"Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in gastric carcinomatosis. Phase II randomized study"

"PIPAC EstoK 01"

INTERVENTIONAL RESEARCH PROTOCOL
RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

Version N°6.0 of 09/08/2021
Project code number: **P160951J** / EUDRACT No. **2018-004755-20**

Coordinating Investigator : Pr Clarisse EVENO
Chirurgie Digestive et Oncologique
Hôpital Universitaire Claude Huriez
Place de Verdun, 59037 Lille Cedex France
Tel. 03 20 44 44 07
Email : clarisse.eveno@gmail.com

Scientific Director: Pr Marc POCARD
Chirurgie viscéral et digestive
Hôpital Pitié-Salpêtrière
47-83 Boulevard de l'Hôpital, 75013 Paris
Email : marc.pocard@gmail.com

Sponsor: AP-HP and by delegation:
Delegation for Clinical Research and Innovation (DRCI)
Hôpital Saint-Louis
1, avenue Claude Vellefaux 75010 PARIS
DRCI head office project advisor: **Karine SEYMOUR**
Tel: 01 44 84 17 42
Email: karine.seymour@aphp.fr

Entity responsible for monitoring the trial:
Unité de Recherche Clinique (URC)
Hôpital Saint-Louis 75010 Paris
1, avenue Claude Vellefaux 75010 PARIS

Methodologist: **Matthieu RESCHE-RIGON**
Email : matthieu.resche-rigon@univ-paris-diderot.fr

URC head office project advisor:
Chafia ABBOU-BENIHADDADENE
Email : chafia.benihaddadene@univ-paris-diderot.fr

Tel. 0142499742

Délégation à la Recherche Clinique et à l'Innovation (DRCI)
Hôpital Saint Louis 75010 PARIS

INTERVENTIONAL RESEARCH PROTOCOL
RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

PROTOCOL SIGNATURE PAGE

Research code number: **P160951J**

Title: Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in gastric carcinomatosis. Phase II randomized study. "PIPAC_EstoK 01"

Version N°6.0 of: 09/08/2021

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

Coordinating Investigator:
Pr Clarisse EVENO
Chirurgie Digestive et Oncologique
Hôpital Universitaire C. Huriez
Place de Verdun,
59037 Lille Cedex

Date: ……/……/……..
Signature:

Sponsor
Assistance Publique-Hôpitaux de Paris
Delegation of Clinical Research and Innovation
Hôpital Saint Louis
1 avenue Claude Vellefaux
75010 PARIS

Date: ……/……/……..
Signature:

The study was approved by the Ethic committee (CPP) of **31/07/2019** and authorised by the ANSM on **26/07/2019**.

TABLE OF CONTENTS

SUMMARY

Full title	Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in gastric carcinomatosis. Phase II randomized study.
Acronym	PIPAC EstoK 01
Coordinating Investigator	Clarisse EVENO, PU-PH, Digestive Surgery Department, Claude Huriez hospital, CHU of Lille
Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	Peritoneal metastasis is a common pattern in advanced gastric cancer leading to a terminal condition in a very short time. Whatever recent progress regarding systemic chemotherapy using multi drugs association median survival is limited to 6 months with altered quality of life (QoL) after 4 months for all patients. We postulated that a new innovative health technology for delivering intraperitoneal pressurized aerosol of chemotherapy (Doxorubicin and Cisplatin) during laparoscopy can transform that situation offering to double the survival with QoL preservation. Interestingly, PIPAC procedure is made to be applied repeatedly, every 6 weeks (+/- 2 weeks). This therapeutic strategy allows to improved IP drugs impregnation and maintained IV chemotherapy meanwhile. Our PIPAC Estok 01 project is supported by the six main carcinomatosis national centers and should gather medical and surgical teams that daily support peritoneal carcinomatosis. To demonstrate the efficacy of PIPAC procedure in gastric carcinomatosis and make a radical shift in management of these patients that will break with past strategies.
Main objective and primary endpoint	<u>Main objective of the clinical study</u> The primary objective is to evaluate and compare 24-month progression free-survival in patients with peritoneal carcinomatosis of gastric cancer treated either with IV chemotherapy and pressurized intraperitoneal aerosol chemotherapy (PIPAC) or with IV chemotherapy alone, with preservation of quality of life. <u>Primary endpoint</u> The primary endpoint corresponds to the 24-month progression free-survival, defined as the number of patients with no clinical or morphological sign of progression or death 24 months after the treatment.
Secondary objectives and endpoints	Secondary Objectives and assessment criteria • **Patients related:** - The morbidity will be evaluated on post-operative day 30 by the Clavien–Dindo classification (I to V) (17) and the Comprehensive Complication Index, ranging from 0 to 100 and calculated on a website (https://www.assessurgery.com/about_cci-calculator) (19) - Evaluation of treatment-related toxicity based on CT CAE classification (V5.0) - Postoperative pain measured using a numeric

	rating scale from 0 to 10 from post-operative day 0 to day 2, every 6 hours (not obligatory during sleeping and night break). - Quality of life evaluated at each visit by the patient with the EORTC QLQ-STO22 questionnaire, specific to gastric cancer (Annexe 19.8) and with EORTC QLQ-C30 questionnaire (annexe 19.7). - Quality of health status evaluated at each visit by the patient with the EQ-5D-5L questionnaire (Annexe 19.6) • **Treatment related:** - Feasibility of 3 successive PIPAC procedures defined as the possibility to perform 3 PIPAC with no problem of access to the peritoneal cavity • **Disease related:** - Overall survival at 24 months defined as the time from randomization to death - Secondary resecability rate defined as an IPC ≤ 8 at laparoscopy after the treatment
Design of the trial	Prospective, multicenter, randomized, open-label, controlled, parallel-group, Phase II clinical trial designed to evaluate the effects of PIPAC with doxorubicin and cisplatin on patients with gastric peritoneal metastasis and PCI>8.
Population of trial subjects	Major subjects with peritoneal carcinomatosis of gastric cancer
Inclusion criteria	**Patients related:** 1. Age ≥ 18 years 2. Performance status (WHO) < 2 3. White blood cells > 3.500 /mm^3; neutrophils > 1.500 /mm^3; platelets > 100.000 /mm^3 4. Creatinemia < 1.5 mg/dL and creatinine clearance> 60 mL/min, and Serum total bilirubin< 2 mg/dL (5. An acceptable nutritional condition with BMI > 18.5 kg/m^2 and/or Albumin > 30 g/l and/or pre-albumin > 110 mg/l 6. Effective contraception for patients of childbearing age 7. Written consent obtained prior any act of the research 8. Patient with social insurance **Disease related:** 9. Patient having synchronous or metachronous peritoneal (or ovarian) metastasis (pathologically proven), of a gastric and/or Siewert III adenocarcinoma cancer including ADCI (adenocarcinoma with independent cells) and/or linitis 10. Patients with or without primary gastric tumor can be included 11. PCI (Peritoneal Cancer Index) > 8
Exclusion criteria	**Patients related:** 1. Weight loss > 20% of total body weight in the last

	three months 2. Presence of uncontrolled comorbidities including severe chronic disease or organ insufficiency 3. Contraindication to any drug contained in the chemotherapy regimen, according to summary of product characteristic's (RCP) 4. Contraindication to CISPLATIN IV and DOXORUBICIN IV according the Summary of Product Characteristics in force: allergies, severe toxicity to Cisplatin (renal function impairment: contraindicated if the calculated (Cockcroft formula) or measured creatinine clearance is less than 60 mL/min; the only measure of creatinine does not adequately reflect renal function; cisplatin has cumulative nephrological toxicity) or Doxorubicin (risk of cardiotoxicity that can occur immediately or delayed with sinus tachycardia and/or electrocardiogram abnormalities)….(Cf RCP on the following website : http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0289737.htm) 5. Complete deficiency of the enzyme dihydropyrimidine dehydrogenase. 6. For patients in arm A (PIPAC), the debulking surgery (out of ovariectomy or omentectomy) is not permitted during PIPAC surgical procedure scheduled in accordance with the protocol (3 successive PIPAC). The debulking surgery after these 3 PIPAC procedures is authorized. 7. Pregnancy or breastfeeding 8. Patient under guardianship **Disease related:** 9. Any other malignancies within the last 5 years (other than curatively treated basal cell carcinoma of the skin and/or in situ carcinoma of the cervix) or other systemic metastases (liver, lung, bone, brain or lombo-aortic lymph node involvement) 10. Pleural effusion requiring evacuation for respiratory failure 11. Small bowel occlusion with no possible food intake 12. Ascites > 3 liters 13. Participation in other clinical trials for the treatment of gastric peritoneal metastasis in the year preceding inclusion
Investigational medicinal product(s)	Intraperitoneal pressurized aerosol of chemotherapy of Cisplatin 10.5 mg/m^2 and Doxorubicin 2.1 mg/m^2 during laparoscopy were given for 30 min at 37°C and 12 mmHg at 6-weeks (+/- 2 weeks) intervals. At least 3 successive PIPAC are scheduled by the protocol. The patient will receive PIPAC procedure until progression, toxicity or non-feasibility of the procedure. The research is opened by the sponsor only in centers that already practice the PIPAC procedure as part of the treatment. The investigators who will be declared as part of this research will have to undergo training in the use of this new PIPAC procedure

Comparator treatment	Patient will receive standard poly chemotherapy proposed by the oncologist as EOX (epirubicin, oxaliplatin, and capecitabine), ECX (epirubicin, cisplatin, and capecitabine), FOLFOX, FOLFIRI, ECF (epirubicin, cisplatin, and fluorouracil) or FLOT, or any new standard validated during the study, until progression or toxicity.
Interventions added for the trial	1) Every PIPAC is a surgical procedure, performed under general anaesthesia with biopsy of tumor on peritoneum. Patient is generally hospitalized one night before and two days after each PIPAC procedure. Intraperitoneal pressurized aerosol of chemotherapy of Cisplatin 10.5 mg/m^2 and Doxorubicin 2.1 mg/m^2 during laparoscopy were given for 30 min at 37 °C and 12 mmHg at 6 +/-2 weeks intervals. 3 successive PIPAC are scheduled. 3) Explorative laparoscopy for final assessment will be performed if there is no patient progression on clinic and radiological assessment.
Risks added by the trial	Risk D
Scope of the trial	Peritoneal carcinomatosis of gastric cancer
Number of subjects included	94 patients (47 in each arm)
Number of sites	20 Participating national centres
Duration of the trial	Specify: - inclusion period: 36 months - participation period (treatment+follow-up): 24 months - total duration: 60 months
Number of enrolments expected per site and per month	0.*13* patients/ month/ centre
Statistical analysis	The 24-month progression free-survival will be estimated using Kaplan Meier estimator on the total sample and per arm. Estimation with 95% Confidence Intervals (CI) will be given. Test between survival curves will be performed using Logrank test. Hazard Ratio will be estimated using Cox model. Sensitivity analyses will be performed considering per protocol population.
Sources of funding for the trial	INCa PHRC K 2016
Trial will have a Data Monitoring Committee	Yes

1 SCIENTIFIC JUSTIFICATION FOR THE TRIAL

1.1 Hypothesis for the study

Peritoneal metastasis from gastric cancer often remains undiagnosed until it reaches an advanced stage. Despite curative management combining perioperative systemic chemotherapy, cytoreductive surgery, and Hyperthermic Intra Peritoneal Chemotherapy, treated patients' 5-year survival rate remains under 20% when patients are carefully selected. Palliative intravenous chemotherapy in patients with non-resectable cancer is frequently associated with poor long-term benefit and an estimated survival time below 1 year. Recently, two retrospectives studies reported that pressurized intraperitoneal aerosol chemotherapy (PIPAC) improves patients' overall survival without impairing their quality of life. This promising result needs however to be studied on large randomized clinical trial to validate the effect of PIPAC on survival and quality of life of patients with gastric peritoneal metastasis.

1.2 Existing knowledge relating to the condition under investigation

Current management of peritoneal metastasis of gastric cancer
Peritoneal metastasis is a common phenomenon in advanced gastric cancer and leads to a terminal condition in a very short time. Despite recent progress regarding systemic chemotherapy using multi-drugs associations, median survival time is limited to 6 months with altered quality of life (QoL) after 4 months for all patients. (1) To date, the only hope of prolonged survival is associated with either a rare cancer mutation on a specific gene that expresses HER2 (Human Epidermal Growth factor Receptor 2) (2) or the possibility to have a complete cytoreductive surgery (CRS) combined with intraperitoneal chemotherapy. However, CRS and HIPEC (hyperthermic intraperitoneal chemotherapy) are not always suited for this type of tumor and are only beneficial for patients who present limited peritoneal carcinomatosis (peritoneal cancer index PCI ≤ 8). (3,4) Taken together, these elements urge for a new therapeutic approach and strategy to develop treatments that fit better the conditions and outcomes of advanced gastric cancer with peritoneal carcinomatosis.

An innovative strategy: PIPAC
Carcinomatosis is known to have limited chemosensitivity because of poor drugs tissue penetration. Numerous preclinical and pharmacokinetic studies have demonstrated that the administration chemotherapy directly into the peritoneal cavity results in a several-fold increase in drug concentration within abdominal cavity compared with intravenous treatment. Similarly, a new innovative technology for intraperitoneal chemotherapy delivery, Pressurized intraperitoneal Aerosol Chemotherapy (PIPAC) was shown to significantly improve the conditions of administration and patient's outcome and survival with preserved QoL. This technique consists in delivering cytotoxic drugs by a pressurized aerosol directly into the abdominal cavity. (5) PIPAC is applied through laparoscopic access and a normothermic capnoperitoneum is established with a pressure of 12 mmHg. A cytotoxic solution is nebulized with a micropump into the abdominal cavity for 30 minutes. This treatment has been used for peritoneal metastasis of various origins, with encouraging results in gastric cancer with median survival from 13 to 15 month. (6-8)
Applying an aerosol in the peritoneal cavity allows for a homogeneous distribution of the chemotherapeutic agent within the abdomen. In addition, an artificial pressure gradient is generated to overcome tumor interstitial fluid pressures, which can often represent an obstacle in cancer therapy. The use of PIPAC results in higher local drugs concentration compared with conventional intraperitoneal or intravenous chemotherapy. (9) At the same time, the plasma concentration of the chemotherapeutic agent remains low, reducing potential side effects and organ toxicity. Recent experimental studies strengthen these findings and show that the main advantage of aerosol chemotherapy delivery in a close compartment reside in the high local drug penetration rate that counteracts the high pressure of the interstitial peritoneal metastasis which reduces significantly secondary effect of systemic passage in patient (10). Interestingly, PIPAC procedure was designed for repeated applications every 6 weeks (+/- 2 weeks). This therapeutic strategy allows for improved IP

drugs impregnation while maintaining IV chemotherapy. We hypothesize, as suggested by the German team who designed the PIPAC technique, that drugs concentration under PIPAC delivery can be 5 times lower than in hyperthermic intraperitoneal chemotherapy (HIPEC). In our study, after application of Doxorubicin (2.1 mg/m^2 in 50 ml NaCl 0.9%) and Cisplatin (10.5 mg/m^2 body surface in 150 ml NaCl 0.9%), as suggested by Tempfer et *al.* (11) and with a flow rate of 0.7 ml/s, the therapeutic capnoperitoneum is maintained for 30 min at body temperature. PIPAC procedure is repeated three times every 6 weeks (+/- 2 weeks) with a median rate of PIPAC of 2.5/ patient because of possibility of non-access of the abdomen because of adhesions. (18)

Thus, we think that PIPAC could be a valuable approach for the population of subjects with peritoneal carcinomatosis of gastric cancer.

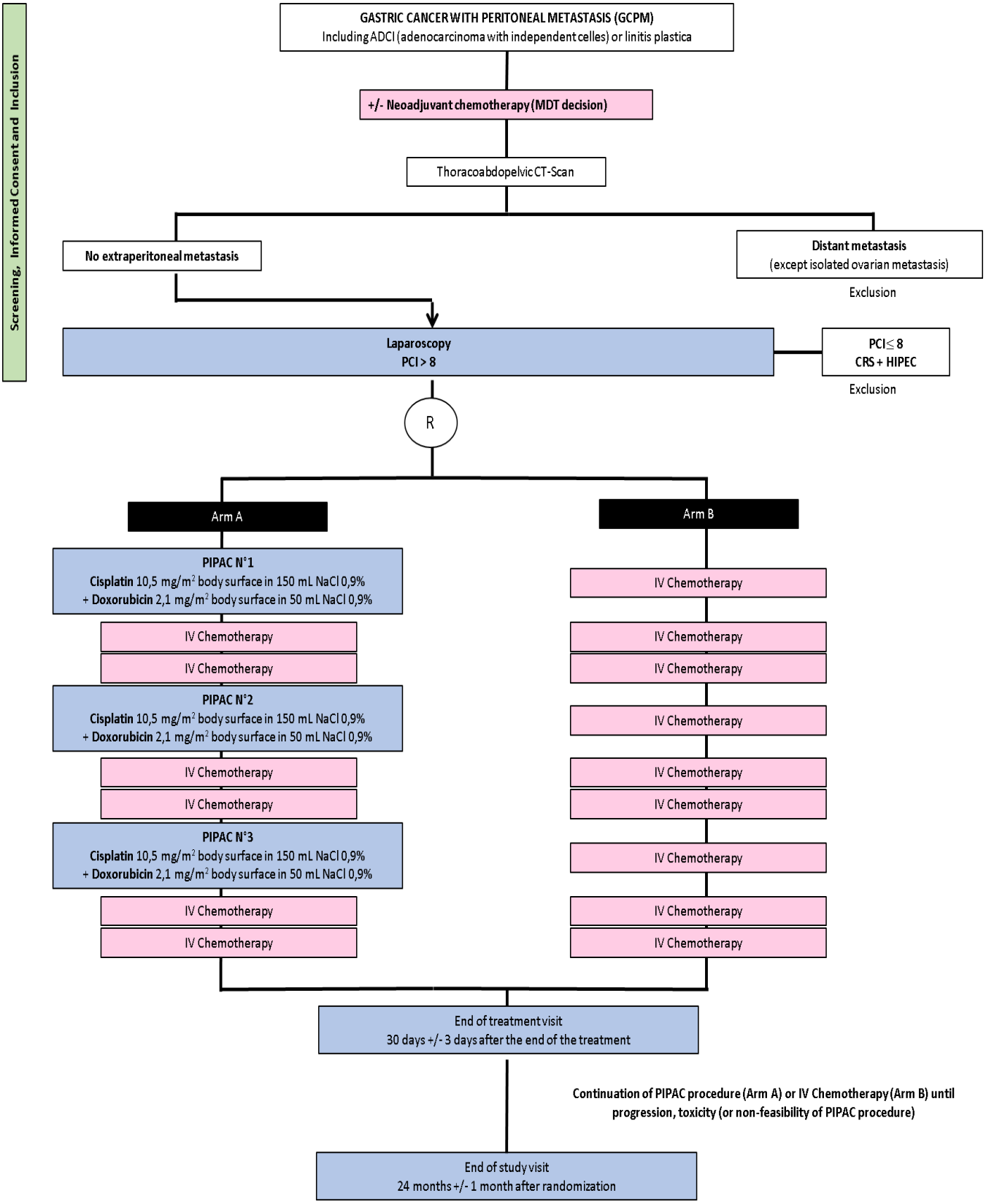
1.3 Summary of relevant pre-clinical and clinical trials

This treatment has been used for peritoneal metastasis of various origins, with encouraging results in gastric cancer with median survival from 13 to 15 month. (6-8)

1.4 Name and description of the investigational medicinal product(s)

In our study, for our PIPAC procedure, a dose of cisplatin at 10.5 mg/m^2 body surface in 150 ml NaCl 0.9% was used, immediately followed by doxorubicin at 2.1 mg/m^2 in 50 ml NaCl 0.9% at 12 mmHg with a flow rate of 0.7 ml/s, the therapeutic capnoperitoneum is maintained for 30 min at body temperature.

1.5 Description and justification of the dosage, route of administration, administration schedule and treatment duration



1.6 Summary of the known and foreseeable benefits and risks for the study participants

Postoperative adverse events were assessed by the CTCAE grading system (12) in most studies. Commonly described CTCAE grade 1–2 events were abdominal pain and nausea. CTCAE grades 3–5 were described in 0–37 per cent; highest rates were described in a study on gastric peritoneal metastases (6). Two deaths were reported by Naziradze et *al.* (6) in patients with gastric cancer (1 lung oedema due to ascites removal, 1 disease progression with bowel invasion), and one death from anasarca by Giger-Pabst et *al.* (13). A direct causative relationship with PIPAC was considered unlikely. Repeated PIPAC applications (at least 2) were possible in 38–82 per cent.

Toxicity and systemic uptake maximal peripheral venous doxorubicin concentrations after PIPAC were 4·0–6·2 ng/ml; half-lives ranged from 86 to 468 min Solass et *al.* (5). Two studies Blanco et *al.* (14) & Robella et *al.* (15) evaluated renal and hepatic toxicity, and inflammatory response. After PIPAC alone, a transient rise in serum γ-glutamyltransferase level was observed. Other liver parameters and renal tests remained within the normal range, and no cumulative toxicity was noted (14). Consistent findings were reported for PIPAC in combination with systemic chemotherapy with regard to absence of hepatorenal toxicity. Leucocytosis and an increase in C-reactive protein level were recorded after most procedures (15).

2 OBJECTIVES

2.1 Primary objective

The primary objective is to evaluate 24-month progression free-survival in patients with peritoneal carcinomatosis of gastric cancer treated either with IV chemotherapy and pressurized intraperitoneal aerosol chemotherapy (PIPAC) or with IV chemotherapy alone, with preservation of quality of life.

2.2 Secondary objectives

The secondary objectives areto allow:

- Patients related:
- The morbidity will be evaluated on post-operative day 30 by the Clavien–Dindo classification (I to V) (17) and the Comprehensive Complication Index, ranging from 0 to 100 and calculated on a website (https://www.assessurgery.com/about_cci-calculator) (19)
- Evaluation of treatment-related toxicity based on CT CAE classification (V5.0)
- Postoperative pain measured using a numeric rating scale from 0 to 10 from post-operative day 0 to day 2, every 6 hours, not obligatory during sleeping and night break.
- Quality of life evaluated at each visit by the patient with the EORTC QLQ-STO22 questionnaire, specific to gastric cancer (Annexe 19.8) and with EORTC QLQ-C30 questionnaire (annexe 19.7).
- Quality of health status evaluated at each visit by the patient with the EQ-5D-5L questionnaire (Annexe 19.6)

- Treatment related:
- Feasibility of 3 successive PIPAC procedures defined as the possibility to perform 3 PIPAC with no problem of access to the peritoneal cavity

- Disease related:
- Overall survival at 24 months defined as the time from randomization to death
- Secondary resecability rate defined as an IPC ≤ 8 at laparoscopy after the treatment

3 DESCRIPTION OF THE TRIAL

3.1 Description of primary and secondary endpoints

3.1.1 Primary endpoint

The primary endpoint corresponds to the 24-month progression free-survival, defined as time from randomization to any progression, recurrence or death.

Progression will be define in case of
1) Clinical progression with either:
- Appearance or increase in volume of ascites to abdominal palpation and/or by taking waist/hip circumference
- Appearance or increase of abdominal pain, define with an visual analogue scale
- Weight loss of more than 10% of total body weight at the time of inclusion

2) Radiological progression with either:
- Appearance or increase (pelvic, peri hepatic or splenic or both) in volume of ascites, defined as peritoneal fluid
- Appearance of extra peritoneal metastasis (liver, lung)
- Increase of peritoneal volume according to RECIST criteria (16), with 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study.

Recurrences are defined as secondary progression (*cf*. supra) after partial or complete response according to RECIST criteria, with 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters or disappearance of all target lesions, respectively

As criteria can be clinical and radiological, all progression or recurrences will be validated during a tumour board meeting.

3.1.2 Secondary endpoints

- Patients related:
- The morbidity will be evaluated on post-operative day 30 by the Clavien–Dindo classification (I to V) (17) and the Comprehensive Complication Index, ranging from 0 to 100 and calculated on a website (https://www.assessurgery.com/about_cci-calculator) (19)
- Evaluation of treatment-related toxicity based on CT CAE classification (V5.0)
- Postoperative pain measured using a numeric rating scale from 0 to 10 from post-operative day 0 to day 2, every 6 hours not obligatory during sleeping and night break.
- Quality of life evaluated at each visit by the patient with the EORTC QLQ-STO22 questionnaire, specific to gastric cancer (Annexe 19.8) and with EORTC QLQ-C30 questionnaire (annexe 19.7).
- Quality of health status evaluated at each visit by the patient with the EQ-5D-5L questionnaire (Annexe 19.6)

- Treatment related:
- Feasibility of 3 successive PIPAC procedures defined as the possibility to perform 3 PIPAC with no problem of access to the peritoneal cavity

- Disease related:
- Overall survival at 24 months defined as the time from randomization to death
- Secondary resecability rate defined as an IPC ≤ 8 at laparoscopy after the treatment

3.2 Research Methodology

3.2.1 Design of the trial

A randomized phase II offers the answer for the PIPAC security, tolerance and efficacy. A major survival effect is expected. A limited survival increase is not acceptable because of the necessity to deliver the drug using a general anesthesia.

- Comparative
- Randomised
- Controlled
- Control group: reference medicinal product, IV chemotherapy
- Superiority
- No blinding (open label)
- With 2 treatment arms (IV chemotherapy with or without pressurized intraperitoneal aerosol chemotherapy (PIPAC))
- With 2 parallel groups
- Subjects distributed between groups at a ratio of (1:1)

3.2.2 Number of participating sites

The trial involves multiple sites (and hospital) in France (n= 19).
The subjects will be recruited: in hospital out-patients.

3.2.3 Identification of the subjects

The subjects participating in this study will be identified as follows:
Site number (3 digits) - Sequential selection number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the trial.

3.2.4 Randomisation

When selected, the patient eligibility will be evaluated from inclusion and non-inclusion criteria. Once the consent will be signed by the patient and investigator (after information), the patient will be included and randomised by connecting the eCRF. The patient identification number will be allocated.

Randomization of patients will be centralized and carried out using a computerized system in the eCRF website according to a predefined randomization list. Distribution in the two groups will be made in a 1:1 ratio.
The randomization list will be designed by the URC Saint-Louis. Each list will be based on permutation blocks, the size of which will be unknown to practitioners involved in patient accrual. All inclusion and non-inclusion criteria will be checked before randomization.

4 PROCEDURE FOR THE TRIAL

- Before any examination or intervention may be carried out for the trial, the investigator must obtain the *free, informed and written consent of the subject participating in the trial. T*he patient is informed before signing the consent.

Subjects participating in the clinical studies described in article L.1121-1(1° paragraph) of the Code de la Santé Publique are eligible for prior medical examination appropriate for the trial.

4.1 Screening visit (day - 45 to -1 before start of treatment)

Prior to trial entry, the investigators (or designated assistant) will explain the nature of the trial, its purpose, procedures, expected duration, alternative therapies, as well as the benefits

and risks. Each patient will be given the opportunity to ask questions and will be informed on the right to withdraw from the trial at any time without prejudice. Functions of organ systems must be documented before inclusion, as outlined in the inclusion criteria, including:

- they fulfil the inclusion criteria defining eligibility;

AND

- the evaluation of organ functions has not revealed any non-inclusion criteria as defined above.

A pre-surgery anaesthesiology visit will be performed

During the screening visit, assessments will be performed as day-hospital sessions, as follows, and to verify inclusion and non-inclusion criteria:

1. A complete physical examination will be performed and will include the examination of abdomen, rectal and pelvis, Performance Status evaluation weight at the time of the inclusion visit, usual weight, weight loss, height, BMI, waist and hip circumference, body surface area, and evaluation of abdominal pain with EVA scale.
2. Laparoscopy to evaluate PCI score and volume of ascite. Please note that if all other criteria are validated, it is authorized to include patient before laparoscopy, and randomized during per operative time.

3. Assessment of following blood samples:
    - Haematology (White Blood Cells count, total neutrophils, haemoglobin, and platelet count),
    - Clinical chemistry (Sodium, potassium,glycemia, creatinine, creatinine clearance (Cockcroft and Gault formula), bilirubin (total,), AST, ALT, albumin, pré-albumin, alkaline phosphatase, LDH, CPK, GGT).
    - Screening for DPD deficiency (dihydropyrimidine dehydrogenase) ANSM recommendation April 2019: measurement of uracilemia to prevent serious toxicities to 5-FU and prodrugs.
    - Tumor biomarkers (ACE and CA19-9)
    - All females of childbearing potential will have a serum pregnancy test at selection visit. A positive urine pregnancy test requires a serum β-HCG test. If positive, the patient will not be included in the study.
4. Thoraco-Abdomino-Pelvic CT scan (with evaluation according RECIST criteria). It could be performed within 45 days prior to the first treatment administration.
5. Optionals: Upper intestinal endoscopy, endoscopic ultrasound, and MRI

Subjects that have met all eligibility criteria will be ready to begin study.

Briefly state, for example in table format:

- who informs the participating subjects about the trial and obtains their consent
- at what exact time the subjects are informed, and whether their consent is obtained immediately or after they have had time to consider their participation;

The procedure for informing subjects and obtaining their consent should be described in detail in the section on "Ethical and Legal Considerations"

Whose consent must be obtained	Who informs the individual and collects their consent	When is the individual informed	When is the individual's consent collected
• the subject participating in the trial;	• the investigator, oncological surgeon • his representative visite	• Screening visit;	• after one week and before randomisation

4.2 Inclusion visit (Day -30 to day 0 before start of treatment)

- Verification of inclusion and exclusion criteria
- Written informed consent will be obtained from the patient
- All females of childbearing potential will have a serum pregnancy test before first dose of study drug (≤72 hrs). A positive urine pregnancy test requires a serum HCG test. If positive, the patient must be excluded from the study
- Evaluation of the quality of life (using the QLQ-STO22, EQ-5D-RL and QLQ-C30),
- Assessment of toxicity (using CTC AE version 5.0)
- Medical past history
- Randomization: can be done during laparoscopy if needed (it provides the possibility to perform the PIPAC procedure immediately if randomization in arm A)

4.3 Arm A: experimental arm

- At each PIPAC:
    - From 2 to 5 days hospitalization
    - Pre-surgery anaesthesiology visit (only on the first and third PIPC)
    - Score ASA
    - Clinical examination: weight, waist and hip circumference, ascites, and evaluation of abdominal pain with EVA scale.
    - PCI Score
    - Biological assessment:
        - Clinical chemistry: Creatinine, Albumin, Pre-albumin
        - Tumor biomarkers (ACE and CA19-9)
    - Evaluation of pain (EVA scale) during 48 hours, every 6 hours not obligatory during sleeping and night break
    - Tissues biopsy and Anatomopathologicals results

- At each cycle of chemotherapy:
    - Clinical examination: weight, waist and hip circumference, ascites
    - Chemotherapy agents
    - Start date and end date of the cycle (with notification of any report or interruption of the treatment)
    - Biological assessment:
        - Biological evaluation as usually done in the investigational centers
        - Tumor biomarkers (ACE and CA19-9)

Assessment of toxicity (using CTC AE version 5.0)
Please note that the chemotherapy treatment could be done in a chemotherapy center near from patient's residency

Please note that in case of weekly regimen of chemotherapy (Taxol or other), there will be 3 cures of IV chemotherapy between each PIPAC (instead of 2 scheduled for the others protocols of chemotherapy)

- Follow-up - Day 30 (+/- 3 days) after each PIPAC
    - Clinical exam: examination of abdomen, rectal and pelvis, Ascites, Performance Status evaluation and an evaluation of the quality of life (using the QLQ-STO22, EQ-5D-RL and QLQ-C30), weight, waist and hip circumference, and evaluation of abdominal pain with EVA scale.
    - Morbidity that will be evaluated by the Clavien–Dindo classification (I to V) (17) and the Comprehensive Complication Index calculated on a website (https://www.assessurgery.com/about_cci-calculator/)
    - Assessment of toxicity (using CTC AE version 5.0)
    - Assessment of following blood samples:
        - Haematology (White Blood Cells count, total neutrophils, haemoglobin, and platelet count),

- Clinical chemistry (Sodium, potassium, glycemia, creatinine, creatinine clearance (Cockcroft and Gault formula), bilirubin (total), AST, ALT, albumin, pré-albumin, alkaline phosphatase, LDH, CPK, GGT).
- Tumor biomarkers (ACE and CA19-9)
- Optionals: TAP CT scan, upper intestinal endoscopy, endoscopic ultrasound, and MRI

4.4 Arm B: control arm

- At each cycle:
  - Clinical examination: weight, waist and hip circumference, ascites
  - Chemotherapy agents
  - Start date and end date of the cycle (with notification of any report or interruption of the treatment)
  - Biological assessment:
    - Biological evaluation as usually done in the investigational centers
    - Tumor biomarkers (ACE and CA19-9)
  - Assessment of toxicity (using CTC AE version 5.0)
- Please note that the chemotherapy treatment could be done in a chemotherapy center near from patient's residency

- Please note that in case of weekly regimen of chemotherapy (Taxol or other), there will be 12 cures of IV chemotherapy (instead of 9 scheduled for the others protocols of chemotherapy)

- Please note that PIPAC is not allowed in this treatment arm unless there is disease progression.

4.5 End of treatment visit (30 days +/- 3 days after the end of treatment) – Arm A and B

This visit will occur after:
- The 3 PIPAC procedures associated with chemotherapy for patients in arm A
- 9 cycles of chemotherapy for patients in arm B

And contain:
- Clinical exam: examination of abdomen, rectal and pelvis, Ascites, Performance Status evaluation and an evaluation of the quality of life (using the QLQ-STO22, EQ-5D-RL and QLQ-C30), weight, waist and hip circumference, and evaluation of abdominal pain with EVA scale.
- Explorative laparoscopy obligatory for arm B, and for patients randomized in Arm A who stopped the PIPAC procedures)
- Tissues biopsy and Anatomopathologicals results
- Assessment of toxicity (using CTC AE version 5.0)
- Assessment of following blood samples:
  - Haematology (White Blood Cells count, total neutrophils, haemoglobin, and platelet count),
  - Clinical chemistry (Sodium, potassium, glycemia, creatinine, creatinine clearance (Cockcroft and Gault formula), bilirubin (total), AST, ALT, albumin, pré-albumin, alkaline phosphatase, LDH, CPK, GGT).
  - Tumor biomarkers (ACE and CA19-9)
- Thoraco-Abdomino-Pelvic CT scan (with evaluation according RECIST criteria)
- Optionals: Upper intestinal endoscopy, endoscopic ultrasound, and MRI

Thereafter, patients continue the treatment (PIPAC procedure, Arm A or IV Chemotherapy Arm B) until progression, toxicity or non-feasibility of the PIPAC procedure.

4.6 Follow-up visits (every 3 months +/- 7 days after randomization) - Arm A and B

The entire visit will be done by the investigator.

At each visit, the patient will undergo:

a) Clinical exam: examination of abdomen, rectal and pelvis, Ascites, Performance Status evaluation and an evaluation of the quality of life (using the QLQ-STO22, EQ-5D-RL and QLQ-C30), weight, waist and hip circumference and evaluation of abdominal pain with EVA scale.
b) Assessment of following blood samples:
    i. Haematology (White Blood Cells count, total neutrophils, haemoglobin, and platelet count),
    ii. Clinical chemistry (Sodium, potassium, glycemia, creatinine, bilirubin (total), AST, ALT, albumin, pré-albumin, alkaline phosphatase, LDH, CPK, GGT).
    iii. Tumor biomarkers (ACE and CA19-9)
c) TAP CT scan (with evaluation according RECIST criteria)

4.7 End of study visit (24 months +/- 1 month after randomization)

The end of study visit will occur at 24 months (+/- 1 month) after randomization or in case of early withdrawal (if the patient accept that data will be still collected for the study)

At this visit:

a) Clinical exam: examination of abdomen, rectal and pelvis, Ascites, Performance Status evaluation and an evaluation of the quality of life (using the QLQ-STO22, EQ-5D-RL and QLQ-C30), weight, waist and hip circumference and evaluation of abdominal pain with EVA scale.
b) Assessment of following blood samples:
    i. Haematology (White Blood Cells count, total neutrophils, haemoglobin, and platelet count),
    ii. Clinical chemistry (Sodium, potassium, glycemia, creatinine, bilirubin (total,), AST, ALT, albumin, pré-albumin, alkaline phosphatase, LDH, CPK, GGT).
    iii. Tumor biomarkers (ACE and CA19-9)
c) TAP CT scan (with evaluation according RECIST criteria)
d) Explorative laparoscopy, only for patients randomized in Arm B
e) Optionals: Upper intestinal endoscopy, endoscopic ultrasound, and MRI

4.8 Expected length of participation, chronology and duration of the study.

Randomization will be performed during the inclusion visit.

Maximum period between screening and enrolment	1 month
Length of Inclusion period	36 months
Duration of participation for each subject, of which:	
• Treatment period:	3 months
• Follow-up period:	Until death or 21 months
Total study duration:	60 months

4.9 Table or diagram summarising the chronology of the study

	Screening visit	Inclusion visit	PIPAC treatment	Chemotherapy Treatment (arm A and B)	Follow up visits during treatment (only arm A)	Post treatment visit (arm A and B)	Follow up visit (arm A and B)	End of study visit (arm A and B)
	Days -45 to -1	Days -30 to day 0 if randomization in PIPAC arm)	Day 0, then every 6 weeks +/-2 weeks	At each cycle	Day 30 (+/- 3 days) after each PIPAC	30 days (+/- 3 days) after end of treatment	Every 3 months (+/- 7 days)	24 months (+/- 1 month)
Randomisation		x						
Written signature of informed (I) consent (C)	X (I)	X (C)						
Past medical history		x						
Clinical exam (height-weight-BMI-Waist/Hip circumference)	x		x	x	x	x	x	x
Verification of inclusion/exclusion criteria	x	x						
EVA scale	x				x	x	x	x
Laboratory test (biochemistry, hematology, albumin ,pre-albumin, ACE, CA 19-9)	x		x	x	x	x	x	x
Deficiency of DPD evaluation	x							
Pregnancy test	x	X*						
Explorative laparoscopy	x**	x	x			x***		x*****
Questionnaires(QLQ-C30/EQ-5D-RL/QLQ-STO22)		x			x	x	x	x
Post operative morbidity evaluation (Dindo Clavien classification and CCI)					x****			
TAP Ct scan	x				*(optional)*	x	x	x
Toxicity assessment (CT CAE V5.0)		x		x	x	x		

* Pregnancy test : 72 heures before first dose of study drug

** Explorative laparoscopy : randomization could be realizedduring explorative laparoscopy

*** Except for patients randomized in Arm A who continue the PIPAC procedures

**** Post-operative evaluation : Dindo Clavien classification and Comprehensive complication index (https://www.assessurgery.com/about_cci-calculator)

***** Only for patients randomized in Arm B. If no progressive disease has been confirm on clinical, biological and/or radiological signs and confirm during tumour board meeting, an explorative laparoscopy will be perform at 2

month.

4.10 Distinction between standard care and research

TABLE: "Standard care" vs. "added interventions" required specifically for the study

Procedures and treatments to be provided during the study	Procedures and treatments associated with standard care	Procedures and treatments added for the study
PIPAC (arm A)	Intra venous Chemotherapy	Pre surgery anaesthesiology visit
		PIPAC procedure (3 days hospitalization and general anaesthesia every PIPAC)
		Explorative laparoscopy for the end of treatment visit (except for patients randomized in Arm A who continue the PIPAC procedures) and the end of study visit (only for patients in control arm) will be performed
		biopsies
Consultations	Every 3-month consultation	
Blood samples	Standard as described below	
Imaging, etc.	Chest and abdomen CT scan	

4.11 Biological samples

Not applicable

4.12 Termination and exit rules

4.12.1 Criteria and procedures for prematurely terminating the study treatment

Patients can be withdrawn from the study under the following circumstances: death, initiation of alternate anti-tumor therapy (if progression), toxicity (cf paragraph 6.5), non-compliance (including loss of patient to follow-up), and voluntary withdrawal. After initiation of alternate anti-tumor therapy, toxicity e.g. normally patients receive an End of treatment (EOT) and are excluded e.g. from per-protocol Analysis (PP) but not from the study, they will receive further follow up examinations and could be evaluated in the intention to treat population (ITT).

4.12.1.1 Different situations

- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the subject's source file and the case report form (CRF)
- Premature termination of treatment, but the subject remains enrolled in the study until the end of the subject's participation: the investigator must document the reason
- Premature termination of treatment and exit from the study.

The investigator must:

- Document the reason(s)
- Collect all endpoints at the moment the subject exits from the study, if the subject agrees
- Schedule further follow-up visits, especially in case of a serious adverse event.

4.12.1.2 Criteria and procedure for premature withdrawals and exits from the study

- Subjects may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a subject from the study for any safety reason or if it is in the subject's best interests.

➔Subject lost to follow-up: the subject cannot be located. The investigator must make every effort to reconnect with the subject (and record his attempts in the source file), at least to determine whether the subject is alive or dead

If a subject exits the trial prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

The case report form must list the various reasons why the subject exited or was withdrawn from the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Other medical problem (Non feasibility of PIPAC procedure)
- ☐ Subject's personal reasons
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

4.12.2 Monitoring subjects after the premature termination of treatment

If a subject exits the study prematurely, and if the subject agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment).

If a subject exits the trial this will in no way affect the standard care received for his/her condition.
In case of severe adverse events, the investigator must notify the sponsor and monitor the subject for 6 months following the premature termination of treatment. If treatment is stopped prematurely due to a serious adverse event, a serious adverse event report will be sent by e-mail at eig-vigilance.drc@aphp.fr to the sponsor. The serious adverse reaction will be monitored until it is resolved.

4.12.3 Procedure for replacing subjects

During the inclusion period patient prematurely exiting the study will be replace.

4.12.4 Full or partial cancellation of the study

AH-HP (the sponsor) or the Competent Authority (ANSM) may prematurely discontinue all or part of the trial, temporarily or permanently, upon the recommendation of the Data Monitoring Committee in the following situations:

- first, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the two treatment arms, requiring a reassessment of the benefit-risk ratio for the trial.
- similarly, AH-HP, as the sponsor, or the Competent Authority (ANSM) may prematurely cancel the trial due to the discovery of unexpected facts or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved.
- AP-HP, as the sponsor, reserves the right to permanently suspend enrolment at any time if the enrolment targets have not been met.

In case of trial discontinuation strategies will be decided according to the sponsor and Data Monitoring Committee:

- Premature and immediate discontinuation of treatment in all subjects, as soon as the decision is taken
- Subjects are permitted to discontinue their treatment

Irrespective of the reason for cancellation of the trial, describe the follow-up care that subjects still enrolled on the trial will receive. In particular, state whether the participating subjects must be monitored until the end of their participation, as stated by the protocol.

If the study is cancelled prematurely, AP-HP will inform the Competent Authority (ANSM) and the Institutional Review Board of its decision within 15 days, together with justification for the decision and any recommendations from the Data Monitoring Committee.

5 ELIGIBILITY CRITERIA

5.1 Inclusion criteria

Patients related:

1. age ≥ 18 years
2. Performance status (WHO) < 2
3. White blood cells > 3.500 /mm^3; neutrophils > 1.500 /mm^3; platelets > 100.000 /mm^3
4. Creatinemia < 1.5 mg/dL and creatinine clearance > 60 mL/min and serum total bilirubin < 2 mg/dL
5. An acceptable nutritional condition with BMI > 18.5 kg/m^2 and/or Albumin > 30 g/l and/or pre-albumin > 110 mg/l
6. Effective contraception for patients of childbearing age
7. Written consent obtained prior any act of the research
8. Patient with social insurance

Disease related:

9. Patient having synchronous or metachronous peritoneal (or ovarian) metastasis (pathologically proven), of a gastric and/or Siewert III adenocarcinoma cancer including ADCI (adenocarcinoma with independent cells) and/or linitis
10. Patients with or without primary gastric tumor can be included
11. PCI > 8

5.2 Exclusion criteria

Patients related:

1. Weight loss > 20% of total body weight in the last three months
2. Presence of uncontrolled comorbidities including severe chronic disease or organ insufficiency
3. Contraindication to CISPLATIN IV and DOXORUBICIN IV according the Summary of Product Characteristics in force:

allergies, severe toxicity to Cisplatin (renal function impairment: contraindicated if the calculated (Cockcroft formula) or measured creatinine clearance is less than 60 mL/min; the only measure of creatinine does not adequately reflect renal function; cisplatin has cumulative nephrological toxicity) or Doxorubicin (risk of cardiotoxicity that can occur immediately or delayed with sinus tachycardia and/or electrocardiogram abnormalities)….(Cf summary of product characteristics on the following website : http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0289737.htm)

4. Complete deficiency of the enzyme dihydropyrimidine dehydrogenase.
5. For patients in arm A (PIPAC), the debulking surgery (out of ovariectomy or omentectomy) is not permitted during PIPAC surgical procedure scheduled in accordance with the protocol (3 successive PIPAC). The debulking surgery after these 3 PIPAC procedures is authorized.
6. Pregnancy or breastfeeding
7. Patient under guardianship

Disease related:

8. Any other malignancies within the last 5 years (other than curatively treated basal cell carcinoma of the skin and/or in situ carcinoma of the cervix or other systemic metastases (liver, lung, bone, brain) or lombo-aortic lymph node involvement
9. Pleural effusion requiring evacuation for respiratory failure
10. Small bowel occlusion with no possible food intake
11. Ascitis > 3 liters
12. Participation in other clinical trials for the treatment of gastric peritoneal metastasis in the year preceding inclusion

5.3 Recruitment methods

Feasibility of the study: French surgeon are leader in carcinomatosis field.

The 19 surgical centers enrolled in our study are the French leader in management of peritoneal metastasis of digestive origins. Three of those teams routinely perform CRS and HIPEC for gastric carcinomatosis. Thereby, active cohort of patients is already referred to surgeon and oncologist of those centers. All centers have legibility in carcinomatosis with academicals teaching (Inter university degree) and many published paper on large multi-centric cohort of peritoneal metastasis of various. The 6 major centers have included the majority of patients in a national trial using oxaliplatin during surgical colonic carcinomatosis resection with hyperthermia (ACCORD-15 PRODIGE-7 PHRC 2006). That PHRC had successfully included all patients required.
In addition, all French digestive surgeon that have been trained to perform PIPAC procedure in Germany with Professor Marc Reymond are group leader in there hospital and responsible of inclusion in our study. No competition study on PIPAC procedure has been implemented in France. Finally, as active members of scientific community; diffusion of information about our study design will be provided by:

- RENAPE (French Network for Rare Peritoneal Malignancies)
- FRENCH (Fédération de Recherche en Chirurgie)
- FFCD (Fédération Francophone de Cancérologie Digestive)
- GERCOR (Group Coopérateur Multidisciplinaire en Oncologie)

All that clinical research groups have been associated with the construction of the project and wait the future results. If our Phase II study is conclusive, we will be able, with the support of those groups, to conduct a national Phase III study of greatest impact.

	Number of subjects
Total number of subjects to be included	94
Number of sites	20
Enrolment period (months)	36
Number of subjects/site	4.7
Number of subjects/site/month	0.13 patients/ month/ center

6 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

6.1 Control Arm

In advanced gastric cancer, chemotherapy is the standard palliative treatment in patients with an acceptable clinical status because it provides better survival and quality of life than supportive care. Combination of epirubicin, cisplatin, and fluorouracil (ECF) is a standard procedure widely used today. In the past decade, more drugs, including oral fluorouracil, docetaxel, oxaliplatin, and irinotecan, have proved to be effective for this indication. New first-line regimens demonstrated equivalence (epirubicin, cisplatin, and capecitabine [ECX]; epirubicin, oxaliplatin, and capecitabine [EOX]; and mFOLFOX) or superiority (docetaxel, cisplatin, and fluorouracil [DCF]) to CF or ECF. (12-14) FOLFIRI has been recently compared to ECX with a better time-to treatment failure. (1) FLOT who is an association of fluorouracil, leucovorin, oxaliplatin, and docetaxel has shown interesting results in patients with limited metastatic disease (15) and is currently evaluated in a Phase III randomized study 5-

fluorouracil and oxaliplatin with or without docetaxel in first-line chemotherapy advanced gastric cancer (GASTFOX study, 16) Long-term benefit remains poor with overall survival still less than 1 year (7 to 9 months in most studies).

Patient will receive standard poly chemotherapy proposed by the oncologist as EOX, ECX, FOLFIRI, FOLFOX, ECF or FLOT, or any new standard validated during the study, until progression or toxicity. All patients can be included, even in case of more than one line of chemotherapy.

Please note that in case of weekly regimen of chemotherapy (Taxol or other), there will be 12 cures of IV chemotherapy (instead of 9 scheduled for the others protocols of chemotherapy)

Chemotherapy can be done near from patient residency.

The data (biochemistry, hematology, albumin, pre-albumin, ACE, CA 19-9, Pregnancy test, Toxicity assessment) requested by the protocol will be collected by the recruiting center from oncologists and presented in a report containing also the results of examinations.

6.2 Experimental Arm : PIPAC

Pressurized intraperitoneal aerosol chemotherapy (PIPAC):
After insufflation of a 12 mmHg of capnoperitoneum at 37°C, two balloons safety trocars (10 and 12mm) are inserted into the abdominal wall. A biopsy is taken for pathologic confirmation of PC during the first procedure and all following procedures in order to ascertain tumor regression grade (17). Ascites volume is documented and ascites is removed. Then, a nebulizer CAPNOPEN© (Reger Medizintechnik, GmbH, Villingendorf, Germany) is connected to an intravenous high-pressure injector and inserted into the abdomen. The tightness of the abdomen is documented via a zero-flow of CO_2. Safety house is used to entirely cover the abdomen. A continuous suction is performed under the house by a surgical smoke extractor providing a second level of security in case of leak during the vaporization. Injection parameters are set at a flow rate of 30 ml/min and a maximum upstream pressure of 300 psi in the high-pressure injector. The injection is remote-controlled to minimize personnel exposure. The safety protocol with checklist containing all safety aspects as described previously (18) was systematically double-checked before administration of cytostatics. After application of Doxorubicin (2.1 mg/m^2 in 50 ml NaCl 0.9%) and Cisplatin (10.5 mg/m^2 body surface in 150 ml NaCl 0.9%) with a flow rate of 0.7ml/s, the therapeutic capnoperitoneum is maintained for 30 min at body temperature. Then, the chemotherapy aerosol is exhausted over a closed surgical smoke extractor. Finally, trocars are retracted and laparoscopy ended. No drainage of the abdomen is applied. The PIPAC procedure is repeated three times every 6 weeks (+/- 2 weeks) with a median rate of PIPAC of 2.5/ patient because of possibility of non-access of the abdomen because of adhesions (18).
Patients can continue the PIPAC procedures until progression, toxicity or non-feasibility of the procedure.

Please note that in case of weekly regimen of chemotherapy (Taxol or other), there will be 3 cures of IV chemotherapy between each PIPAC (instead of 2 scheduled for the others protocols of chemotherapy)

6.3 Traceability information for the investigational medicinal product(s)

Not Applicable (NA)

6.4 Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including emergency medications

For Cisplatin:
- Contra-indicated associations: Phenytoin (if introduced as a prophylaxis for the convulsive effect of certain anticancer drugs) and Yellow fever vaccine
- Associations not recommended: Live attenuated vaccines (except yellow fever).

- Associations subject to precautions for use: Phenytoin (in case of treatment prior to chemotherapy), antihypertensives based on furosemide, hydralazine, diazoxide and propranolol, nephrotoxic and ototoxic substances.

For Doxorubicin:
- Associations to be considered: Sorafenib and Verapamil

6.5 Safety plan

6.5.1 - For patients receiving the PIPAC surgical technique:

Uncommon surgical complication during explorative laparoscopy preceding PIPAC application is bowel injury. In that case, bowel will be repaired and PIPAC procedure will be cancelled.
Expected Adverse Events related to PIPAC

- General disorders: Fatigue, transitory increase of CRP with a peak in postoperative day 2 and without manifest infection
- Gastrointestinal toxicities: Abdominal pain, nausea, vomiting, abdominal pressure, mild loss of appetite.
- Renal disorders: frequent urination, transitory increase of creatinine of <10%
- Very rare: Toxic skin reaction, neuropathy

The most serious, but theoretical, surgical complication is extravasation of gas outside the intraperitoneal region. This could be prevented with 3 level of security:

1) Utilization of special laparoscopy port with intra and extra abdominal balloons. The monitoring of the absence of gas leak is measure by laparoscopy insufflator.
2) Second level is a plastic bag that cover the patient with active suction under it, linked to a carbon filter that is for unique use.
3) The third level is application of aerosol chemotherapy from outside the operative room (OR) with a remote system.

To prevent systemic toxicities, drastic compliance to inclusion criteria is mandatory, including verification just before surgery of the major functions (cf supra).
During PIPAC, in case of allergy to Cisplatin and Doxorubicin, up to a cardiac arrest, emergency procedure will be initiated including to stop chemotherapy application from outside of the OR, reentry in OR of the surgeon with protective equipment, evacuation of abdominal pneumoperitoneum. Immediately after this, anesthesiologist and his team can come inside the OR to provide adequate care.

Dose adjustments for PIPAC

- Non hematological

Creatinine clearance will be checked prior to i.p. cisplatin administration, and i.p. cisplatin will be administered only if creatinine clearance is > 60 ml/min. In addition, the following dose reduction guidelines will apply.

<table>
<tr><th colspan="3">Dose modification table for PIPAC of Cisplatin and Doxorubicin</th></tr>
<tr><td>AE Grade</td><td>Dose modifications for cisplatin</td><td>Dose modifications for doxorubicine</td></tr>
<tr><td>Grade 3 Abdominal pain</td><td>Administer a morphine pump during the procedure for 2 days during the procedure until grade 2 of abdominal pain</td><td>Administer a morphine pump during the procedure for 2 days during the procedure until grade 2 of abdominal pain</td></tr>
<tr><td>Grade 3 Fatigue</td><td>Dose reduction to Cisplatin 7.5 mg/m² until the end of the treatment</td><td>Dose reduction to Doxorubicin 1.5 mg/m² until the end of the treatment</td></tr>
<tr><td>Grade 3 Ascites</td><td colspan="2">- If symptomatic with invasive procedure indicated
OR
- If infection documented clinically and microbiologically with IV antibiotic, antiviral or antifungal radiology or operative intervention indicated
PIPAC will be stopped</td></tr>
</table>

Grade 2 AEs related to PIPAC	If recovered within 15 days the next PIPAC will be done
	If not recovered within 15 days stop PIPAC definitively
If grade 3-4 toxicities are maintained at the next PIPAC, PIPAC will be stopped	

For other toxicities, dose management and reductions of the systemic chemotherapy will follow the same guidelines as for the control group.

6.5.2 - For all patients receiving IV chemotherapy:

Measures to prevent and/or treat toxicities related to the administered chemotherapies will be in compliance with the SmPC of the concomitant received chemotherapies. (see annex 19.4 & 19.5)

- Dose reduction measures and discontinuation of chemotherapies will be in compliance with the SmPC of the concomitant received chemotherapies. (see annex 19.4 & 19.5)

A general toxicity management plan with WHO toxicity grades, relevant for most of the chemotherapies will also be done. (see table 2)

6.6 Effective birth control pregnancy and breastfeeding:

6.6.1 Effective birth control pregnancy and breastfeeding:

- Protocol require a contraception method(s) and length for patients and their partners in compliance with the SmPC of the concomitant received chemotherapies.
    - Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study drug.
    - Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of ovulary cycle) after PIPAC or IV chemotherapy.
    - Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) after PIPAC or IV chemotherapy.
    - Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section. Investigators shall counsel WOCBP, and male subjects who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. At a minimum, subjects must agree to the use one highly effective method of contraception.

- Protocol require a wash out period for at least 90 days for breastfeeding after study in compliance with the SmPC of the concomitant received chemotherapies.

- Protocol require fertility preservation measure in compliance with the SmPC of the concomitant received chemotherapies.

6.6.2 Use of Cisplatin and Doxorubicin for patient with PIPAC surgery:

- Protocol require an effective contraception method for both woman and man patients treated and their partners for at least 90 days after last PIPAC surgery.

- Protocol require a 90 days wash out period for breastfeeding after last PIPAC surgery.

- Protocol state at least those patients have to be informed of the risk of infertility following PIPAC surgery.

- Protocol require that if a patient wishes to have a child after PIPAC surgery has been completed, it is advisable to consult a geneticist. Since both cisplatin and doxorubicin treatment can cause permanent sterility, patients who wish to have children later on should be informed of the possibilities of cryopreservation of the semen and eggs before treatment.

7 EFFICACY ASSESSMENT

The primary endpoint corresponds to the 24-month progression free-survival, defined as time from randomization to any clinical (ascites, abdominal pain, weight loss > 10% of total body weight) and/or morphological signs (systemic metastases, ascites, progression with RECIST criteria) of recurrence (local or systemic) or death.

RECIST criteria the response to treatment in solid tumor, defined as complete response (CR) if disappearance of all lesions, partial response (PR) if ≥30% decrease in the sum of longest diameters of targeted lesions, progressive disease (PD) if >20% increase in the sum of longest diameters od stable disease (SD) if neither PR or PD. (16)

- Laparoscopy for final evaluation

If no progressive disease has been confirm on clinical, biological and/or radiological signs and confirm during tumour board meeting, an explorative laparoscopy will be perform at 24 month (only for patients randomized in Arm B).

Peritoneal cancer index (PCI) and ascites volume are documented and tumour biopsy is taken in order to ascertain tumour regression. Ascites volume is documented and ascites is removed. Importantly, decision to perform this last laparoscopy will be optional and made in accordance to the referring physician, surgeon or oncologist.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable assessment. If the patient has no evaluable visits or does not have a baseline assessment they will be censored at day 1 unless they die within two visits of baseline. The PFS time will always be derived based on imagery assessment dates not visit dates. The primary analysis will be based on investigator-recorded assessments.

Secondary endpoints

- Patients related:
- The morbidity will be evaluated on post-operative day 30 by the Clavien–Dindo classification (I to V) (17) and the Comprehensive Complication Index, ranging from 0 to 100 and calculated on a website (https://www.assessurgery.com/about_cci-calculator) (19)
- Evaluation of treatment-related toxicity based on CT CAE classification (V5.0)
- Postoperative pain measured using a numeric rating scale from 0 to 10 from post-operative day 0 to day 2, every 6 hours, not obligatory during sleeping and night break
- Quality of life evaluated at each visit by the patient with the EORTC QLQ-STO22 questionnaire, specific to gastric cancer (Annexe 19.8) and with EORTC QLQ-C30 questionnaire (annexe 19.7).
- Quality of health status evaluated at each visit by the patient with the EQ-5D-5L questionnaire (Annexe 19.6)

- Treatment related:
- Feasibility of 3 successive PIPAC procedures defined as the possibility to perform 3 PIPAC with no problem of access to the peritoneal cavity

- Disease related:

- Overall survival at 24 months defined as the time from randomization to death
- Secondary resecability rate defined as an IPC ≤ 8 at laparoscopy after the treatment

8 SPECIFIC COMMITTEES FOR THE TRIAL

Depending on the type of research, one or more specific committees may be required.

The possible committees are:

English name	French name	Description
Data Monitoring Committee (DMC) Data Safety Monitoring Board (DSMB)	Comité de surveillance indépendant (CSI)	Members independent from the investigator
Steering Committee	Comité de Pilotage Comité Scientifique	Investigators, sponsor, etc.

List the members of the Steering Committee and Scientific Committee.

NB: the Data Monitoring Committee (DMC) is described in section on Vigilance.

8.1 Scientific Committee

Members: specialists in the condition and treatments under investigation, biostatisticians, methodologists. It is often set up by the Steering Committee, with the addition of particular skills.
Role: determine the objective, write the protocol, recommend changes to the protocol during the trial.
Specify:

- Members of the committee: Dr Eveno (Investigator), Pr Pocard, Pr Resche-Rigon
- Missions: determine the objective, write the protocol, recommend changes to the protocol during the trial.
- Operating procedures: Make meeting when necessary

8.2 Steering Committee

Members: Coordinating Investigator, one of more other investigators, biostatistician, the sponsor's appointed representatives for the trial.
Role:

- Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.
- Propose procedures to be followed during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority.

- Members of the committee: Dr Eveno, Pr Pocard, Pr Resche-Rigon, Mrs Seymour DRCI-Siège, Mme ABBOU (DRCI-URC)
- Missions: Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.
- Operating procedures: Make meeting when necessary

8.3 Data Safety Monitoring Board (DSMB)

See section 11.2.4 below

9 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

Supplementary risks will be added in the PIPAC arm concerning the laparoscopy and intra peritoneal chemotherapy.

Analysis of literature:

Feasibility, safety and tolerance of repeated PIPAC treatment were confirmed by 6 Good Clinical Practice (GCP) (20, 21, 26–29) and 17 cohort studies (30–46). Surgical complications (intra- and postoperative) were exceptional (2% and 1%, respectively), and mortality rate was 1.25% (0.5% related to PIPAC procedure). Across all studies, adverse events (CTCAE >2) occurred after 9% (GCP) - 15% (confirmatory evidence) of procedures (most common: bowel obstruction 0-5%, bleeding 0-4%, abdominal pain 0-4%), whereas mortality was 1.25%.

Regarding adverse events (CTCAE>2):

- One colon perforation (CTCAE grade 3) occurred among the 15 patients included in the phase 1 trial (21).
- In the phase 2 trial CTCAE grade 3 toxicities occurring in 53 patients were as follows trocar hernia (n=2), bowel obstruction (n=1), abdominal pain (n=2), hematoma (n = 1), intraoperative bleeding (n = 1) and cystitis with urosepsis (n = 1) (20)
- The prospective case series of 18 women having undergone at least one PIPAC reported adverse events (CTCAE>2) in 5 patients (30). The AE related or potentially related to PIPAC were: recto-vaginal fistula (n = 1); postoperative small bowel perforation (n=1); intraoperative colon lesion (n=1); small bowel fistula (n=1). Of note, 3 events occurred in women who had both CRS and PIPAC (recto-vaginal fistula; postoperative small bowel perforation and small bowel fistula).
- The retrospective cohort study of 99 patients undergoing PIPAC reported adverse events (CTCAE>2) in 20 patients (31). These AE were: bowel obstruction (n=1); small bowel perforation (n=1); small bowel fistula (n=1); colon perforations (n=2); anaemia (n=4); sepsis (n=2); trocar metastasis (n=1); breast cancer (n=1); bowel anastomosis insufficiency (n=1); hypertension (n=1); bile duct stenosis (n=1); respiratory insufficiency (n=4) . Of note, the five surgical complications CTCAE grade 3/4 (small bowel perforation, colon perforation, bowel anastomosis insufficiency, trocar metastasis) occurred in women who had both CRS and PIPAC. No perioperative or in-house mortality occurred.

Of note, a recent report demonstrated severe hypersensitivity reactions to platinum in 3% of patients, which could all be managed without further complications (47)

9.1 Safety endpoints

- The morbidity will be evaluated on post-operative day 30 by the Clavien–Dindo classification (I to V) (17) and the Comprehensive Complication Index, ranging from 0 to 100 and calculated on a website (https://www.assessurgery.com/about_cci-calculator) (19).
- Treatment-related toxicity at 30 days of each PIPAC procedure
- Feasibility of 3 successive PIPAC procedures
- The time of discontinuation defined as the time from randomization to therapy change or dose reduction because of progression of disease or intolerance or adverse effects or patient refusal or death.

9.2 Recording and reporting adverse events

9.2.1 Definitions

According to Article R1123-46 of the French Public Health Code:

- Adverse event

Any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the clinical trial or with the investigational product.

- Adverse reaction to an investigational medicinal product

Any adverse event occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational medicinal product

- Serious adverse event or reaction

Any adverse event or reaction that at any dose of medication, results in death, threatens the life of the research subject, requires hospitalisation or prolongs hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity.

- Unexpected adverse reaction to an investigational medicinal product

Any adverse reaction to the product, whose nature, severity, frequency or outcome is inconsistent with the safety information described in the Reference Safety Information (summary of product characteristics, or the investigator's brochure if the product is not authorised).

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for clinical trial sponsors (ANSM):

- Emerging safety issue

Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials..
For the clinical trials involving the first administration or use of an investigational medicinal product in healthy volunteers, any serious adverse reaction.

Examples:

a) any clinically significant increase in the frequency of an expected serious adverse reaction
b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports
c) any new safety issue relating to the conduct of the clinical trial or the development of the investigational medicinal product, that may impact the safety of the trial subjects.

Examples:

- a serious adverse event likely to be related to the interventions and the trial's diagnostic procedures and which may impact the conduct of the clinical trial,
- a significant risk on the trial subjects such as ineffectiveness of the investigational medicinal product in treating a life-threatening illness under investigation,
- significant safety results from a recently completed non-clinical study (such as a carcinogenicity study),
- the premature termination, or temporary suspension, of a trial conducted on the same investigational medicinal product in another country, for safety reasons,
- an unexpected serious adverse reaction associated with a non-experimental medication required for the conduct of the clinical trial, (e.g. challenge agents, rescue treatment)

d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, that may affect the safety of the trial subjects

e) any suspected unexpected serious adverse reaction (SUSAR) reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication.

9.2.2 The role of the investigator

The investigator must **assess the seriousness criteria of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).

The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the severity** of the adverse events by using:
- General terms:
  - Mild: tolerated by the patient, does not interfere with daily activities
  - Moderate: sufficiently uncomfortable to affect daily activities
  - Serious: preventing daily activities

The investigator must assess the **causal relationship** between the serious adverse events and the investigational medicinal product and the study procedure(s).

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following causality terms:
- Certain
- Probable/likely
- Possible
- Unlikely (not ruled out).

These terms are defined as follows (extracted from the WHO-UMC causality categories, version dated 17/04/2012).

Table N°2: WHO-UMC causality categories (extract)

Causality term	Assessment criteria*
Certain	· Event or laboratory test abnormality, with plausible time relationship to drug intake ** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake ** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake ** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with
** Or study procedures

9.2.2.1 Serious adverse events that require a notification without delay by the investigator to the sponsor

As per article R.1123-49 of the French Public Health Code (CSP), the investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any serious adverse event which occurs during a trial as described in Article L.1121-1(1) CSP, except those which are listed in the protocol (11.2.2.2.2) and, if applicable, in the investigator's brochure as not requiring a notification without delay.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening
3- requires inpatient hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

The serious adverse events listed below are especially monitored by the sponsor:

- Deaths during the 60th postoperative days;
- Severe hemorrhage (Grade III and IV - CTC-AE V5.0);
- Severe hemodynamic failure (Grade III and IV - CTC-AE V5.0);
- All visceral failure: renal insufficiency necessitate dialysis, respiratory failure needed respiratory assistance, liver failure (bilirubin >10N), brain failure;
- Home parenteral nutrition more than 1 month;
- All infectious complications (intra-abdominal abscess);
- Grade 4 thrombopenia (<25,000), neutropenia (<500 PN), transfusion (more than 4 RBCU);
- Diarrhea > 15 stools per day after 21 days;
- All adverse effect affecting life prognosis or leading to permanent or temporary serious incapacity.
- Every death or complication of grade III/IV of the Common Toxicity Criteria (CTC-AE V5.0) of the National Cancer Institute occurring within 60 days of surgery will be an event for the analysis of postoperative morbidity and mortality. Complications of Grade 3 are those that require special treatment invasive (surgery, drainage, interventional radiology of the gesture) or readmission to hospital. Complications of Grade 4 will be those that require a shift in Intensive Care Unit ICU (presence of at least two organ failures in a broad sense).

9.2.2.2 Specific features of the protocol

9.2.2.2.1Other events that require the investigator to notify the sponsor without delay

- Adverse events judged as being "medically significant"

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these adverse events, according to the same modalities and within the same timeline as for serious adverse events (see above).

- In utero exposure

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any pregnancy that occurs during the trial, even if not associated with an adverse event.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be reported to the sponsor.

- **Exposure via breastfeeding**

Exposure via breastfeeding occurs if an infant or child could have been exposed *via* the breast milk of a mother being treated with an investigational medicinal product.
Even if such exposure is not associated with an adverse event, the investigator must always notify the sponsor without delay on the day when the investigator becomes aware of any exposure via breastfeeding.

9.2.2.2.2Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are simply recorded in the case report form**.** A CRF extraction of these serious adverse events will be realized every 6 months.

- Normal and natural course of the condition:

- Mild to Moderate abdominal pain (grade 1-2 according to the CTCAE scale)
- Mild to Moderate nausea (grade 1-2 according to the CTCAE scale)
- Moderate systemic inflammation with fever < 38°5, white blood count < 16000, CRP < 50
- Death related to cancer and that is not related to “Serious adverse events that require a notification without delay by the investigator to the sponsor

- Some events require special monitoring in the PIPAC arm:

- Trocar hernia
- Bowel injury
- Hemorrhage
- Dissemination of chemotherapy in abdominal wall within the trocar
- Intraoperative bleeding
- Bowel sclerosis
- Hypersensitivity reactions to platinum compounds
- AE related to a PIPAC C/D malfunctioning

- In both study arms, AE leading to a treatment permanent discontinuation will be monitored.

The primary objective of the trial is progression free survival and overall survival is a secondary endpoint. The mortality rate of the condition under investigation is 50 % at 2 years.
If there is any imbalance between the randomization groups or the mortality rate is higher than expected affecting the safety of trial subjects and which requires the sponsor to take urgent safety measures, the ANSM will be informed about the emerging safety issue without delay.

- Special circumstances
  - Hospitalisation for a pre-existing illness or condition
  - Hospitalisation for a medical or surgical treatment scheduled prior to the trial
  - Admission for social or administrative reasons
  - Transfer to the emergency ward (< 12 hours)

- Adverse events during the trial possibly related to the treatments/acts prescribed as part of the patient's standard care

The investigator as health care professional must notify these events to the appropriate health surveillance institution according to the situation. Examples: Agence Régionale de Santé, quality department of your hospital, Centre Régional de Pharmacovigilance, local correspondent of the materiovigilance unit (ANSM), etc.

9.2.2.3 Period during which the investigator must send notification of SAEs to the sponsor without delay

The investigator notifies the sponsor without delay of all the serious adverse events listed in the corresponding section:
- starting from the date on which the subject signs the consent form
- throughout the whole follow-up period intended by the trial
- until 4 weeks after the end of the subject's treatment with the investigational medicinal product.

- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear at long term after exposure to the medication, such as cancers or congenital abnormalities)

9.2.2.4 Procedures and deadlines for notifying the sponsor

The investigator should initially complete a SAE reporting form (contained in the case report form). This report must be signed by the investigator.

The investigator must complete every section of the SAE form so that the sponsor can carry out the appropriate assessment.

The initial report sent to the sponsor must be rapidly followed up by one or more additional written reports describing the course of the event and any complementary information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results of additional exams, etc.). These documents must be anonymized. In addition, the investigator must state the study acronym and the number and initials of the study participant on each paper.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has terminated his participation in the trial.

The initial report, the SAE follow-up reports, and all other documents must be sent to the sponsor by e-mail (**eig-vigilance.drc@aphp.fr**) to the sponsor's safety department. It is possible to send the SAE to the Safety department by fax to the sponsor's safety department, fax N°. +33 (0)1 44 84 17 99 only in case of unsuccessful attempt to send the SAE by e-mail and in order to avoid duplicates

For trials which use e-CRF
- the investigator completes the SAE report form in the e-CRF, then validates, prints and signs the form before sending it by fax;
- In case of failure to connect to the e-CRF, the investigator should complete, sign and send the SAE report form to the safety Department. As soon as the connection is restored, the investigator must complete the SAE report form in the e-CRF.

The investigator must comply with all requests for additional information from the sponsor.
For all questions relating to an adverse event report, the safety Department can be contacted via email at vigilance.drc@aphp.fr.
For cases of *in utero* exposure, the investigator will complete the initial notification and follow-up report forms for pregnancy exposure during trial participation".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy ends, and must notify the sponsor of the outcome of the pregnancy, using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy report form, the SAE follow-up forms and any other documents will be sent to the sponsor using the same modalities as described above.
If it was the father who was exposed, the investigator must obtain the mother's permission before collecting information about the pregnancy.

9.2.3 Role of the sponsor

The sponsor, represented by its safety Department, shall continuously assess the safety of each investigational medicinal product throughout the trial.

9.2.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all reported adverse events,
- the **causal relationship** between these adverse events and investigational medicinal product and study procedures and any other treatments,

All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.

- the **expectedness assessment** of the serious adverse reactions

Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.
The sponsor, acting through its safety Department, assesses the expectedness of the serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product(s):
Refer to the SmPCs for Cisplatine Accord 1 mg/mL and Adriblastine 10 mg, enclosed in Annexe 19.4

❖ For serious adverse events likely to be related to the IV standard poly chemotherapy (auxiliary medicinal products):

- refer to the SmPC in force for each product

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency).

- The sponsor must send the initial report without delay upon receipt of the unexpected serious adverse reaction if it is fatal or life-threatening, or otherwise within 15 days from receipt of any other type of unexpected serious adverse reaction;
- The sponsor must provide all relevant additional information by sending follow-up reports, within 8 calendar days following receipt.

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).
The sponsor must notify all the investigators about any information that could adversely affect the safety of the trial subjects.

9.2.3.2 Analysis and declaration of other safety data

This relates to any new safety data that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.

The sponsor will inform the competent authority and the Ethics committee without delay after becoming aware of the emerging safety issue and, if applicable, describe which measures have been taken.

Following the initial declaration of emerging safety issue, the sponsor will declare to ANSM any additional relevant information about the new safety issues in the form of a follow-up report, which must be sent no later than 8 days after becoming aware of the information.

9.2.3.3 Annual safety report

The sponsor must prepare once yearly throughout the trial duration an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- an analysis of safety data concerning trial subjects
- a description of the patients included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- cumulative summary tabulation of all the serious adverse events that have occurred since the beginning of the clinical trial,

The report must be transmitted to ANSM no later than 60 days after the anniversary date corresponding to the date of authorization of the clinical trial by ANSM.

9.2.4 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) can be set up by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of a DSMB to the Competent Authority (ANSM) and to the Ethics committee.

A DSMB will be set up for this trial. The DSMB must hold its first meeting before the first subject is enrolled.

The members of the DSMB are:

Name	Address / phone / mail	Specialty
Mr Jérémie LEFEVRE	Service de Chirurgie générale et digestive Hôpital Saint-Antoine 184 rue du faubourg Saint-Antoine 75571 Paris Cedex 12, France Faculté de Médecine Sorbonne Université Paris VI Email : jeremie.lefevre@aphp.fr	Professeur des universités-Praticien Hospitalier Chirurgie générale et digestive
Mme Belin Lisa	Hôpitaux Universitaires Pitié-Salpêtrière Charles Foix 47-83 Boulevard de l'Hôpital 75013 PARIS Tel : 01.42.16.05.14 Email : lisa.belin@aphp.fr	Assistant Hospitalo-Universitaire Biostatistiques
Mr Thiery ANDRE (président du CSI)	Hôpital Saint-Antoine 184 rue du Faubourg Saint-Antoine 75012 Paris Tel : 06.61.77.07.08/01.49.28.23.44 Email : thierry.andre@aphp.fr	Professeur des universités-Praticien Hospitalier Cancérologie

All missions as well as the precise operating procedures of the DSMB are described in the DSMB charter of the clinical trial.

The DSMB has a consultative role. The final decision concerning the conduct of the clinical trial relies on the sponsor.

10 DATA MANAGEMENT

10.1 Data collection

10.2 Identification of data recorded directly in the CRFs which will be considered as source data

Source documents, defined as any original document or object through which the existence or accuracy of a data or fact recorded during the research can be proven, shall be kept by the investigator or the hospital, if it concerns a hospital medical record, for 15 years.

10.3 Right to access source data and documents

10.3.1.1 Access to data

In accordance with GCP:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures.
- the investigators will ensure the persons in charge of monitoring and auditing the clinical trial and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

10.3.1.2 Source documents

The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the trial. Source documents will be kept by the investigator, or by the hospital in the case of hospital medical records, for the statutory period.

List the types of source documents relevant to the trial (medical files, original laboratory test results, medical imaging reports, etc.).

10.3.1.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code).
During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised.
Under no circumstances will the names and addresses of the subjects be shown.
Only the subject's initials will be recorded, along with an identification code specific to the study indicating the order of enrolment.
The sponsor will ensure that each subject has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

10.4 Data processing and storage of documents and data

10.4.1 Identification of the data processing manager and the location(s)

Mrs Claire Pacheco data manager from SBIM in St Louis Hospital Paris will be responsible for data entry and the relevant procedures.

Matthieu Resche Rigon from SBIM in Saint Louis Hospital Paris will conduct the statistical analysis

10.4.2 Data entry

Data will be entered electronically via a web browser.

10.4.3 Data processing (CNIL, the French Data Protection Authority) in France

- - If the trial is governed by the CNIL "Reference Method" (MR-001):

This trial is governed by the CNIL "Reference Method for processing personal data for clinical studies" (MR-001, amended). AP-HP, the study sponsor, has signed a declaration of compliance with this "Reference Method"

10.4.4 Archiving

The specific documents for a clinical trial on a medicinal product for human use will be archived by the investigator and the sponsor for 15 years after the end of the trial.

This indexed archiving includes, in particular:

- A sealed envelope containing the originals of all information sheets and consent forms signed by all individuals at the site who participated in the study for the investigator;
- One copy of all the information sheets and signed consent forms signed for all individuals at the site who participated in the study for the sponsor;
- "Study" binders for the Investigator and the sponsor, containing:
  - all successive versions of the protocol (identified by version no. and date), and its appendices
  - the ANSM authorisations and CPP decisions
  - correspondence
  - the enrolment list or register
  - the appendices specific to the study
  - the final study report
- The data collection documents

.

10.5 Ownership of the data

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

11 STATISTICAL ASPECTS

This study is a prospective, multicenter, randomized, open-label, controlled, parallel-group, Phase II clinical trial designed to evaluate the effects of PIPAC with oxaliplatin on patients with gastric peritoneal metastasis and PCI>8.

The following analysis sets will be considered:

- Intent-to-treat (ITT) defined as all randomized patients in the study and in their randomized group whatever the eligibility criteria and treatment received). This will refer to the primary analyses.
- Safety population: ITT population receiving at least one PIPAC
- Per protocol set: Includes all subjects from the intent-to-treat set without any major violations which could affect the evaluation of the primary efficacy endpoint. This will be used as secondary, exploratory or sensitivity analyses
- Safety set: Includes all subjects who take any amount of study drug.

As a general strategy, continuous efficacy and safety endpoints will be summarized using summary measures (median and interquartile range). Frequency distributions (counts and percentages) will be used to summarize categorical endpoints. Similarly, characteristics of patients will be presented using summary measures (median and interquartile range for quantitative characteristics and counts and percentages for categorical characteristics)

Analyses by treatment group will be presented according to the treatment to which subjects were randomized

11.1 Disposition of the Study Subjects

The disposition of subjects will be described with summaries by treatment group of the number of subjects enrolled, the number of subjects treated, and the number of subjects for whom study drug was permanently discontinued (including the reasons for discontinuation).

11.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized globally and by treatment group.

11.3 Exposure to Study Treatment and Compliance

Frequency distributions of the number of received PIPAC will be presented by treatment group. Treatment duration and treatment compliance for all randomized subjects will be described by treatment group.

11.4 Planned statistical methods, including the timetable for any planned interim analyses

11.4.1 Analysis of Primary Efficacy Endpoint

The 24-month progression free-survival will be estimated using Kaplan Meier estimator on the total sample and per arm. Estimation with their 95% Confidence Intervals (CI) will be given. Test between survival curves will be performed using Logrank test. Hazard Ratio will be estimated using Cox model. Centre effect will be assessed and tested using random effect model. If the test is significant, Hazard Ratio between groups will be estimated using Cox model with Random effect.

Sensitivity analysis will be carried out by adjusting the treatment effect on the fact the patient is in first line of treatment or not. Subgroup analyses on patients in first line of treatment or not will be carried out. Quantitative and qualitative interactions will be assessed using Gail and Simon interaction tests.

Primary analysis will be performed in Intent-to-treat. Sensitivity analyses will be performed considering per protocol population.

11.4.2 Analysis of Secondary Endpoints

Patients related:

- The morbidity at day 30. Proportion by groups and globally will be estimated. 95% CI will be given. Proportions will be compared between groups using Fisher test
- The Comprehensive Complication Index will be described by median and Interquartile range by groups and globally. Distributions will be compared by Wilcoxon tests.
- Postoperative pain measured using a numeric rating scale from 0 to 10 from post-operative day 0 to day 2, every 6 hours.will be described by median and Interquartile range by groups and globally. Comparisons between groups will be performed using a linear random effect model including groups as explicative variable and patient as random effect. Wald test of the group effect will be performed.
- Quality of life evaluated monthly by the patient with the EORTC QLQ-STO22 questionnaire, specific to gastric cancer will be described by median and Interquartile range by groups and globally. Comparisons between groups will be performed using a linear random effect model including groups as explicative variable and patient as random effect. Wald test of the group effect will be performed. Similar analyses will be performed for QLQ-C30 and EQ-5D-5L.

Treatment related:

- Global treatment-related toxicity. Proportion by groups and globally will be estimated. 95% CI will be given. Proportions will be compared between groups using Fisher test. Precise description of toxicity will be given according to the randomization groups

- feasibility of 3 successive PIPAC procedures. Proportion of patients with 3 successive PIPAC procedures will be estimated with 95% CI within the PIPAC arm.

Disease related:
- Overall survival (OS) at 24 months defined as the time to death. The OS will be estimated using Kaplan Meier estimator on the total sample and per arm. Estimation with their 95% Confidence Intervals (CI) will be given. Test between survival curves will be performed using Logrank test. Hazard Ratio will be estimated using Cox model.

- Secondary resecability rate defined as an IPC ≤ 8 at laparoscopy after the treatment. Proportion by groups and globally will be estimated. 95% CI will be given. Proportions will be compared between groups using Fisher test

11.4.3 Analysis of Safety

Safety analyses will involve examination of the incidence, severity, and type of treatment emergent adverse events reported, changes in vital signs and laboratory test results.

11.4.4 Adverse Events

Adverse events reported during the study will be coded using a MedDRA dictionary. Incidence of treatment-emergent adverse events will be summarized by treatment group and the following:

- System organ class and preferred term
- System organ class, preferred term and severity

These summaries will be presented for the following subsets:

- Serious adverse events
- All adverse events
- Drug-related adverse events
- Adverse events resulting in discontinuation of study drug
- Outcome of adverse events
- Action taken

For tables reporting adverse events by severity, if a subject has multiple occurrences of an adverse event with the same organ class and preferred term, the most severe event will be presented.
A summary and by-subject listing will be provided for all subjects who experienced any adverse events, serious adverse events, or adverse events resulting in discontinuation of study drug.

11.5 Hypotheses for calculating the required number of subjects, and the result

Considering a survival analysis using a two-sided log-rank test, we fixed our bilateral type I error at 5% and we aimed a power of 85%. We assumed a median progression free survival in the control arm of 6 months and an expected median survival in the PIPAC arm of 12 months. Thus, we need to observe 78 events corresponding to a sample size of 94 patients to be enrolled (equally balanced in each arm).

11.6 State whether subjects who exit the study prematurely will be replaced and in what proportion.

During the inclusion period patient prematurely exiting the study will be replace.

11.7 Anticipated level of statistical significance

All test will be 2-sided at the 0.05 level.

11.8 Method for taking into account missing, unused or invalid data

In case of missing data multiple imputation by chained equation will be performed with at least 20 imputed dataset. Complete case analyses will be performed as sensitivity analyses.

12 QUALITY CONTROL AND ASSURANCE

Every clinical study managed by AP-HP is ranked according to the projected risk incurred by the study participants using a classification system specific to AP-HP-sponsored clinical trials.

12.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the trial. The sponsor must have a quality assurance system for monitoring the implementation of the study at the research centres.

For this purpose, the sponsor shall appoint Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study sites, after completing their initial visits.
The purpose of monitoring the study, as defined in the Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the research subjects are safe, protected and their rights are being met
- the data being recorded is accurate, complete and consistent with the source documents
- the study is carried out in accordance with the current version of the protocol, with GCP and with all statutory and regulatory requirements.

12.1.1 Strategy for site opening

The strategy for opening the sites is determined using the tailored monitoring plan.

12.1.2 Scope of site monitoring

For this study, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, the sponsor in agreement with the coordinating investigator, has agreed on a logistical score and impact and the corresponding study monitoring level of risk D.

The various levels are described in the Human Research Trial monitoring charter.

12.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCD and in accordance with Good Clinical Practice as well as with the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the study protocol and its procedures
- quality of the data collected in the case report forms: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

If differential quality control is used (i.e. level of quality control depends on the risk incurred by the subjects), provide the necessary details.

12.3 Case Report Form

The case report forms should only contain the data needed to analyse the trial and publish the results. All other data needed to monitor the subject during and after the trial are recorded in the medical file.

All information required by the protocol must be entered in the case report forms. The data must be collected as and when it is obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given instructions for using this tool.
Using on-line case report forms means the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, there are consistency checks to ensure the data are verified immediately upon being entered. The investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

12.4 Management of non-compliances

Any events that occur as a result the investigator or any other individual involved in conducting the study failing to comply with the protocol, standard operating procedures, good clinical practice or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

The sponsor has its own procedures for managing these non-compliances.

12.5 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the basis of medical secrecy.

An audit can be carried out at any time by independent individuals appointed by the sponsor. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the trial agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study.

12.6 Principal Investigator's declaration of responsibility

Before starting the trial, each investigator will give the sponsor’s representative a signed and dated copy of his/her curriculum vitæ and RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will agree to comply with legislation and to conduct the trial in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a declaration of responsibility (standard DRCD document) which will be sent to the sponsor's representative.
The investigators and their co-workers will sign a delegation form specifying each person's role.

13 ETHICAL AND LEGAL CONSIDERATIONS

13.1 Methods for informing and obtaining consent from the research participants

NB:
If the investigational medicinal product has been granted Marketing Authorisation in France, use this section to compare and, if applicable, describe and justify any relevant differences in terms of safety between the patient information sheet and the package leaflet (Article R.5121-148), as regards any contraindications, undesirable effects and warnings/precautions for use.

Describe **in detail** the method for informing and obtaining consent from the persons taking part in the trial, especially when subjects are unable to give their own consent.
Depending on the type of trial and the categories of subjects, provide the following information:

- **Who will be informed?** the subject
- Who will give their consent? the subject
- When? Before inclusion visit
- **How?** Information sheet given to the subject and oral explanation.
- **Who will obtain the consent?** The investigator or his representative~~]~~.

As well as the consent required by Article L.1122-1-1 of the French Public Health Code, special consent is required when the study involves genetic testing of the participants. If this applies, describe the procedure for informing the subjects and obtaining their consent.

As an exception, pursuant to *Article L.1122-1*, certain information about the diagnosis of the study participant may be withheld, in their interests. [Explain the reasons or delete if not applicable]

Standard paragraph for trials of adults capable of giving their consent

In accordance with Article L.1122-1-1 of the French Public Health Code, no research can be carried out on a person without his/her free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.

The person will be given the sufficient time ~1 week between receiving the information and being asked to sign the consent form.

The person’s free and informed written consent will be obtained by the investigator, or by a doctor representing the investigator, before the person is enrolled on the trial (before randomisation).

The information sheet and a copy of the consent form signed and dated by the research subject and by the investigator or the doctor representing the investigator, will be sent to the individual prior to being enrolled on the trial.

In addition, the investigator will specify in the research participant’s medical file the methods used for obtaining their consent as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

13.2 Prohibition of concomitant clinical studies participation and exclusion period after the trial, if applicable

Whilst participating in this trial, subjects may not take part in any other clinical study without first speaking to the doctor in charge of this trial.

13.3 Legal obligations

13.3.1 The sponsor's role

Assistance Publique Hôpitaux de Paris (AP-HP) is the sponsor of this study and has delegated powers to its Clinical Research and Development Department (DRCD) in order to conduct the study in accordance with Article L.1121-1 of the French Public Health Code. AP-HP reserves the right to terminate the study at any time for medical or administrative reasons. In this case, the investigator will be informed accordingly.

13.4 Request for approval from the Institutional Review Board

AP-HP, as sponsor, obtains prior approval from the Institutional s Review Board for its clinical trials of medicinal products for human use, within the scope of the Board's authority and in accordance with statutory and regulatory requirements.

13.5 Request for approval from the ANSM

AP-HP, as sponsor, obtains prior authorisation from the ANSM for its clinical trials of medicinal products for human use, within the scope of the ANSM's authority and in accordance with statutory and regulatory requirements.

13.6 Procedures relating to data protection regulations

The computer file used for research has been implemented in accordance with French (amended French Data Protection Act) and European (General Data Protection Regulation - GDPR) regulations.

Commitment to comply with “Reference Methodology” MR-001
This research is governed by the CNIL (French Data Protection Agency) “Reference Methodology for processing personal data used within the scope of health research” (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this “Reference Methodology”

13.7 Modifications to the trial

Any substantial amendment made to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to implementing the amendment, approval from the Institutional Review Board and authorisation from the ANSM, within the scope of their respective authorities.
The information sheet and the consent form can be revised if necessary; in particular, if there is substantial amendment to the study or if adverse reactions occur.

13.8 Final study report

The final study report referred to in CSP Article R.1123-67 is written and signed by the sponsor and the investigator. A report summary, meeting the competent authority’s guidelines, has to be sent to the competent authority and Institutional Review Board within one year of the end of the trial i.e. the end of the participation of the last study participant.

14 FUNDING AND INSURANCE

14.1 Sources of funding for the trial

The sources of funding for the trial (PHRC-K), INCA

14.2 Insurance

As per Article L.1121-10 of the French Public Health Code, insurance policies must cover the third party liability of the sponsor and all collaborators, and insure them against the financial consequences of any damage caused by the human research trial.

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own third party liability as well as the third party liability of all the doctors involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the study participant and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GERLING through BIOMEDIC-INSURE, covering its own third party liability and that of any collaborator (doctor or research staff), in accordance with Article L.1121-10 of CSP.

15 PUBLICATION

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and name the sponsor AP-HP (DRCI) and the source of funding, if funded by a call for tenders (e.g. national or regional PHRC); a copy of the publication must be sent to the sponsor (see below for rules governing affiliation, and naming the sponsor and funders).

15.1 Mention of AP-HP affiliation for projects sponsored or managed by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is not important
- However, if the trial is funded by an internal call for tenders at the AP-HP, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon
- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France

15.2 Mention of the AP-HP manager (DRCI) in the acknowledgements of the text

- "The sponsor was *Assistance Publique – Hôpitaux de Paris* (Clinical Research and Development Department)"

15.3 Mention of the funder in the acknowledgements of the text

- If PHRC: "The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2016 (Ministry of Health)"

If an AP-HP internal call for tenders: "The study was funded by a grant from Assistance Publique – Hôpitaux de Paris"

16 BIBLIOGRAPHY

1. Guimbaud R, Louvet C, Ries P et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) study. J Clin Oncol. 2014 Nov 1;32(31):3520-6.

2. Bang YJ, Van Cutsem E, Feyereislova A et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010 Aug 28;376(9742):687-97.

3. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359–74.

4. Chia CS, You B, Decullier E, Vaudoyer D, Lorimier G, Abboud K, Bereder JM, Arvieux C, Boschetti G, Glehen O; BIG RENAPE Group. Patients with Peritoneal Carcinomatosis from Gastric Cancer Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Is Cure a Possibility? Ann Surg Oncol. 2016 Jun;23(6):1971-9.

5. Solass W, Kerb R, Mürdter T, Giger-Pabst U, Strumberg D, Tempfer C, Zieren J, Schwab M, Reymond MA.. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol. 2014;21:553-9.

6. Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond MA. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Low-Dose Cisplatin and Doxorubicin in Gastric Peritoneal Metastasis. Gastrointest Surg. 2016 Feb;20(2):367-73.

7. Khomyakov V, Ryabov A, Ivanov A, Bolotina L, Utkina A, Volchenko N, Kaprin A. Bidirectional chemotherapy in gastric cancer with peritoneal metastasis combining intravenous XELOX with intraperitoneal chemotherapy with low-dose cisplatin and Doxorubicin administered as a pressurized aerosol: an open-label, Phase-2 study (PIPAC-GA2). Pleura and Peritoneum 2016; 1(3): 159–166

8. Alyami M, Gagniere J, Sgarbura O, Cabelguenne D, Villeneuve L, Pezet D, Quenet F, Glehen O, Bakrin N, Passot G. Multicentric initial experience with the use of the pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the management of unresectable peritoneal carcinomatosis. Eur J Surg Oncol. 2017 Nov;43(11):2178-2183.

9.Solass W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. Surg Endosc. 2012;26:1849-55.

10. Eveno C, Haidara A, Ibrahim A, Pimpie C, Mirshahi M, Pocard M. Experimental pharmacokinetics evaluation of chemotherapy delivery by PIPAC for colon cancer: first evidence for efficacy. Pleura & Peritoneum 2017; 2(2) :103-9.

11. Tempfer CB, Giger-Pabst U, Seebacher V, Petersen M, Dogan A, Rezniczek GA. A phase I, single-arm, open-label, dose escalation study of intraperitoneal cisplatin and doxorubicin in patients with recurrent ovarian cancer and peritoneal carcinomatosis. Gynecol Oncol. 2018;150(1):23-30

12. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

US Department of Health and Human Services, National Institutes of Health, National Cancer Institute: Bethesda, 2009

13. Giger-Pabst U, Solass W, Strumberg, D, Zieren J, Reymond M. Erste klinische Ergebnisse der 'Pressurized IntraPeritoneal Aerosol Chemotherapy' (PIPAC) bei Patienten mit Magenkarzinom und fortgeschrittener Peritonealkarzinose. Z Gastroenterol 2013; 51: K364

14. Blanco A, Giger-Pabst U, Solass W, Zieren J, Reymond MA. Renal and hepatic toxicities after pressurized intraperitoneal aerosol chemotherapy (PIPAC). Ann Surg Oncol 2013; 20: 2311–2316.

15. Robella M, Vaira M, De Simone M. Safety and feasibility of pressurized intraperitoneal aerosol chemotherapy (PIPAC) associated with systemic chemotherapy: an innovative approach to treat peritoneal carcinomatosis. World J Surg Oncol 2016; 14: 128

16. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors (RECIST Guidelines). J Natl Cancer Inst 2000;92:205–16.

17. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug;240(2):205-13

18. Solass W, Giger-Pabst U, Zieren J, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC): occupational health and safety aspects. Ann Surg Oncol. 2013;20:3504- 11.

19. Slankamenac K1, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg. 2013 Jul;258(1):1-7.

20. Tempfer CB, Winnekendonk G, Solass W, Horvat R, Giger-Pabst U, Zieren J, et al. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: A phase 2 study. Gynecol Oncol. mai 2015;137(2):223-8.

21. Tempfer CB, Giger-Pabst U, Seebacher V, Petersen M, Dogan A, Rezniczek GA. A phase I, single-arm, open-label, dose escalation study of intraperitoneal cisplatin and doxorubicin in patients with recurrent ovarian cancer and peritoneal carcinomatosis. Gynecol Oncol. 2018;150(1):23-30.

26. Intraperitoneal Aerosol Chemotherapy in Gastric Cancer - (PIPAC-GA01) [Internet]. [cité 4 mars 2019]. Disponible sur: https://clinicaltrials.gov/ct2/show/NCT01854255

27. Khomyakov V, Ryabov A, Ivanov A, Bolotina L, Utkina A, Volchenko N, et al. Bidirectional chemotherapy in gastric cancer with peritoneal metastasis combining intravenous XELOX with intraperitoneal chemotherapy with low-dose cisplatin and Doxorubicin administered as a pressurized aerosol: an open-label, Phase-2 study (PIPAC-GA2). Pleura Peritoneum. 2016;1(3):159–166.

28. Graversen M, Detlefsen S, Bjerregaard JK, Fristrup CW, Pfeiffer P, Mortensen MB. Prospective, single-center implementation and response evaluation of pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastasis. Ther Adv Med Oncol. 2018;10:1758835918777036.

29. Study of Efficacy and Safety of Laparoscopic Intra-abdominal Chemotherapy (PIPAC) Performed in Patients With Peritoneal Carcinomatosis From Colorectal, Ovarian, Gastric Cancer and Primary Peritoneal Tumors (PI-CaP) [Internet]. [cité 4 mars 2019]. Disponible sur: https://clinicaltrials.gov/ct2/show/NCT02604784

30. Tempfer CB, Celik I, Solass W, Buerkle B, Pabst UG, Zieren J, et al. Activity of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with cisplatin and doxorubicin in women with recurrent, platinum-resistant ovarian cancer: preliminary clinical experience. Gynecol Oncol. févr 2014;132(2):307-11.

31. Tempfer CB, Rezniczek GA, Ende P, Solass W, Reymond M-A. Pressurized Intraperitoneal Aerosol Chemotherapy with Cisplatin and Doxorubicin in Women with Peritoneal Carcinomatosis: A Cohort Study. Anticancer Res. déc 2015;35(12):6723-9.

32. Khosrawipour T, Khosrawipour V, Giger-Pabst U. Pressurized Intra Peritoneal Aerosol Chemotherapy in patients suffering from peritoneal carcinomatosis of pancreatic adenocarcinoma. PloS One. 2017;12(10):e0186709.

33. Odendahl K, Solass W, Demtröder C, Giger-Pabst U, Zieren J, Tempfer C, et al. Quality of life of patients with end-stage peritoneal metastasis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. oct 2015;41(10):1379-85.

34. Robella M, Vaira M, De Simone M. Safety and feasibility of pressurized intraperitoneal aerosol chemotherapy (PIPAC) associated with systemic chemotherapy: an innovative approach to treat peritoneal carcinomatosis. World J Surg Oncol. 29 avr 2016;14:128.

35. Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond M-A. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Low-Dose Cisplatin and Doxorubicin in Gastric Peritoneal Metastasis. J Gastrointest Surg Off J Soc Surg Aliment Tract. févr 2016;20(2):367-73.

36. Kurtz F, Struller F, Horvath P, Solass W, Bösmüller H, Königsrainer A, et al. Feasibility, Safety, and Efficacy of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) for Peritoneal Metastasis: A Registry Study. Gastroenterol Res Pract. 2018;2018:2743985.

37. Demtröder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond M-A. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Colorectal Dis Off J Assoc Coloproctology G B Irel. avr 2016;18(4):364-71.

38. Graversen M, Detlefsen S, Bjerregaard JK, Pfeiffer P, Mortensen MB. Peritoneal metastasis from pancreatic cancer treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC). Clin Exp Metastasis. 2017;34(5):309-14.

39. Hübner M, Teixeira Farinha H, Grass F, Wolfer A, Mathevet P, Hahnloser D, et al. Feasibility and Safety of Pressurized Intraperitoneal Aerosol Chemotherapy for Peritoneal Carcinomatosis: A Retrospective Cohort Study. Gastroenterol Res Pract. 2017;2017:6852749.

40. Alyami M, Gagniere J, Sgarbura O, Cabelguenne D, Villeneuve L, Pezet D, et *al.* Multicentric initial experience with the use of the pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the management of unresectable peritoneal carcinomatosis. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. nov 2017;43(11):2178-83.

41. Falkenstein TA, Götze TO, Ouaissi M, Tempfer CB, Giger-Pabst U, Demtröder C. First Clinical Data of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) as Salvage Therapy for Peritoneal Metastatic Biliary Tract Cancer. Anticancer Res. 2018;38(1):373-8.

42. Gockel I, Jansen-Winkeln B, Haase L, Rhode P, Mehdorn M, Niebisch S, et al. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in Gastric Cancer Patients with Peritoneal Metastasis (PM): Results of a Single-Center Experience and Register Study. J Gastric Cancer. déc 2018;18(4):379-91.

43. Horvath P, Beckert S, Struller F, Königsrainer A, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastases of pancreas and biliary tract cancer. Clin Exp Metastasis. oct 2018;35(7):635-40.

44. Jansen-Winkeln B, Thieme R, Haase L, Niebisch S, Pommer C, Lyros O, et al. [Perioperative safety of intraperitoneal aerosol chemotherapy : Analysis of our first 111 pressurized intraperitoneal aerosol chemotherapy (PIPAC) procedures]. Chir Z Alle Geb Oper Medizen. févr 2019;90(2):137-45.

45. Giger-Pabst U, Demtröder C, Falkenstein TA, Ouaissi M, Götze TO, Rezniczek GA, et al. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) for the treatment of malignant mesothelioma. BMC Cancer. 18 2018;18(1):442.

46. Willaert W, Sessink P, Ceelen W. Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC). PLEURA PERITONEUM. 2017;2(3):121-8.

47. Siebert M, Alyami M, Mercier F, Gallice C, Villeneuve L, Bérard F, et al. Severe hypersensitivity reactions to platinum compounds post-pressurized intraperitoneal aerosol chemotherapy (PIPAC): first literature report. Cancer Chemother Pharmacol. mars 2019;83(3):425-30.

17 ANNEXES (LIST OF ADDENDA)

Every addendum and the log of addenda versions are attached, independently of the protocol. Every addendum can be modified (change of addendum version) without modifying the version of the protocol.

17.1 List of Investigators (in appendix)

17.2 Serious Adverse Events report form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une recherche impliquant la personne humaine portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par courriel à l'adresse eig-vigilance.drc@aphp.fr. Il est à noter qu'il est possible de transmettre les EIG au secteur Vigilance par télécopie au +33 (0) 1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi des EIG par mail (afin d'éviter les doublons).

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

1. Identification de la recherche	
Acronyme : PIPAC EstoK 01	**Date de notification :** |__|__| |__|__| |2|0|__|__| jj mm aaaa
Code de la Recherche : P160951J	**Date de prise de connaissance de l'EIG par l'investigateur :** |__|__| |__|__| |2|0|__|__| jj mm aaaa
Risque : D	

Titre complet de la recherche : Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) dans la carcinose gastrique : Étude randomisée de phase II.

2. Identification du centre investigateur

Nom de l'établissement :	Investigateur (nom/prénom) : .....
Ville et code postal :	Tél : ..... Fax : .....
Service :	E-mail : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__|__|__| - |__| - |__|
n°centre – n° ordre de sélection – initiale nom – initiale prénom

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance :
|__|__| |__|__| |__|__|__|__|
jj mm aaaa

Age : |__|__|__|ans

Date de signature du consentement : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Date de randomisation : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
.....
.....
.....
.....
.....
.....
.....

Groupe : ☐ Chimiothérapie en IV + PIPAC
☐ Chimiothérapie en IV

Cycle de chimiothérapie au moment de la survenue de l'EIG :
Numéro : |__|__| Date de début : |__|__| |__|__| |2|0|__|__|

4. Médicament(s) expérimental(aux) (ME) ou produit(s) assimilé(s) [préciser le(s)quel(s)] avant la survenue de l'EIG

PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :
Référence GED : REC-DTYP-0192

(barrer l'encadré si traitement non débuté)					
Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie[(1)]	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours[(2)]	Date de fin *(jj/mm/aaaa)*
Cisplatine	………	………	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Adriblastine Autre, précisez …	………	………	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

5. Procédures et actes ajoutés par la recherche ***(ex. : biopsies, IRM …)*** ***(barrer l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG
Chirurgie exploratrice (cœlioscopie) avant randomisation	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
PIPAC N°1 ☐ Non applicable	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
PIPAC N°2 ☐ Non applicable	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
PIPAC N°3 ☐ Non applicable	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
Chirurgie exploratrice (cœlioscopie) finale	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐

Acronyme : PIPAC Estok 01

Référence de la personne se prêtant à la recherche : |___|___|___| - |___|___|___|___|___| - |___| - |___|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

6. Traitement comparateur = chimiothérapie IV [préciser quel(s) médicament(s)] avant la survenue de l'EIG ***(barrer l'encadré si traitement non débuté)***							
Nom commercial (de préférence) ou Dénomination Commune Internationale *	Voie[(1)]	Posologie (préciser l'unité ex : mg/j)	Dates d'administration *(du jj/mm/aa au jj/mm/aa)*	En cours [(2)]	Indication	***Action prise*** *0 : poursuite sans modification de la posologie* *1 : arrêt* *2 : diminution de la posologie* *3 : augmentation de la posologie* *4 : ne sais pas*	***Causalité de l'EIG*** *0 : non lié au médicament* *1 : lié au médicament* *2 : ne sais pas*
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

Agents chimiothérapiques:

1. Acide Folinique
2. Doxorubicine (Caelyx)
3. Adriamycine (Adriablastine)
4. Gemcitabine (Gemzar)
5. Bévacizumab (Avastin)
6. Irinotecan (Campto)
7. Campécitabine (Xeloda)
8. Mitomycine C (MMC)
9. Carboplatine (Paraplatine)
10. Oxaliplatine (Eloxatine)
11. Cetuximab (Erbitux)
12. Paclitaxel (Taxol)
13. Cisplatine
14. Pemetrexed (Almita)
15. Daunorubicine (Tomox)
16. 5-Fluoro Uracile (5-FU)
17. Docetaxel (Taxotere)
18. Topotecan (Hycamtin)
19. Autres

7. Médicament(s) <u>concomitant(s)</u> au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable
(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)

⇨ **Annexe jointe au présent formulaire :** ☐ Oui ☐ Non

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie[1]	Posologie (préciser l'unité ex : mg/j)	Dates d'administration *(du jj/mm/aa au jj/mm/aa)*	En cours [2]	Indication	***Action prise*** *0 : poursuite sans modification de la posologie 1 : arrêt 2 : diminution de la posologie 3 : augmentation de la posologie 4 : ne sais pas*	***Causalité de l'EIG*** *0 : non lié au médicament 1 : lié au médicament 2 : ne sais pas*
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

8. Evènement indésirable grave [EIG]

<u>Diagnostic</u> : ☐ Définitif ☐ Provisoire

.....

.....

.....

<u>Date de survenue des premiers symptômes</u> : |__|__| |__|__| |_2_|_0_|__|__|

Préciser lesquels :

.....

<u>Organe(s) concerné(s)</u> :

.....

.....

.....

.....

.....

.....

<u>Date d'apparition</u> de l'EIG :

|__|__| |__|__| |_2_|_0_|__|__|

jj mm aaaa

Heure de survenue : |__||__| hh |__||__| min

☐ *donnée manquante*

<u>Délai</u> entre la date de la dernière administration du ME/produit assimilé ou la date de procédure/acte ajouté par la recherche et la date de survenue de l'EIG :

|__||__| / |__||__| |__||__|

jj hh min

<u>Critères de gravité</u> :

☐ Nécessite ou prolonge l'hospitalisation :

du |__|__| |__|__| |_2_|_0_|__|__|

au |__|__| |__|__| |_2_|_0_|__|__| ☐ *en cours*

☐ Décès

☐ Mise en jeu du pronostic vital

☐ Incapacité ou handicap important ou durable

☐ Anomalie ou malformation congénitale

☐ Autre(s) critère(s) médicalement significatif(s), préciser :

.....

.....

<u>Degré de sévérité</u> :

<u>CTCAE (v5.0)</u> : ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

L'évènement a-t-il conduit à :

☐ aucune mesure prise concernant le ME

☐ diminution de la posologie du ME ☐ augmentation de la posologie du ME

☐ arrêt définitif du ME

☐ arrêt transitoire du ME, date de reprise : |__|__| |__|__| |_2_|_0_|__|__|

☐ ne sais pas

Récidive de l'EIG après ré-administration : ○ Non ○ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|

○ Non applicable

Des mesures symptomatiques ont-elles été prises ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|Préciser : .....

L'évènement a-t-il conduit à une <u>levée d'insu</u> ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__| ☐ Non applicable

L'évènement fait-il suite à :

- une erreur médicamenteuse ? ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|

- un surdosage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|	
- un mésusage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|	
- autre (préciser) : ……	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|	

PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :

Référence GED : REC-DTYP-0192

Acronyme : **PIPAC Estok 01**

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Evolution de l'événement

☐ **Décès**
○ sans relation avec l'EIG
○ en relation avec l'EIG
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

☐ **Sujet non encore rétabli**, préciser :
○ Etat stable ○ Amélioration ○ Aggravation

☐ **Résolu :**
○ sans séquelles
○ avec séquelles, préciser lesquelles :
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
|__|__| |__|__|
hh min

☐ **Evolution inconnue**

9. Autre(s) étiologie(s) envisagée(s)

☐ Non ☐ Oui Si oui, préciser : ……
……
……

10. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés]……
……
……

11. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)

Lié à la recherche :

☐ **Oui :** ☐ **au(x) médicament(s)/produit(s) assimilé(s) de la recherche : le(s)quel(s) ?**

Lequel : Cisplatine …… ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

Lequel : Adriblastine …… ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

☐ **au(x) médicament(s) de la chimiothérapie IV : le(s)quel(s) ?**

Lequel : …… ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

Lequel : …… ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

Lequel : …… ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

Lequel : …… ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

☐ **à la (aux) procédure(s)/acte(s) de la recherche : la/le(s)quel(les) ?**

La/lequel(le) : PIPAC (anesthésie générale, chirurgie et/ou procédure de vaporisation) ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

La/lequel(le) : Chirurgie exploratrice (cœlioscopie) avant randomisation ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

La/lequel(le) : Chirurgie exploratrice (cœlioscopie) finale ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

☐ **Non :** ☐ **à la progression de la maladie faisant l'objet de la recherche :** carcinome d'origine gastrique non résécable
☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) : ……**
☐ **à une maladie intercurrente, laquelle : ……**
☐ **autre, préciser : ……**

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature	Nom : Signature	

17.3 PREGNANCY NOTIFICATION FORM

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS ***Notification et suivi d'une grossesse apparue au cours d'une recherche portant sur un Médicament ou produit assimilé***	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE INTERNE :** Référence GED : REC-DTYP-0185

Ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par courriel à l'adresse eig-vigilance.drc@aphp.fr. Il est à noter qu'il est possible de transmettre les EIG au secteur Vigilance par télécopie au +33 (0) 1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi des EIG par mail (afin d'éviter les doublons).

1. Identification de la recherche

Acronyme : **PIPAC EstoK 01**
Code de la recherche : **P160951J**

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance de la grossesse par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Titre complet de la Recherche : **Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) dans la carcinose gastrique : Étude randomisée de phase II.**

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : Fax :

3. Identification de la personne présentant une grossesse

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
(n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Date de naissance : |__|__| |__|__| |___|___|__|__|

Date de signature du consentement : |__|__| |__|__| |2|0|__|__|

Date de randomisation : |__|__| |__|__| |2|0|__|__|

Groupe de randomisation : ☐ Chimiothérapie en IV + PIPAC
☐ Chimiothérapie en IV

Date des dernières règles : |__|__| |__|__| |2|0|__|__|

Et/ou date début de grossesse : |__|__| |__|__| |2|0|__|__|

Cas particulier d'une exposition paternelle : ☐ Oui ☐ Non

Accord de la femme enceinte pour recueillir les informations sur la grossesse : ☐ Oui ☐ Non ☐ NA

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser unités OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite

Autre (préciser) :

4. Antécédents maternels

Médicaux :	**Chirurgicaux :**

Obstétricaux : |__|__| geste |__|__| pare

Préciser si fausse couche, grossesse extra-utérine, interruption de grossesse (médicale ou volontaire), mort *in utero*, malformation congénitale, pathologie congénitale/néonatale non malformative, … (*nombre, date et nature/raison si applicable).*

PARTIE RESERVEE AU PROMOTEUR
REFERENCE INTERNE :
REC-DTYP-0192

5. Médicament(s) expérimental (aux) administré(s) ou non pendant la grossesse ou s'il s'agit une exposition paternelle					
Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
Cisplatine	………	………	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Adriblastine	………	………	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Autre, précisez ……………………………	………	………	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

6. Procédures et actes ajoutés par la recherche *(Barrez l'encadré si procédures et actes non réalisés)*	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la grossesse	Au cours de la grossesse
Chirurgie exploratrice (cœlioscopie) avant randomisation	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
PIPAC N°1 ☐ Non applicable	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
PIPAC N°2 ☐ Non applicable	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
PIPAC N°3 ☐ Non applicable	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
Chirurgie exploratrice (cœlioscopie) finale	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐

7. Traitement comparateur = chimiothérapie IV [préciser quel(s) médicament(s)] avant la survenue de l'EIG
(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale *	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Dates d'administration *(du jj/mm/aa au jj/mm/aa)*	En cours (2)	Indication	***Action prise*** *0 : poursuite sans modification de la posologie 1 : arrêt 2 : diminution de la posologie 3 : augmentation de la posologie 4 : ne sais pas*	***Causalité de l'EIG*** *0 : non lié au médicament 1 : lié au médicament 2 : ne sais pas*
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			

(2) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

Agents chimiothérapiques:

1. Acide Folinique
2. Doxorubicine (Caelyx)
3. Adriamycine (Adriablastine)
4. Gemcitabine (Gemzar)
5. Bévacizumab (Avastin)
6. Irinotecan (Campto)
7. Campécitabine (Xeloda)
8. Mitomycine C (MMC)
9. Carboplatine (Paraplatine)
10. Oxaliplatine (Eloxatine)
11. Cetuximab (Erbitux)
12. Paclitaxel (Taxol)
13. Cisplatine
14. Pemetrexed (Almita)
15. Daunorubicine (Tomox)
16. 5-Fluoro Uracile (5-FU)
17. Docetaxel (Taxotere)
18. Topotecan (Hycamtin)
19. Autres

8. Médicament(s) concomitants administré(s) au moment de la grossesse

(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ ***Oui*** ☐ ***Non applicable)***

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

9. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

☐ Autres examens. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

10. Grossesse en cours ☐ (envoyer par mail un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale)

ou issue de la grossesse ☐ (compléter ci-dessous)

Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J

☐ Fausse couche
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Grossesse extra-utérine
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Interruption de grossesse → Raison :
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Accouchement : ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :

Souffrance fœtale : ☐ Non ☐ Oui, précisez :

Mort-né : ☐ Non ☐ Oui, précisez :

Placenta normal : ☐ Oui ☐ Non, précisez :

Liquide amniotique : ☐ Clair ☐ Autre, précisez :

Anesthésie : ☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune

11. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et l'envoyer par mail)

Sexe : ☐ Masculin ☐ Féminin

Poids : |__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm

APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____

Malformation(s) congénitale(s) : ☐ Non ☐ Oui, précisez :

Pathologie(s) congénitale(s)/néonatale(s) non malformative(s) : ☐ Non ☐ Oui, précisez :

Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : ☐ Non ☐ Oui, précisez : ☐ Non applicable

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature :	Nom : Signature :	

17.4 Reporting special situation PIPAC form

Direction de la Recherche Clinique, de l'Innovation, des relations avec les universités et les organismes de recherche (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Fiche de signalement d'une situation spéciale**	Unité de Recherche Clinique Hôpital Saint-Louis 75010 Paris 1, avenue Claude Vellefaux 75010 Paris Tél : 01 42 49 97 42

Dès la prise de connaissance par l'investigateur d'une situation spéciale, celui-ci doit la reporter dans le cahier d'observation électronique (eCRF).

Code projet : P160951J EudraCT : 2018-004755-20 Nom et N° du centre : ……	Titre complet de la recherche : "Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in gastric carcinomatosis. Phase II randomized study" (« PIPAC EstoK 01 ») Notification initiale : ☐ Rapport de suivi : ☐ **N° du suivi** |__|__|

1) Informations sur le patient (si applicable) : ☐ NA

Référence de la personne :

|__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg

Taille : |__|__|__| cm

Date de naissance : |__|__| |__|__| |__|__|__|__|
jj mm aaaa

Age : |__|__|__|ans

Date de Cœlioscopie : |__|__| |__|__| |__|__|__|__|
jj mm aaaa

Date d'inclusion/randomisation :
|__|__| |__|__| |__|__|__|__|
jj mm aaaa

☐ Groupe expérimental (PIPAC + Chimiothérapie IV)

☐ Groupe contrôle (Chimiothérapie IV)

2) Description du (ou des) DM concerné(s) :

- Nom : ……
- Fabricant : ……
- Numéro de lot / numéro de série : ……
- Date de début d'utilisation : |__|__| |__|__| |_2_|_0_|__|__|
- Date de fin d'utilisation : |__|__| |__|__| |_2_|_0_|__|__|
- Date de péremption : |__|__| |__|__| |_2_|_0_|__|__|
- Autre précision, si nécessaire : ……

3) Type de situation spéciale / cocher la(les) case(s) correspondante(s) :

☐	Abus	*Utilisation excessive intentionnelle, persistante ou sporadique d'un médicament ou d'un dispositif qui est accompagnée par des réactions physiques ou psychologiques nocives.*
☐	Erreur	*Toute utilisation non conforme involontaire survenant à un niveau quelconque dans le circuit du médicament ou du dispositif (de la fabrication, à la prescription et à l 'administration du dispositif). Cette définition inclut les erreurs causées par tout acte de soin, d'ordre chirurgical ou de diagnostic.* ☐ à risque ☐ potentielle ☐ avérée
☐	Mésusage	*Situation où le médicament ou le dispositif est intentionnellement utilisé de manière inadaptée sans suivre les règles de conformité d'utilisation du produit (ex : voie d'administration/posologie ou indication différentes de celles listées dans le document de référence).*
☐	Surdosage	*Toute administration d'une quantité donnée (ou diffusée, relarguée, ...) lors d 'une administration, ou de manière cumulative, qui est au-dessus de la dose maximale recommandée selon les règles de conformité ou d'utilisation du produit. Un jugement clinique devra toujours être appliqué.* ☐ surdosage réel : dû à une quantité brute trop importante ☐ surdosage relatif : dû aux facteurs prédisposants du patient tels que insuffisance rénale, hypoalbuminémie
☐	Incident *(article R5212-15 du Code de la Santé Publique)*	*Réaction nocive et non voulue se produisant lors de l'utilisation d'un dispositif médical conformément à sa destination ; réaction nocive et non voulue résultant d'une utilisation d'un dispositif médical ne respectant pas les instructions du fabricant ; tout dysfonctionnement ou toute altération des caractéristiques ou des performances d'un dispositif médical ; toute indication erronée, omission et insuffisance dans la notice d'instruction, le mode d'emploi ou le manuel de maintenance.* ☐ mineur : fonction-information dégradée, sans risque pour le patient ☐ majeur/sévère : DM inutilisable sans risque pour le patient ☐ critique : information dégradée ou/et DM inutilisable, avec risque pour le patient)
☐	Autre	Préciser :

Description de la situation :
Date de survenue : |__|__| |__|__| |_2_|_0_|__|__|
Date de détection (si différente) : |__|__| |__|__| |_2_|_0_|__|__|

.....
.....
.....
.....
.....
.....

La situation spéciale décrite a-t-elle induit un/des Evènement(s) Indésirable(s) (EI) ?

☐ Non

☐ Oui, préciser : .....

☐ Grave : merci de remplir un formulaire de notification d'EIG ☐ Non grave : merci de compléter l'eCRF

Si oui, dès la prise de connaissance par l'investigateur d'une situation spéciale ayant conduit à la survenue d'un EIG, cette fiche de signalement doit être dûment complétée, signée, jointe au formulaire de notification d'EIG correspondant et retournée sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre les documents au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail.
NB : Ne pas transmettre par télécopie les documents initialement transmis avec succès par courriel pour éviter les doublons.

4) Mesures correctives prises :

.....
.....
.....
.....
.....
.....

Une déclaration de pharmaco/matériovigilance a-t-elle été réalisée ? ☐ Non ☐ Oui, le |__|__| |__|__| |_2_|_0_|__|__|

Le fabricant a-t-il été informé de l'incident ?
☐ donnée manquante
☐ non, aucune information n'a été transmise au fabricant
☐ oui, une information a été transmise au fabricant le _ _ / _ _ / _ _ _ _ (jj/mm/aaaa) (cf. pièce jointe si disponible)

5) Devenir de la situation spéciale :
☐ résolue ☐ en cours investigation* ☐ persistante* *(*suivi requis)*

6) Conclusion : Selon l'investigateur, la cause de cette situation spéciale est :
☐ Confusion de dénomination commerciale/commune
☐ Défaut d'information (mode d'emploi, notice, circuit...)
☐ Défaut qualité (conditionnement, étiquetage, aspect, ...)
☐ Comportement du patient
☐ Autre : préciser : .....

7) Auteur de la déclaration
Investigateur ☐ Autre ☐
Nom du déclarant :

Tel/Fax :
Mail :
Nom, date et signature de l'investigateur :

17.5 Include the SCP

Specify here that the SCP must have been obtained from the EMA website (http://www.ema.europa.eu/ema/), or from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php); otherwise, use the SCP from Vidal.

17.6 Expected toxicity and dose adjustments:

1. Toxicité(s) liée(s) à l'épirubicine et adaptation de dose

Sa prescription ne doit pas être faite en cas d'insuffisance cardiaque ou coronarienne symptomatique. C'est la raison pour laquelle une échographie cardiaque avec mesure de la fraction d'éjection est à demander à l'inclusion. Les cycles de traitement peuvent être espacés en cas de manifestations toxiques et notamment de toxicité hématologique. En cas d'atteinte hépatique (bilirubinémie ≥ 35 micromoles/l), la dose administrée sera réduite selon le schéma suivant:

Bilirubine (micromoles/l)	Dose à administrer (en pourcentage de la dose théorique)
>50	0 (ne pas administrer)
35-50	50
<35	100

En cas d'insuffisance rénale, la dose administrée sera réduite, compte tenu de la possibilité d'accumulation

2. Toxicité(s) liée(s) au cisplatine et au 5FU et adaptation de dose

Un bilan biologique est réalisé avant tout début de cure. La chimiothérapie ne sera administrée que si : PNN > 1500/mm^3 Plaquettes > 100 000 mm^3 Toutes toxicités muqueuses (mucite, conjonctivite, rhinite, diarrhée) revenues à un grade < 1, syndrome Mains Pieds revenu à un grade < 1, Asthénie revenue à un grade < 1 Après reprise de la chimiothérapie, les doses seront celles présentes dans les tableaux ci-dessous :

Toxicité avant chaque cycle					
	Grade (NCI CTC V4)	Adaptation du cisplatine	Adaptation de 5FU	Adapatation epirubicine	Adapatation capecitabine
Toxicité hématologique					
1 000/ mm3 < PNN < 1500/ mm3	2	100%	100%	100%	100%
50 000/ mm3< plaquettes < limite inférieure de la normale	1 ou 2	100%	100%		
PNN < 1 000/ mm3	3 ou 4	75%	75%	75% si gr 4	75% si gr 4
Plaquettes < 50 000 /mm3	3 ou 4	75%	75%	75% si gr 4	75% si gr 4
Toxicité non hématologique					
Mucite ou diarrhée	3 ou 4	75%	75%	75% si gr 4	75% si gr 3 50% si gr 4
Syndrome main pied avec ulcération	3 ou 4	100%	75%		Cf ci dessous
Asthénie	3 ou 4	75%	75%		
Conjonctivite	3	100%	75%		
Rhinite	2	100%	75%		

En cas de toxicité rénale (clairance de la créatinine < 50 ml/min) la 2ème injection de cisplatine sera annulée et la créatininémie contrôlée aussi souvent que nécessaire jusqu'à normalisation.

Pour le 5FU comme pour le Cisplatine la chimiothérapie ne sera prescrite qu'après récupération à un grade < 1. Si les toxicités réapparaissent malgré la réduction de dose, diminuer la dose de 50% de la dose initiale. Si persistance malgré cette diminution, arrêt du traitement.

3. Toxicité(s) liée(s) à la capecitabine et adaptation de dose

La toxicité due à l'administration de Xeloda peut être contrôlée par un traitement symptomatique et/ou par une modification de la posologie (interruption du traitement ou réduction de la dose). Une fois la dose réduite, celle-ci ne devra pas être augmentée

ultérieurement. Pour les toxicités considérées comme ne pouvant probablement pas devenir graves ou menacer le pronostic vital, par exemple l'alopécie, l'altération du goût, les modifications unguéales, le traitement peut être poursuivi à la même dose, sans diminution ni interruption. Les doses de Xeloda non prises en raison de la toxicité ne sont pas remplacées. Les modifications posologiques recommandées en cas de toxicité figurent dans le tableau suivant :

Toxicité Grades*	Modification de la dose au cours d'un cycle de traitement	Ajustement posologique pour le cycle suivant /dose (% de la posologie initiale)
□ Grade 1	Maintenir la posologie	Maintenir la posologie
□ Grade 2		
- 1ére apparition	Interrompre le traitement jusqu'à retour au grade 0-1	100 %
- 2e apparition		75 %
- 3e apparition		50 %
- 4e apparition	Arrêter le traitement définitivement	Sans objet
□ Grade 3		
- 1ére apparition	Interrompre le traitement jusqu'à retour au grade 0-1	75 %
- 2e apparition		50 %
- 3e apparition	Arrêter le traitement définitivement	Sans objet
□ Grade 4		
- 1ére apparition	Arrêter le traitement définitivement	50 %
	ou Si le médecin juge qu'il est souhaitable dans l'intérêt du patient de continuer, interrompre le traitement jusqu'à retour au grade 0-1	
- 2e apparition	Arrêter le traitement définitivement	Sans objet

Hématologie : Les patients présentant une neutropénie < 1,5 x 10^9/L et/ou une thrombocytopénie < 100 x 10^9/L à l'initiation du traitement ne doivent pas être traités par Xeloda. Si des analyses biologiques, non programmées, effectuées au cours d'un cycle de traitement, révèlent une neutropénie inférieure à 1,0 x 10^9/L ou que le taux de plaquettes chute à une valeur inférieure à 75 x 10^9/L, le traitement par Xeloda doit être interrompu.

4. Toxicité(s) liée(s) au FOLFOX, FOLFIRI ou association FOLFOXIRI et adaptation de dose

Les produits seront préparés selon les Bonnes Pratiques en Chimiothérapie. Les traitements seront pris dans le stock habituel de la pharmacie. L'utilisation de G-CSF prophylactique est associée (4 à 5 jours à débuter à J4).
Adaptation des doses: En cas de réduction de doses nécessaire, les posologies réduites seront maintenues ultérieurement. En cas de toxicité de grade 4 récurrente à l'identique malgré une diminution de dose, l'investigateur et le patient peuvent discuter ensemble d'un éventuel arrêt du traitement. Les doses d'acide folinique ne sont jamais modifiées, sauf arrêt si allergie. L'adaptation des doses du protocole FOLFOXIRI suivra les RCP du produit :
- Concernant les toxicités hématologiques :

SELON LE BILAN BIOLOGIQUE À J15

NFS à J15	RETARD DE CYCLE	RÉDUCTION DE DOSE		
		Irinotécan (CPT-11)	Oxaliplatine (L-OHP)	LV5FU
PNN ≥ 1.5 x 10^9 /l et plaq ≥ 100 x10^9 /l	Pas de retard de cycle	Pas de réduction de dose		
PNN < 1.5 x 10^9 /l	Retarder le traitement jusqu'à PNN ≥ 1500 (jusqu'à J22 ou J29 si nécessaire) et discuter reprise du cycle avec G-CSF	1er épisode : réduction de dose à 150 mg/m² 2ème épisode : maintien de la dose à 150 mg/m² 3ème épisode: arrêt de l'irinotécan	1er épisode : pas de réduction de dose 2ème épisode : réduire la dose à 60 mg/m²	1er épisode : pas de réduction de dose
Plaquettes < 100 x10^9 /l	Retarder le traitement jusqu'à récupération (plaquettes ≥100x10^9 /l). En cas de non récupération à J29, arrêt du traitement	1er épisode : pas de réduction de dose 2ème épisode : diminuer la dose à 150 mg/m²	1er épisode : diminuer la dose à 60 mg/m² 2ème épisode : maintien de la dose réduite 3ème épisode : arrêt de l'oxaliplatine	1er épisode : diminuer la dose de la perfusion continue de 25% (900 mg/m²/j)

SELON LA TOXICITÉ HEMATOLOGIQUE PENDANT L'INTERCURE (NADIR)

ÉVENEMENTS	REDUCTION DE DOSE AU CYCLE SUIVANT
-Neutropénie fébrile isolée -Neutropénie grade 4 de plus de 7 jours -Infection avec neutropénie de grade 3-4 concomitante	1er épisode : réduire la dose d'irinotécan à 150 mg/m² et ajouter G-CSF 2ème épisode : réduire aussi le FU continu à 2000mg/m² et la dose d'oxaliplatine à 60 mg/m² 3ème épisode : arrêt de la chimiothérapie préopératoire
Thrombopénie grade 3-4	1er épisode : réduire la dose d'oxaliplatine à 60 mg/m² 2ème épisode : réduire aussi la dose d'irinotécan à 150 mg/m² et la dose de 5-FU continu de 25 % 3ème épisode : arrêt de la chimiothérapie préopératoire

- **Concernant les toxicités digestives :**

ÉVENEMENTS	REDUCTION DE DOSE AU CYCLE SUIVANT
-Diarrhée grade 3-4 isolée ou -Diarrhée + fièvre et/ou neutropénie grade 3-4	1er épisode : réduire la dose d'irinotécan à 150 mg/m² 2ème épisode : réduire aussi la dose d'oxaliplatine à 60 mg/m² et réduire la dose de 5FU continu de 25 % (900 mg/m²/j) 3ème épisode : arrêt de l'irinotécan
Diarrhée résistante (> 48 h) en dépit des hautes doses de lopéramide	Pas de réduction de dose d'irinotécan ni d'oxaliplatine ni de 5-FU après récupération sauf si diarrhée de grade 3-4, ou diarrhée + fièvre et/ou neutropénie de grade 3-4

- Concernant les mucites ou l'érythrodermie palmoplantaire. En cas de toxicité grade 3-4, une réduction de posologie de 25 % du 5-FU continu (900 mg/m²/j) sera réalisée pour les cures suivantes.

- Concernant la toxicité cardiaque. En cas d'angine de poitrine ou d'infarctus du myocarde, le traitement par 5-FU sera définitivement arrêté.

- Concernant la neuropathie périphérique. Pour limiter le risque de neurotoxicité, il est conseillé d'utiliser le gluconate de Calcium 1g et le sulfate de Magnésium 1g en 15 minutes juste avant la perfusion d'oxaliplatine, perfusions à répéter aux mêmes doses à la fin de la perfusion d'oxaliplatine. La dose d'oxaliplatine peut être adaptée selon le tableau ci-dessous:

Toxicité	Durée de la toxicité		
	≤ 7 jours	> 7 jours et < 14 jours	Persistante entre les cycles*
Paresthésies/dysesthésies sans altération fonctionnelle (grade 1 NCI)	Aucune modification	Aucune modification	Aucune modification
Paresthésies/dysesthésies avec altération fonctionnelle mais ne gênant pas les activités de la vie quotidienne (grade 2 NCI)	Aucune modification	Aucune modification	65 mg/m²
Paresthésies/dysesthésies avec douleurs ou altération fonctionnelle gênant les activités de la vie quotidienne (grade 3 NCI)	65 mg/m²	65 mg/m²	Arrêt
Paresthésies/dysesthésies persistantes, invalidantes	NA	NA	Arrêt
TOXICITE AIGUE : dysesthésies laryngo-pharyngées ou autre toxicité aiguë invalidante	Allonger la durée de la perfusion suivante à 6 heures Ajouter (si ce n'était pas déjà fait) 1g de Gluconate de Calcium et 1g de sulfate de magnésium 15mn avant la perfusion d'oxaliplatine, perfusions à renouveler à la fin de la perfusion d'oxaliplatine		

*Si l'oxaliplatine est arrêté pour neurotoxicité, l'irinotécan et le 5-FU seront poursuivis.

- Concernant l'élévation de la bilirubine: En cas d'élévation de la bilirubine, il est nécessaire d'en rechercher la cause et de prévoir, si médicalement indiquée, une adaptation de dose de l'irinotécan.

ÉVENEMENTS	REDUCTION DE DOSE AU CYCLE SUIVANT
27 µmol/l (16 mg/L)< Bilirubine = 50 µmol/l	réduire la dose d'irinotécan à 50%
Bilirubine > 50 µmol/l (29 mg/L)	Arrêter l'irinotécan

- Concernant l'anémie: En cas d'anémie (par ex. taux d'hémoglobine 11 g/dl), des transfusions ou un traitement par érythropoïétine sera mis en route à la discrétion du clinicien. **Dans la mesure où il a été observé chez certains patients traités par érythropoïétine une augmentation de fréquence d'accidents thromboemboliques notamment lorsque le taux d'hémoglobine est supérieur à 13 g/dl, une surveillance accrue de la numération sanguine sera effectuée. D'autre part, comme avec tout facteur de croissance, on ne peut pas exclure totalement le risque de croissance tumor**ale avec les érythropoïétines.

- Concernant la prophylaxie des nausées et vomissements

Nausées et vomissements aigus : avant l'administration de l'oxaliplatine à J1 une association de corticoïdes (30 mn avant) (si absence de diabète), d'anti 5HT3 (sétron, 15 min avant) et d'aprépitant (Emend®) est recommandée

Rappel: l'aprépitant (125 mg/80 mg) est un substrat, un inhibiteur modéré et un inducteur du CYP3A4. Il est également inducteur du CYP2C9. Il faut donc réduire la dose de corticoïdes avec l'aprépitant :
- la dose de déxaméthasone IV et orale doit être réduite de 50% ;
- la dose de méthylprednisolone IV et orale doit être réduite de 25% (Aapro MS, Walko CM Annals of oncology 2010).

L'efficacité des contraceptifs hormonaux peut être réduite pendant l'administration d'aprépitant et au cours des 28 jours qui suivent. Des méthodes contraceptives alternatives ou complémentaires doivent être utilisées au cours du traitement par aprépitant et pendant les 2 mois qui suivent la dernière prise d'aprépitant.

o Nausées et vomissements retardés : Une prévention des nausées et vomissements retardés est recommandée, utilisant l'aprépitant et des corticoïdes. En cas de diabète, l'utilisation des corticoïdes est déconseillée.

- Concernant l'alopécie: Les casques hypothermiques sont possibles et efficaces pendant le Campto®, mais l'oxaliplatine administré au préalable peut augmenter le désagrément du casque.

- Concernant les autres toxicités: Toute autre toxicité grade 2, exceptées l'anémie et l'alopécie, pourra justifier une réduction de dose si indiquée médicalement, par exemple réduction de l'irinotécan à 150 mg/m2 et/ou d'oxaliplatine à 60 mg/m^2 et/ou le 5-FU de 25 % en fonction du type de toxicité.

- Traitement du syndrome cholinergique : En cas de syndrome cholinergique aigu (hypersudation, hypersalivation, troubles visuels, larmoiements, myosis, crampes abdominales, diarrhée précoce) une injection par voie sous cutanée de 0,25mg d'atropine sera réalisée à titre curatif (sauf si contreindication : glaucome à angle fermé, dysurie sévère sur hypertrophie prostatique) puis ensuite à titre préventif aux cures suivantes, sauf contre-indication pour les patients traités par irinotécan.

- Traitement de l'extravasation :
Des réactions sévères liées à une extravasation de l'irinotécan ou d'oxaliplatine ont été rapportées (Kretzschmar A et al. 2010). Les recommandations d'ordre général en cas d'extravasation sont les suivantes :
- arrêter immédiatement la perfusion,
- ne pas retirer l'aiguille ou le cathéter,
- aspirer par la même aiguille le maximum de produit infiltré,
- appliquer de la glace sur la zone infiltrée pendant 15 à 20 minutes toutes les 4 à 6 heures pendant 72 h,
- corticothérapie locale,
- vérifier régulièrement le site infiltré pendant les jours suivants, afin de vérifier si quelque traitement est nécessaire. Ne pas hésiter à prendre un avis chirurgical en cas de doute.

- Traitement des diarrhées tardives

o Traitement prophylactique : Aucun traitement prophylactique ne doit être donné, en particulier le lopéramide ne doit pas être administré de façon prophylactique. Cependant les patients doivent arrêter tout traitement laxatif et éviter les aliments et les boissons qui sont connus pour accélérer le transit intestinal. o Traitement curatif :
 dès la 1ère selle liquide ou molle le patient doit prendre immédiatement 2 capsules de lopéramide per os puis 1 capsule toutes les 2 h pendant au moins 12 h après la dernière selle liquide, sans dépasser un traitement total d'une durée de 48 h. La prise de boissons riches en électrolytes sera indiquée aussi au patient pendant tout l'épisode de diarrhée.

 En cas de persistance de la diarrhée plus de 48 h en dépit du traitement recommandé par lopéramide, une antibiothérapie à large spectre (fluoroquinolone) sera entreprise pour une durée systématique de 7 jours et après avis médical.

 En cas de diarrhée persistante et/ou sévère, le patient sera hospitalisé pour réhydratation parentérale et le lopéramide sera remplacé par un autre traitement antidiarrhéique laissé au choix du médecin investigateur.

 L'antibiothérapie orale par fluoroquinolone doit aussi être prescrite en cas de diarrhée grade 4 ou de diarrhée associée à une neutropénie de grade 3-4 ou à une fièvre.

 Les patients qui présentent des vomissements ou une fièvre ou un performance status > 2 concomitant à la diarrhée seront hospitalisés rapidement pour support parentéral. Le lopéramide et la fluoroquinolone doivent être prescrits au patient dès sa sortie d'hôpital afin qu'il ait l'un et l'autre à sa disposition dès l'apparition d'une diarrhée.

- En cas d'allongement de l'intervalle QT/QTc. Si l'ECG montre un allongement de l'intervalle QT/QTc > 500 msec, le traitement par oxaliplatine devra être arrêté et une surveillance ECG rapprochée et adaptée (en continue) en milieu hospitalier devra être mise en place jusqu'à ce que l'avis d'un cardiologue soit obtenu.

17.7 Echelle EQ-5D-RL

Pour chaque rubrique, veuillez cocher UNE case, celle qui décrit le mieux votre s
AUJOURD'HUI.

MOBILITÉ

Je n'ai aucun problème pour me déplacer à pied ❑
J'ai des problèmes légers pour me déplacer à pied ❑
J'ai des problèmes modérés pour me déplacer à pied ❑
J'ai des problèmes sévères pour me déplacer à pied ❑
Je suis incapable de me déplacer à pied ❑

AUTONOMIE DE LA PERSONNE

Je n'ai aucun problème pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes légers pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes modérés pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes sévères pour me laver ou m'habiller tout(e) seul(e) ❑
Je suis incapable de me laver ou de m'habiller tout(e) seul(e) ❑

ACTIVITÉS COURANTES *(exemples: travail, études, travaux domestiques, activités familiales ou loisirs)*

Je n'ai aucun problème pour accomplir mes activités courantes ❑
J'ai des problèmes légers pour accomplir mes activités courantes ❑
J'ai des problèmes modérés pour accomplir mes activités courantes ❑
J'ai des problèmes sévères pour accomplir mes activités courantes ❑
Je suis incapable d'accomplir mes activités courantes ❑

DOULEURS / INCONFORT

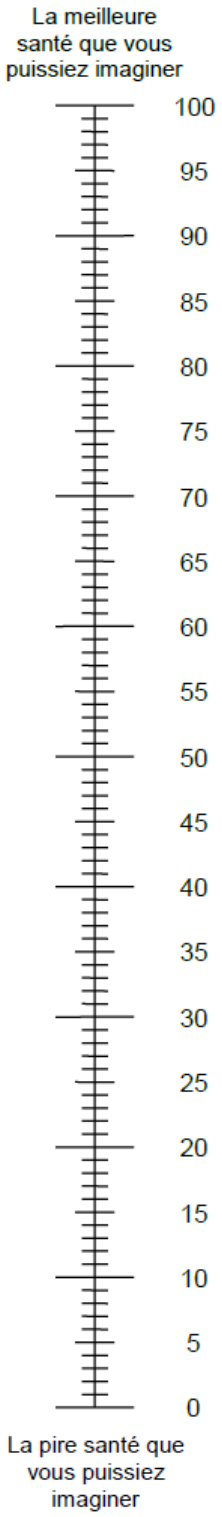
Je n'ai ni douleur ni inconfort ❑
J'ai des douleurs ou un inconfort léger(ères) ❑
J'ai des douleurs ou un inconfort modéré(es) ❑
J'ai des douleurs ou un inconfort sévère(s) ❑
J'ai des douleurs ou un inconfort extrême(s) ❑

ANXIÉTÉ / DÉPRESSION

Je ne suis ni anxieux(se) ni déprimé(e) ❑
Je suis légèrement anxieux(se) ou déprimé(e) ❑
Je suis modérément anxieux(se) ou déprimé(e) ❑
Je suis sévèrement anxieux(se) ou déprimé(e) ❑
Je suis extrêmement anxieux(se) ou déprimé(e) ❑

- Nous aimerions savoir dans quelle mesure votre santé est bonne ou mauvaise AUJOURD'HUI.
- Cette échelle est numérotée de 0 à 100.
- 100 correspond à la meilleure santé que vous puissiez imaginer. 0 correspond à la pire santé que vous puissiez imaginer.
- Veuillez faire un X sur l'échelle afin d'indiquer votre état de santé AUJOURD'HUI.
- Maintenant, veuillez noter dans la case ci-dessous le chiffre que vous avez coché sur l'échelle.

VOTRE SANTÉ AUJOURD'HUI = ☐



17.8 Echelle QLQ-C30

EORTC QLQ-C30 (version 3)

Nous nous intéressons à vous et à votre santé. Répondez vous-même à toutes les questions en entourant le chiffre qui correspond le mieux à votre situation. Il n'y a pas de « bonne » ou de « mauvaise » réponse. Ces informations sont strictement confidentielles.

Merci de préciser :

Vos initiales : ⌊_____⌋

Date de naissance (jour/mois/année) : ⌊__/__/____⌋

La date d`aujourd`hui (jour/mois/année) : 31⌊__/__/____⌋

		Pas du tout	Un peu	Assez	Beaucoup
1.	Avez-vous des difficultés à faire certains efforts physiques pénibles comme porter un sac à provisions chargé ou une valise ?	1	2	3	4
2.	Avez-vous des difficultés à faire une longue promenade ?	1	2	3	4
3.	Avez-vous des difficultés à faire un petit tour dehors ?	1	2	3	4
4.	Êtes-vous obligé(e) de rester au lit ou dans un fauteuil pendant la journée ?	1	2	3	4
5.	Avez-vous besoin d'aide pour manger, vous habiller, faire votre toilette ou aller aux toilettes ?	1	2	3	4

Au cours de la semaine passée :		**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
6.	Avez-vous été gêné(e) pour faire votre travail ou vos activités de tous les jours ?	1	2	3	4
7.	Avez-vous été gêné(e) dans vos activités de loisirs ?	1	2	3	4
8.	Avez-vous eu le souffle court ?	1	2	3	4
9.	Avez-vous ressenti de la douleur ?	1	2	3	4
10.	Avez-vous eu besoin de repos ?	1	2	3	4
11.	Avez-vous eu des difficultés à dormir ?	1	2	3	4
12.	Vous êtes-vous senti(e) faible ?	1	2	3	4
13.	Avez-vous manqué d'appétit ?	1	2	3	4
14.	Avez-vous eu des nausées (mal au cœur) ?	1	2	3	4
15.	Avez-vous vomi ?	1	2	3	4

Passez à la page suivante S.V.P.

Au cours de la semaine passée :	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
16. Avez-vous été constipé(e) ?	1	2	3	4
17. Avez-vous eu de la diarrhée ?	1	2	3	4
18. Étiez-vous fatigué(e) ?	1	2	3	4
19. Des douleurs ont-elles perturbé vos activités quotidiennes ?	1	2	3	4
20. Avez-vous eu des difficultés à vous concentrer sur certaines choses, par exemple, pour lire le journal ou regarder la télévision ?	1	2	3	4
21. Vous êtes-vous senti(e) tendu(e) ?	1	2	3	4
22. Vous êtes-vous fait du souci ?	1	2	3	4
23. Vous êtes-vous senti(e) irritable ?	1	2	3	4
24. Vous êtes-vous senti(e) déprimé(e) ?	1	2	3	4
25. Avez-vous eu des difficultés à vous souvenir de certaines choses ?	1	2	3	4
26. Votre état physique ou votre traitement médical vous ont-ils gêné(e) dans votre vie familiale ?	1	2	3	4
27. Votre état physique ou votre traitement médical vous ont-ils gêné(e) dans vos activités sociales (par exemple, sortir avec des amis, aller au cinéma...) ?	1	2	3	4
28. Votre état physique ou votre traitement médical vous ont-ils causé des problèmes financiers ?	1	2	3	4

Pour les questions suivantes, veuillez répondre en entourant le chiffre entre 1 et 7 qui s'applique le mieux à votre situation

29. Comment évalueriez-vous votre état de santé au cours de la semaine passée ?

1	2	3	4	5	6	7
Très mauvais						Excellent

30. Comment évalueriez-vous l'ensemble de votre qualité de vie au cours de la semaine passée ?

1	2	3	4	5	6	7
Très mauvaise						Excellente

17.9 Echelle QLQ-STO22

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had problems eating solid foods?	1	2	3	4
32. Have you had problems eating liquidised or soft foods?	1	2	3	4
33. Have you had problems drinking liquids?	1	2	3	4
34. Have you had discomfort when eating?	1	2	3	4
35. Have you had pain in your stomach area?	1	2	3	4
36. Have you had discomfort in your stomach area?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
39. Have you had acid indigestion or heartburn?	1	2	3	4
40. Have you had trouble with belching?	1	2	3	4
41. Have you felt full up too quickly after beginning to eat?	1	2	3	4
42. Have you had trouble enjoying your meals?	1	2	3	4
43. Has it taken you a long time to complete your meals?	1	2	3	4
44. Have you had a dry mouth?	1	2	3	4
45. Did food and drink taste different from usual?	1	2	3	4
46. Have you had trouble with eating in front of other people?	1	2	3	4
47. Have you been thinking about your illness?	1	2	3	4
48. Have you worried about your weight being too low?	1	2	3	4
49. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4
51. Have you lost any hair?	1	2	3	4
52. Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4

17.10 Dindo Classification

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.