INTRAPERITONEAL AEROSOLISATION OF ALBUMIN-STABILIZED PACLITAXEL NANOPARTICLES FOR PERITONEAL CARCINOMATOSIS – PHASE I/II STUDY PROTOCOL

1 Trial number

Protocol nr: AGO/2017/003
EudraCT: 2017-001688-20

2 Objective of the study

2.1 Primary objective

To study the safety and efficacy of IV paclitaxel combined with repeated pressurized intraperitoneal aerosol therapy (PIPAC) using albumin bound nanoparticle paclitaxel (nab-pac, Abraxane) in a multicentre, multinational phase I/II trial.

2.2 Primary endpoint

Phase I: Maximally tolerated dose of Abraxane, administered every four weeks using intraperitoneal laparoscopy-assisted aerosolisation (PIPAC)
Phase II: Progression free survival, measured from the day of randomization

2.3 Secondary endpoints

Phase I:

- Surgical morbidity and mortality of laparoscopy
- Technical failure rate
- Pathological response rate
- Pharmacokinetic/Pharmacodynamic analysis
- Quality of life at 2 and 6 months after third PIPAC

Phase II:

- Surgical morbidity and mortality of laparoscopy
- Technical failure rate
- Pathological response rate
- Overall survival
- Disease free survival

3 General information

3.1 Investigators

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4 Introduction

In the European Union, approximately 44000 women are diagnosed with ovarian cancer (OC) every year (eco.iarc.fr/eucan/CancerOne.aspx?Cancer=27&Gender=2). The cancer specific mortality in these patients is over 67%. Ovarian cancer represents the second most common gynecological malignancy (1). Almost 70% of affected women is diagnosed with stage IIIC disease, and only a modest improvement in survival has been achieved over the last two decades. Even after achieving a complete remission induced by a combination of platinum based chemotherapy and surgery, over 85% of patients will develop a peritoneal recurrence originating from peritoneal minimal residual disease. The prognosis of patients with recurrent disease is poor, with a median survival ranging from 12 to 24 months. Platinum resistance eventually occurs in virtually all patients with recurrent OC. It includes patients with a very heterogeneous group of tumors; those who do not respond to first-line therapy (platinum refractory), relapse within 6 months of treatment, or relapse within 6 months of several lines of treatment for recurrent disease. In selected patients with recurrent disease, cytoreductive surgery with or without intraperitoneal (IP) chemotherapy may result in a survival benefit (2,3). However, the morbidity of repeated surgery is considerable, and a complicated postoperative course may render further systemic treatment impossible.

Recently, the technique of laparoscopic pressurized IP aerosol chemotherapy (PIPAC) was introduced in clinical practice (4). During laparoscopy, chemotherapy is delivered as an aerosol, generated by a dedicated micropump connected to a high-pressure injector. Advantages of PIPAC include minimal patient discomfort, possibility of repeated delivery, potential to combine with systemic treatment, and possibility to assess pathological response of peritoneal disease by serial biopsies. A recent prospective cohort study in women with peritoneal carcinomatosis (of which 84% OC) showed that repeated PIPAC resulted in an objective response (histological regression after first procedure) in 76%, a significant decrease in peritoneal cancer index, and a significantly decreased ascites volume (5).

In theory, any cancer drug may be delivered IP as an aerosol. The taxanes are ideal candidates for IP administration because of their activity profile and molecular size. The potential of Taxol™ for IP administration is, however, limited by the local toxicity and potential of hypersensitivity reactions associated with the Cremophor EL™ component. Abraxane® (Celgene) is a novel 130 nm albumin-bound (nab™) nanoparticle formulation of paclitaxel which has demonstrated activity in metastatic breast, pancreatic, and non-small cell lung cancer (6). In platinum resistant OC, a phase II study showed that nab-paclitaxel by intravenous administration has noteworthy single-agent activity and a favorable toxicity profile (7). Preclinical studies have demonstrated that IP administration of nano- and microsized formulations of paclitaxel results in superior antitumor activity against mouse OC xenografts compared to intravenous administration (8).
In clinical studies, paclitaxel has been shown to be highly bound to protein, with Cremophor EL™ further decreasing the unbound fraction of the drug (1,2). The advantage of Abraxane is its water solubility, achieved without the use of Cremophor EL™ and ethanol. Gardner et al. (3) reported that the formulation of Abraxane allowed a much higher fraction of unbound paclitaxel than that of Taxol™, and that the maximal concentration of unbound paclitaxel was ~10-fold higher for Abraxane in their pharmacologic study.
A comparative in vivo study was set up by Kinoshita et al. (4) to evaluate the antitumor activity after intraperitoneal (IP) administration of Abraxane and paclitaxel. Female athymic nude

mice bearing peritoneal carcinomatosis were divided into three groups: a control group (n = 5), an Abraxane (IP) treatment group (n = 5) and a paclitaxel (IP) treatment group (n = 5). Antitumor activity was compared among these three groups at equitoxic doses, as determined by Desai et al (5). After tumor inoculation on day 0, drug treatment was initiated on day 7, and drug was administered once daily for 7 consecutive days. The Abraxane treatment group showed significantly ($p < 0,05$) greater antitumor activity than the paclitaxel treatment group (figure 1). All five mice in the control group developed ascites and died within 19 – 32 days after tumor cell inoculation; the median survival time was 25 days. At equitoxic doses, the median survival time was 96 days for the paclitaxel treatment group and 126 days for the Abraxane treatment group (figure 2). As such, in vivo studies performed in mice have shown the noteworthy antitumor activity of IP administration of Abraxane compared to IP administration of paclitaxel.

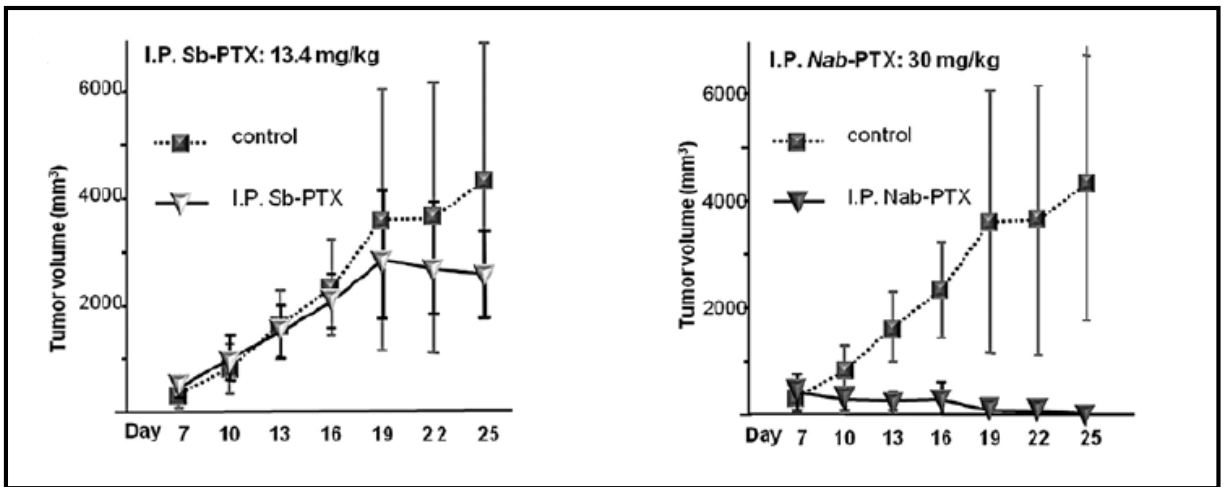
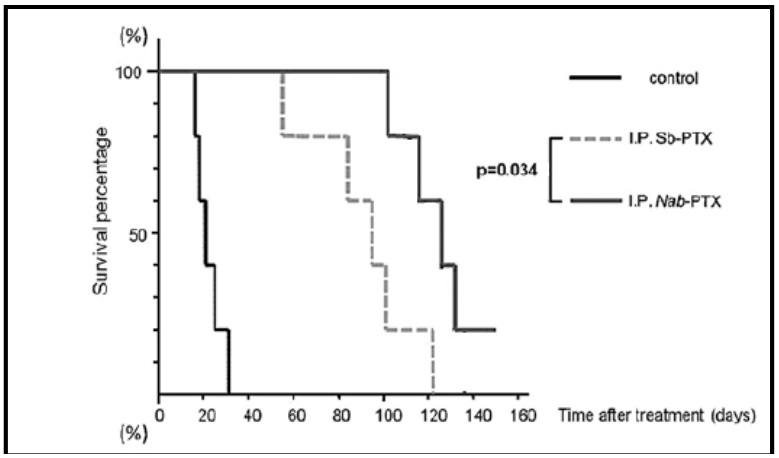


Figure 1: Antitumor activity at equitoxic doses of paclitaxel (Sb-PTX) and Abraxane (Nab-PTX) (4).



Intraperitoneal catheter based delivery of Abraxane® was recently studied in a phase I clinical trial in advanced carcinomatosis patients. The maximum tolerated dose of IP nab-paclitaxel was 140 mg/m²; dose limiting toxicities included grade 3 neutropenia, grade 3 abdominal pain and grade 4 neutropenia. Over the four dose levels, there was a 150-fold pharmacokinetic advantage (intraperitoneal versus plasma) with low intra-patient variability (9).

5 Patients and methods

5.1 Study design

During the phase I part of this study, dose escalation will be combined with pharmacokinetic/pharmacodynamic modelling which incorporates, in addition to plasma, tumor tissue, and peritoneal drug concentrations, biomarkers of toxicity and efficacy including caspase-cleaved cytokeratin 18, CA 125 and human epididymal secretory protein (HE4). During the phase II part of the study, ovarian cancer patients will be randomized to either weekly paclitaxel IV (days 1, 8, 15 every 4 weeks for 6 cycles) or the same schedule combined with three PIPAC treatments (every 4 weeks).

5.2 Intraperitoneal Drug Delivery

5.2.1 Abraxane

5.2.1.1 Composition and dosing

Abraxane® (nanoparticle albumin-bound paclitaxel, nab-pac, ABI-007) is approved in the US and EU for the treatment of metastatic breast cancer, locally advanced or metastatic non-small cell lung cancer (NSCLC), and metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine. The date of issue of marketing authorisation from the European Medicines Agency was 11/01/2008 (Agency product number EMEA/H/C/000778).

The recommended intravenous dose is 100-260 mg/m^2. A recent clinical trial in carcinomatosis patients using repeated intraperitoneal instillation of Abraxane suggested a maximum tolerated dose (MTD) of 140 mg/m^2. Therefore, in the phase I part of the present study, the dose levels for PIPAC will be 35, 70, 90, 112.5, and 140 mg/m^2.

After creation of a CO_2 pneumoperitoneum, the Abraxane® aerosol is generated by a micropump with a 200 µm nozzle (Capnomed GmbH, Villingendorf, Germany) which delivers a polydisperse aerosol with a flowrate of 30 ml/min. The aerosol is left in the peritoneal cavity during 30 minutes and evacuated afterwards.

5.2.1.2 Producer

Celgene Europe Limited, 1 Longwalk Road, Stockley Park, Uxbridge UB11 1DB, United Kingdom

5.2.1.3 Distributor

The drug will be purchased by the participating centers from Celgene.

5.2.1.4 Packaging

Abraxane® is a white to yellow powder for the production of an infusion suspension. Abraxane® is available in glass vials containing 100 mg or 250 mg paclitaxel as albumin-bound nanoparticle formulation.

5.2.1.5 Route of Administration

Abraxane® will be administered into the peritoneal cavity (IP) using the PIPAC-technique.

5.2.1.6 Labelling

This is a commercialized product and the commercially available labelling will be used.
The following particulars will be added to the original packaging, but will not obscure the original labelling:

i) Sponsor: Ghent University Hospital
ii) Study reference code: AGO/2017/003
iii) Subject number
iv) Address & phone number of the sponsor or investigator
v) Direction for use
vi) For clinical trial use only

5.2.1.7 Storage conditions

Abraxane® as a powder:
Unopened vials with Abraxane® are stable up to the date indicated on the package, when the vial is stored in the outer carton to protect the contents from light. The stability of the drug is not affected by either freezing or storage in the refrigerator. No special storage conditions are required for this medicinal product.

Abraxane® in a reconstituted suspension in the vial:
After the first reconstitution, the suspension should be immediately filled into an infusion bag. The chemical and physical stability will be preserved at 2 - 8 °C in the original box and protected against bright light for 8 hours.

Abraxane® in a reconstituted suspension in the infusion bag:
After reconstitution, the reconstituted suspension in the infusion bag should be used immediately. The chemical and physical stability until application was established at a maximum temperature of 25°C for 8 hours.

5.2.1.8 Known side effects of the medication

Abraxane® is currently approved for intravenous (IV) use only. The known side effects after IV administration are listed below. In the present study, Abraxane® is administered intraperitoneally. It is expected that the side effects will be less severe as compared to intravenous administration due to the presence of the peritoneum-blood barrier. To date, only one study has examined IP administration of Abraxane (Cristea et al. Pharmacologic advantage (PA) of intraperitoneal (IP) nab-paclitaxel in patients with advanced malignancies primarily confined to the peritoneal cavity. J Clin Oncol 33, 2015 (suppl; abstr 2553)). Patients received IP nab-paclitaxel on D1, 8, 15 of a 28-day cycle with a 3+3 dose-escalation design, with the dose ranging from 35mg/m^2 - 170mg/m^2. The MTD was established at 140 mg/m^2, with dose limiting toxicities including grade 3 neutropenia resulting in treatment delay >15 days, grade 3 abdominal pain, and grade 4 neutropenia > 7 days. Pharmacokinetic analysis showed a clear advantage of IP administration, with plasma AUC's resulting from IP nab-

paclitaxel at the MTD of 140 mg/m^2 similar to plasma AUC's associated with IV nab-paclitaxel at 100 mg/m^2.

Very common side effects (may affect more than 1 out of 10 patients):

- hair loss (the majority of cases of hair loss occurred within less than one month after the start of treatment with Abraxane®. In addition to this, hair loss is pronounced (more than 50 %) in the majority of cases);
- rash;
- decrease in the number of white blood cells (neutrophilic granulocytes, lymphocytes or leukocytes);
- lack of red blood cells;
- decrease of blood platelets;
- impact on peripheral nerves (pain, numbness, tingling or loss of tactile sensation);
- pain in one or more joints;
- pain in the muscles;
- nausea, diarrhea, constipation, inflammation of the oral mucosa, loss of appetite;
- sickness;
- weakness and fatigue, fever;
- internal dehydration, taste disorders, weight loss;
- decreased potassium levels in the blood;
- depression, sleeping disorders;
- headache;
- shivering;
- difficulty in breathing;
- dizziness;
- swelling of mucous membranes;
- increased liver values;
- pain in the limbs;
- coughing;
- stomach pain;
- nose bleedings.

Frequent side effects (may affect up to 1 out of 10 patients):

- itching, dry skin, nail disorders;
- infection, fever with a decrease of white blood cells (neutrophilic granulocytes), reddening with heat sensation, oror;
- decrease in the number of all blood cells;
- chest pain or throat pain;
- digestive disorders, stomach discomfort;
- stuffy nose;
- back pain, bone pain;
- reduced or difficult muscle coordination;
- difficulty reading, increased or decreased tear flow, loss of eyelashes;
- changes of heart rate or heart rhythm, heart failure;
- decreased or increased blood pressure;
- redness or swelling at the entrance of the needle into the skin;
- anxiety;

- infections of the lungs;
- urinary tract infection;
- intestinal narrowing, colon inflammation, bile duct inflammation;
- acute renal failure;
- increased bilirubin concentration in blood;
- hemoptysis;
- dry mouth, swallowing complaints;
- muscle weakness;
- blurred vision.

Occasional side effects (may affect up to 1 out of 100 patients):

- weight gain, increase of lactate dehydrogenase in blood, impaired renal function, increased glucose level in blood, increased phosphate level in blood;
- reduced or absent reflexes, involuntary movements, pain along a nerve, fainting, dizziness while standing, trembling, paralysis of the facial nerve;
- irritated, painful, red or itchy eyes, reduced eyesight, blurred vision due to nasal congestion (cystoid macular edema);
- earache, tinnitus;
- productive cough, shortness of breath when walking or climbing stairs, runny nose or dry nose, reduced breathing, water in the lungs, loss of voice, blood clot in the lungs, dry throat;
- bloating, stomach cramps, aching or sore gums, rectal bleeding;
- painful urination, frequent urination, blood in the urine, inability to hold the urine;
- fingernail pain, fingernail discomfort, fingernail loss, hives, red skin by sunlight, skin discoloration, sweating, night sweats, white areas on the skin, sore spots, swollen face;
- reduced phosphorus levels in the blood, accumulation of water, low albumin levels in the blood, increased thirst, decreased calcium levels in the blood, decreased sodium levels in the blood;
- pain and swelling in the nose, skin infections, infections due to the catheter;
- bruises;
- pain at the tumor site;
- hypotension when standing up, cold hands and feet;
- difficulty walking, swelling;
- allergic reaction;
- decreased liver function, enlarged liver;
- pain in the chest;
- restlessness;
- small hemorrhages caused by blood clots;
- a condition that results in red blood cell destruction and acute kidney failure.

Rare side effects (may affect up to 1 out of 1000 patients):

- skin reaction to another substance or inflammation of the lungs after irradiation;
- blood clot;
- strongly slow pulse, heart attack;
- leakage of drugs out of the veins;

- a disturbance of the cardiac electrical conduction system (atrioventricular block).

Very rare side effects (may affect up to 1 out of 10 000 patients):

- Severe inflammation/rash of the skin and mucous membranes (Stevens-Johnson syndrome, toxic epidermal necrolysis).

5.2.2 Paclitaxel (intravenous use only in the Phase II randomized part)

5.2.2.1 Composition and dosing

Paclitaxel vials contain 30 mg, 100 mg, 150 mg or 300 mg paclitaxel as 6 mg/ml solution.
The following dose will be administered to patients in the phase II trial: 60 mg/m^2 body surface area, repeated 9x over 12 weeks. The total dose will be 540 mg/m^2.

5.2.2.2 Producer

Paclitaxel is available as a generic molecule from numerous manufacturers.

5.2.2.3 Distributor

Local pharmacy of the participating centers

5.2.2.4 Packaging

Concentrate for solution for infusion.
Paclitaxel concentrate for solution for infusion is a clear, colourless or slightly yellow, viscous solution.

5.2.2.5 Route of Administration

Intravenous

5.2.2.6 Labelling

This is a commercialised product and the commercially available labelling will be used.
The following particulars will be added to the original packaging, but will not obscure the original labelling:

i) Sponsor: Ghent University Hospital
ii) Study reference code: AGO/2017/003
iii) Subject number
iv) Address & phone number of the sponsor or investigator
v) Direction for use
vi) For clinical trial use only

5.2.2.7 Storage conditions

Before and after opening: Do not store above 25°C. Store in original package in order to protect from light.
Diluted solutions: Do not refrigerate or freeze diluted solutions.

5.2.2.8 Known side effects of the medication

<u>Cardiovascular</u>

Very common (10% or more): Hypotension
Common (1% to 10%): Bradycardia
Uncommon (0.1% to 1%): Cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, atrioventricular block and syncope, myocardial infarction, hypertension, thrombosis, thrombophlebitis
Rare (0.01% to 0.1%): Cardiac failure
Very rare (less than 0.01%): Atrial fibrillation, supraventricular tachycardia, shock
Frequency not reported: Phlebitis

Dermatologic
Very common (10% or more): Alopecia (90%), rash
Common (1% to 10%): Transient and mild nail and skin changes, discoloration of the nail bed
Rare (0.01% to 0.1%): Pruritus, rash, erythema
Very rare (less than 0.01%): Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet), scleroderma-like reaction

Gastrointestinal
Very common (10% or more): Nausea (52%), mucositis (31%), vomiting, diarrhea mucosal inflammation
Rare (less than 0.1%): Peritonitis, bowel obstruction, bowel perforation, ischemic colitis, pancreatitis
Very rare (less than 0.01%): Pseudomembranous colitis, mesenteric thrombosis, neutropenic colitis, esophagitis, constipation, ascites

Hematologic
Very common (10% or more): Myelosuppression, neutropenia (90%), anemia, thrombocytopenia, leucopenia, bleeding
Rare (less than 0.1%): Febrile neutropenia

Hepatic
Very common (10% or more): Elevated alkaline phosphatase (22%), elevated AST (SGOT) (19%)
Common (1% to 10%): Elevated bilirubin
Very rare (less than 0.01%): Hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome

Hypersensitivity
Very common (10% or more): Minor hypersensitivity reactions (mainly flushing and rash)
Uncommon (0.1% to 1%): Significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic edema, respiratory distress, generalized urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in extremity, diaphoresis, hypertension)
Rare (less than 0.1%): Anaphylactic reactions
Very rare (less than 0.01%): Anaphylactic shock

Immunologic
Very common (10% or more): Infections (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome

Uncommon (0.1% to 1%): Septic shock
Rare (less than 0.1%): Sepsis, pseudomembranous colitis

Local
Common (1% to 10%): Injection site reactions (including localized edema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis)
Rare (less than 0.1%): Phlebitis

Musculoskeletal
Very common (10% or more): Arthralgia/myalgia (44%)
Frequency not reported: Systemic lupus erythematosus, scleroderma

Metabolic
Common (1% to 10%): Severe elevation in aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase (SGOT)), severe elevation in alkaline phosphatase
Uncommon (0.1% to 1%): Severe elevation in bilirubin
Rare (0.01% to 0.1%): Dehydration, increased blood creatinine
Very rare (less than 0.01%): Anorexia
Frequency not reported: Tumor lysis syndrome

Nervous system
Very common (10% or more): Neurotoxicity (mainly peripheral neuropathy)
Rare (0.01% to 0.1%): Motor neuropathy (with resultant minor distal weakness)
Very rare (less than 0.01%): Autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), optic nerve disturbance, grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia

Ocular
Very rare (less than 0.01%): Optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended
Frequency not reported: Macular edema, photopsia, vitreous floaters

Oncologic
Very rare (less than 0.01%): Acute myeloid leukemia, myelodysplastic syndrome

Other
Rare (0.01% to 0.1%): Asthenia, pyrexia, edema, malaise
Very rare (less than 0.01%): Ototoxicity, hearing loss, tinnitus, vertigo

Psychiatric
Very rare (less than 0.01%): Confusional state
Respiratory
Rare (0.01% to 0.1%): Pneumonia, dyspnea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure
Frequency not reported: Bronchospasm

5.2.3 Number of subjects

Phase I:

- Total study sample size: 20
- Target inclusion in Belgium: maximally 20 (depending on participation of other centers)

Phase II:

- Total sample size: 50
- Target inclusion in Belgium: 10

5.2.4 Inclusion- and exclusion criteria

5.2.4.1 Inclusion criteria

- Phase I study: patients with advanced carcinomatosis from ovarian, gastric, breast, or pancreatic origin.
- No concurrent taxane based systemic chemotherapy
- Phase II study: platinum resistant or refractory recurrent ovarian cancer or primary peritoneal carcinoma, FIGO stage IIIB or C.
- Selected stage IV patients with very limited metastatic disease are eligible for inclusion
- Age over 18 years
- Adequate performance status (Karnofsky index > 60%)
- Absence of intestinal or urinary obstruction
- Limited size of the majority of peritoneal tumor implants (< 5 mm)
- Absent or limited ascites
- Ability to understand the proposed treatment protocol and provide informed consent
- Expected life expectancy more than 6 months
- Laboratory data
    - Serum creatinine ≤ 1.5 mg/dl or calculated GFR (CKD-EPI) ≥ 60 mL/min/1.73 m²
    - Serum total bilirubin ≤ 1.5 mg/dl, except for known Gilbert's disease
    - Platelet count > 100.000/µl
    - Hemoglobin > 9g/dl
    - Neutrophil granulocytes > 1.500/ml
    - Blood coagulation parameters within normal range
- Absence of alcohol and/or drug abuse
- No other concurrent malignant disease
- Written informed consent

5.2.4.2 Exclusion criteria

- Concurrent systemic taxane therapy until three weeks before the first experimental treatment
- Pregnancy or breast feeding. Women who can become pregnant must ensure effective contraception
- Active bacterial, viral or fungal infection
- Active gastro-duodenal ulcer
- Parenchymal liver disease (any stage cirrhosis)
- Uncontrolled diabetes mellitus
- Psychiatric pathology affecting comprehension and judgement faculty

- General or local (abdominal) contra-indications for laparoscopic surgery
- Documented intolerance or allergy to paclitaxel

5.2.5 Replacement of subjects

Patients who drop out from the study will be replaced until the target accrual is reached.

6 Experimental procedures

6.1 Phase I part

1. Baseline assessment

- Staging

- CT, 18F-FGD-PET-CT, and/or total body diffusion weighed MRI, according to local practice
- Serum tumor markers: CA125, CEA, CA19.9, CA15.3

- Quality of life assessment: patients will be asked to fill in the QLQ-C30, QLQ-OV28, and/or the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaires preoperatively (outpatient visit or hospital admission), at week 2 after each of the three PIPAC procedures, and at month 2 and 6 after the third PIPAC procedure.

2. Experimental treatment

Patients will undergo laparoscopy and PIPAC as per local procedural protocol. After creation of a CO_2 pneumoperitoneum, the Abraxane® aerosol is generated by a micropump with a 200 µm nozzle (Capnomed GmbH, Villingendorf, Germany) which delivers a polydisperse aerosol with a flow rate of 30 ml/min. The aerosol is left in the peritoneal cavity during 30 minutes and will be evacuated afterwards. The dose of Abraxane will be escalated (35, 70, 90, 112.5, and 140 mg/m^2) until the MTD is observed.

3. Plasma and tissue samples for PK/PD modelling

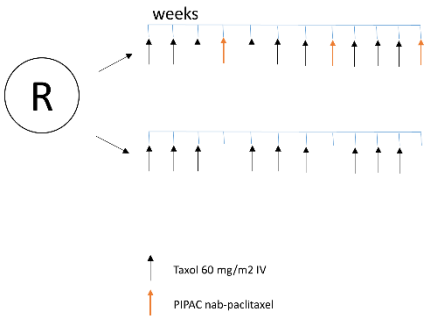
- Tumor tissue samples will be collected (5x5x5 mm) before and at the end of the aerosol delivery after each PIPAC procedure.
- Plasma samples (5 ml) will be collected preoperatively and at
- 15, 30, 60 min, 1.5, 2, 4, 8, 12 and 24 h, and after day 7, 28, 35, 56, 63, 84 and 91 after the first PIPAC procedure.

- 4. Plasma samples for systemic toxicity assessment

  Blood samples (5 ml) will be collected preoperatively and 12 h, 24 h and 7 days after each PIPAC procedure.

6.2 Phase II part

Patients with recurrent OC will be randomized (1:1) to receive either weekly paclitaxel alone or weekly paclitaxel combined with PIPAC using nab-paclitaxel, using the dose identified from the phase I part.
Randomization will be central (computer generated) and stratified according to treatment center.



Quality of life assessment: patients will be asked to fill in the QLQ-C30, QLQ-OV28, and/or the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaires preoperatively (outpatient visit or hospital admission), at week 6 and 12, and after 3 months, 6 months, 1 year, and 2 years.

7 Statistical analysis

Phase I
In the phase I study we determine the maximum tolerated dose (MTD) (and associated dose-limiting toxicity (DLT)) that will next be tested in a randomized phase II study. The target probability of DLT is set on 50%. In order to optimize the balance between safety and efficacy at this stage, we will design the study following a two-stage TITE-CRM (ref: Cheung, Ying Kuen. Dose finding by the continual reassessment method. CRC Press, 2011). In a two-stage TITE-CRM, an initial design is followed until the first DLT occurs. From that moment, TITE-CRM updates an initial prior estimate of the probabilities of DLT based on all available information. Patients are assigned the dose whose estimated probability of DLT at that time is closest to the target probability. This method allows for continuous, staggered accrual of patients.

Dose limiting toxicity (DLT) will be defined as any of the following:

1. Any Grade 3 or 4 non-hematologic toxicity excluding fatigue and controllable nausea, vomiting, abdominal pain, and diarrhea
2. Grade 4 thrombocytopenia
3. Grade 4 neutropenia lasting more than 7 days or associated with fever
4. Failure to perform more than one PIPAC due to toxicity
5. Surgical complication Dindo-Clavien grade IIIB or higher

Only DLT's that take place within 14 weeks of the start of the treatment, are taken into account for selecting the MTD.

In the phase I study we examine 5 therapeutic dose levels: 35, 70, 90, 112.5, and 140 mg/m^2 with a priori estimated chance of DLT at each of the doses under study is 10%, 20%, 25%, 35% and 40%, respectively. For safety reasons, however, the prior estimate used by TITE-CRM is 80%, 85%, 90%, 95%, 98%. This allows for the use of an initial design with a moderate pace of escalation (35 - 35 - 70 - 70 - 90 - 90 - 90 - 112.5 - 112.5 - 112.5 - 140 - 140 - 140 - 140 - 140 - 140 - 140 - 140 - 140 - 140 mg/m2), while preserving the logical escalation rules of escalating only one dose at a time and not escalating when the previous patient had a DLT. Results of this design have been simulated under a number of possible true values for the chance of DLT at each of the dose levels examined. These simulations show that in case of relatively low probabilities of DLT, this design is only moderately efficient in identifying the optimal dose. When true probabilities of DLT are high, however, this design results in reasonably low chances of selecting a dose with a probability of DLT higher than the target. In the second example below for instance, where doses 112.5 and 140 mg/m^2 have real probability of DLT of respectively 60% and 70%, these doses where selected as optimal respectively 6% and 0% out of the 1000 simulations.

For each simulation, a sample size of 20 patients was assumed and 1000 runs were performed. As an example of low probabilities of DLT: with true probabilities of DLT equal to 15%, 20%, 25%, 30% and 45% over the 5 increasing dose levels under study, the ordered doses 35, 70, 90, 112.5, and 140 mg/m^2 were identified as optimal dose respectively 0.4%, 4.6%, 34.2%, 48.5% and 12.3% of the time. With high true probabilities of DLT 30%, 40%, 50% 60%, 70%, the ordered doses were identified as optimal dose respectively 17%, 39.3%, 37.7%, 6%, 0% of the time.

Phase II

Once the final dose has thus been selected, the randomized phase II will start. No patients of phase I will be incorporated. To screen for effectiveness of the treatment under study, the phase IIB will be designed to have 80% power to detect an improvement in progression free survival time (PFS) from a median 3.5 to 6 months, when performing a one-sided log rank test at the 20% significance level. Based on a PH-assumption (HR=0.60), 44 events are needed. Based on a log rank test and with a loss to follow up of 5%, a sample size of 48 is needed with an accrual of 30 months and a follow up of 6 months. With a foreseen accrual of 20 patients per year, this seems feasible.

8 Randomisation/blinding

During the Phase II part of the trial, eligible patients will be randomized 1:1 to one of both treatment arms using sealed envelopes. The randomization will be stratified on treating center. For each center, a variable length block design will be prepared with block sizes 2 and 4. Within each block, the patients are randomly assigned to one of both arms, where the balance is maintained within each block. Given the specifics of the trial, blinding of either the investigators or the participants is not possible.

9 Prior and concomitant therapy

Patients should not receive other taxanes therapy until three weeks before the first experimental treatment.

10 Adverse event reporting

General considerations

Data Safety Monitoring Committee (DMC)

Composition

1. Prof. Dr. Sylvie Rottey

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Radiation Oncologist

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3. Prof. dr. Tom Loeys

Statistician

Department of Data-analysis
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Role

The DMC will, based on independent assessment of trial data as they become available, safeguard patient safety and trial integrity. The DMC will take decisions on trial continuation, protocol adaptation, or discontinuation based on efficacy or futility.

The experimental treatment involves the instillation of chemotherapy during a standard of care surgical procedure. Therefore, attribution of toxicity and morbidity to either the chemotherapy (intervention) or the surgery (standard of care) will not always be possible.

In the phase II part of the study, patients will undergo weekly low dose paclitaxel IV treatment until one week before each PIPAC treatment. The toxicity from low dose weekly paclitaxel is relatively mild. In a phase II trial by Markman et al., serious adverse events were relatively uncommon (neuropathy-grade 2: 21%; grade 3: 4%; and grade 3 fatigue: 8%).[1] Since paclitaxel does not exhibit cumulative toxicity and the plasma half-life after a systemic dose of 80 mg/m^2 was estimated at approximately 12 hours, it is anticipated that the toxicity or morbidity of PIPAC will not be affected by the antecedent IV treatment.[2] Conversely, pharmacokinetic studies with IV nab-paclitaxel showed that at the clinical dose range of 80 to 300 mg/m^2, the mean terminal half-life ranges from 13 to 27 hours. Therefore, the proposed interval between the PIPAC procedure and resumption of IV paclitaxel seems feasible.

Surgical complications will be scored according to the Dindo-Clavien classification.
Possibly drug related toxicity will be scored using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

Reporting of Adverse Events

List of abbreviations

AE	Adverse Event
CA	Competent Authority
EC	Ethics Committee
SAE	Serious Adverse Event
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction

Adverse events (AE)

The following information will be recorded:

- nature of adverse event
- date and time of occurrence and disappearance
- intensity: mild, moderate or severe
- frequency: once, continuous or intermittent
- decision regarding study: continuation or withdrawal
- relation to the study medication (see below)

AE's will be recorded from the first drug administration until 30 days after the last PIPAC procedure.

Special attention will be given to those subjects who have discontinued the trial for an AE, or who experienced a severe or a serious AE.

Definitions of Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Avent (SAE)
Any untoward medical occurrence that at any dose:
- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
or
- is a congenital anomaly/birth defect.

Note: Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

Unexpected adverse event
An adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Life-threatening
Any event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Associated with the use of the drug
An adverse event is considered associated with the use of the drug if the attribution is possible, probable or definitive.

Attribution definitions

Not related
An adverse event which is not related to the use of the drug.

Unlikely

An adverse event for which an alternative explanation is more likely - e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

Possible
An adverse event which might be due to the use of the drug. An alternative explanation - e.g. concomitant drug(s), concomitant disease(s), - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

Probable
An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely - e.g. concomitant drug(s), concomitant disease(s).

Definitely
An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

Reporting of adverse events

Adverse events will be reported between the first PIPAC and 30 after the last PIPAC procedure. All AEs and SAE's will be recorded in the patient's file and in the CRF. All SAE's will be reported as described below.

Medical events that occur between signing of the Informed Consent and the first intake of trial medication will be documented on the medical and surgical history section and concomitant diseases page of the CRF.
SAE's occurring within a period of 30 days following the last intake of trial medication will also be handled as such if spontaneously reported to the investigator.

All serious adverse events (SAE) and pregnancies occurring during clinical trials must be reported by the local Principal Investigator and local Ethical Committee within 2 working days after becoming aware of the SAE. This reporting is done by using the appropriate SAE form. It is the responsibility of the local Principal Investigator to report the local SAE's to the local EC.

In case the investigator decides the SAE is a SUSAR (Suspected Unexpected Serious Adverse Reaction), Bimetra Clinics will report the SUSAR to the Central EC and the CA within the timelines as defined in national legislation. The National Coordinating Investigator reports the SUSAR to all National Coordinating Investigators.

In case of a life-threatening SUSAR the entire reporting process must be completed within 7 calendar days. In case of a non-life-threatening SUSAR the reporting process must completed within 15 calendar days. The first report of a serious adverse event may be made by telephone, e-mail or facsimile (FAX).

The investigator must provide the minimal information: i.e. trial number, subject's initials and date of birth, medication code number, period of intake, nature of the adverse event and investigator's attribution.
This report of a serious adverse event by telephone must always be confirmed by a written, more detailed report. For this purpose the appropriate SAE form will be used. Pregnancies occurring during clinical trials are considered immediately reportable events. They must be reported as soon as possible using the same SAE form. The outcome of the pregnancy must also be reported.

If the subjects are not under 24-hour supervision of the investigator or his/her staff (out-patients, volunteers), they (or their designee, if appropriate) must be provided with a "trial card" indicating the name of the investigational product, the trial number, the investigator's name and a 24-hour emergency contact number.

Annual Safety Reporting

Bimetra Clinics will ask the National Coordinating Investigator for an annual report containing an overview of all SSARs (Suspected Serious Adverse Reaction) and a summary regarding the safety of the trial subjects. Bimetra Clinics will send this report to the Central EC and the CA within the timelines as defined in national legislation. The National Coordinating Investigator will pass this annual report to all National Coordinating Investigators.

11 Quality control and quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.
A study monitor is responsible for visiting the institution at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The nature and extent of the monitoring will be captured in a monitoring plan. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the workbooks. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.
Quality control of the data in the CRF will be done by comparing the data in source documents with the data in the CRF by a person who was not involved in completing the CRF. There will be no medical data recorded in the CRF which are not mentioned in the medical file of the patients.

12 Indemnity insurance

Ghent University Hospital will undersign a no fault insurance within Belgium.

13 Publication policy

The decision whether, when, and where to publish the results of the trial will be the responsibility of the principal investigator. The PI will, however, involve the co-investigators prior to making any decision. Co-authorship of any scientific output will be offered to participating co-investigators, with the exact author order to be based on number of included patients and in consensus.

14 Independent Ethics Committee (IEC) / Institutional Review Bord (IRB)

This trial can only be undertaken after full approval of the protocol and addenda has been obtained from the IEC/IRB. This document must be dated and clearly identify the protocol, amendments (if any), the informed consent form and any applicable recruiting materials and subject compensation programs approved.
During the trial, the following documents will be sent to the IEC/IRB for their review:

- reports of adverse events that are serious, unexpected and associated with the investigational drug
- all protocol amendments and revised informed consent form (if any).

Amendments should not be implemented without prior review and documented approval / favorable opinion form the IEC/IRB except when necessary to eliminate an immediate hazard to trial subjects or when the change involves only logistical or administrative aspects of the trial.
Reports on, and reviews of the trial and its progress will be submitted to the IEC/IRB by the investigator at intervals stipulated in their guidelines.
At the end of the trial, the investigator will notify the IEC/IRB about the trial completion.

15 ICH/GCP guidelines

This trial will be conducted in accordance with the protocol, current ICH-GCP guidelines and applicable law(s).
Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

16 Subject information and informed consent

Prior to entry in the trial, the investigator must explain to potential subjects or their legal representatives the trial and the implication of participation. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Participating subjects will be told that their records may be accessed by competent authorities and by authorized persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF), the subjects or legally acceptable representatives are authorizing such access.
After this explanation and before entry to the trial, written, dated and signed informed consent should be obtained from the subject or legally acceptable representative. The ICF should be provided in a language sufficiently understood by the subject. Subjects must be given the opportunity to ask questions.
The subject or legally acceptable representative will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry to the trial, consent should be appropriately recorded by means of either the subject's or his/her legal representative's dated signature or the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the ICF must be given to the subject.
In case the subject or legally acceptable representative is unable to read, an impartial witness must attest the informed consent.
Subjects who are unable to comprehend the information provided or pediatric subjects can only be enrolled after consent of a legally acceptable representative.

17 Case Report Forms

The source documents are to be completed at the time of the subject’s visit. The CRFs are to be completed within reasonable time after the subject’s visit.
The investigator must verify that all data entries in the CRFs are accurate and correct. If certain information is Not Done, Not Available or Not Applicable, the investigator must enter "N.D." or "N.AV." or "N.AP", respectively in the appropriate space.

18 Direct access to source data / documents

The investigator will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

19 Data handling and record keeping

The investigator and sponsor specific essential documents will be retained for at least 20 years. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirement(s).

20 Signature page

Investigator:

Name: _____

Title: _____

Signature: _____

Date: _____

Investigator:

Name: _____

Title: _____

Signature: _____

Date: _____

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Appendix A – Performance status criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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