INTRAOPERATIVE INTRAPERITONEAL CHEMOPERFUSION TO TREAT PERITONEAL MINIMAL RESIDUAL DISEASE IN STAGE III OVARIAN CANCER: A RANDOMIZED PHASE II TRIAL

Study Protocol

1 Trial number

Protocolnummer: AGO/2015/002
EudraCTnummer: **2015-000418-23**

2 Aim

The aim of this randomized, double-blinded phase II trial is to study the effect of cytoreductive surgery (CRS) and efficacy of cisplatin-based intraoperative intraperitoneal chemoperfusion (IPEC) in patients with primary or recurrent serous epithelial ovarian cancer (OC), in order to treat peritoneal minimal residual disease (pMRD). Additionally, we aim to study the pharmacodynamics of IP drug delivery, the value of different doses of cisplatin and hyperthermic administration.

3 Endpoints

- Primary:
    - Tissue penetration distance of cisplatin in peritoneal tumor tissue nodules
- Secondary:
    - Postoperative morbidity and mortality (within 30 days after debulking)
    - Quality of Life (before and after debulking + 3, 6 and 12months after debulking)
    - Pharmacokinetics of cisplatin in peritoneal perfusate and plasma samples
    - Pharmacodynamics: Pt DNA adduct formation
    - Overall survival, disease free survival, peritoneal recurrence free survival (24 months after debulking)
    - Effects of (H)IPEC on peritoneal cytology
    - Translational research: analyzing gene expression of selected biomarkers for Pt sensitivity, stromal density and composition of tumor slices.

4 General information

4.1 Investigator(s)

- Trial coordinator: Wim Ceelen, MD, PhD, Ghent University Hospital, Department of GI Surgery, De Pintelaan 185, 9000 Ghent, Belgium. Tel +32 9332 6251. Fax +32 9332 6251 wim.ceelen@ugent.be

- Co-investigators:

  - Ghent University Hospital

    - Wouter Willaert, MD, Ghent University Hospital, Department of GI Surgery. De Pintelaan 185, 9000 Ghent, Belgium. Tel +32 9332 8950 wouter.willaert@ugent.be
    - Carlier Charlotte, PhD student, Ghent University Hospital, Department of GI Surgery. De Pintelaan 185. 9000 Ghent, Belgium. Tel+32 9332 5524 charlotte.carlier@ugent.be
    - Philippe Tummers, MD, PhD, Ghent University Hostpital, Department of Uro-gynaecology. De Pintelaan 185, 9000 Ghent, Belgium. Tel +32 9332 03 38 Philippe.Tummers@ugent.be
    - Hannelore Denys, MD, PhD, Ghent University Hospital, Department of Internal medicine. De Pintelaan 185, 9000 Ghent, Belgium. Tel +32 9332 5184 Hannelore.Denys@ugent.be
    - Amin Makar, MD, PhD, Ghent University Hospital, Department of gynaecological-oncology/senology. De Pintelaan 185, 9000 Ghent, Belgium. Tel +32 495 60 12 21 Amin.makar@pandora.be

  - Hospital Network Antwerp Middelheim (ZNA)
    - Amin Makar, MD, PhD, Hospital Network Antwerp (ZNA) Middelheim, Department of gynaecological-oncology/senology. Lindendreef 1, 2020 Antwerp, Belgium Tel +32 3280 30 03 or +32 495 60 12 21 amin.makar@zna.be

Opmerking [HDP1]: Gelieve hier ook de investigators van de andere sites toe te voegen.

Opmerking [CC2]: Dit kan ik u pas meedelen als de andere centra formeel bevestigen

4.2 Sponsor

There is no industrial sponsor. There is only funding from “Vlaamse Liga tegen kanker (VLK)”.

4.3 Departments/laboratories involved in the study

- Ghent University Hospital

- Wim Ceelen, Department of GI Surgery, De Pintelaan 185, 9000 Ghent, Belgium. Tel +32 9332 6251. Fax +32 9332 6251 wim.ceelen@ugent.be
- Philippe Tummers, Department of Uro-gynaecology. De Pintelaan 185, 9000 Ghent, Belgium. Tel +32 9332 03 38 Philippe.Tummers@ugent.be

- Hannelore Denys, Department of Internal medicine. De Pintelaan 185, 9000 Ghent, Belgium. Tel +32 9332 5184 Hannelore.Denys@ugent.be
- Frank Vanhaecke, Department of analytical chemistry. Krijgslaan 281 S12, 9000 Ghent, Belgium. Tel +32 9264 48 48 Frank.Vanhaecke@ugent.be

4.4 Estimated duration of the study

- Estimated date start recruitment: 01/04/2015
- Estimate date end of the study: 01/01/2018

5 Background

5.1 Peritoneal Carcinomatosis from ovarian cancer

With more than 20.000 new cases annually in the United States and more than 65.000 new cases annually in Europe, ovarian cancer (OC) represents the second most common gynecological malignancy and main cause of death.(1-3) In comparison to other common solid cancers, OC is often diagnosed in an advanced stage, because of a lack of specific symptoms at earlier stages. Consequently, almost 70% of patients are diagnosed with stage IIIC OC, of which the majority (~90%) are of epithelial origin. Despite the fact that OC is usually widespread throughout the peritoneal cavity at the time of diagnosis, the disease generally remains confined to the peritoneal cavity.(4) Although significant research efforts have been made over the last 3 decades and despite the frequency and potential morbidity of peritoneal recurrence in advanced OC, only a modest improvement in treatment, prevention or survival has been achieved. This is explained by the fact that even after successful initial treatment, most patients (~80%) will eventually develop recurrent peritoneal disease, which can only arise from peritoneal minimal residual disease (pMRD), left after primary cytoreductive surgery (CRS).(3, 5, 6) Recently, the addition of intraoperative intraperitoneal chemoperfusion (IPEC) to the combination of CRS and systemic chemotherapy has been demonstrated to be beneficial, as OC usually remains confined to the peritoneal cavity.(6)

The epidemiology and risk factors for PC in OC are well established. While the incidence of OC is low before the menopause, it rises afterwards with a median age at the time of diagnosis of 60-63 years. The lifetime risk of OC is approximately 1 in 70 in developed countries, but there are women with a much higher risk. The most important risk factor is a strong family history of breast or ovarian cancer, although a genetic predisposition (mostly germline mutations in tumor suppressor genes BRCA1 and/or BRCA2) is only present in only 10-15% of patients. For women with a BRCA1 or BRCA2 mutation, the risk of an OC is approximately 39-46% and 12-20%,

respectively. Other factors like null parity, late menopause, early menarche and alcohol lead also to an increased risk, while breast feeding, oral contraceptives, pregnancy and tubal ligation are associated with a reduced risk of OC.(7, 8)

5.2 Current first-line treatment of Stage III ovarian cancer

1.2.1 Cytoreductive (debulking) surgery

Most patients with ovarian cancer are diagnosed with advanced stage disease (stage III or IV) and when untreated, the outlook of these patients is poor, with a long-term survival (>10 years) of approximately 10-30% for women older than 65 years.(9, 10) Currently, complete debulking surgery (cytoreductive surgery, CRS) combined with systemic carboplatin/paclitaxel-based chemotherapy is the standard of care for primary OC.(7) The goal of CRS is to remove all macroscopically visible disease, since this has been shown to be associated with significantly increased overall survival (OS) and progression free survival (PFS) in patients with advanced OC.(4, 9, 11)

1.2.2 Neo-adjuvant chemotherapy

When tumor dissemination is too extensive and optimal primary CRS impossible, neo-adjuvant chemotherapy has been proposed in order to reduce tumor load and reduce postoperative complications. Vergote and colleagues compared the effect of neo-adjuvant chemotherapy followed by interval CRS with primary CRS followed by platinum-based chemotherapy, in patients with stage IIIC or IV OC. This study showed a higher rate of post-operative adverse effects in the group treated with primary CRS followed by chemotherapy. Residual tumor nodules of one cm or less were found in 41,6% of patients treated with primary CRS and in 80.6% of patients treated with interval CRS. Additionally, the hazard ratio (HR) for death was 0.98 (90% confidence interval [CI], 0.84 to 1.13; P=0.01 for non-inferiority) and the HR for progressive disease was 1,01 (90% CI, 0.89 to 1.15), when comparing the group treated with interval CRS with the group treated with primary CRS. In conclusion, this study demonstrates first that neo-adjuvant therapy followed by interval CRS was not inferior to primary CRS followed by adjuvant chemotherapy and second that performing maximal cytoreduction remains the strongest independent variable for overall survival, whether administered at primary or at interval CRS.

1.2.3 Intraperitoneal chemotherapy

Since OC rarely spreads systemically, intraperitoneal (IP) chemotherapy might offer a benefit, since its pharmacokinetic advantage allows to achieve higher concentrations into the peritoneal cavity, as compared to i.v. therapy.(7) Several large randomized trials have demonstrated a statistically significant survival benefit associated with IP-platinum based chemotherapy as a first-line treatment after primary CRS (Table 1). (3, 9) Kyrgiou et al. showed in a meta-analysis of multiple treatments, that the best survival in women with OC is obtained with a combination of IP

administration of platinum and a taxane. They calculated that a platinum and taxane combination with IP administration resulted in a 55% relative risk reduction (95% confidence interval [CI] = 39% to 67%) for mortality as compared with nonintraperitoneal monotherapy.(10) Another meta-analysis by Hennessy et al., confirmed a benefit for catheter based IP chemotherapy in OS in patients with small (< 1cm) or no residual disease after surgery. Nevertheless, adjuvant IP chemotherapy through a catheter is currently not universally accepted as a standard treatment, mainly because of the potential for locoregional toxicity, port or catheter malfunction, and infection.(4, 8)

Table 1. Randomized controlled trials of IP-platinum based chemotherapy as a first-line treatment after CRS, in women with primary stage III OC

Author	Year	N eligible patients	Setting	OS (months)	PFS (months)
Alberts[12]	1996	546	IV cyclophosphamide (600mg/m^2) + IP cisplatin (100mg/m^2) *OR* IV cyclophosphamide (600mg/m^2) + cisplatin (100mg/m^2)	IP arm: 49 95% CI [42-56] IV arm: 41 95% CI [34-47]	-
Markman[13]	2001	462	IV carboplatin (AUC9) + paclitaxel (135mg/m^2) + IP cisplatin (100mg/m^2) *OR* IV paclitaxel (135mg/m^2) + cisplatin (75mg/m^2)	IP arm: 63 IV arm: 52 RR 0.81 P=0.05 by log-rank test One-tail	IP arm: 28 IV arm: 22 RR 0.78 P=0.01 by log-rank test One-tail
Armstrong[14]	2003	415	IV paclitaxel (135mg/m^2) + IP paclitaxel (60mg/m^2) + cisplatin (100mg/m^2) *OR* IV paclitaxel (135mg/m^2) + cisplatin (75mg/m^2)	IP arm:65.6 IV arm: 49.7 P=0.03 by log-rank test	IP arm:23.8 IV arm:18.3 P=0.05 by log-rank test

IV intravenous, *IP* intraperitoneal, *OS* overall survival, PFS progression free survival, *CI* 95% confidence interval, *RR* relative risk

1.2.4 Intraperitoneal Cisplatin

Cisplatin (*cis*-diamminedichloroplatinum [II]) is among the most frequently used chemotherapeutic agents for the treatment of solid tumors and has a molecular weight of approximately 300 and a high $AUC_{i.p.}/AUC_{plasma}$ ratio ranging from 12-22. (1, 6, 15, 16) It executes its cytotoxic activity via formation of intra- and interstrand crosslinks in DNA, whereby the two major reaction products are guanine-guanine (Pt-[GG]) and adenine-guanine (Pt-[AG]) intrastrand crosslinks. These crosslinks results in inhibitory effects on DNA replication and transcription, which subsequently trigger apoptosis.(17) Recently, Bianga and colleagues demonstrated with laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) that cisplatin (75mg/m^2, 42°C, 90min)

penetrates deeper into tumor tissues (3-5mm), while oxaliplatin is mostly found at the periphery of the tumors. Therefore, cisplatin could provide a higher tumor drug concentration in pMRD.(8, 18) The efficacy of cisplatin is enhanced by the addition of hyperthermia (thermal sensitization). Raaphorst et al. showed that a combination of mild hyperthermia (40-41°C) and low doses of cisplatin is a more effective treatment, due to the inhibition of DNA damage repair by hyperthermia. This synergistic effect persists at least for 2 hours. Other studies have confirmed that hyperthermia is a good sensitizer for cisplatin treatment.(19, 20)

5.3 Hyperthermic intraperitoneal chemoperfusion (HIPEC)

HIPEC was first described in an animal model in 1974 by Euler (21).The first clinical application of combined cytoreduction and HIPEC was reported in 1980 by Spratt and co-workers, who treated a 35 years-old man, suffering from pseudomyxoma peritonei (PMP) with extensive surgery followed by IP chemoperfusion of thiotepa under hyperthermic conditions using a delivery system consisting of a heat exchanger and pump (22). After the procedure, the drains were left in place and 5 days later another HIPEC procedure with methotrexate was performed. In that publication, the authors stressed the importance of removing free floating cancer cells by the microfilters in the perfusion circuit. The advantage of intraoperative chemoperfusion, as opposed to adjuvant, is the possibility to achieve optimal chemotherapy exposure of all peritoneal surfaces at risk. The use of hyperthermia is based on several observations. First, hyperthermia is selectively cytotoxic for malignant cells.(23) Second, the cytotoxicity of several chemotherapeutic agents (e.g. cisplatin) is enhanced by hyperthermia via different mechanisms like: increased cell membrane permeability, increased production of free oxygen radicals, increased DNA alkylation and increased activity at low pH.(9, 11, 19, 24) Third, hyperthermia enhances tissue perfusion and oxygenation, and may improve drug penetration. Los et al. demonstrated a significant increase in peritoneal tumor Pt concentrations when IP cisplatin therapy was combined with regional hyperthermia (41.5 °C) in a rat colon cancer model.(25)

Although prospective, randomized controlled trials have demonstrated a significant benefit of CRS followed by HIPEC in colon cancer with PC and high-grade gastric cancer, there's only one prospective, randomized trial published up to now of HIPEC for PC in OC patients by Spiliotis et al.(6, 26, 27) On the other hand a number of non-randomized small trials have been published. Table 2 summarizes the most important trials presenting survival data in patients with primary advanced or recurrent OC treated with CRS and HIPEC.(3)

These results were summarized in two systematic reviews. Bijelic and colleagues found a median OS ranging from 22-54 months, a median disease free survival (DFS) ranging from 10-26 months, a significant morbidity of 5-36% and a median mortality of 3%.(11) Chua et al. found a similar median OS ranged from 22-64 months, a median PFS varied from 10-57 months, similar rates of severe perioperative morbidity ranged from 0-40% and mortality rates varied from 0-10% and are associated with treatment.(28)

Recently, Spiliotis et al.compared the effect of CRS followed by HIPEC and systemic chemotherapy with CRS followed by systemic chemotherapy in women with recurrent EOC, after initial debulking and systemic chemotherapy. Noteworthy, in the HIPEC group there was no difference in mean survival between patients with platinum-sensitive versus platinum-resistant disease (26.6 vs. 26.8 months, p=0,287). This was in contrast to the non-HIPEC group, where there was a statistically significant difference in mean survival between platinum-sensitive versus platinum-resistant disease (15.2 vs. 10.2 months, p<0.002).(27) At this time, several other prospective, randomized controlled trials were initiated to compare outcomes of CRS (interval or secondary) with or without HIPEC and are currently recruiting participants (Table 3).

Table 2. Results of trials presenting survival data in patients with primary advanced or recurrent OC treated with cytoreductive surgery followed by hyperthermic intraperitoneal chemoperfusion.

Author	Year	N	Disease type	CR (%)	Mortality (%)	Morbidity (%)	OS (months)	DFS/PFS (months)
Zanon[29]	2004	30	Recurrent or advanced primary	-	3.3	16.7	28.1	17.1
Reichman[30]	2005	13	Recurrent or advanced primary	38	None	-	-	15.4
Rufian[31]	2006	33	Recurrent or advanced primary	52	None	36	48[a]	-
Raspagliesi[32]	2006	40	Persistent recurrent	82	None	5	414[a]	23.9[a]
Cotte[33]	2007	81	Chemoresistent recurrent	55	2.5	136	28.4	19.2
Helm[34]	2007	18	Persistent recurrent	61	5.5	17	31	10
Di Giorgio[35]	2008	47	Advanced primary or recurrent	59	4.2	21.3	24	20
Fagotti[36]	2009	25	Recurrent	92	None	28	-	10
Tentes[37]	2010	29	Recurrent	58.6	3.4	21.4	-	-
Deraco[38]	2011	26	Primary advanced	65.2	3.8	15.2	60.7	15.2
Bakrin[39]	2012	246	Recurrent/ persistent	92.2	0.37	11.6	48.9	-
Ceelen[3]	2012	42	Recurrent	50	None	21	37	13
Bakrin[40]	2013	566	Recurrent or advanced primary	74.9	0.8	31.3	Recurrent: 45.7 Advanced: 354	-
Cascales[41]	2013	91	Recurrent or advanced primary	80.2	None	27	-	-

CR macroscopically complete (CC-0) resection, *mortality* 30-day or in-hospital mortality, *morbidity* major morbidity rate, OS median overall survival, DFS median disease-free survival, PFS median progression-free survival

[a] Mean

Table 3. Published and ongoing prospective, randomized controlled trials (Spiliotis, OVHIPEC, HORSE and CHIPOR)

Clinical trial	N patients	Eligible ages	Setting	End points
Spiliotis [27]	120	[18-70]	-Recurrent OC - Second-line systemic chemotherapy + maximal CRS -With OR without HIPEC	- OS [a]: - 26.7m HIPEC versus - 13.4m non-HIPEC p < 0.006 -Three-year survival: -75% HIPEC versus -18% non-HIPEC p < 0.01
OVHIPEC[42] (Dutch)	280	[18 - 76]	-Primary OC -Interval CRS -With OR without HIPEC	Primary: - RFS Secondary: - toxicity/morbidity - OS - tumor response after chemotherapy - QoL
HORSE[43] (Italian)	158	[18 - 70]	-Recurrent OC -Secondary CRS -With OR without HIPEC	Primary: - PFI Secondary: - OS - morbidity - mortality
CHIPOR [44] (French)	444	[18 - …]	-Recurrent OC -Second-line systemic chemotherapy + maximal CRS -With OR without HIPEC	Primary: - OS Secondary: - RFS

RCT randomized controlled trial, *OC* ovarian cancer, *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemoperfusion, *RFS* recurrence free survival, *OS* overall survival, *QoL* Quality of life, *PFI* progression-free interval, *m* months
[a] mean

Generally, the quality of available evidence is low, but it is reasonable to assume that in selected patients in whom complete or optimal CRS can be achieved, HIPEC could be a feasible addition to the standard treatment of systemic chemotherapy and surgery, with potential benefits and significant prolongation of survival in patients suffering from primary or recurrent OC.

6 Patients and methods

6.1 Patient selection criteria

❖ Inclusion criteria

- Tumor type
  - Biopsy proven serous epithelial ovarian carcinoma or peritoneal carcinoma
- Primary or recurrent disease
- Extent of disease
  - Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis (FIGO stage III)
  - Stage IV with unilateral pleural fluid allowed
  - Complete or nearly complete macroscopic cytoreduction at the time of surgery (CC-0 or CC-1) deemed possible based on imaging, laparoscopy, or both
- Second-line patients; platinum sensitive
- Age over 18 years
- No major cardiac or respiratory disease
- Absent or limited (<500ml) clinical ascites
- Adequate performance status (Karnofsky index > 70%)
- Adequate mental faculty, allowing to understand the proposed treatment protocol and provide informed consent
- Expected life expectancy more than 6 months
- Laboratory data
  - Serum creatinine $\leq$ 1.5 mg/dl or a calculated GFR (CKD-EPI) $\geq$ 60 mL/min/1.73 m^2
  - Serum total bilirubin $\leq$ 1.5 mg/dl, except for known Gilbert's disease
  - Platelet count > 100.000/µl
  - Hemoglobin > 9g/dl
  - Neutrophil granulocytes > 1.500/ml
  - International Normalized Ratio (INR) $\leq$ 2
- Absence of alcohol and/or drug abuse
- No other concurrent malignant disease
- No inclusion in other clinical trials interfering with the study protocol
- No concurrent chronic systemic immune or hormone therapy, except neoadjuvant chemotherapy
- Absence of any severe organ insufficiency
- No pregnancy or breast feeding
- Written informed consent

❖ Exclusion criteria

- Severe or uncontrolled cardiac insufficiency, including recent (< 6 months) occurrence of myocardial infarction, the presence of congestive cardiac insufficiency, of symptomatic angor in spite of optimal medical care, of cardiac arrhythmia requiring medical treatment presenting insufficient rhythm control, or uncontrolled arterial hypertension
- Pregnancy or breast feeding
- Platinum resistant (relapse > 12 months after completion of Pt containing therapy) or refractory disease
- Active bacterial, viral or fungal infection
- Active gastro-duodenal ulcer
- Parenchymal liver disease (any stage cirrhosis)
- Uncontrolled diabetes mellitus
- Severe obstructive or restrictive respiratory insufficiency
- Psychiatric pathology capable of affecting comprehension and judgment faculty
- Tumor in the presence of obstruction
- Evidence of extra-abdominal disease (with the exception of unilateral malignant pleural effusion) or extensive liver metastasis
- Peritoneal cancer index (sPCI) ≥ 25

6.2 Methods

6.2.1 Patient selection and staging

Staging is performed as per standard of care, but should minimally include CT scan of the chest and abdomen and CA125 measurement.
Other imaging techniques (DWI-MRI, ^{18}F-FDG-PET-CT) and diagnostic laparoscopy are optional.

6.2.2 Neoadjuvant therapy

Neoadjuvant therapy is performed as the current standard of care (carboplatin and paclitaxel). The duration and treatment schedule are decided by the treating oncologist. Ideally, 3 or 4 courses are administered before surgery and IPC. A minimal waiting period of two or three weeks should be respected for weekly and three-weekly scheduled chemotherapy, respectively, between the last dose of chemotherapy and the date of surgery.

6.2.3 Surgery

6.2.3.1 Assessment and confirmation of optimal resectability

The extent of the disease is reported and scored as the simplified peritoneal cancer index (sPCI).

6.2.3.2 Peritoneal fluid sampling

Samples (50 ml) are obtained of ascites or of NaCl 0.9% instilled into the peritoneal cavity and vigorously moved between the abdominal contents. Three samples are taken at different time points: before surgery, after completion of surgery, and after completion of IPC.

6.2.3.3 Cytoreductive surgery

A combination of organ resections and peritonectomies is performed aiming to achieve optimal (macroscopically complete) resection. Two tumor nodules resected during surgery will be kept for analysis and serves as controls, and two other parietal peritoneal index nodules will be left during chemoperfusion, and are resected for analysis after the IPC.

6.2.3.4 Intraperitoneal chemoperfusion

The open (coliseum) technique is used as per standard of care, and a semi-closed circuit created consisting of inflow- and outflow drains, temperature probes, heat exchanger, and a peristaltic pump. When optimal cytoreduction is achieved, patients will be randomized to normothermic

(37°C) or hyperthermic (41°C) chemoperfusion immediately before installation of the IPC system, using sealed envelopes. Chemoperfusion duration is 90 minutes, starting from the addition of drug to the circuit.

- **Drug regimen, administration way and composition**

Cisplatin is used in a dose of 120 mg/m^2 or 75mg/m^2, dissolved in a balanced peritoneal dialysis solution (Physioneal™ 1.36, Baxter). The volume of the perfusate is calculated as 2 liters/m^2 body surface area (BSA).

A systemic sodium-thiosulfate (Na2S2O3) solution is administered IV 20 minutes before start of the chemoperfusion (4g/m^2, dissolved in 150ml NaCl 0,9%) and during 6 hours after completion of the chemoperfusion (12g/m^2 dissolved in 1000ml NaCl 0,9%), in order to prevent nephrotoxicity.

An adjusted hydration and urinary workup have to be carried out during the first 24hours following infusion. Administration of cisplatin has been associated with aberrant concentrations of the serum electrolytes (Mg, K, Na, Ca), including a symptomatic hypomagnesaemia. Hence, it is recommended to check these serum concentrations during and after each treatment.

- **Producer**

Hospira Benelux BVBA. Noorderplaats 9, 2000 Antwerpen.

- **Distributor**

Cisplatin Hospira 50 mg/50 ml Onco-Tain : BE 197486.
Cisplatin Hospira 100 mg/100 ml Onco-Tain : BE 197495.

- **Packaging**

Solution for injection. Cisplatin Hospira 50 mg/50 ml Onco-Tain: 1 glass vial containing 50 mg cisplatin/50 ml. Cisplatin Hospira 100 mg/100 ml Onco-Tain: 1 glass vial containing 100 mg cisplatin/100 ml. The following particulars will be added to the original vial, but will not obscure the original labelling: '*For clinical trial use only*', study reference code, study site, study participant and investigator's name

- **Storage conditions**

Storage beneath 25°C and protect against light.

In-use stability: from a microbiological point of view, unless dilution has taken place in controlled and validated aseptic conditions, the product should be used immediately. If not used immediately, storage times and conditions for use are the responsibility of the user.

The resulting solution should not be stored in the refrigerator, due to precipitation.

- **Known side effects of the medication**

- Nephrotoxicity:
    - Kidney failure
    - Hyperuricaemia
- Ototoxicity
- Neurotoxicity:
    - Peripheral neurotoxicity
- Hematological toxicity:
    - Myelosuppression
    - Leucopenia
    - Thrombocytopenia
    - Anaemia
- Gastro-intestinal toxicity:
    - Emetogenesis
    - Diarrhea
    - Nausea
- Liver and bile disease:
    - Increased transaminases: serum glutamate-oxaloacetate transaminase (SGOT)

6.2.3.5 Postoperative care and follow-up

Postoperative care and follow up are performed as per current standard treatment and protocols. The Dindo-Clavien classification will be used to score post-operative complications until 3 months after surgery and (H)IPEC. Participants of the study will be asked to fill in a cancer-specific (C30) and disease-specific (OV28) questionnaire, on specific time points (before and after debulking and after 3, 6 and 12 months) to analyze the quality of life. In appendix you can find the EORTC questionnaires and manuals.

6.2.4 Analytical Methods

6.2.4.1 Cisplatin Tumor Tissue penetration

Two index nodules (min. 7mm diameter) of the parietal peritoneum will be removed after chemoperfusion and a cross-section of each index nodule will be made to obtain a cylinder-shaped tumour sample, according to a protocol described in literature.(45) One cylinder-shaped tumor sample will be stored at -80°C, thereafter pieces of different thickness will be cut using a freezing microtome (Leica CM3050s, Leica Biosystems) subsequently Pt distribution will be analyzed in tumor homogenates, using acid digestion and pneumatic nebulization inductively coupled plasma-mass spectrometry (PN-ICP-MS). Chemical analysis will be performed at the Department of Analytical Chemistry, Faculty of Sciences, Ghent University (F. Vanhaecke). The second cylinder-

shaped tumor nodule will be stored half formalin-fixed and paraffin-embedded for histology and half snapfrozen (-196°C) in RNase-free tubes to analyze gene expression of selected biomarkers for Pt sensitivity.

6.2.4.2 Cisplatin Pharmacokinetics in peritoneal perfusate and plasma samples

One plasma and one perfusate sample will be taken before chemoperfusion (T=0). Other perfusate and plasma samples will be taken after 20, 40and 60 min and after 1, 10, 20, 30, 45, 60, 75, 90 and 105 min of chemoperfusion, respectively. Plasma samples will also be taken after 2, 3, 4, 6, 8, 12 and 24 hours post chemoperfusion, for Pt determination. Since there is a difference between the pharmacokinetics of free and total Pt in plasma and there are certain amount of proteins present in ascites fluid, ultrafiltration will be used to separate the free from the protein-bound Pt.(46, 47) The Pt concentrations will be determined in plasma and perfusate by an Xseries 2 quadrupole-based PN-ICP-MS (Thermo-Scientific, Bremen, Germany) respectively after an acid digestion step in a MLS-1200 Mega, microwave digestion system (Milestone Inc, Sorisole, Italy) or after a two-step sample dilution. In order to eliminate variations, arising from changes in the density of blood, the samples will be weighted and the Pt concentration will be calculated per gram instead of per millliter of blood. Afterwards, the latter will be converted again in milliliter since this is necessary for the PKPD modeling.

The primary endpoint in this study is to estimate the tumor penetration of cisplatin following HIPEC administration. In order to achieve a reliable estimate of this tumor-penetration we will build a PKPD model describing cisplatin intraperitoneal, plasma and tumor kinetics simultaneously. Similar to our earlier published model, describing paclitaxel PKPD following IPEC administration in rats, this model will be used to estimate systemic (i.e. blood) and tumor exposure following (H)IPEC dosing and will provide the necessary power to estimate the potential difference in tumor penetration between the normothermic and hyperthermic perfusion. (45)

6.2.4.3 Cisplatin Pharmacodynamics

A pharmacodynamic model will be built (collaboration with dr P. Colin, FFW) relating Pt concentration to Pt DNA adduct formation in tumor slices. PK/PD modeling will be done using the LAPLACE estimation algorithm with interaction in NONMEN® software (version 7.2, GloboMax LLC, Hanover, MD, USA). Furthermore, systemic toxicity (hematological / nephrological), following HIPEC administration will be incorporated in the model (in terms of serum creatinine, blood urea nitrogen (BUN), kalium and absolute neutrophil count and platelet count) to study the onset and duration of Pt-related toxicities following HIPEC.(48)

6.2.5 Oncological Endpoints

6.2.5.1 Peritoneal cytology

Samples will be centrifuged and HE staining will be performed. Cytology results are compared before versus after surgery and IPC.

2.2.5.2 Local (peritoneal) and systemic recurrence

Follow up duration will be minimally one year after surgery/IPC. Patients will be followed as per standard protocol. The date and location of first recurrence and/or death will be recorded. Actuarial Kaplan Meier estimates will be calculated for peritoneal recurrence free survival, disease free survival or progression free survival, and overall survival.

6.2.6 Translational research

6.2.6.1 2.2.6.1 Gene expression analysis of selected biomarkers and composition of tumor slices

Tumor tissue, plasma and peritoneal perfusate samples will be obtained. Gene expression (RT-PCR) of selected biomarkers (ERCC1, GSTP1, MGMT, XPD and BRCA1) will be analyzed for the Pt sensitivity, and also stromal density and composition of tumor slices (collagen density, fibroblast proliferation) will be investigated, in women undergoing treatment for stage III ovarian cancer.

- Histology/immunohistochemistry (IHC):
  - Collagen density (sirius red staining) and fibroblast proliferation (α-SMA)
  - DNA intrastrand adduct formation of Pt-[GG] with Mab R-C18

- Gene expression (resected peritoneal metastases) of:
  - Excision Repair Cross-Complementation group 1 **(ERCC1)**
  - Glutathione S-transferase P enzyme **(GSTP1)**
  - Methylguanine MethylTransferase enzyme **(MGMT)**
  - Xeroderma Pigmentosum D **(XPD)**
  - BReast CAncer gene 1 **(BRCA1)**
  - Copper Transporter 1 **(CTr1)**

- Circulating (serum) biomarkers: before neoadjuvant Tx, before surgery, before adjuvant Tx, and after completion of adjuvant Tx
  - CA 125
  - cCK18

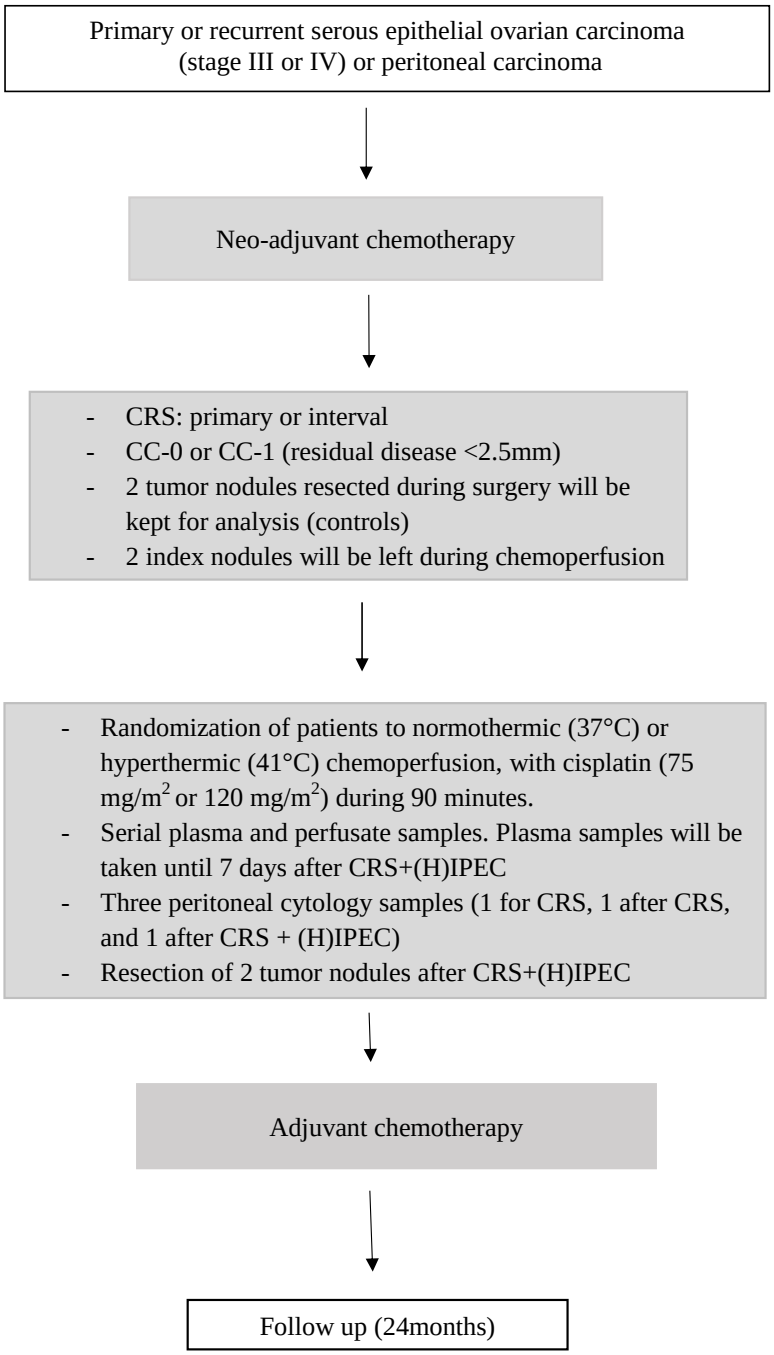
6.2.6.2 Preservation of resected tumor tissue for further research purposes

Resected tumor nodules are rinsed with saline (0.9% NaCl), snap-frozen in liquid nitrogen and stored at –80°C. Afterwards, tumor dissociation will be performed based on commercially available protocols (Macs product line, Miltenyi Biotec, The Netherlands) or based on a technique employing cancer tissue-originated spheroids (CTOS)[39]. Resulting primary cancer cells will be cultured in culture media supplemented with Rho kinase inhibitors and fibroblast feeder cells to retain lineage commitment and normal growth potential[40;41]. In-vitro sensitivity assessments against currently used compounds (paclitaxel, cisplatin), based on established protocols (MTT assay) will be performed on the primary cultures and results will be evaluated against genotyping information on 34 genes associated with the expression of drug-transporters and drug-metabolizing enzymes (VeraCode® ADME Core Panel, Illumina, US).

7 Trial Design

This is a randomized, double-blinded, phase II study.

The study flowchart is illustrated in figure 1.



8 Statistical analysis

a. Statistical design, randomization and blinding

This study is a randomized, double-blinded phase II trial. The primary objective is to study the penetration of cisplatin in tumor tissue nodules, which are resected after CRS and (H)IPEC, in patients with stage III ovarian cancer. Patients will be randomized after CRS to the normothermic (37°C) or hyperthermic (41°C) treatment and within this two groups, there will be another randomization in terms of dose of cisplatin (75mg/m^2 or 120mg/m^2). Randomization will be performed by drawing sealed envelopes and this will be done by the perfusionist. There will be two papers in these envelopes: one paper with the patient code (not secret), and one paper with the treatment (secret, only known by the perfustionist). In the case of a SUSAR the perfusionist knows which treatment the patient has received and this may be reported to people involved by safety reporting to national authorities, to people who carry out safety assessments during the study and to ethics and safety Committees.(49)

b. Sample size

A sample size of 48 patients (N=12/group) was calculated to detect an effect size of 10%, with a significance level of 0.05 ($\alpha = 0.05$) and of power of 0.8 ($\beta = 0.80$). A total of 60 patients will be included in order to account for the estimated drop-out rate of 25% post randomization. Patients will be followed-up to 24 months postoperatively. An interim analysis will be made and used to estimate the power to detect significant differences in tumor penetration between the normo- and hyperthermic cohort and will be used to derive the final sample size of the study.

c. Statistical Analysis

i. Primary endpoint:

The H_0 hypothesis is that hyperthermia (41°C) doesn't enhance the Pt penetration in tumor tissue nodules. On the contrary, the H_a hypothesis is that hyperthermia does enhance the Pt penetration in tumor tissue nodules. Differences between the groups will be analyzed with a t-test.

ii. Secondary endpoints:

1. Overall survival, disease free survival and time to peritoneal recurrence will be calculated using the Kaplan Meier product limit method, and differences will be assessed with the Logrank and Cox proportional hazards analyses. Survival will be measured from the date of surgery to progression or death.

2. Three months postoperative morbidity and mortality will be analyzed using effect methods (95% confidence interval)

3. Differences between groups will be analyzed with Chi square, Fisher exact, t-test and U-test if appropriate.

   All calculations and plotting will be performed with IBM SPSS®, version 20.

9 Safety Monitoring

Adverse events will be monitored and reported on an ongoing basis during the 3 months postoperative period using the Dindo-Clavien classification. Toxic effects during the pre- and postoperative chemotherapy regimens will be categorized using the CTCAE, Version 4.0. The worst event for each patient will be described. Both events related and unrelated to treatment will be recorded. Clinical and laboratory data will be tabulated and compared to normal ranges for the institution.

10 Forms and procedure for collecting data

Individual anonymized patient data will be extracted from the medical record onto paper case report forms (CRF). The local investigator will also report all adverse events in the source documents and CRFs. The SAEs will be reported within time periods specified in the protocol.
The information from the individual CRF's will be entered into a specifically designed MS Access database.

Opmerking [HDP3]: Gelieve mee in te dienen.

Dit moet juist nog nagekeken worden door prof. Ceelen

11 Adverse event reporting

a. Definitions

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 the end of the trial.
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 judgment 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).

b. Reporting procedure

Reporting of adverse events

Adverse events will be reported between the first dose administration of trial medication and the last trial related activity.
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) occurring during clinical trials must be reported by the local Principal Investigator within 2 working days after becoming aware of the SAE to:

- The local EC
- Bimetra Clinics of the University Hospital Ghent
- The National Coordinating Investigator (in case of multicenter trials)

This reporting is done by using the appropriate SAE form. For the contact details, see below.

It is the responsibility of the local Principal Investigator to report the local SAE's to the local EC.

- 1/ 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 local Principal Investigators.
- 2/ 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 within the timelines as defined in national legislation. The National Coordinating Investigator reports the SUSAR to all local Principal 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 be completed within 15 calendar days.

The first report of a serious adverse event may be made by telephone, e-mail or facsimile (FAX).

Contact details of Bimetra Clinics:
e-mail: bimetra.clinics@uzgent.be

tel.: 09/332 05 00
fax: 09/332 05 20

Contact details of the National Coordinating Investigator:
e-mail: wim.ceelen@ugent.be
tel.: 09/332 62 51
fax: 09/332 15 03

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.

c. Expected side effects

Systemic administration of cisplatin is associated with severe side effects, which are dose dependent. These side effect includes emetogenesis, ototoxicity, myelosuppression and nephrotoxicity.(15) The latter forms the major systemic toxicity of cisplatin. In this study, cisplatin will be administered IP where a peritoneal plasma barrier is present, the given dose remains low (120mg/m^2, literature describes doses up to 250mg/m^2) and sodium-thiosulfate ($Na_2S_2O_3$) is given during HIPEC as antidote.(50) Therefore the systemic concentration of the drug will remain low and is considered to be safe.(50-53)

12 Ethical considerations

d. Patient protection

The responsible investigators will ensure that the study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ref:http://www.ifpma.org/pdfifpma/e6.pdf).

The protocol will be submitted to Ethical Committee of Ghent University Hospital as Central Committee, and to the Local Ethical Committees of all participating centers.

e. Subject identification

After inclusion in the study, the investigator will assign each subject a unique identifier to protect the subject's identity and this will be used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data. Only those investigators involved in the study will have access to the trial database allowing identification of each participant. All data

collected on a patient's health for the purpose of research will be kept confidential. The patient's identity will never be disclosed.

f. Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, and that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent will be obtained for all patients included in the study before they are registered in the study. The informed consent procedure conforms to the ICH guidelines on Good Clinical Practice.

13 References

1. Grosso G, Rossetti D, Coccolini F, Bogani G, Ansaloni L, Frigerio L. Intraperitoneal chemotherapy in advanced epithelial ovarian cancer: a survey. Archives of gynecology and obstetrics. 2014;290(3):425-34.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA: a cancer journal for clinicians. 2014;64(1):9-29.
3. Ceelen WP, Van Nieuwenhove Y, Van Belle S, Denys H, Pattyn P. Cytoreduction and hyperthermic intraperitoneal chemoperfusion in women with heavily pretreated recurrent ovarian cancer. Annals of surgical oncology. 2012;19(7):2352-9.
4. Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2013;24 Suppl 6:vi24-32.
5. Heintz AP, Odicino F, Maisonneuve P, Quinn MA, Benedet JL, Creasman WT, et al. Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2006;95 Suppl 1:S161-92.
6. de Bree E, Helm CW. Hyperthermic intraperitoneal chemotherapy in ovarian cancer: rationale and clinical data. Expert review of anticancer therapy. 2012;12(7):895-911.
7. Halkia E, Spiliotis J, Sugarbaker P. Diagnosis and management of peritoneal metastases from ovarian cancer. Gastroenterology research and practice. 2012;2012:541842.
8. Hennessy BT, Coleman RL, Markman M. Ovarian cancer. Lancet. 2009;374(9698):1371-82.
9. Ceelen WP, Hesse U, de Hemptinne B, Pattyn P. Hyperthermic intraperitoneal chemoperfusion in the treatment of locally advanced intra-abdominal cancer. The British journal of surgery. 2000;87(8):1006-15.
10. Kyrgiou M, Salanti G, Pavlidis N, Paraskevaidis E, Ioannidis JP. Survival benefits with diverse chemotherapy regimens for ovarian cancer: meta-analysis of multiple treatments. Journal of the National Cancer Institute. 2006;98(22):1655-63.
11. Bijelic L, Jonson A, Sugarbaker PH. Systematic review of cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis in primary and recurrent ovarian cancer. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2007;18(12):1943-50.
12. Alberts DS, Liu PY, Hannigan EV, O'Toole R, Williams SD, Young JA, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. The New England journal of medicine. 1996;335(26):1950-5.
13. Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001;19(4):1001-7.
14. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. The New England journal of medicine. 2006;354(1):34-43.
15. Wang D, Lippard SJ. Cellular processing of platinum anticancer drugs. Nature reviews Drug discovery. 2005;4(4):307-20.
16. Pavlov MJ, Kovacevic PA, Ceranic MS, Stamenkovic AB, Ivanovic AM, Kecmanovic DM. Cytoreductive surgery and modified heated intraoperative intraperitoneal chemotherapy (HIPEC) for advanced and recurrent ovarian cancer -- 12-year single center experience. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2009;35(11):1186-91.
17. Liedert B, Pluim D, Schellens J, Thomale J. Adduct-specific monoclonal antibodies for the measurement of cisplatin-induced DNA lesions in individual cell nuclei. Nucleic acids research. 2006;34(6):e47.
18. Bianga J, Bouslimani A, Bec N, Quenet F, Mounicou S, Bouyssiere B, et al. Complementary of MALDI and LA ICP mass spectrometry for platinum anticancer imaging in human tumor. doi: 10.1039/c4mt00131a. Metallomics. 2014.
19. Orsolic N, Car N. Quercetin and hyperthermia modulate cisplatin-induced DNA damage in tumor and normal tissues in vivo. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2014;35(7):6445-54.
20. Raaphorst GP, Yang DP. The evaluation of thermal cisplatin sensitization in normal and XP human cells using mild hyperthermia at 40 and 41 degrees C. Anticancer research. 2005;25(4):2649-53.
21. Euler J, Prieschi.A, Wenzl J, Sauerman.G, Klockler K, Kretschm.G. HYPERTHERMIC PERITONEAL PERFUSION IN ASCITES TUMORS IN RATS. Wien Klin Wochenschr. 1974;86(8):220-5.

22. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer research. 1980;40(2):256-60.
23. Hildebrandt B, Wust P, Ahlers O, Dieing A, Sreenivasa G, Kerner T, et al. The cellular and molecular basis of hyperthermia. Critical Reviews in Oncology Hematology. 2002;43(1):33-56.
24. Raaphorst GP, Yang DP. The evaluation of thermal cisplatin sensitization in normal and XP human cells using mild hyperthermia at 40 and 41 degrees C. Anticancer Research. 2005;25(4):2649-53.
25. Los G, Sminia P, Wondergem J, Mutsaers PH, Havemen J, ten Bokkel Huinink D, et al. Optimisation of intraperitoneal cisplatin therapy with regional hyperthermia in rats. European journal of cancer (Oxford, England : 1990). 1991;27(4):472-7.
26. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003;21(20):3737-43.
27. Spiliotis J, Halkia E, Lianos E, Kalantzi N, Grivas A, Efstathiou E, et al. Cytoreductive Surgery and HIPEC in Recurrent Epithelial Ovarian Cancer: A Prospective Randomized Phase III Study. Annals of surgical oncology. 2014.
28. Chua TC, Robertson G, Liauw W, Farrell R, Yan TD, Morris DL. Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery in ovarian cancer peritoneal carcinomatosis: systematic review of current results. Journal of cancer research and clinical oncology. 2009;135(12):1637-45.
29. Zanon C, Clara R, Chiappino I, Bortolini M, Cornaglia S, Simone P, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for recurrent peritoneal carcinomatosis from ovarian cancer. World journal of surgery. 2004;28(10):1040-5.
30. Reichman TW, Cracchiolo B, Sama J, Bryan M, Harrison J, Pliner L, et al. Cytoreductive surgery and intraoperative hyperthermic chemoperfusion for advanced ovarian carcinoma. Journal of surgical oncology. 2005;90(2):51-6; discussion 6-8.
31. Rufian S, Munoz-Casares FC, Briceno J, Diaz CJ, Rubio MJ, Ortega R, et al. Radical surgery-peritonectomy and intraoperative intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis in recurrent or primary ovarian cancer. Journal of surgical oncology. 2006;94(4):316-24.
32. Raspagliesi F, Kusamura S, Campos Torres JC, de Souza GA, Ditto A, Zanaboni F, et al. Cytoreduction combined with intraperitoneal hyperthermic perfusion chemotherapy in advanced/recurrent ovarian cancer patients: The experience of National Cancer Institute of Milan. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2006;32(6):671-5.
33. Cotte E, Glehen O, Mohamed F, Lamy F, Falandry C, Golfier F, et al. Cytoreductive surgery and intraperitoneal chemo-hyperthermia for chemo-resistant and recurrent advanced epithelial ovarian cancer: prospective study of 81 patients. World journal of surgery. 2007;31(9):1813-20.
34. Helm CW, Toler CR, Martin RS, 3rd, Gordinier ME, Parker LP, Metzinger DS, et al. Cytoreduction and intraperitoneal heated chemotherapy for the treatment of endometrial carcinoma recurrent within the peritoneal cavity. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2007;17(1):204-9.
35. Di Giorgio A, Naticchioni E, Biacchi D, Sibio S, Accarpio F, Rocco M, et al. Cytoreductive surgery (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of diffuse peritoneal carcinomatosis from ovarian cancer. Cancer. 2008;113(2):315-25.
36. Fagotti A, Paris I, Grimolizzi F, Fanfani F, Vizzielli G, Naldini A, et al. Secondary cytoreduction plus oxaliplatin-based HIPEC in platinum-sensitive recurrent ovarian cancer patients: a pilot study. Gynecologic oncology. 2009;113(3):335-40.
37. Tentes AA, Korakianitis OS, Kakolyris S, Kyziridis D, Veliovits D, Karagiozoglou C, et al. Cytoreductive surgery and perioperative intraperitoneal chemotherapy in recurrent ovarian cancer. Tumori. 2010;96(3):411-6.
38. Deraco M, Kusamura S, Virzi S, Puccio F, Macri A, Famulari C, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as upfront therapy for advanced epithelial ovarian cancer: multi-institutional phase-II trial. Gynecologic oncology. 2011;122(2):215-20.
39. Bakrin N, Cotte E, Golfier F, Gilly FN, Freyer G, Helm W, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for persistent and recurrent advanced ovarian carcinoma: a multicenter, prospective study of 246 patients. Annals of surgical oncology. 2012;19(13):4052-8.
40. Bakrin N, Bereder JM, Decullier E, Classe JM, Msika S, Lorimier G, et al. Peritoneal carcinomatosis treated with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for advanced ovarian carcinoma: a French multicentre retrospective cohort study of 566 patients. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2013;39(12):1435-43.

41. Cascales Campos P, Gil J, Parrilla P. Morbidity and mortality outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with primary and recurrent advanced ovarian cancer. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2014;40(8):970-5.
42. http://clinicaltrials.gov/show/NCT00426257.
43. http://clinicaltrials.gov/show/NCT01539785.
44. http://clinicaltrials.gov/show/NCT01376752.
45. Colin P, De Smet L, Vervaet C, Remon JP, Ceelen W, Van Bocxlaer J, et al. A Model Based Analysis of IPEC Dosing of Paclitaxel in Rats. Pharmaceutical research. 2014;31(10):2876-86.
46. Zivanovic O, Abramian A, Kullmann M, Fuhrmann C, Coch C, Hoeller T, et al. HIPEC ROC I: A phase i study of cisplatin administered as hyperthermic intraoperative intraperitoneal chemoperfusion followed by postoperative intravenous platinum-based chemotherapy in patients with platinum-sensitive recurrent epithelial ovarian cancer. International journal of cancer Journal international du cancer. 2015;136(3):699-708.
47. Dakwar GR, Zagato E, Delanghe J, Hobel S, Aigner A, Denys H, et al. Colloidal stability of nano-sized particles in the peritoneal fluid: towards optimizing drug delivery systems for intraperitoneal therapy. Acta biomaterialia. 2014;10(7):2965-75.
48. Perez-Ruixo C, Valenzuela B, Peris JE, Bretcha-Boix P, Escudero-Ortiz V, Farre-Alegre J, et al. Neutrophil dynamics in peritoneal carcinomatosis patients treated with cytoreductive surgery and hyperthermic intraperitoneal oxaliplatin. Clinical pharmacokinetics. 2013;52(12):1111-25.
49. http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_nl.pdf.
50. Markman M, D'Acquisto R, Iannotti N, Kris M, Hakes T, Bajorin D, et al. Phase-1 trial of high-dose intravenous cisplatin with simultaneous intravenous sodium thiosulfate. Journal of cancer research and clinical oncology. 1991;117(2):151-5.
51. Guastalla JP, Vermorken JB, Wils JA, George M, Scotto V, Nooij M, et al. Phase II trial for intraperitoneal cisplatin plus intravenous sodium thiosulphate in advanced ovarian carcinoma patients with minimal residual disease after cisplatin-based chemotherapy--a phase II study of the EORTC Gynaecological Cancer Cooperative Group. European journal of cancer. 1994;30A(1):45-9.
52. Leitao DJ, Blakley BW. Quantification of sodium thiosulphate protection on cisplatin-induced toxicities. The Journal of otolaryngology. 2003;32(3):146-50.
53. van Rijswijk RE, Hoekman K, Burger CW, Verheijen RH, Vermorken JB. Experience with intraperitoneal cisplatin and etoposide and i.v. sodium thiosulphate protection in ovarian cancer patients with either pathologically complete response or minimal residual disease. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 1997;8(12):1235-41.