with systemic cisplatin administration to mice model

The protocol described in example 3 has been reproduced, except that three groups of 6-10 mice were compared:

- (i) untreated negative control,
- (ii) mice injected IV with 1.5 mg/kg cisplatin in a three-week cycle (one administration in weeks 1 and 3, week 2 is a week-off),
- (iii) mice treated with a combination of cisplatin DPI according to example 2 at a dose of 0.5 mg/kg cisplatin prepared in example 1 and cisplatin IV at 1.5 mg/kg in a

three-week cycle (three administration in weeks 1 and 3, week 2 is a week-off).

As it can be seen in figure 4, a decrease in tumor growth for the two cisplatin-treated groups compared with the untreated control group was observed. This decrease was significant for the combination (iii) ($p < 0.05$, 1-way ANOVA) but not for the cisplatin IV (ii) ($p > 0.05$, 1-way ANOVA). Data are presented as the mean ratio of bioluminescence signals related to day 3 post graft $\pm$ SEM.

As it can be seen in figure 5, a significant increase in survival rates ($p < 0.05$, Log-rank Test) for the two cisplatin-treated groups compared with the untreated control group was observed. Significant increase in survival rates ($p < 0.05$, Log-rank Test) for the combination compared with cisplatin IV was also observed.

Example 5.- Combination of cisplatin DPI with systemic cisplatin and paclitaxel administration to mice model

The protocol described in example 3 has been reproduced, except that three groups of 6-10 mice were compared:

- (i) untreated negative control,
- (ii) mice injected IV with a platinum doublet composed of 1.5 mg/kg cisplatin and 10 mg/kg paclitaxel in a three-week cycle (one administration in weeks 1 and 3, week 2 is a week-off),
- (iii) mice treated with a combination of cisplatin DPI from example 1 at a dose of 0.5 mg/kg cisplatin (from example 1) and the platinum doublet in a three-week cycle (three administration in weeks 1 and 3, week 2 is a week-off).

A decrease in tumor growth with the combination group (iii) compared with the untreated control group and with group (ii) was observed as well as a significant increase in survival rates ($p < 0.05$, Log-rank Test) for the combination group (iii) compared with the untreated control group and group (ii) was observed.

Example 6. Combination of cisplatin DPI with systemic immunotherapy

The protocol described in example 3 has been reproduced, except that three groups of 6-10 mice were compared:

- 5 (i) untreated negative control,
- (ii) mice injected intraperitoneally (IP) with an anti-PD1 antibody (RMP 1-14, Bioceros, Utrecht, The Netherlands) in a two-week cycle (four administrations in weeks 1, week 2 is a week-off),
- 10 (iii) mice treated with cisplatin DPI from example 1 at a dose of 0.5 mg/kg cisplatin (from example 1) in a three-week cycle (three administration in weeks 1 and 3, week 2 is a week-off) and injected intraperitoneally (IP) with an anti-PD1 antibody (RMP 1-14, Bioceros, Utrecht, The Netherlands) in a two-week cycle (four administrations
- 15 in weeks 1, week 2 is a week-off).

A decrease in tumor growth with the combination group (iii) compared with the untreated control group and with group (ii) was observed as well as a significant increase in survival rates ($p < 0.05$, Log-rank Test) for the combination group (iii) compared with the untreated control group and group (ii) was observed.

Example 7. Combination of cisplatin DPI with systemic chemotherapy and systemic immunotherapy

The protocol described in example 3 has been reproduced, except that three groups of 6-10 mice were compared:

- 25 (i) untreated negative control,
- (ii) mice injected intraperitoneally (IP) with an anti-PD1 antibody (RMP 1-14, Bioceros, Utrecht, The Netherlands) in a two-week cycle (four administrations in weeks 1, week 2 is a week-off),
- 30

- 5 (iii) mice treated with a combination of cisplatin DPI at a dose of 0.5 mg/kg cisplatin and cisplatin IV at 1.5 mg/kg in a three-week cycle (three administration in weeks 1 and 3, week 2 is a week-off) and injected intraperitoneally (IP) with an anti-PD1 antibody (RMP 1-14, Bioceros, Utrecht, The Netherlands) in a two-week cycle (four administrations in weeks 1, week 2 is a week-off).

A decrease in tumor growth with the combination group (iii) compared with the untreated control group and with group (ii) was observed as well as a significant increase in survival rates ($p < 0.05$, Log-rank Test) for the combination group (iii) compared with the untreated control group and group (ii) was observed.

Example 8. Combination of cisplatin DPI with systemic platinum doublets and systemic immunotherapy

15 The protocol described in example 4 has been reproduced, except that four groups of 6-10 mice were compared:

- (i) untreated negative control,
- (ii) mice injected intraperitoneally (IP) with 250 μ g of anti-PD1 antibody (RMP 1-14, Bioceros, Utrecht, The Netherlands) in a two-week cycle (four administrations in weeks 1, week 2 is a week-off),
- 20 (iii) mice injected IV with a platinum doublet composed of 1.5 mg/kg cisplatin and 10 mg/kg paclitaxel in a three-week cycle (one administration in weeks 1 and 3, week 2 is a week-off),
- 25 (iv) mice treated with a combination of cisplatin DPI at a dose of 0.5 mg/kg cisplatin and the platinum doublet in a three-week cycle (three administration in weeks 1 and 3, week 2 is a week-off) and the anti-PD1 antibody in a two-week cycle (four administrations in weeks 1, week 2 is a week-off).
- 30

A decrease in tumor growth the combination group (iv) compared with the untreated control group and with group (ii) and (iii) was observed as well as a significant increase in survival rates ($p < 0.05$, Log-rank Test) for the combination group (iv) compared with untreated the untreated
5 control group and group (ii) and (iii) was observed

Example 9. Demonstration of the absence of environmental contamination with the kit for inhaled chemotherapy described in the invention, compared with a conventional kit for inhalation.

The kit of the present invention was compared to a conventional
10 kit in terms of environmental contamination.

a. Procedure to collect the environmental contamination from the use of a conventional kit composed with an RS.01 dry powder inhaler (RPC Plastiap, Osnago, Italy), a size 3 HPMC capsule (Quali-V-I, Qualicaps, Madrid, Spain) containing 20 mg cisplatin formulation (prepared in Example 1).

15 Briefly, a size 3 HPMC capsule (Quali-V-I, Qualicaps) was hand-filled with about 20 mg powder (prepared according to Example 1). The device was then prepared and use as directed in the instructions to the patient.

All the following preparation steps were performed over a glass crystallizer of about 20 cm diameter in order to collect the powder being at the
20 origin of the environmental contamination. The capsule was placed into a RS.01 dry powder inhaler (RPC Plastiap), the device was closed and the capsule pierced. The device was placed in the apparatus described in the European Pharmacopeia 9.02 for dose collection. This apparatus is capable of quantitatively capturing the delivered dose. To simulate patient's inhalation, a
25 flow rate of 100 ± 5 L/min measured using a DFM3 flow meter (Copley Scientific, Nottingham, UK) was obtained with two HCP5 air pumps (Copley Scientific, Nottingham, UK) connected in series to a TPK critical flow controller (Copley Scientific, Nottingham, UK). The critical flow controller was used to ensure a deposition time of 2.4 s at 100 L/min and a critical flow with a P3/P2 ratio < 0.5 ,
30 as required by the European Pharmacopeia 9.02.

The device was opened, the capsule removed and the device reclosed. The powder fraction responsible for environmental contamination (i.e. the powder remaining in the crystallizer, the gloves of the investigator, outside the device and outside the capsule) was recovered with extensive washing with DMF and analyzed for its platinum content using the electrothermal atomic absorption spectrometry (ETAAS) validated method described by Levet et al (Levet et al, Int J Pharm 2016).

b. Procedure to collect the environmental contamination from the use of the kit of the present invention composed with an adapted RS.01 dry powder inhaler (Plastiape), a size 3 HPMC capsule (Quali-V-I, Qualicaps) containing 20 mg cisplatin formulation (prepared in Example 1)

Briefly, a size 3 HPMC capsule (Quali-V-I, Qualicaps) was hand-filled with about 20 mg powder (prepared according to Example 1). The device was then prepared as directed in the instructions to the patient.

All the following preparation steps were performed over a glass crystallizer of about 20 cm diameter in order to collect the powder being at the origin of the environmental contamination. The capsule was placed into a RS.01 dry powder inhaler (RPC Plastiape), the device was closed and the capsule pierced. The device was placed in the apparatus described in the European Pharmacopeia 9.02 for dose collection. This apparatus is capable of quantitatively capturing the delivered dose. To simulate patient's inhalation, a flow rate of 100 ± 5 L/min measured using a DFM3 flow meter (Copley Scientific, Nottingham, UK) was obtained with two HCP5 air pumps (Copley Scientific, Nottingham, UK) connected in series to a TPK critical flow controller (Copley Scientific, Nottingham, UK). The critical flow controller was used to ensure a deposition time of 2.4 s at 100 L/min and a critical flow with a P3/P2 ratio < 0.5 , as required by the European Pharmacopeia 9.02.

The device was then immediately sealed, i.e. isolated from the environment.

The powder fraction responsible for environmental contamination (i.e. the powder remaining in the crystallizer, the gloves of the investigator and outside the device) was recovered with extensive washing with

DMF and analyzed for its platinum content using the electrothermal atomic absorption spectrometry (ETAAS) validated method described by Levet et al (Levet et al, Int J Pharm 2016).

5 The powder fraction responsible for environmental contamination collected with the kit of the present invention was significantly lower than with the conventional kit ($p < 0.05$, Student t-test, $n = 5$).

It should be understood that the present invention is not limited to the described embodiments and that variations can be applied without going outside of the scope of the appended claims.

10 For example, it has been described that the chemotherapy by inhalation is used in a polytherapy after. Of course, it is also foreseen that the chemotherapy by inhalation is administered before a

CLAIMS

1. Kit for an inhaled chemotherapy comprising:
 - a) a series of single hermetically packaged therapeutic doses of a dry powder for inhalation containing at least one anti-neoplastic agent
5 chosen in the group of platinum drugs such as carboplatin, cisplatin, oxaliplatin, or nedaplatin) with a lipid matrix and optionally a PEGylated excipient and
 - b) a series of disposable dry powder inhaler devices,
wherein
 - 10 i) each single hermetically packaged therapeutic dose having a close state and an open state,
 - ii) each disposable dry powder inhaler device having an open position and a close position,
 - iii) each single hermetically packaged therapeutic dose being provided
15 for being accommodated in said close state in one disposable dry powder inhaler device of said series of disposable dry powder inhaler devices in said open position,
 - iv) and each single hermetically packaged therapeutic dose being also provided for being in said open state only when said one disposable
20 said tight dry powder inhaler device is in said close position.
2. Kit for an inhaled chemotherapy according to claim 1, wherein said single hermetically packaged therapeutic dose is a capsule or a blister.
3. Kit for a inhaled chemotherapy according to any of the claims 1 to 2,
wherein the lipid matrix is a matrix of pure or a mixture of triglycerides,
25 such as for example tristearin, hydrogenated vegetal oil (e.g. hydrogenated castor oil) or any hydrophobic glyceride derivative having values of Log P higher than 5, preferably comprised between 14 and 25, more particularly between 18 and 25 and preferably around 20, as measured using the shake-flask method.
- 30 4. Kit for an inhaled chemotherapy according to any of the claims 1 to 3, wherein the PEGylated excipient is derived from vitamin E or from

phospholipids, such as tocopheryl polyethylene glycol succinate (TPGS) or distearoyl phosphoethanolamine polyethylene glycol 2000 (DSPE-mPEG-2000).

5. Kit for a inhaled chemotherapy according to any of the claims 1 to 4,
5 wherein said disposable dry powder inhaler device comprises a dispersion chamber in fluid connection with an inhalation channel and connected to an entry by means of a channel for accommodating said single hermetically packaged therapeutic dose in a loading chamber inside said disposable dry powder inhaler device, said entry comprising
10 locking means provided to isolate the outside environment from the inside of the disposable dry powder inhaler device, said disposable dry powder inhaler device comprising opening means provided to open the single hermetically packaged therapeutic dose only when the locking means are activated and isolating the outside environment from the
15 inside of the disposable dry powder inhaler device.
6. Kit for an inhaled chemotherapy according to any of the claims 1 to 4, wherein said disposable dry powder inhaler device is ready to use and comprises a dispersion chamber in fluid connection with an inhalation channel and connected to cavity accommodating said single
20 hermetically packaged therapeutic dose inside said disposable dry powder inhaler device.
7. Kit for a inhaled chemotherapy according to any of the claims 1 to 6, wherein said single hermetically packaged therapeutic dose comprises a therapeutic dose in the form of a dry and fine powder having a
25 granulometric distribution PSD d_{50} lower than or equal to 15 μm , preferably lower than or equal to 10 μm , preferably lower than or equal to 5 μm , and a d_{90} lower than or equal to 30 μm , preferably lower than or equal to 15 μm , preferably lower than or equal to 10 μm and more preferably lower than or equal to 7 μm , and optionally a volume mean
30 diameter $D[4,3]$ lower than or equal to 20 μm , preferably lower than or equal to 15 μm , preferably lower than or equal to 10 μm , preferably lower than or equal to 6 μm .

8. Kit for an inhaled chemotherapy according to any of the claims 1 to 7, wherein each single hermetically packaged therapeutic dose has a powder weight comprised between 1 and 100 mg, preferably between 5 and 75 mg, more preferably between 10 and 50 mg.
- 5 9. Kit for an inhaled chemotherapy according to any of the claims 1 to 8, wherein each single hermetically packaged therapeutic dose comprises between 0.1 and 90 mg, preferably between 1 mg and 40 mg of said anti-neoplastic agent.
- 10 10. Kit for an inhaled chemotherapy according to any of the claims 1 to 9, wherein each single hermetically packaged therapeutic dose comprises from 10 to 99.9 mg, preferably between 10 and 49 mg of said lipid matrix.
- 15 11. Kit for an inhaled chemotherapy according to any of the claims 1 to 10, wherein each single hermetically packaged therapeutic dose comprises from 0.01 to 5 mg, preferably between 0.05 mg and 1 mg of PEGylated excipient.
12. Kit for an inhaled chemotherapy according to any of the claims 1 to 11, to be used in a polytherapy.
- 20 13. Kit for an inhaled chemotherapy according to claim 12, wherein said polytherapy comprises one therapy chosen in the group consisting of intravenous infusion or oral chemotherapy, immunotherapy, targeted therapy, hormonotherapy, tumor ablative surgery, ablative surgery for removing a part of or a full organ bearing a tumor, a curative surgery, a radiotherapy and their combination and one chemotherapy by inhalation as additional therapy.
- 25 14. Kit for an inhaled chemotherapy according to claim 13, wherein said therapy comprises at least intravenous infusion or oral chemotherapy or an immunotherapy provided to be administered for a series of cycles, each cycle comprising an administration period and an off-period, said chemotherapy by inhalation being provided to be administered during
30 said off-period of or before the said therapy.

15. Kit for an inhaled chemotherapy according to claim 14, wherein said administration period extends over less than one day, preferably over a period of time between 3 to 6 hours, and where said off-period extends over a period of time from 2 to 5 weeks, preferably from 2 to 4 weeks, more preferably between 2,5 and 3,5 weeks and particularly over about 3 weeks $\pm$ 2 days.
16. Kit for a inhaled chemotherapy according to any of the claims 12 to 15, wherein said chemotherapy by inhalation is provided to be administered at a rate of at least 1 single hermetically packaged therapeutic dose/week of off-period, preferably of at least 3 single hermetically packaged therapeutic doses/week of off-period, preferably of at least 5 single hermetically packaged therapeutic doses/week of off-period, possibly 7 single packaged therapeutic doses/week of off-period for a daily dosage regimen, optionally in an equally spread manner over said off-period,
17. Kit for an inhaled chemotherapy according to claim 12 or claim 13, wherein said polytherapy comprises at least tumor ablative surgery, ablative surgery for removing a part of or a full organ bearing a tumor, a curative surgery, or a radiotherapy followed by a recovery period, said chemotherapy by inhalation being provided to be administered before the said therapy or after said recovery period of the said therapy.
18. Kit for a inhaled chemotherapy according to claim 17, wherein said chemotherapy by inhalation is provided to be administered at a rate of at least 1 single hermetically packaged therapeutic dose/week of off-period, preferably of at least 3 single hermetically packaged therapeutic doses/week of off-period, preferably of at least 5 single hermetically packaged therapeutic doses/week of off-period, possibly 7 single packaged therapeutic doses/week of off-period for a daily dosage regimen, optionally in an equally spread manner over said week after said recovery period or before said recovery period.
19. Use of a kit for an inhaled chemotherapy according to any of the claims 1 to 11, in a polytherapy.

20. Use of a kit for an inhaled chemotherapy according to claim 19, wherein said polytherapy comprises one therapy chosen in the group consisting of intravenous infusion or oral chemotherapy, immunotherapy, targeted therapy, hormonotherapy, tumor ablative surgery, ablative surgery for removing a part of or a full organ bearing a tumor, a curative surgery, a radiotherapy and their combination and one chemotherapy by inhalation as additional therapy.
21. Use of a kit for an inhaled chemotherapy according to claim 20, wherein said therapy comprises at least intravenous infusion or oral chemotherapy or an immunotherapy provided to be administered for a series of cycles, each cycle comprising an administration period and an off-period, said chemotherapy by inhalation being provided to be administered during said off-period of said therapy or before the said therapy.
22. Use of a kit for a inhaled chemotherapy according to claim 21, wherein said administration period extends over less than one day, preferably over a period of time between 3 to 6 hours, and where said off-period extends over a period of time from 2 to 5 weeks, preferably from 2 to 4 weeks, more preferably between 2,5 and 3,5 weeks and particularly over about 3 weeks $\pm$ 2 days.
23. Use of a kit for a inhaled chemotherapy according to any of the claims 21 or 22, at a rate of at least 1 single hermetically packaged therapeutic dose/week of off-period, preferably of at least 3 single hermetically packaged therapeutic doses/week of off-period, preferably of at least 5 single hermetically packaged therapeutic doses/week of off-period, possibly 7 single packaged therapeutic doses/week of off-period for a daily dosage regimen, optionally in an equally spread manner over said off-period.
24. Use of a kit for a inhaled chemotherapy according to claim 19 or 20, wherein said polytherapy comprises at least tumor ablative surgery, ablative surgery for removing a part of or a full organ bearing a tumor, a curative surgery, or a radiotherapy followed by a recovery period, said

chemotherapy by inhalation being provided to be administered after said recovery period of said therapy or before the said therapy.

25. Use of a kit for a inhaled chemotherapy according to claim 24, wherein said chemotherapy by inhalation is provided to be administered at a rate of at least 1 single hermetically packaged therapeutic dose/week, preferably of at least 3 single hermetically packaged therapeutic dose/week, preferably of at least 5 single hermetically packaged therapeutic dose/week, more preferably of at least 7 single hermetically packaged therapeutic doses/week, optionally in an equally spread manner over said week after said recovery period or before the said therapy.
26. Therapeutic treatment against lung cancer comprising the steps of administering an inhaled chemotherapy in a polytherapy comprising at least one therapy chosen in the group consisting of intravenous infusion or oral chemotherapy, immunotherapy, targeted therapy, hormonotherapy, tumor ablative surgery, ablative surgery for removing a part of or a full organ bearing a tumor, a curative surgery, a radiotherapy and their combination said inhaled chemotherapy being an additional therapy.
27. Therapeutic treatment against lung cancer according to claim 26, wherein said therapy comprises at least intravenous infusion or oral chemotherapy or an immunotherapy provided to be administered for a series of cycles, each cycle comprising an administration period and an off-period, said chemotherapy by inhalation being provided to be administered during said off-period of said therapy or before the said therapy.
28. Therapeutic treatment against lung cancer according to claim 27, wherein said administration period extends over less than one day, preferably over a period of time between 3 to 6 hours, and where said off- period extends over a period of time from 2 to 5 weeks, preferably from 2 to 4 weeks, more preferably between 2,5 and 3,5 weeks and particularly over about 3 weeks $\pm$ 2 days.

29. Therapeutic treatment against lung cancer according to any of the claims 27 or 28, wherein chemotherapy by inhalation is provided to be administered at a rate of at least 1 single hermetically packaged therapeutic dose/week of off-period, preferably of at least 3 single hermetically packaged therapeutic doses/week of off-period, possibly 7 single packaged therapeutic doses/week of off-period for a daily dosage regimen, optionally in an equally spread manner over said off-period.
30. Therapeutic treatment against lung cancer according claim 26, wherein said polytherapy comprises at least tumor ablative surgery, ablative surgery for removing a part of or a full organ bearing a tumor, a curative surgery, or a radiotherapy followed by a recovery period, said chemotherapy by inhalation being provided to be administered before said therapy or after said recovery period of the said therapy.
31. Therapeutic treatment against lung cancer according to claim 30, wherein said inhaled chemotherapy is administered at a rate of at least 1 single hermetically packaged therapeutic dose/week of off-period, preferably of at least 3 single hermetically packaged therapeutic doses/week of off-period, preferably of at least 5 single hermetically packaged therapeutic doses/week of off-period, possibly 7 single packaged therapeutic doses/week of off-period for a daily dosage regimen, optionally in an equally spread manner over said off-period, after said recovery period.
32. Therapeutic treatment against lung cancer according to any of the claims 26 to 31, wherein said lung cancer is a small cell lung cancer.
33. Therapeutic treatment against lung cancer according to any claims 26 to 31, wherein said lung cancer is a non-small cell lung cancer.

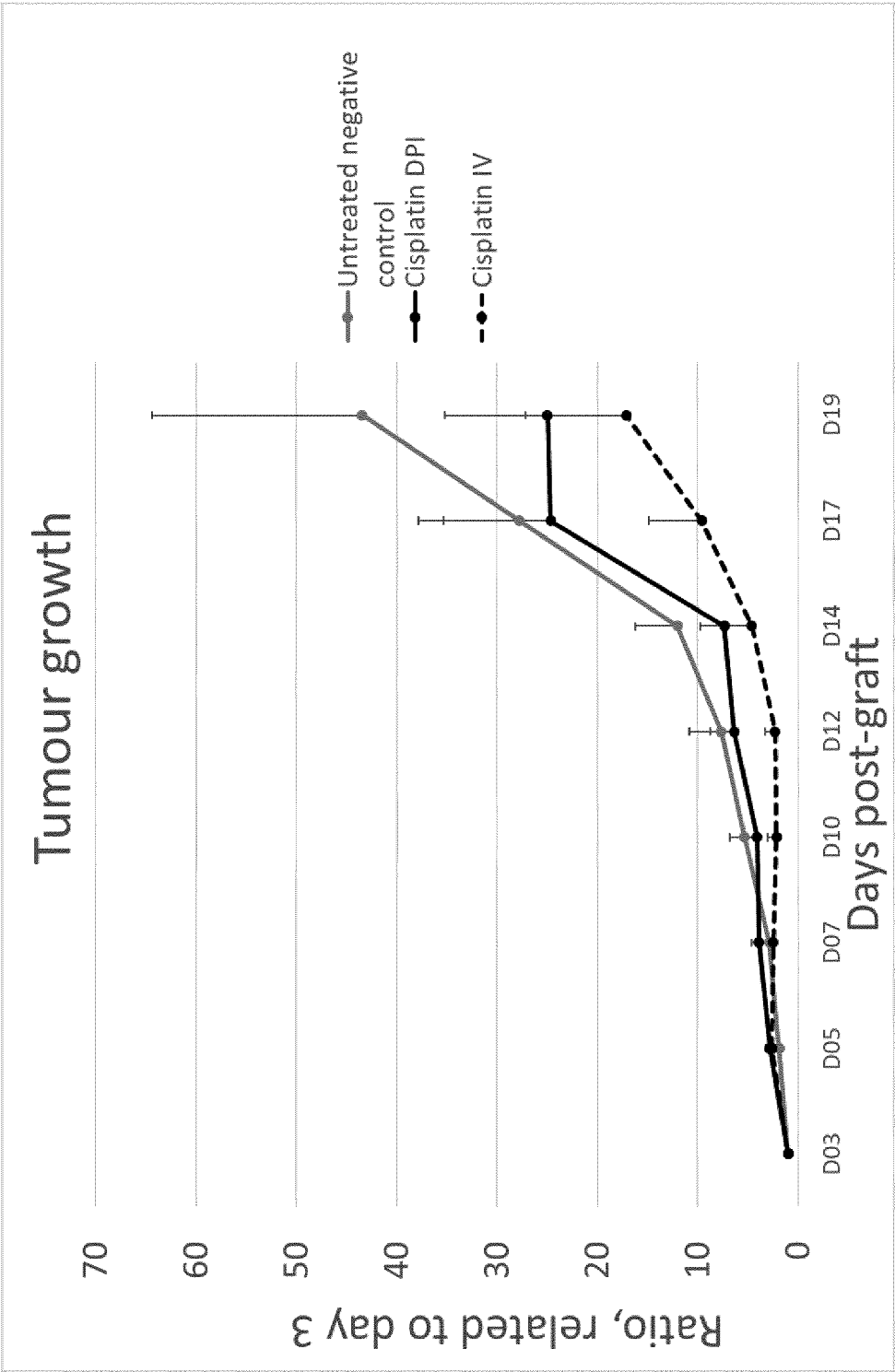


Figure 1

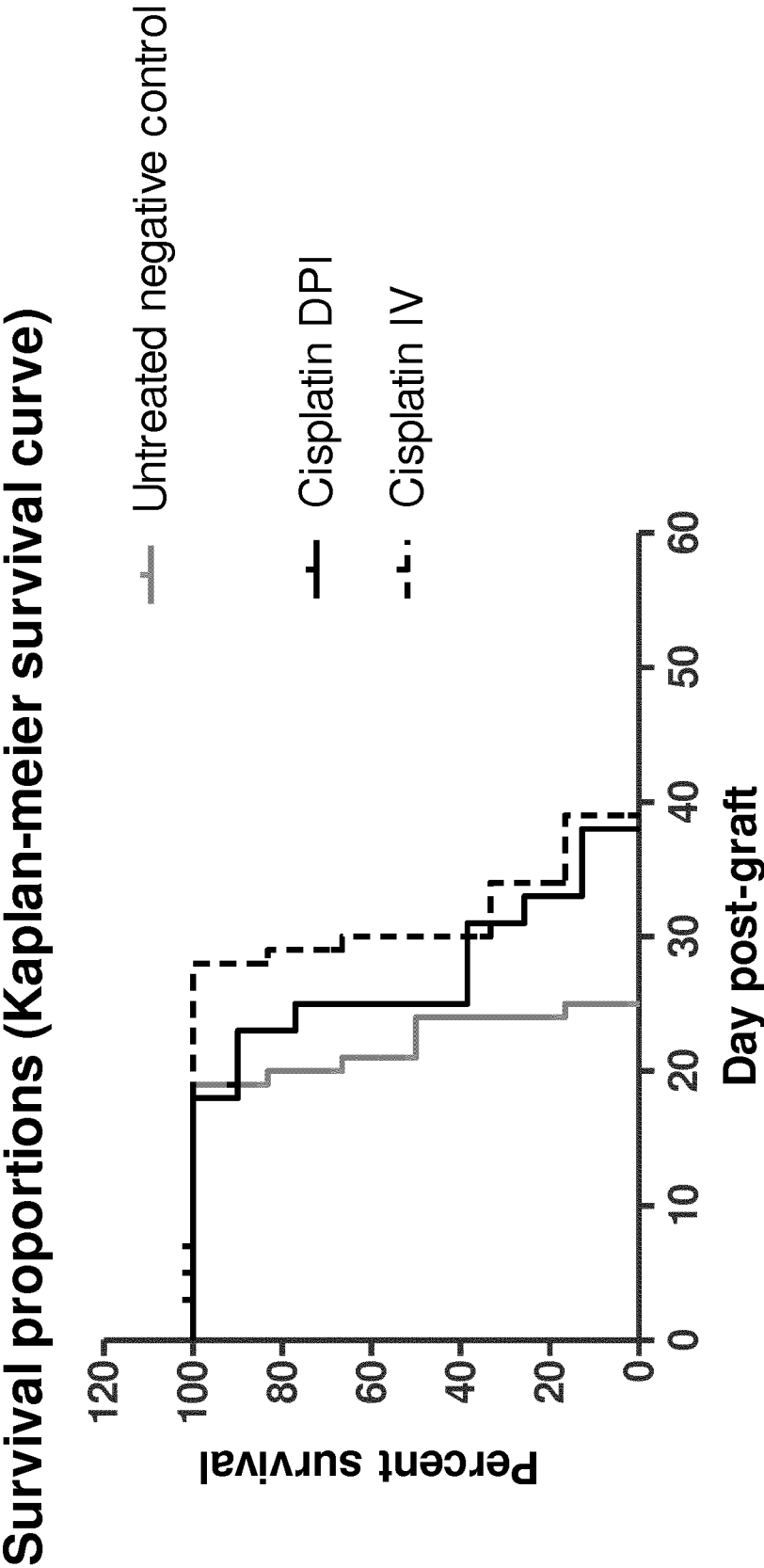


Figure 2

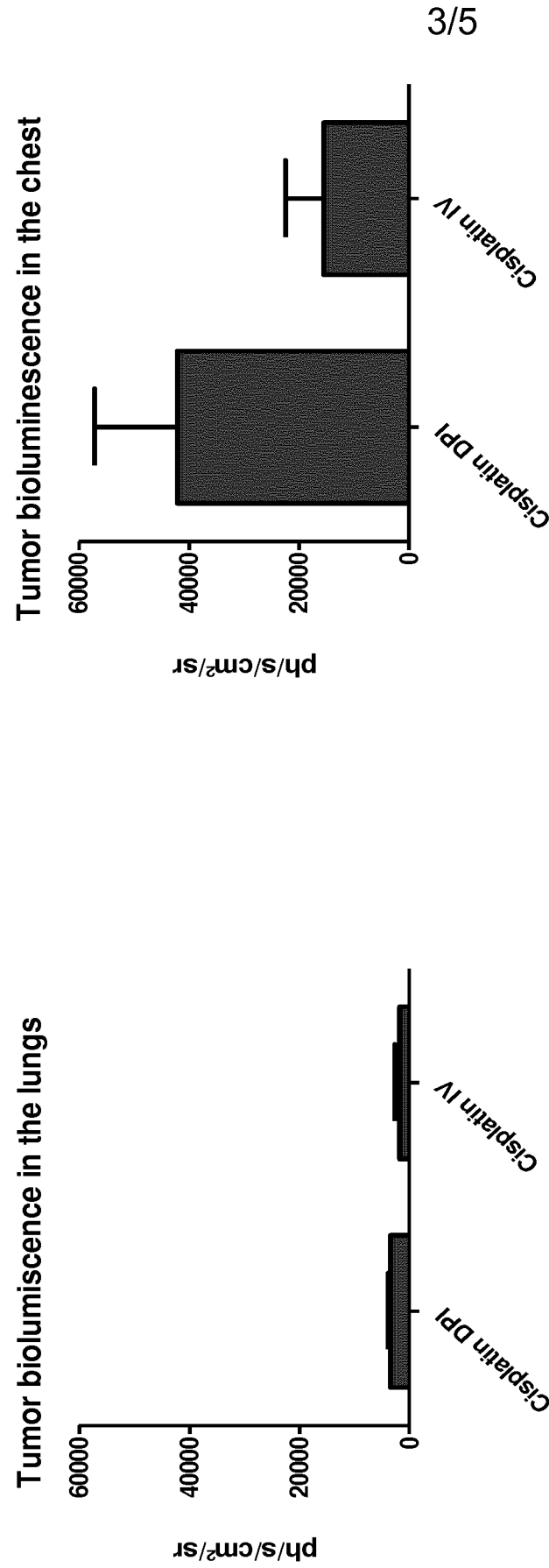


Figure 3

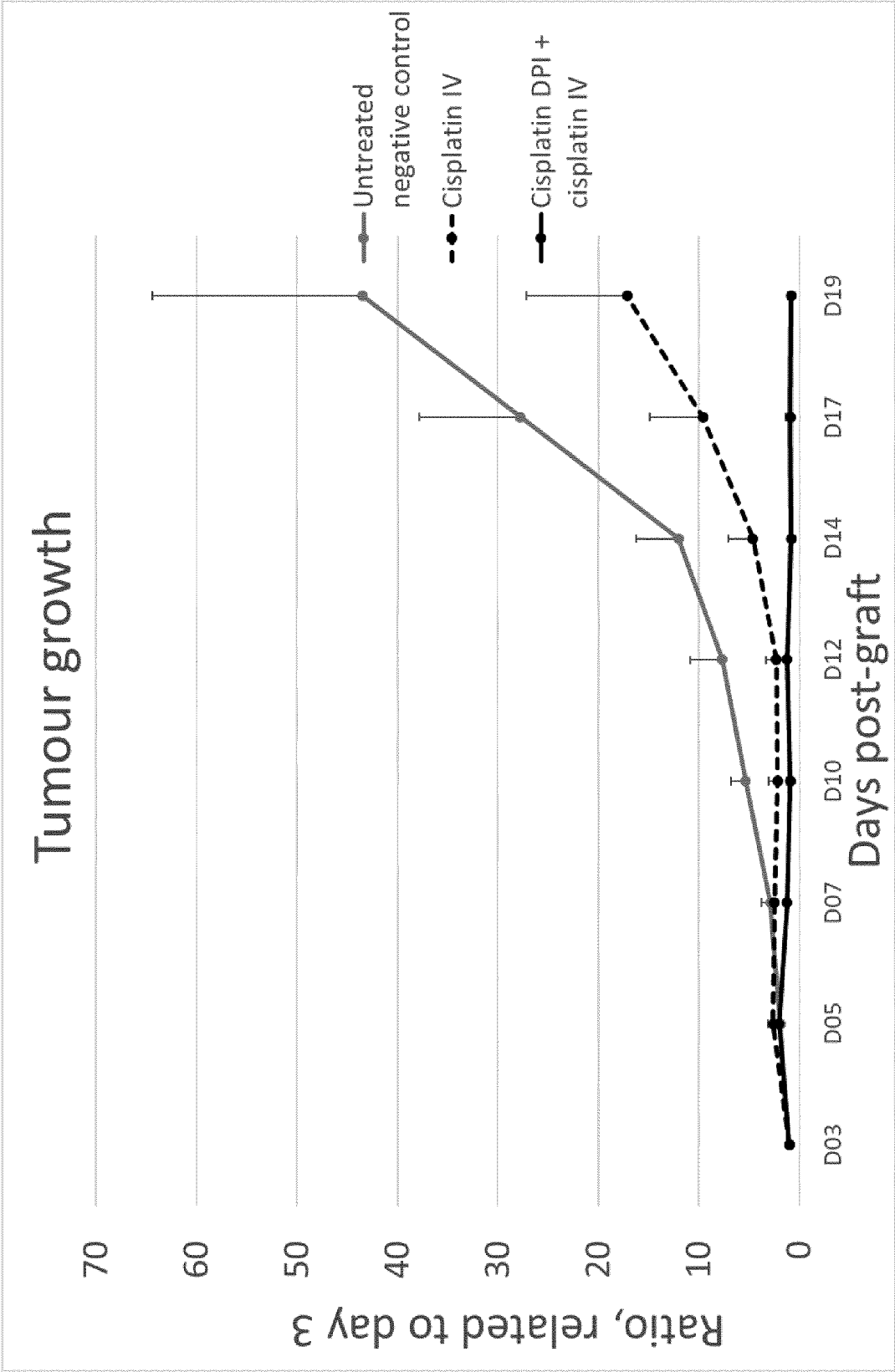


Figure 4

Survival proportions (Kaplan-meier survival curve)

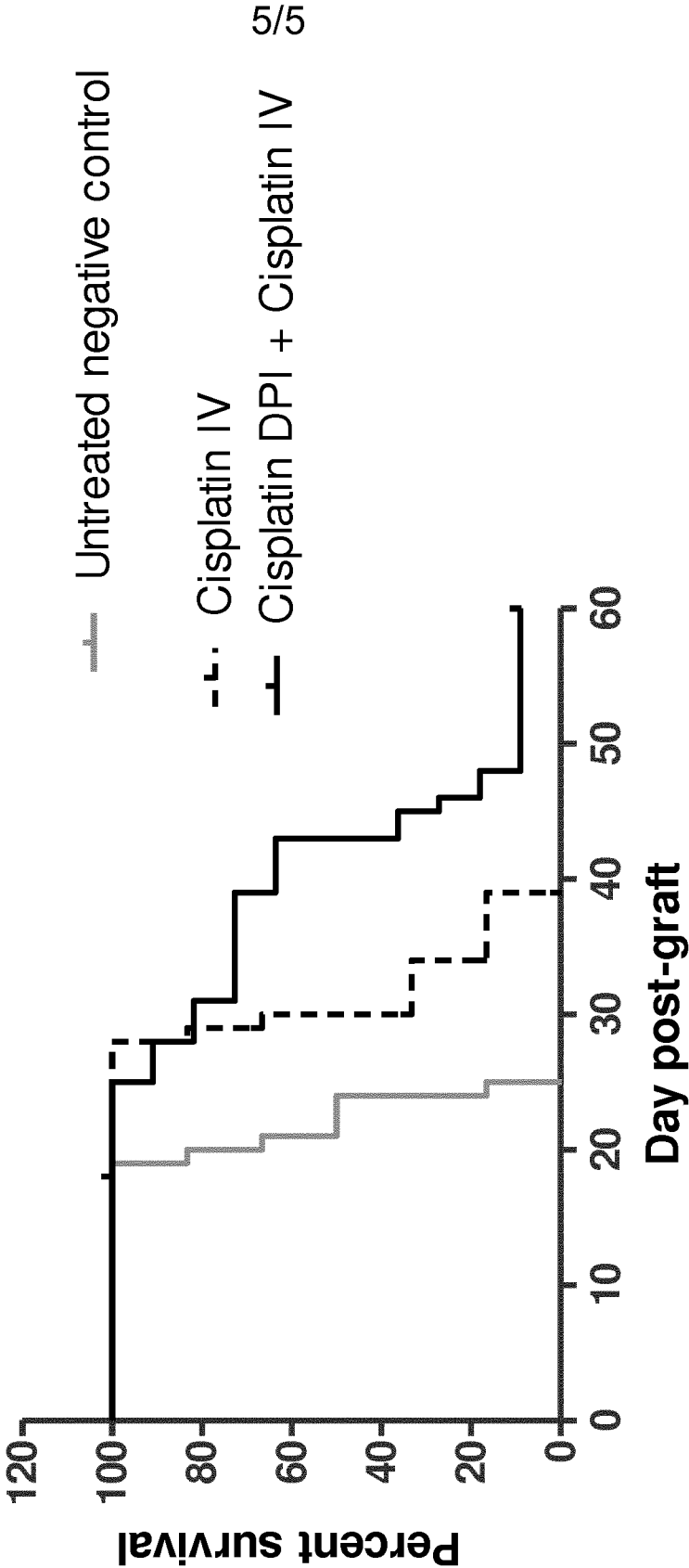


Figure 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/097140

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 A61K33/24 A61P35/00 A61K33/243 A61K9/14
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EP0-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/065522 A1 (PILKIEWICZ FRANK G [US] ET AL) 22 March 2007 (2007-03-22) paragraphs [0002], [0011] - [0012], [0057], [0063], [0064]; examples 1-2 -----	1-33
Y	LEVET VINCENT ET AL: "Platinum pharmacokinetics in mice following inhalation of cisplatin dry powders with different release and lung retention properties", INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER, NL, vol. 517, no. 1, 19 December 2016 (2016-12-19), pages 359-372, XP029878094, ISSN: 0378-5173, DOI: 10.1016/J.IJPHARM.2016.12.037 the whole document ----- -/--	1-33



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

21 August 2019

Date of mailing of the international search report

28/08/2019

Name and mailing address of the ISA/

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Authorized officer

Estañol, Inma

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/097140

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	VINCENT LEVET ET AL: "Development of controlled-release cisplatin dry powders for inhalation against lung cancers", INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 515, no. 1-2, 11 October 2016 (2016-10-11), pages 209-220, XP055584532, NL ISSN: 0378-5173, DOI: 10.1016/j.ijpharm.2016.10.019 the whole document -----	1-33
A	US 2007/122350 A1 (PILKIEWICZ FRANK G [US] ET AL) 31 May 2007 (2007-05-31) paragraphs [0009], [0010] -----	1-33
A	US 2005/107287 A1 (PILKIEWICZ FRANK G [US] ET AL) 19 May 2005 (2005-05-19) paragraph [0036] -----	1-33

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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