TITLE "Multicenter, randomized clinical trial to evaluate the efficacy and safety of hyperthermic intraperitoneal chemotherapy (HIPEC) with Mitomycin C associated with surgery in the treatment of locally advanced colorectal carcinoma."

Nº EudraCT: 2015-001801-15

Code protocol: FCO-HIP-2015-01

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GENERAL INFORMATION

A. Test Identification: Title: “Multicenter, randomized clinical trial to evaluate the efficacy and safety of hyperthermic intraperitoneal chemotherapy (HIPEC) with Mitomycin C associated with surgery in the treatment of locally advanced colorectal carcinoma.” EudraCT No.: 2015-001801-15 Protocol code: FCO-HIP-2015-01 Version: 1.3 of January 31, 2018

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PROTOCOL SUMMARY

1.0 Development phase: Phase III

1.1. Study disease: colon and rectal cancer

1.2 Objectives of the study:

1.2.1 Main objective: To evaluate the efficacy of hyperthermic intraperitoneal chemotherapy (HIPEC) with Mitomycin C associated with extended cytoreductive surgery by locoregional control (LC) in the treatment of locally advanced colorectal carcinoma (cT4).

1.2.2 Secondary objectives: 1) To assess the effect on overall survival (OS) of adding HIPEC with Mitomycin C to extended surgery at 12 months and 3 years.

2) To assess the effect on disease-free survival (DFS) of adding HIPEC with Mitomycin C to extended surgery at 12 months and 3 years.

3) Evaluate the safety (morbidity and mortality) of adding HIPEC to extended surgery for cT4NxM0 colorectal carcinoma.

4) Evaluate the quality of life in patients who have received HIPEC associated with extended surgery in colorectal carcinoma.

1.3. Study design: Clinical, multicenter, randomized and open trial to evaluate the efficacy and safety of hyperthermic intraperitoneal chemotherapy (HIPEC) with Mitomycin C associated with extended cytoreductive surgery in the treatment of locally advanced colorectal carcinoma.

1.4 Description of treatment groups: Experimental Group: Cytoreductive surgery + target organ surgery + HIPEC Control Group: Cytoreductive surgery + target organ surgery

1.5. Number of patients / Allocation to treatment: N= 200. Assignment to treatment 100/100.

1.6. Variables:

1.6.1 Efficiency: - Primary variable: Locoregional control (LC) in months (time to locoregional recurrence/carcinomatosis) and rate of locoregional disease control (LC%) (% of patients without signs of locoregional recurrence) at 12 months and 3 years .

Secondary variables: 1) Peri- and post-operative morbidity using the CTCAE adverse event classification system and peri-operative mortality, up to 30 and 90 days post-intervention. 2) Overall survival (OS) in months and survival rate (% OS at 12 months, 3 years). 3) Disease-free survival (DFS) in months and disease-free period rate (% DFS at 12 months, 3 years). 4) Effect on the quality of life of patients using the QLQ-C30 and QLQ-CR29 questionnaires.

1.6.2 Security: The safety of both treatment groups will be assessed as a secondary endpoint as follows: • Peri- and post-operative morbidity through the CTCAE adverse event classification system and peri-operative mortality, up to 30 and 90 days post-intervention. • Incidence and severity of adverse events (AEs).

1.7. Study Population: Patients diagnosed with cT4NxM0 locally advanced colorectal cancer. 1.7.1 Selection criteria: Patients who meet ALL the inclusion criteria and NO exclusion criteria will be prospectively included in the study

Inclusion criteria:

1) Patients of both sexes, aged ≥18 years and ≤75 years.

2) Adenocarcinoma of the colon, sigmoid and recto-sigma junction that present cT4a/b according to the seventh TNM edition of the American Joint Committee on Cancer (AJCC).

3) Lymph node extension: N0, the presence of N1/2 according to AJCC TNM 7th edition is allowed as long as they can be resected.

4) Metastatic extension: M0.

5) Karnofsky index >70 or Performance status ≤2.

6) Informed consent duly completed.

Exclusion criteria:

1) Presence of metastases (M1), in case of liver or peritoneal metastases at the time of surgery, the patient will be excluded from the trial and treated according to their new stage.

2) Presence of unresectability criteria.

3) Urgent intervention for obstruction or perforation if there is tumor removal, previous interventions such as referrals without removal of the primary tumor or drainage of collections prior to scheduled surgery will be accepted.

4) Extraperitoneal rectal cancer (medium-low) (avoiding neoadjuvant alterations).

5) Coexistence of another malignant neoplastic disease (synchronous tumors of the upper colon and rectum are accepted as long as the stage is equal to or less than the tumor treated).

6) Severely impaired liver, kidney, or cardiovascular function.

7) Intolerance to treatment.

8) Administration of chemotherapy prior to the trial (use of neoadjuvant therapy is ruled out).

9) Women in gestational period or lactating.

1.7.2 Study withdrawal criteria 1. Withdrawal of the patient's informed consent. 2. Protocol deviation. If the researchers consider it appropriate from the clinical point of view due to worsening of symptoms. 3. Administrative decision made by the researchers, sponsor or a regulatory authority. 4. Loss of contact during follow-up. 5. Serious adverse event (SAE) or clinically relevant. 6. Unexpected Serious Adverse Reaction (SARI)

1.8. Treatment under study: Drug: Mitomycin C Dose: 30 mg/m2 in 4 liters of infusion fluid Guideline: single dose Pharmaceutical Form: Powder for injectable solution. The product, before reconstitution, is a purple-blue, crystalline powder. Administration Route: Intraperitoneal Pharmacotherapeutic group: Mitomycin ATC code: L01DC03

1.9. Administration of treatments: Experimental group: will receive intraperitoneal Mitomycin C in hyperthermia in 4000cc of 1.5% dextrose for 60 minutes after completing cytoreductive and target organ surgery.

1.10. Study Procedures: The total expected duration of each patient in the study will be 36 months and the following visits and procedures will be performed:

Cronogram visits	**Selection**	**Basal**	**V1**	**1º-7º PO day**	**Month 1**	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**	**Month 30**	**Month 36**
Patient selection	X											
Preoperative evaluation	X											
Consent inform	X											
Treatment and surgery			X									
Clinical evaluation	X			X	X	X	X	X	X	X	X	X
Tumoral Markers: CEA and CA 19.9	X					X	X	X	X	X	X	X
Blood analytic	X			X	X							
Morbidity analysis		X	X	X	X	X	X	X	X	X	X	X
CT/MRI	X						X	X	X	X	X	X
QLQ-C30/CR29		X			X		X	X		X		X

Table 1. Visits.

1.11. Statistic analysis:

1.11.1. Sample size determination

The calculation of the sample size of the clinical trial is based on the regional control rate of the disease (LC rate %) at 36 months after the intervention (main end point). We have assumed that the proportion of patients in the treatment group with local control of the disease (LC rate %) at 36 months is 82% (peritoneal recurrence in 18% at 36 months) and that the proportion of patients in the group control with local control of the disease (LC rate %) at 36 months is 64% (peritoneal recurrence in 36% at 36 months). With this estimation (error α = 0.05, power = 0.80, double tail) the calculated sample size is 190 patients, 95 patients in each arm. Contemplating an approximate loss of 5% of patients, the definitive N is 200 patients.

1.11.2. Statistical methods - Descriptive analysis for quantitative variables by calculating arithmetic means (m) and typical or standard deviations (SD); and for qualitative variables by calculating counts of percentages and proportions (%). -Determination of the goodness of fit to a normal distribution (normal data) using the Shapiro-Wilk test. The homogeneity of variances will also be checked using Levene's test. -Comparison of the mean values of the quantitative variables between the two groups using Student's t-test (parametric test) or Mann-Whitney U-test (non-parametric test). -Comparison of proportions between the different groups using chi-square tests for contingency tables; in the case of 2 x 2 tables, the chi-square statistic with Yates' correction will be used, and when some expected frequency is ≤ 5, Fisher's exact test will be applied.

-Association between quantitative variables by calculating Pearson's linear correlation coefficients (parametric test) or Spearman's correlation (non-parametric test), as appropriate. - Analysis of locoregional control rate, disease-free time and overall survival will be based on the intention-to-treat population. Survival curves will be studied using the Kaplan-Meier method and comparison using Log-Rank to analyze the effect of the different factors on survival. - Multiple logistic regression analysis to evaluate the risk factors in the recurrence of the disease as well as mortality. Hazard ratios and their corresponding 95% confidence intervals will be estimated using Cox models. - Previous analyzes will be stratified according to: laparoscopic approach yes/no, closed/open or semi-open HIPEC, K-Ras mutation (yes/no), definitive pT (T3b/T4a/T4b), pN0/N1 lymph node involvement /N2 and degree of differentiation (good/moderate/little-signet ring-mucinous).

All hypothesis tests will be two-sided. And in all the statistical tests, "significant" values will be considered those whose confidence level is 95% ($p<0.05$).

1.12. Workplan The expected total duration of the trial is 5 years from the inclusion of the first patient: • Preparation of the protocol. Application for authorization to the AEMPS. Evaluation request to the CEIm: 2 months. • Start of the study: the first patient is expected to be included: November 2015. • Patient recruitment/inclusion period: 24 months from the end of opening of centers. • Treatment period: each included patient will receive treatment for: 1 day. • Follow-up period per patient: 36 months. • Intermediate analysis with the first 100 patients recruited. • Completion of the study: May 2022. Statistical analysis and writing of the final report: September 2022.

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1. BACKGROUND AND JUSTIFICATION OF THE STUDY

1.1 Background

Colorectal cancer (CRC) is one of the most frequent neoplasms in our environment, with a growing trend observed in the last decade. According to data from the International Agency for Research on Cancer (IARC), in Spain in 2008, 16,896 cases of colon and rectal cancer were diagnosed in men and 12,005 in women, with an overall incidence of 45.7 cases per 100,000 inhabitants per year. . This represents the second most frequent neoplasm in our country with a mortality rate of 21%, being the second most frequent cause of death from cancer in our country (1).

The prognosis of colon and rectal cancer is primarily established using the TNM or Dukes staging systems. These classification systems have their limitations, especially when most patients are included in stages II and III, which are very heterogeneous categories. Other pathological variables have been investigated as prognostic tools in these stages, such as lymphatic and venous invasion, histological type, degree of differentiation, peritumoral lymphocytic infiltration, resection margin status, number of resected nodes, and the tumor location. The most relevant histological characteristic (pT4) has also been recognized as an important prognostic factor in locoregional recurrence and survival (2). Shepherd et al.(3) established transserous invasion with local peritoneal involvement (LPI) as a significant risk factor for peritoneal recurrence in colorectal cancer, establishing type 3 LPI (tumor present on the peritoneal surface with inflammatory reaction, mesothelial hyperplasia and/or erosion or ulceration) and LPI 4 (free tumor cells on the peritoneal surface with evidence of ulceration in the visceral peritoneum) as corresponding to pT4 in the TNM classification with equal risk of locoregional recurrence.

In this sense, if we assess the prognosis of patients with pT4, we observe that overall survival at 5 years is 20% (for T1-2 it is 91%), obtaining a prognosis similar to that of patients with N2 and M1. This leads us to consider the pT category by itself, as a prognostic factor in survival. The same does not occur with other typified prognostic factors such as lymphatic and venous invasion in the piece. In this way, the TNM categories are distorted in survival figures, because, when we stratify in pT4, there is a variation in the survival of patients with stage II from 80% at 5 years, it decreases to 50%. % at 5 years when pT4 is present. In stage III the effect is similar, survival is 56% at 5 years, reducing with the presence of pT4 to 30% at 5 years, being in N2 37% at 5 years. In stage IV, pT4 is not a prognostic factor in survival (2).

The addition of adjuvant therapy in stages II is controversial today, being applicable to those patients with risk factors of which the one that determines a worse prognosis is the presence of category T4; In this way, several studies have observed that patients with T4N0M0 (II) have a worse prognosis than T1 N1 M0 (III), so lymph node invasion is not only the main prognostic factor, as postulated in the TNM and Dukes classifications. Until now, only a few retrospective studies consider the addition of adjuvant therapy to be beneficial in patients with stage II and pT4 based on 5-FU (2).

Hompes et al. (4) through their epidemiological study in patients with T4 assessed the probability of peritoneal recurrence in 379 patients undergoing surgery for pT4 colorectal cancer and stages II and III, ruling out T4 with distant metastases. For these patients, local recurrence and appearance of peritoneal carcinomatosis was 15.6% at 12 months after surgery, while for T3 it was 4.5% at 12 months ($p = 0.008$). Locoregional recurrence in patients with T3 was 20% at 5 years, while for T4 it was 40% at 5 years, of which in 62% of them it was the only location of metastasis. It is this 26% of all T4 who could have benefited from adjuvant

treatment with hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of surgical resection, because survival in those patients who recurred with peritoneal carcinomatosis was only 6% at 5 years (4).

1.2 Preclinical and clinical experience: HIPEC acquired its expansion thanks to the application and diffusion of peritonectomy procedures associated with HIPEC in the treatment of peritoneal metastases in colorectal cancer, which was developed by P.H Sugarbaker (5). This procedure allows complete cytoreduction of all visible lesions in the abdomen, after which the application of intraperitoneal chemotherapy in hyperthermia allows high concentrations of chemotherapy to achieve destruction of microscopic lesions with minimal systemic adverse effects.

The application of this therapeutic modality has made it possible to significantly improve survival in patients with carcinomatosis of colonic origin, passing globally from 23 months and 13% at 5 years with the best systemic chemotherapy up to 62 months and 51% at 5 years. , supporting these results until reaching levels of evidence IA (6-8) . Today, new concepts are being studied in the application of intraperitoneal chemotherapy, either as early postoperative administration (EPIC), as neoadjuvant or adjuvant, or the application of intraperitoneal chemotherapy in hyperthermia as chemoprophylaxis or adjuvant in locally advanced or high-risk tumors. develop carcinomatosis, a widespread concept in gastric carcinoma.

In this line, the French group of the Gustave Roussy Institute investigates (9) the performance of a second-look surgery and HIPEC for those patients with a high risk of developing peritoneal carcinomatosis of colonic origin 12 months after the first intervention. Of these, 56% had peritoneal disease at the time of the second surgery and could be treated by cytoreductive surgery and HIPEC, increasing their survival compared to those who did not receive HIPEC. After this preliminary study, the Prophylochip study was launched in France to compare standard follow-up with second-look surgery + HIPEC.

This same concept of applying HIPEC in adjuvant therapy has also been more extensively studied for locally advanced gastric tumors with serosal involvement, improving the prognosis of these patients (10).

Tentes et al. (11) conducted a study on the application of HIPEC with Mitomycin C or oxaliplatin on 41 patients and EPIC on 63, with a 3-year survival rate of 100% in the HIPEC group, with the patients included being T3 and T4 and finding a clear superiority of HIPEC in terms of survival compared to EPIC.

Sammartino et al. (12) propose something similar in their study, the application of HIPEC with oxaliplatin for mucinous T3/T4 colorectal carcinoma and compare it with a control group with standard surgery. They only recruited 25 patients in the experimental group with a recurrence at 36 months of 4% compared to 22% in the control group, with the reservation that targeting surgery was performed in the experimental group (surgery extended to omentectomy, oophorectomy bilateral in postmenopausal women and appendectomy) and in the control group no.

The suggestion by Hompes et al. (4) and also by Baratti et al. (13) to add HIPEC as an adjuvant or as a second look to risk groups is not new, but it has not been extensively studied, only a few pilot studies have been able to conclude survival benefits and, above all, safety of the treatment provided. In this sense, only one long prospective study carried out by Noura et al. (14) explored the effects of HIPEC in patients with colorectal carcinoma with positive peritoneal lavage as prevention for their locoregional recurrence, concluding that HIPEC with Mitomycin C seemed effective in preventing peritoneal recurrence and prolonging survival, achieving a reduction from 50% in the non-HIPEC group to 12% in the HIPEC group with no increase in morbidity and mortality.

1.3 Justification of the study: The approach of our study is aimed at the search for an effective and safe treatment to prevent the appearance of peritoneal disease after tumor resection, increasing locoregional control of the disease, disease-free period and survival, in patients with pT4NxM0 colorectal carcinoma. with the use of hyperthermic intraperitoneal chemotherapy (HIPEC) with Mitomycin C and surgery extended to target organs, establishing the differences with the control group (surgery extended to target organs). Thus, HIPEC meets the expectation of a locally aggressive treatment with minimal side effects that has also provided clear benefits in terms of survival in patients with advanced cancer disease.

This would suggest the potential benefit that HIPEC would provide as adjuvant or chemoprophylaxis to improve disease-free survival and therefore overall survival in patients with locally advanced colorectal carcinoma (pT4) with little associated morbidity. This option is attractive for professionals who face peritoneal recurrences every day after performing extremely complex surgeries, but its application is difficult today due to the increase that it would entail in economic cost and resources, which leads us to the need of its administration and evaluation within clinical trials, which, in order to obtain adequate power and significance, need to be multicenter, carried out in centers with specialized Oncology Surgery Units and extensive experience in peritoneal carcinomatosis that perform cytoreduction procedures and HIPEC.(15-18).

This set of Oncology Surgery Units focused on the treatment of disseminated peritoneal disease (GECOP Group under the auspices of the SEOQ) is the field of implementation of the study that we present. The GECOP group was born to respond to the need to find a union between those groups that embarked on the treatment of disseminated peritoneal disease with peritonectomy and HIPEC procedures, each of the constituent Units becoming points of reference for referral of highly complex patients such as those who are eligible for said treatment (digestive, gynecological or peritoneal carcinomatosis). The application of HIPEC as adjuvant therapy in locally advanced carcinomas with risk of subsequent development of carcinomatosis is a topic that is always on the rise, both within our national group of GECOP and in the international community, where it is currently the trend of the different trials clinics launched by different groups of advanced cancer surgery.

2. OBJECTIVES OF THE STUDY

2.1. Main goal

To evaluate the efficacy of hyperthermic intraperitoneal chemotherapy (HIPEC) with Mitomycin C associated with extended cytoreductive surgery by locoregional control (LC) in the treatment of locally advanced colorectal carcinoma (cT4).

2.2. Secondary Objectives

1) To assess the effect on overall survival (OS) of adding HIPEC with Mitomycin C to extended surgery at 12 months and 3 years.

2) To assess the effect on disease-free survival (DFS) of adding HIPEC with Mitomycin C to extended surgery at 12 months and 3 years.

3) To assess the safety (morbidity and mortality) of adding HIPEC to extended surgery for cT4 colorectal carcinoma.

4) Evaluate the quality of life in patients who have received HIPEC associated with extended surgery in colorectal carcinoma.

3. STUDY DESIGN

3.1 Overview of study design

Clinical, multicenter, randomized and open trial to evaluate the efficacy and safety of hyperthermic intraperitoneal chemotherapy (HIPEC) with Mitomycin C associated with extended cytoreductive surgery in the treatment of locally advanced colorectal carcinoma.

3.2 Study variables

3.2.1 Efficacy Variables Main variable: Locoregional control (LC) in months (time to locoregional recurrence/carcinomatosis) and rate of locoregional disease control (LC%) (% of patients without signs of locoregional recurrence) at 12 months and 3 years.

Secondary variables: 1) Peri- and post-operative morbidity using the CTCAE adverse event classification system and peri-operative mortality, up to 30 and 90 days post-intervention. 2) Overall survival (OS) in months and survival rate (% OS at 12 months, 3 years). 3) Disease-free survival (DFS) in months and disease-free period rate (% DFS at 12 months, 3 years). 4) Effect on the quality of life of patients using the QLQ-C30 and CR29 questionnaire.

3.2.2 Security Variables

The safety of both treatment groups will be assessed as a secondary endpoint as follows:

• Peri- and post-operative morbidity through the CTCAE adverse event classification system and peri-operative mortality, up to 30 and 90 days post-intervention.

• Incidence and severity of adverse events (AEs).

3.3 Randomization and masking

It is planned to include a total of 200 patients who will be divided into two groups:

• Treatment Group: 100 patients

• Control Group: 100 patients

Patients will be randomly assigned to one of two treatment groups in a 1:1 ratio, using a random assignment list generated by a dedicated computer system.

This is an open study, so blinding is not necessary. As it is an application of intraoperative treatment, it is not possible to mask the patient or the doctor, due to the inherent characteristic of the surgical technique and to the fact that the patient systematically receives a hospital discharge report with a description of the surgical procedure carried out. cape. Knowledge of the applied technique does not influence the variables under study.

3.4 Participating centers

Spanish centers with the capacity to perform HIPEC (see Annex 3).

3.5 Work plan

The expected total duration of the trial is 60 months, from the inclusion of the first patient:

• Preparation of the protocol. Application for authorization to the AEMPS. Evaluation request to the CEIm: 2 months

• Start of the study: After obtaining authorization from the AEMPS and a favorable opinion from the CEIm, the first patient is expected to be included in 2015.

• Patient recruitment/inclusion period: 2 years from the opening of the last center

• Treatment period: each included patient will receive treatment in a single session.

• Follow-up period per patient: 36 months after finishing treatment.

• An interim study will be carried out after the recruitment of patient 100.

• Completion of the study (last contact of the last patient included): 2022.

• Statistical analysis and writing of the final report: two months after the last patient.

The expected total duration of each patient in the study is 36 months. Each patient will make a total of 14 visits, in the following sequence (see table 1):

● Selection period.

● Inclusion and randomization period: baseline.

● Treatment period.

● Follow-up period: 1st, 2nd, 3rd, 4th and 7th postoperative days, 1, 3, 6, 12, 18, 24, 30 and 36 months.

The trial visits are described below:

Screening Visit (VS)

- (Day -15): Inform the patient about the study and obtain their Informed Consent. Evaluation of inclusion and exclusion criteria. Clinical history and physical examination, vital signs, laboratory samples, pre-anesthetic study and radiological study.

- Baseline inclusion and randomization visit (V0): Review of the inclusion and exclusion criteria, randomization. Quality of life questionnaires will be provided to patients.

- Visit 1 (V1): surgical procedure and treatment.

- Visits V2-V6 (1st, 2nd, 3rd, 4th and 7th postoperative days): the first visits will be hospitalized, where safety variables, laboratory tests and physical examination will be evaluated.

- Visits V7-V14 (at one month, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months): performing clinical examination, laboratory samples (month 1), tumor markers (month 3, month 6, month 12, month 18, month 24, month 30 and month 36) and evaluation by CT/MRI thoraco-abdomino-pelvic imaging tests (6, 12, 18, 24, 30, 36).

3.6 Termination and interruption of the study

The study will be terminated when the last patient included in the trial has made the last follow-up visit or withdraws from it for the reasons indicated in Section 4.3. ”Criteria for termination and withdrawal from the study by the subjects”.

If the study is terminated prematurely or is suspended, the sponsor must promptly inform the investigators, the participating center and the regulatory authorities of the termination or suspension and the reasons for it. In addition, the promoter must promptly inform the CEIm and provide the justification for the termination or suspension, as specified by the relevant legal requirements.

Whether the study is completed or terminated prematurely, the sponsor must ensure that trial reports are prepared and provided to regulatory agencies as specified by applicable legal requirements.

Whether the study is completed or terminated prematurely, the sponsor must ensure that trial reports are prepared and provided to regulatory agencies as specified by applicable legal requirements.

4. STUDY POPULATION

4.1 General characteristics

Patients diagnosed with locally advanced adenocarcinoma of the colon and upper rectum.

4.2 Selection criteria

Patients who meet ALL the inclusion criteria and NO exclusion criteria will be prospectively included in the study.

Inclusion criteria:

1) Patients of both sexes, aged ≥18 years and ≤75 years.
2) Adenocarcinoma of the colon, sigmoid and recto-sigma junction that present cT4a/b according to the seventh TNM edition of the American Joint Committee on Cancer (AJCC).
3) Lymph node extension: N0, the presence of N1/2 according to AJCC TNM 7th edition is allowed as long as they can be resected.
4) Metastatic extension: M0.
5) Karnofsky index >70 or Performance status ≤2.
6) Informed consent duly completed.

Exclusion criteria:

1) Presence of metastases (M1), in case of liver or peritoneal metastases at the time of surgery, the patient will be excluded from the trial and treated according to their new stage.
2) Presence of unresectability criteria.
3) Urgent intervention for obstruction or perforation if there is tumor removal, previous interventions such as referrals without removal of the primary tumor or drainage of collections prior to scheduled surgery will be accepted.
4) Extraperitoneal rectal cancer (medium-low) (avoiding neoadjuvant alterations).
5) Coexistence of another malignant neoplastic disease (synchronous tumors of the upper colon and rectum are accepted as long as the stage is equal to or less than the tumor treated).
6) Severely impaired liver, kidney, or cardiovascular function.
7) Intolerance to treatment.
8) Administration of chemotherapy prior to the trial (use of neoadjuvant therapy is ruled out).
9) Women in gestational period or lactating.

4.3 Subject termination and withdrawal criteria

A subject will be considered to have completed the trial at the last scheduled follow-up visit.

Any subject who does not follow the study procedure, has not followed up, or for whom no further information is available since the date of withdrawal or last contact will be classified as “withdrawal” from the study.

The reasons for the withdrawal will be analyzed in full accordance with the principles of Bioethics, in terms of guaranteeing the rights of patients and autonomous and informed decision.

Patients may withdraw at any time throughout the study, for any reason, and without prejudice to future medical treatment.

Although patients can withdraw without having to explain why, as soon as a patient has decided to do so, the investigators will try to contact subjects who do not return for scheduled visits or check-ups and establish that the patient's decision is a choice. informed, as well as to check to what extent the patient might be willing to continue to participate in the study on a limited basis, e.g. whether they would be willing to continue to be contacted or seen, in order to obtain follow-up information .

In the event of premature withdrawal, the investigator will perform all examinations scheduled for the end-of-study visit.

The relevant information for the withdrawal will be documented in the CRD. The investigator will indicate whether the decision to withdraw from the study was made by the patient or by the investigator and indicate which of the following possible reasons led to withdrawal:

1. Patient request and withdrawal of informed consent.
2. Protocol violation or deviation.
3. If the researchers consider it appropriate, from the clinical point of view, due to worsening of the patient's disease state.
4. Administrative decision made by the investigators, sponsor or a regulatory authority.
5. Loss of contact during follow-up.
6. Unexpected Serious Adverse Reaction (SARI).
7. Serious Adverse Event (SAE).
8. Any adverse or intercurrent event that is considered intolerable by the patient or incompatible with the continuation of the study according to the investigator.
9. Suspected pregnancy or positive pregnancy test result. Any suspected pregnancy should be promptly followed by a confirmatory serum pregnancy test.

A clear distinction must be made between subjects who withdraw from the study due to SAE/ARGI and those who do so for other reasons. Investigators will follow subjects who withdraw due to an SAE/RAGI until the event has resolved.
In case of withdrawal from the study, patients will be treated according to existing protocols and at the discretion of the investigator.

4.4 Patient substitution
Retired patients will not be replaced.

4.5 Identification of patients
All patients who have signed the informed consent will receive a code number, which will be used to identify them throughout the study.

Patients will be identified by a code that includes the center number followed by a chronological inclusion number for that center (XX-YY).

5. TREATMENT OF THE STUDY
5.1 General description of the investigational medicinal product
The investigational medicinal product (IM) is defined as "a pharmaceutical form of an active substance or placebo that is studied or used as a reference in a clinical trial, including products with a marketing authorization when used or combined (formulated or packaged) differently from the authorized form, or when used for an unauthorized indication, or to obtain more information about the authorized form".

In the present study, the MI consists of Mitomycin. It is an antitumor antibiotic that is activated in tissues, behaving as an alkylating agent that disorganizes deoxyribonucleic acid (DNA) in cancer cells, through the formation of complexes with DNA, and also acts by inhibiting cell division of cancer cells. interfering with DNA biosynthesis.

Drug: Mitomycin
Dose: 30mg/ M2 /4 Liter of perfusion fluid (dextrose 1.5%)
Guideline: Single intraoperative dose

Pharmaceutical Form: Powder for injectable solution. The product, before reconstitution, is a purple-blue, crystalline powder.
Administration Route: Intraperitoneal
Pharmacotherapeutic group: Mitomycin
ATC code: L01DC03

5.2 Manufacturing and labeling

Mitomycin C will be manufactured and supplied by the Hospital Pharmacy Service of each participating center, following the Good Manufacturing Practices (GMP).
The containers used for the test will be identified by means of a label, in accordance with current GMP, GCP guidelines and current national legal requirements.

5.3 Shipping, storage and accounting

The investigational medication will be received by the investigator or the pharmacist (if applicable) and they will be responsible for handling and storing it safely and appropriately.

The MI must be stored in the Pharmacy Service of each participating center, in a closed facility, with access limited to authorized personnel of the center and under physical conditions that meet the specific requirements of the investigational product.

The investigator or pharmacist should keep current temperature records to document proper storage during the course of the trial.

When requested by the researcher, the responsible staff of the Pharmacy Service will prepare the investigational medication in accordance with the current protocol, ensuring optimal safety conditions at all times. Once the medication is prepared, it will be sent to the operating room for intraoperative administration.
The investigator must ensure that MI is administered only to patients participating in this study.

The MI should not be used outside the context of this study protocol. The investigator or authorized personnel are required to document the receipt, dispensing, and return of all IMs received during this study.

The medication should not be used after the expiration date printed on the outer container.

At the end of each patient's participation in the study, all remaining MI must be returned to the Promoter for an accurate accounting of MI delivered and returned.

A record should be kept of receipt, use, return, loss, or other disposition of IM. The investigator or, where applicable, the pharmacist, must sign the reception forms. The investigator or pharmacist, or other appropriately trained person at the investigational site, must keep records on delivery to the site, inventory at the site, use by each patient, and return to the IM Promoter. These records should include dates, quantities, lot numbers, and unique code numbers assigned to IMs and patients. Investigators must keep records documenting that patients received the doses specified in the protocol. In addition, they must reconcile all IM received from the Promoter. It is the investigator's responsibility to explain any discrepancies in the MI accounting.

All remaining MI will be collected and returned to the Promoter for destruction at the end of the study.

5.4 Administration of investigational medication (experimental group only)

Mitomycin C will be administered intraoperatively intraperitoneally in continuous perfusion by means of a hyperthermia machine for 60 minutes at a temperature of 42-43ºC, in a solution of 4000cc of 1.5% dextrose at a dose of 30mg/M2. (HIPEC).

Once cytoreduction has been completed, including a complete cytoreduction of the tumor plus removal of target organs such as the greater omentum, ileocecal appendix, round ligament and bilateral oophorectomy in postmenopausal women, hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) with Mitomycin C will be administered. The solution containing the cytostatic it will be administered in the abdominal cavity (Mitomycin C at a dose of 30 mg/m2 for every 4 liters of 1.5% dextrose solution) for 60 minutes. During the perfusion time, which will be maintained at an intra-abdominal temperature between 42-43ºC by means of a heat exchanger, all internal anatomical structures of the peritoneal cavity will be uniformly exposed to chemotherapy. Two infusion pumps will send the chemotherapy solution with a high flow rate (1l/min) into the abdomen through two infusion catheters and will extract it through four suction drains placed in the abdominal cavity (subdiaphragmatic and pelvic). Through a smoke evacuator, the air will be extracted under a plastic cover that will isolate the bell-shaped cavity, thus avoiding possible contamination of the air in the operating room by cytotoxic aerosols. When the intraoperative infusion is finished, all fluid will be aspirated from the abdomen.

5.5 Dose Modification and Management of Toxicity

The dose will depend on the calculation of body surface at a rate of 30mg/M2/4 liters. Patients with nephropathy, liver disease or pregnant women will not be included, so no dose modification is required.

5.6 Risks and precautions in the use of investigational medication

The possible adverse reactions and the contraindications, warnings and precautions for use are collected in the Technical Data Sheet (FT) of Mitomycin C.

5.7 Concomitant medication

It is defined as any medication other than the investigational medication of the trial.

Concomitant treatments will be recorded in the patient's CRF and the name of the drug, the total daily dose, the route of administration, the start and end dates, as well as the reason for administration will be specified.

Patients receiving any prohibited concomitant medication or any medication in a dosage that is not permitted and cannot be discontinued or reduced will not be eligible to participate in the study.

5.7.1 Concomitant medication allowed

The following concomitant treatments are allowed during the study:

- Any chronic treatment of the patient will be allowed.
- Thus, the administration of adjuvant therapy will be allowed through schemes based on fluoropyrimidines (5-FU, Capecitabine), platinum (Oxaliplatin).
- Possibility of adjuvant radiotherapy if the protocol of the center or in a multidisciplinary session is decided.

• Monoclonal antibodies such as bevacizumab and cetuximab.

5.7.2 Concomitant medication prohibited

The treatments prohibited throughout the study are:

• Neoadjuvant chemotherapy/radiotherapy treatment.

5.7.3 Interactions with other treatments

The following treatments are not recommended during the entire active treatment phase:

• They do not exist.

5.8 Overdose

There is no known antidote for Mitomycin C overdose.

In case of overdose, the patient should be closely monitored and any manifested toxicities treated.

5.9 Modification of treatment regimens due to adverse events

In the case of AA, its impact on the patient and the relationship with the administered investigational drug will be assessed.

5.10 Destruction of investigational medication

At the end of the trial, unused investigational products will be disposed of.

If destruction takes place at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, site policy. Destruction must be properly documented.

6. STUDY PROCEDURES

6.1 Procedures for the selection and inclusion of patients

Before carrying out any study activity, patients will be asked to read and sign an informed consent form that has been approved by a Drug Research Ethics Committee (CEIm) and that meets the regulatory requirements. Patients will be given time to review any study-related information provided by the investigator. As part of the informed consent procedure, patients will be allowed to ask the investigator any questions about the possible risks and benefits of participating in the study.

To participate in the study, patients must meet ALL inclusion criteria, and NO exclusion criteria.

Once the selection criteria are confirmed and the patient is considered suitable to participate in the study, they will be randomly assigned to a treatment group.

The investigator will document in the CRF the fulfillment of the selection criteria of the subjects considered to participate in the study. In addition, you must maintain a list of inclusion and patient identification codes.

6.2 Procedures per visit

SELECTION VISIT (VS) (Day -15)
The following evaluations and studies will be carried out:

• Inform the patient about the trial and obtain their informed consent in writing, signed and dated.
• Document demographic data.
• Evaluation of the selection criteria.
• Document the patient's medical history.
• Perform a physical examination (including height, weight, vital signs).
• Blood sample to carry out complete blood count, biochemistry, coagulation, tumor markers (according to normal clinical practice).
• Radiological study by thoraco-abdomino-pelvic MRI/CT (PET or other imaging technique will be allowed if necessary for staging) according to usual clinical practice).
• Check the patient's current methods of birth control and perform serum pregnancy testing for women of childbearing potential (if applicable).
• Concomitant medications or non-pharmacological therapies, including the reason for administration.
• Make an appointment for the next visit.

BASELINE OR INITIAL VISIT (V0)
The baseline visit can take place up to 15 days after the screening visit when all the results of the screening evaluation are available.

The following evaluations will be carried out:
• Hospitalization.
• Reassessment of inclusion and exclusion criteria.
• Perform a physical examination (including height, weight, vital signs).
• Inclusion in the trial, randomization and treatment assignment.
• Document the patient's medical history.
• Blood sample.
• Quality of life questionnaire QLQ-C30 and QLQ CR29.

VISIT 1 (Surgical intervention and treatment)
• Surgical treatment and HIPEC.
• Record of possible adverse events.

VISIT 2 (1st postoperative day)
• Clinical examination.
• Analytics (biochemistry, blood count and coagulation).
• Record of possible adverse events.

VISIT 3 (2nd postoperative day)
• Clinical examination.
• Analytics (biochemistry, blood count and coagulation).
• Record of possible adverse events.

VISIT 4 (3rd postoperative day)
• Clinical examination.
• Analytics (biochemistry, blood count and coagulation).
• Record of possible adverse events.

VISIT 5 (4th postoperative day)
- Clinical examination.
- Analytics (biochemistry, blood count and coagulation).
- Record of possible adverse events.

VISIT 6 (7th postoperative day)
- Clinical examination.
- Analytics (biochemistry, blood count and coagulation).
- Record of possible adverse events.

VISIT TO THE HOSPITAL DISCHARGE
Carried out by the principal investigator and collaborators on the hospitalization floor:
- Clinical examination.
- Analytics (biochemistry, blood count and coagulation).
- Record of possible adverse events.
- Record of hospital stay (days).
- Record of postoperative morbidity.

VISIT 7 (1 month post-treatment)
- Clinical examination.
- Analytics (biochemistry, blood count and coagulation).
- Record of possible adverse events.
- Questionnaire QLQ-C30 and CR29.

VISIT 8 (3 months post-treatment)
- Clinical examination.
- CEA and CA 19.9 tumor markers.
- Record of possible adverse events.

VISIT 9 (6 months post-treatment)
- Clinical examination.
- CEA and CA 19.9 tumor markers.
- CT/MRI thoraco-abdomino-pelvic.
- Record of possible adverse events.
- Questionnaire QLQ-C30 and CR29.

VISIT 10 (12 months post-treatment)
- Clinical examination.
- CEA and CA 19.9 tumor markers.
- CT/MRI thoraco-abdomino-pelvic.
- Record of possible adverse events.
- Questionnaire QLQ-C30 and CR29.

VISIT 11 (18 months post-treatment)
- Clinical examination.
- CEA and CA 19.9 tumor markers.
- CT/MRI thoraco-abdomino-pelvic.
- Record of possible adverse events.

VISIT 12 (24 months post-treatment)
- Clinical examination.

• CEA and CA 19.9 tumor markers.
• CT/MRI thoraco-abdomino-pelvic.
• Record of possible adverse events.
• Questionnaire QLQ-C30 and CR29.

VISIT 13 (30 months post-treatment)
• Clinical examination.
• CEA and CA 19.9 tumor markers.
• CT/MRI thoraco-abdomino-pelvic.
• Record of possible adverse events.

VISIT 14 (36 months post-treatment)
• Clinical examination.
• CEA and CA 19.9 tumor markers.
• CT/MRI thoraco-abdomino-pelvic.
• Record of possible adverse events.
• Questionnaire QLQ-C30 and CR29.

6.3 Biological samples

6.3.1 Blood samples.
During the trial, several extractions will be performed to determine the blood count, biochemistry, coagulation and serum levels of tumor markers CEA and Ca19.9 (extractions in accordance with routine clinical practice).
Estas determinaciones se realizarán en el Servicio de Análisis Clínicos de cada hospital participante.

The extraction, storage and confidentiality of the same will be carried out in accordance with the regulations for the use and storage of biological samples contained in Title V of Law 14/2007, of July 3, on biomedical research and the REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of April 27, 2016 regarding the protection of natural persons with regard to the processing of personal data and the free circulation of these data and Organic Law 3/2018, of 5 December, Protection of Personal Data and guarantee of digital rights.

7. SAFETY ASSESSMENT / ADVERSE EVENTS
7.1 Safety assessment
The principal investigator will be responsible for detecting and documenting adverse events (AEs) throughout the study.

It is the responsibility of the principal investigator to report all AEs in the CRF, both observed by him or spontaneously reported by the participants, regardless of the relationship with the investigational medication.

All AEs must be reported during all phases of the study and followed until resolution or until an adequate explanation is found, even if the patient has completed study treatment. Likewise, reports will be made periodically on the AEs that occurred during the study, including an evaluation of causality, severity and intensity.

Patients will be informed of the possible adverse reactions of the investigational medication through the Patient Information Sheet, as well as their commitment to report any adverse event they experience. They will be provided with a contact form with the study investigators for this purpose. At all study visits, patients will be questioned about the presence of new AAs or about the evolution of pre-existing ones.

7.2 Definition of adverse event

An adverse event (AE) is any occurrence that is detrimental to the health of a patient or clinical trial subject treated with a drug, even if it is not necessarily related to said treatment.
Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbation of a pre-existing one) temporarily associated with the use of an investigational product. In the case of marketed medicines, the lack of expected benefits (ie, lack of efficacy), abuse and misuse are also included.

AAs include the following:

• Significant or unexpected worsening or exacerbation (either an increase in the frequency of onset or intensity of the disease) of a pre-existing chronic or intermittent disease, as well as of the disease or indication under study.
• New diseases detected or diagnosed after administration of the investigational product, even though they may have been present before the trial began.
• Signs, symptoms or clinical sequelae of a suspected interaction.
• Signs, symptoms or clinical sequelae of a suspected overdose of the investigational product or concomitant medication.
• Lack of efficacy, understood as a significant failure of the expected pharmacological or biological action.

AEs may encompass events that occurred before or after treatment as a result of protocol-specified procedures (eg, modification of the subject's previous treatment or testing).
Pregnancies occurring during the trial will also be considered AA and will be followed up.

7.3 Definition of serious adverse event

A serious adverse event (SAE) is any experience that suggests a significant risk, contraindication, side effect, or precaution.

This is an AA that, at any dose, meets at least one of the following criteria:

• Causes death (death is a consequence, not an event, so death cannot be considered as an identification of the adverse event).
• Is life-threatening (the term “life-threatening” refers to an event that posed an immediate risk of death to the patient at the time it occurred and not an event that hypothetically could have caused death if it had been more intense).
• Requires hospital admission or extension of current hospitalization (in general, “hospitalization” means that the subject has been admitted, at least one night, in the hospital or in the emergency room, for observation or to receive treatment that could not have been performed in the doctor's office or on an outpatient basis Complications that occur during hospitalization are AE if they prolong hospitalization or meet any other severity criteria, in this case the event being an SAE.

- Causes significant or permanent disability/incapacity (this definition does not include experiences that may be considered less medically relevant, such as headache, nausea, vomiting, diarrhoea, flu, or accidental trauma (e.g., sprained ankle), which may interfere with or prevent the development of the functions of daily life and that, however, do not constitute a substantial alteration of these).
- Causes a congenital abnormality or birth defect.

For notification purposes, suspected AEs that are considered medically important will also be treated as serious, even though they do not meet the above criteria, or require an intervention to prevent any of the consequences indicated above, and those that lead to the transmission of an infectious agent through the medicine.

Pregnancies occurring during the trial will also be considered SAEs.

7.4 Definition of adverse reaction

An adverse reaction (AR) is any harmful and unintended reaction to an investigational drug, regardless of the dose administered.

Unlike an AE, in the case of an AR there is a suspected causal relationship between the drug under investigation and the adverse event.

7.5 Definition of serious and unexpected adverse reaction

An unexpected adverse reaction (RAI) is any AR whose nature, intensity or consequences do not correspond to the information regarding the drug (eg the Investigator's Manual in the case of an investigational drug not authorized for marketing, or the File Product technique in the case of an authorized drug).

The unexpected character of an adverse reaction is based on the fact that it has not been previously observed and will not be based on what could be anticipated based on the pharmacological properties of the drug. The concept of Serious Unexpected Adverse Reaction (SARI) has been described above and in Section 7.3 of the protocol.

7.6 Analytical abnormalities and other abnormal evaluations

The results of the laboratory tests will be recorded in the CRD.

Laboratory abnormalities or other assessments (e.g., vital signs) that are abnormal and clinically significant in the investigator's judgment, detected during the trial or present at Visit 0 or baseline and significantly worsening after the start of the trial, will be recorded. as AA (serious or non-serious if they meet the corresponding definition). However, laboratory abnormalities or other clinically significant abnormal evaluations that are associated with the disease under study, unless judged by the investigator to be more severe than expected for the subject's condition or present or detected early of the trial and do not worsen, they will not be reported as AA.

In the event of unexplained abnormal laboratory test values that are clinically significant, repeat testing and follow-up will be performed until values are restored to the normal range, return to baseline, and/or a finding is found. clear explanation of the anomaly.

7.7 Intensity evaluation

The severity of all AEs will be graded according to the National Cancer Institute (NCI-CTCAE) criteria, version 4.0, on a five-point scale (grades 1 to 5) and will be recorded in detail on the CRD.

An AE described as “severe” should not be confused with a “serious” AE. Intensity is a category used to qualify the intensity of an adverse event and both non-serious AEs and SAEs can be

classified as intense or severe. An adverse event is defined as serious when it produces one of the predefined outcomes described in Section 7.3 of the protocol.

7.8 Assessment of causality

The Principal Investigator will assess the causal relationship of the AE to the study medication.

If there are reasonable suspicions indicating that the study medication has a causal relationship with the AE, that is, there are facts (indications) or arguments that suggest said relationship, the causality algorithm used by the Spanish Pharmacovigilance System (Karch and Modified Lasagna) that uses 5 criteria:

- Temporal Sequence (ST), reasonable with the administration of the drug.
- Prior Knowledge (CP). Follows a known response pattern to the suspect drug.
- Evolution after withdrawal (RT). Disappears or decreases when treatment is stopped or the dose is reduced.
- Effect of re-exposure (RX). It recurs when the drug is reintroduced.
- Alternative cause (AC). Natural history of underlying diseases, concomitant treatments or other risk factors.

The total imputability score classifies the causal relationship into 5 categories:

- UNLIKELY……..……..≤ 0
- CONDITIONAL……..……1-3
- POSSIBLE……..……4-5
- LIKELY……..6-7
- DEFINED……..…..≥ 8

The causal relationship will be DEFINED if the AE is related to the administration of the drug, improves when it is suppressed and reappears with its readministration without being able to be explained by other causes; PROBABLE if it is related to the administration of the drug, it improves when it is stopped without being able to be explained by other causes; POSSIBLE when related to drug administration but can be explained by other causes; CONDITIONAL when there is a causal relationship with the administration of the drug but it does not coincide with the AE of the drug and can be explained by alternative causes. Finally, UNLIKELY or there is no causal relationship (unrelated) if there is no time sequence, it does not coincide with the AE described for the drug and it can be explained by other causes.

7.9 Collection and monitoring of adverse events

The principal investigator will collect all AEs that occur from the time the patient signs the informed consent until the last follow-up visit, including those caused by trial procedures.

All AEs will be recorded in the patient's medical record and in the CRF.

These may be self-reported by the patient or may be revealed through open questions, explorations, or assessments during interviews at study visits. In order to avoid reporting bias, patients should not be asked about the specific manifestation of one or more AE.

After the initial collection of data on the AE, the researcher must actively follow the evolution of each patient and provide new information on their situation. In this sense, all AAs will be monitored until their resolution, until the problem is stabilized, an alternative explanation is found, or until it is impossible to trace the subject.

At the end of the patient's participation in the study, only the following AEs will be followed up:

• SAA and RAGI still present
• Non-serious AEs related to investigational product or trial procedures still present until resolved or until an alternative explanation is found or subject follow-up becomes impossible.

Once resolved, the AA page in the CRF will be updated. The investigator will ensure that the follow-up includes as many additional investigations as necessary to elucidate the nature and causality of the AE. This may include additional laboratory tests or tests, histopathological examinations, or consultation with other healthcare professionals.

7.10 Reporting of serious adverse events

All AEs that are serious and manifest during the course of the study, regardless of the treatment group in which they occur, must be reported to the sponsor within one business day (24 hours) from the time the investigator be aware of the event.

The notification form must always be completed in as much detail as possible, with all the specific information available, and must be signed by the investigator. The minimum information in the initial report includes: patient identification, adverse event identification, onset date, reason considered serious, causal relationship to study medication, name of person originally reporting the event, and all event-specific information available. In case the investigator does not have all the information about the SAE, he will not wait to receive it before reporting the event. The additional information must be notified in the same form within 24 hours after its knowledge.

The preferred method for the promoter to receive this information is to send a fax with the notification form:

FIBICO Pharmacovigilance Unit
Fax: +34 957 76 35 71

In exceptional circumstances, and in the absence of a fax machine, notification by email or telephone is accepted, with a copy of the form being sent by express mail (or attached to the email message). Initial notification by email or phone does not replace the need for the investigator to complete, sign, and return the notification form within the timeframes noted above.

The sponsor will review the form received and, if applicable, request additional information from the investigator.

If the investigator receives additional information about the SAE, or the SAE is resolved or unlikely to change, a follow-up report should be completed and also faxed to FIBICO's Pharmacovigilance Unit within 24 hours of completion. your knowledge.
All cases of pregnancy are considered SAEs and therefore must be notified according to the procedure described above.

The immediate notification of the SAE in the form will be in addition to the collection of these data in the patient's clinical history and in the CRD.

The promoter can delegate tasks to third parties, although the ultimate responsibility will remain with the promoter.

The sponsor will not actively look for ADRs attributable to either medication or trial procedures that occur after the subject's participation in the trial has ended. However, if the researcher communicates them, the sponsor will collect and process them accordingly. Such cases will be subject to expedited notification as required by regulatory authorities.

The sponsor must expeditiously notify all information that could modify the risk/benefit ratio of the investigational drug, or determine changes in its administration schedule or in the conduct of the trial, for example:

• A qualitative change or an increase in the percentage of appearance of the expected SARs, which is considered clinically important.
• RAGI that occur after the completion of a clinical trial and that are reported by the investigator to the sponsor.
• New events related to the conduct of the trial or the development of the investigational drug and that are likely to affect the safety of the subjects, such as:
• SAEs that may be associated with the trial procedures and that may affect the performance of the trial.
• A significant risk to subjects such as the lack of efficacy of an investigational drug used for the treatment of a life-threatening disease.
• Important new safety findings from new animal studies (such as carcinogenicity).
• Any premature termination or temporary stoppage of a clinical trial with the same investigational drug for safety reasons, carried out in another country and by the same sponsor.
• RAGI related only to an NMI that are considered relevant as they are not subject to the general rules of expedited notification of individual RAGI cases.
• Any recommendation of the Data Monitoring Committee, which is relevant to the safety of the subjects.

This relevant information must be notified as soon as possible and no later than 15 days after the promoter has become aware of it. In addition, if additional relevant information is obtained, it must be notified as quickly as possible.

The sponsor must communicate to all the investigators involved any information that may affect the safety of the trial subjects, as soon as possible. You will also be informed, throughout the study, of any safety issues that impact the conduct of the clinical trial or the development of the product, including the interruption of the development program or changes to the protocol related to safety.

The study will meet all local regulatory requirements. It will also meet all the requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A.

7.11 Expedited notification of RAGIs to health authorities / RECs

The sponsor, through the FIBICO Pharmacovigilance Unit, is responsible for notifying the AEMPS, the CEIs involved and the Autonomous Communities where the trial is carried out, of all the RAGI that are collected in the study, following the procedure indicated in the current legislation.

For suspected RAGI that occur in Spanish territory, only the official Spanish language of the State will be accepted and the RAGI notification form included in the investigator's file will be used.

The maximum period for notification of an individual case of suspected RAGI will be 15 calendar days from the moment in which the promoter became aware of it. When the suspicion of RAGI has caused the death of the patient, or put his life in danger, the promoter will send the information within a period of 7 calendar days from the moment in which he becomes aware of it. It will complete said information, as far as possible, in the following 8 days.

This information should include an evaluation of the importance and implication of the findings, including previous relevant experience with the same or similar drugs.

The notification may be made by fax (+34 918225076), by post or in person at the AEMPS (Parque Empresarial Las Mercedes Edificio 8, C/ Campezo 1 - 28022 Madrid) addressed to the Clinical Trials Area of the General Subdirectorate of Medicines for Human Use. Suspected adverse reactions will be accompanied by an accompanying letter.

The AEMPS will make public the date from which it will accept the electronic notification sent by the promoters. Likewise, the AEMPS will determine the deadline from which it will not accept notifications in digital or paper format, except for justified reasons. Until then, promoters may continue to make notifications in paper format, without prejudice to the fact that in the case of RAGI notifications occurring outside of Spain, when the RAGI is notified to Eudravigilance, additional notification to the AEMPS is not necessary.

Each of the RECs involved in a clinical trial must be notified of all the RAGI that have occurred in the participating subjects in the centers in their area of influence.

Likewise, the competent body of each of the Autonomous Communities where the test is carried out must be notified of suspected RAGI occurring in the health centers of their Community. In both cases, the RAGI notification form will be used for this.

The sponsor will annually send the researchers the information on the RAGI in an aggregated form in a list together with a brief analysis of the data provided.

7.12 Annual Safety Reports

The annual safety reports that will include the RAGIs and AAGs collected in the study since the patient is randomized, will be sent by FIBICO to the AEMPS (Clinical Trials Area of the General Subdirectorate of Medicines for Human Use), the Autonomous Communities and the CEIs, within the terms established in current legislation.

7.13 Treatment of adverse events

Treatment of any adverse event is at the discretion of the investigator and is based on current Good Clinical Practice standards. Any medication administered to treat an AE will be listed on the subject's CRF.

7.14 Pregnancy

According to ICH Guideline M3, precautions should be taken to minimize risk to the fetus or embryo when women of childbearing potential are included in clinical studies. These precautions include performing a serum pregnancy test at the baseline evaluation to rule out

pregnancy, the use of highly effective contraceptive measures and continued monitoring in case of pregnancy.

If a pregnancy occurs during the patient's participation in the clinical trial, it will be considered an SAE and the investigator will record the information about the pregnancy on the CRF. In addition, the patient will be followed up to determine the outcome of the pregnancy (also including premature termination of the pregnancy).

Pregnancy complications and voluntary termination for medical reasons and spontaneous abortions should also be reported using the serious adverse event report.

The investigator shall immediately notify the sponsor of any SAE related to pregnancy or the newborn/child that he or she considers may be related to the investigational medicinal product during the trial and after the patient has completed the trial.

Any pregnancy that occurred during the study and its outcome should be recorded and followed up to rule out abnormalities or congenital malformations. Information will be collected on:

- Normal birth, spontaneous or therapeutic abortion (any congenital anomaly detected in the aborted fetus must be documented) stillborn fetus, congenital anomaly
- Neonatal deaths occurring within 30 days of birth
- Death of an infant after 30 days if suspected by the investigator to be related to in utero exposure to study medication

All infants born after fetal exposure should be followed for the first 12 months after delivery.

7.15 Deaths

Deaths occurring during treatment with the investigational product or within 12 weeks of discontinuation of treatment, whether or not considered treatment-related, should be reported.

All deaths considered to be related to study drug at any time will be reported as SAEs, regardless of time since last dose of investigational product.

8. STATISTICAL METHODOLOGY

8.1 Analysis data sets

8.1.1 Intention-to-treat (ITT) population

The ITT population is defined as all randomized patients, whether or not they received the MI. Patients will be classified according to the treatment group to which they have been randomised, regardless of the actual treatment received. This population provides the basis for the main efficacy analyses.

8.1.2 Population per protocol (PP)

The PP dataset consists of all patients from the ITT dataset without any major protocol deviations. This is the group of patients who participated in the study as planned.

Major deviations from the protocol are defined as:

- Failure to comply with the inclusion and exclusion criteria.
- Taking prohibited medications.

Minor deviations:
• Failure to comply with the visit dates.
• Missed value of the main criterion without premature suspension.
• Failure to comply with the protocol design.
• Any other deviation during the course of the study.

8.1.3 Security data set
The safety data set encompasses all patients included in the study who have received at least one dose of any study drug.

8.2 Determination of sample size
The calculation of the sample size of the clinical trial is based on the regional control rate of the disease (LC rate %) at 36 months after the intervention (main end point). We have assumed that the proportion of patients in the treatment group with local control of the disease (LC rate %) at 36 months is 82% (peritoneal recurrence in 18% at 36 months) and that the proportion of patients in the group control with local control of the disease (LC rate %) at 36 months is 64% (peritoneal recurrence in 36% at 36 months).
With this estimation (error α = 0.05, power = 0.80, double tail) the calculated sample size is 190 patients, 95 patients in each arm. Contemplating an approximate loss of 5% of patients, the definitive N is 200 patients.

8.3 Types of analysis
- Descriptive analysis for quantitative variables by calculating arithmetic means (m) and typical or standard deviations (SD); and for qualitative variables by calculating counts of percentages and proportions (%).
- Determination of the goodness of fit to a normal distribution (normal data) using the Shapiro-Wilk test. The homogeneity of variances will also be checked using Levene's test.
- Comparison of the mean values of the quantitative variables between the two groups using Student's t-test (parametric test) or Mann-Whitney U-test (non-parametric test).
- Comparison of proportions between the different groups using chi-square tests for contingency tables; in the case of 2 x 2 tables, the chi-square statistic with Yates' correction will be used, and when some expected frequency is ≤ 5, Fisher's exact test will be applied.
- Association between quantitative variables by calculating Pearson's linear correlation coefficients (parametric test) or Spearman's correlation (non-parametric test), as appropriate.
- Survival curves will be studied using the Kaplan-Meier method and comparison using Log-Rank to analyze the effect of the different factors on survival.

Todos los contrastes de hipótesis serán bilaterales. Y en todas las pruebas estadísticas se considerarán valores “significativos" aquéllos cuyo nivel de confianza sea del 95% ($p<0,05$).

9. ADMINISTRATIVE OBLIGATIONS

9.1 Source documents
The source documents are any document, original, electronic or paper data records from which the patient's CRF data is obtained.

9.2 Data collection and management

The Principal Investigator must maintain a list of appropriately qualified individuals to whom they have delegated study tasks. All persons authorized to make entries and/or corrections to the CRFs will be listed on the delegation of authority form, signed by the sponsor.

Researchers must complete a CRD for each patient participating in the trial, where all the data requested in this study will be collected, including laboratory data.

All forms must be completed clearly and legibly. Corrections should be made by crossing out the incorrect entry (without erasing or rendering it illegible), inserting the correct information, date, and initials of the investigator or authorized delegate making the correction, next to the corrected portion. Investigators will ensure the accuracy, completeness, readability, and timeliness of the data in the CRDs and in all requested records.

Once the study has been completed by the patient, the principal investigator will sign the CRF and deliver it to the sponsor (or designated technical personnel) for their file. This also applies to CRFs for subjects who do not complete the study.

All data necessary for analysis and communications will be entered into a validated database. The closure of the database will take place when the data management quality control procedures have been completed.

The monitor will verify adherence to the protocol and its integrity, coherence and accuracy of the data entered in the CRD, in addition to ensuring that the clinical trial is carried out in accordance with the Good Clinical Practice (GCP) Standards, and all applicable regulatory requirements. .

Adequate and accurate records shall be maintained so that the performance of the trial is fully documented and the subsequent verification of the trial data.

9.3 Investigator's file / Conservation of documents

Adequate and accurate records must be kept by the investigator to allow the study to be fully documented and so that the study data can be subsequently verified. These documents should be classified into two different categories: the investigator's study file and the patient's original clinical documentation.

The investigator's study file will contain the protocol and amendments, the approval of the CEIm and the competent authorities along with correspondence, the model informed consent form, medication records, team resumes, authorization forms and other appropriate documents and correspondence.

Original patient clinical documentation will include the patient's hospital records, physician and nursing staff notes, appointment book, original laboratory reports, signed informed consent forms, consultation reports, and screening records. patient inclusion.

The investigator must archive the two types of documents described above for a minimum of 15 years from the date of termination or cancellation of the study or for a longer period, if required by local law. After this period of time, documents may be destroyed in accordance with local law.

If the investigator wishes to assign the study files to another person or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee the requirements established for the filing of any or all of the study documents in the investigation center, the investigator and the sponsor must agree on special measures to keep these documents in a sealed box outside the center, so that can be returned to the investigator in this way, in the event of a regulatory audit. When original documents are required for the continued care of the patient, appropriate copies should be obtained for off-site retention.

The investigator must provide the sponsor, upon request, with the basic data required from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the event that special issues and/or queries arise from regulatory authorities or an audit inspection is required, access to full study documentation is also necessary, provided patient confidentiality is protected.

9.4 Data quality assurance / audits and inspections

To ensure compliance with the Good Clinical Practice Standards and all applicable legal requirements, the sponsor may conduct a quality assurance audit. Regulatory Agencies could also carry out an inspection of this clinical trial. Audits and inspections may occur at any time during the clinical trial or after it has ended. In the event that an audit or inspection is carried out, the investigator and the participating center will agree to allow the auditor or inspector direct access to all records and relevant documentation of the clinical trial (provided that the confidentiality of the subjects is protected). and spend the necessary time, their own and that of their staff, to discuss the results and other relevant matters with the auditor or inspector.

The investigator/institution must facilitate access to the original data/documents for trial monitoring, audits, CEIm reviews and regulatory inspections. In compliance with all applicable regulations, the investigator and the center are required to allow authorized representatives of the study sponsor, the regulatory agency(ies) and the CEIm direct access to the review of the original medical records of the patients for verification of the procedures and data related to the study. This direct access includes the exploration, analysis, verification and reproduction of any records or reports that are important for the evaluation of the study. The investigator is required to inform and obtain the subject's consent to allow designated representatives access to his or her study-related records without breaching the confidentiality of the subject. Verification of the CRD data must be done by direct inspection of the original documents.

9.5 Posting Policy

The results of this clinical trial may be published or presented at scientific meetings.

The publication conditions will comply with the provisions of article 42 of Royal Decree 1090/2015 of December 4, which regulates clinical trials with medicines, the Ethics Committees for Research with medicines and the Spanish Registry of Studies Clinicians.

Once the study has finished and the statistical report has been prepared, the research team will prepare the final report of the study that will be presented to the CEIm, the AEMPS and the health authorities that request it. This final report will be the basis for the preparation of the manuscripts that are to be published in medical journals.

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9.6 Test monitoring

The monitoring of the study will be carried out according to the recommendations established in the ICH Topic E6 (R2).

The trial monitor will contact the site, prior to subject enrollment, to review the trial protocol and procedures with site staff. In addition, the monitor will be responsible for inspecting CRDs and other pertinent data (provided subject confidentiality is maintained in accordance with legal requirements) at regular intervals throughout the clinical trial for protocol compliance and integrity. consistency and accuracy of the data being entered. The extent, nature, and frequency of site visits will be based on the objective and/or endpoints of the clinical trial, the purpose of the clinical trial, the complexity of the design, and the rate of recruitment.

During these contacts, the monitor:
- Check the progress of the clinical trial and the rate of inclusion of patients.
- Review the data collected from the clinical trial.
- Verify the original documents.
- Will identify any issues and address their resolution.

This will be done in order to verify that:
- The data is authentic, exact and complete
- The safety and rights of subjects are protected.
- The clinical trial is carried out in accordance with the current protocol (and any amendments), the Good Clinical Practice Standards and all applicable legal requirements.

The monitor will be able to access the clinical records of the patients after the researcher requests it. The investigator agrees to allow the monitor direct access to all relevant documents and to spend the necessary time, himself and his team, to discuss the findings and other relevant matters with the monitor.

The investigator must allow the monitor, the sponsor's internal auditors, and representatives of regulatory authorities to inspect all study-related documentation and relevant medical or hospital records for confirmation of the CRF data.

The duties of the monitor are described below:
1. Work in accordance with the promoter's SOPs.
2. Visit the investigator before, during, and after the study to verify compliance with the protocol.
3. Guarantee that the data is recorded correctly and completely.
4. Ensure that informed consent has been obtained from all subjects prior to inclusion in the study.
5. Verify that the researchers and the center where the research will be carried out are suitable for this purpose.
6. Make sure that both the principal investigator and his collaborators have been properly informed and guarantee rapid communication between the investigator and the monitor at all times.
7. Ensure that the storage, distribution and documentation of investigational drugs is safe and adequate.
8. Submit to the sponsor reports of the monitoring visits and all the relevant contacts made with the investigator.

10. REGULATORY AND ETHICAL OBLIGATIONS

10.1 Regulations

This clinical study will be carried out in accordance with the protocol, the principles established in the current revised version of the Declaration of Helsinki (Fortaleza, 2013) (Annex 2) and in accordance with the applicable regulatory requirements, in particular the Tripartite Guide of the ICH "Norms of Good Clinical Practice", the Royal Decree of Clinical Trials 1090/2015, of December 4, which regulates clinical trials with medicines, the Ethics Committees of Research with medicines and the Spanish Registry of Studies Clinicians and Regulation (EU) No. 536/2014 of the European Parliament and of the Council, of April 16, 2014, on clinical trials of medicinal products for human use.

The researcher acknowledges, when signing the protocol, that he adheres to the instructions and procedures described in it and will ensure that the established provisions are strictly complied with.

The promoter will obtain the approval of the Health Authorities (AEMPS), in accordance with all applicable country-specific legal requirements.

The study will not begin until authorization from the AEMPS and approval from the CEIm have been obtained.

The principal investigator is responsible for ensuring that this protocol, the site's informed consent document, and any other information that is presented or made available to prospective subjects (eg, advertisements or information that supports or supplements informed consent) is accurate. reviewed and approved by the CEIm. The researcher agrees to allow the CEIm direct access to all relevant documents. The CEIm must be constituted in accordance with all applicable legal requirements.

10.2 Informed consent

The patient must give their consent before being included in the study. The content and the procedure for obtaining it must be in accordance with all applicable legal requirements.

The investigator is responsible for obtaining the written informed consent of each patient who participates in this study, after having explained in an understandable manner, the nature, objectives, methods, anticipated benefits and possible risks of the study.

The investigator must also explain to patients that they are completely free to refuse to participate in the study or to withdraw from the study at any time, for any reason.

For patients who are unable or incapable of giving legal consent, the written consent of their legally authorized representative must be obtained. In the event that the patient and their authorized legal representative are unable to read, an impartial witness must be present throughout the informed consent process. After the patient and/or their legal representative have verbally given their consent to participate in the study, the witness will sign the document to attest that the information contained in the informed consent form has been fully explained and understood.

The subject of the study will grant their consent, signing the corresponding model. To this end, each model must bear the signature of the investigator and the patient.

The CRDs for this study contain a section to document the patient's informed consent, which must be properly completed.

If new safety information is obtained that results in significant changes to the risk/benefit assessment, the informed consent form will be reviewed and updated, if necessary. All patients, including those already receiving treatment, must be informed of the new results and provided with a copy of the updated informed consent form in order to re-consent to continue in the study.

10.3 Confidentiality

All information related to the study is considered confidential.

In order to guarantee the confidentiality of the study data, only the principal investigator and his team of collaborators, the designated technical personnel, the monitor, the sponsor, the CEIm and the pertinent health authorities will have access to them.

The content of the data collection notebooks, as well as the documents generated during the study and the database, will be protected from unauthorized uses by people outside the research and, therefore, will be considered strictly confidential and will not be disclosed to third parties except those specified in the previous sections.

The promoter guarantees that the data processing will be done with the security measures established in compliance with REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of April 27, 2016 regarding the protection of natural persons in relation to regarding the processing of personal data and the free circulation of these data and by Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights. By signing the informed consent, the participant shows their agreement with this use of the study data. This authorization does not have an expiration date. The participant may withdraw it at any time, but must do so in writing.

All material, information (oral or written), unpublished documentation that is provided to the researchers, including this protocol, the data collection notebooks and the investigator's manual, must be considered the property of the sponsor.

It is the researcher's obligation to consider as confidential and ensure at all times the confidentiality of the documents and results generated during the course of the trial, except for those that the legislation defines as divulgible. The data and/or material of the study may not be disclosed, in whole or in part, by the researcher or his collaborators to any unauthorized person, without the prior and written consent of the sponsor.

The researcher will guarantee that the anonymity of the subjects is maintained and that their identities are protected from unauthorized third parties. To maintain the confidentiality of patient data and to safeguard the doctor-patient relationship, each participating patient will be assigned a unique reference number. In the CRD or other documents presented to the sponsor, the name of the subjects should not appear, using the identification code. The investigator must maintain a record of subject recruitment showing codes and names.

All data and information generated by the center as part of the clinical trial (other than the clinical records of the subjects) will be kept confidential by the investigator and other center personnel. This information and data will not be used by the investigator or other personnel of the center for any purpose other than that of carrying out the trial. These restrictions do not apply to:

- Information that remains publicly available through no fault of the researcher or center staff.
- Information that must be disclosed confidentially to a CEIm exclusively for clinical trial evaluation purposes.
- Information that is necessary to disclose in order to offer adequate health care to a clinical trial subject.
- Results of the clinical trial that can be published as described in the following paragraph.

10.4 Responsibilities according to Good Clinical Practices (GCP)

10.4.1 Responsibilities of the Promoter

The obligations of the Promoter will be the following:

1. Establish Standardized Work Procedures (SOP).
2. Sign the protocol and any modifications to it together with the researcher.
3. Select the most appropriate person to direct the study and ensure that he or she will carry out this task as specified in the protocol.
4. Provide all the basic and clinical information available on the investigational product and update it throughout the study.
5. Request the report by the CEIs and the authorization of the General Directorate of Pharmacy and Health Products, and inform them or request their authorization, as appropriate and without prejudice to the communication to the Autonomous Communities, in case of modifications, violations of the protocol or study discontinuation.
6. Hire a pharmaceutical laboratory to supply the medication to be investigated, ensuring that good manufacturing standards (GMP) have been met and that the samples are properly packaged and labeled.
7. It is also responsible that in the center where the study is carried out there will be a correct procedure for handling, conservation and use of it.
8. Appoint the monitor who will monitor the progress of the study.

9. Communicate to the Health Authorities and the RECs involved in the trial:

a. Serious and unexpected adverse effects that may be related to the treatments under investigation that occurred inside or outside of Spain.

b. Any information derived from animal studies that suggests a significant risk to humans, including any finding of teratogenicity or carcinogenicity. In these cases, the sponsor, together with the researcher, will take the necessary measures to protect the study subjects.

10. Provide the researcher and the RECs when appropriate, any important information, to which they have access during the study.
11. Ensure financial compensation to subjects in case of injury or death related to the study.
12. Agree with the researcher on the obligations regarding data processing, reporting and publication of results. In any case, the promoter is responsable de elaborar informes finales o parciales y comunicarlos a la Dirección General de Farmacia y Productos Sanitarios.

10.4.2 Responsibilities of the Investigator

The investigator's duties are:

1. Agree and sign the project protocol together with the promoter.
2. Know in depth the properties and characteristics of the drugs to be used.
3. Obtain the informed consent of the patients before their inclusion in the study.
4. Collect, record and report data correctly.
5. Immediately notify the promoter of serious or unexpected adverse events.
6. Guarantee that all the people involved in the study will respect the confidentiality of any information about the study subjects.

Failure to comply with the protocol, SOPs, GCP, and/or relevant regulatory requirements by an investigator should lead to prompt intervention, by the sponsor, to ensure compliance.

If monitoring and/or auditing identify serious and/or persistent noncompliance by an investigator, the sponsor must withdraw the investigator from the study. When the investigator is removed due to noncompliance, the sponsor must promptly notify regulatory authorities.

10.5 Insurance

As required by current legislation, and in particular Royal Decree 1090/2015, the sponsor will take out an insurance policy that covers the responsibilities of the sponsor, the principal investigator and their collaborators, and the hospital or center where the study is carried out. clinical trial, before possible damages that affect the patient's health during the study and in the year following its completion.

10.6 Conditions for modifying the protocol

To guarantee the conditions of the study and the interest of the valid statistical analysis of the data, neither the researcher nor the sponsor may alter the conditions of the study agreed upon and stipulated in this protocol.

Any amendment shall be established in writing, indicating the reasons and prior signature of all the agreed parties. The amendment will then become an integral part of the study protocol. In the event that the amendments require the approval of the ethics committees and/or authorities, it will be necessary to obtain it. Any amendment that changes the benefit-risk ratio for the patient must be, once signed by the promoter, submitted for evaluation and approval by the AEMPS and the CEIm.

Modifications to the protocol must be prepared by the sponsor. The investigator will not be able to modify the protocol on his own.

All modifications related to the protocol, the informed consent document or any other information that the CEIm has approved to be delivered to the possible subjects, must be sent to the CEIm for its information and approval, in accordance with the legal requirements, and to the Health Authorities (if necessary). The investigator is responsible for ensuring that the CEIm reviews and approves, where appropriate, these amended documents, and such approval must be obtained before any changes can be made (except, for example, changes necessary to eliminate an immediate risk to study subjects). trial). In the event that an amendment to the informed consent form is made, the investigator must follow all applicable legal requirements related to its use, including obtaining CEIm approval of the amended document, before new subjects give their consent. to participate in the clinical trial using this version of the form.

10.7 Conditions to end the study

If the trial is terminated prematurely or suspended, the sponsor must promptly inform the investigator and regulatory authorities of the termination or suspension and the reason for it. The sponsor or investigator must promptly inform the CEIm and provide the reason for the termination or suspension, as specified by the relevant regulatory requirements. Both the sponsor and the investigator reserve the right to terminate their participation in the study under the circumstances agreed upon in the contract with the center. If this is necessary, both parties will decide the procedures individually, after review and consultation. At the time of termination of the study, the sponsor and the investigator will ensure that due consideration is given to the protection of the interests of the patients.

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12. ANNEXES

All annexes are provided as separate documents.

Annex 1. Information sheet for the subject and informed consent
Annex 2. Declaration of Helsinki of the World Medical Association
Annex 3. List of participating centers
Annex 4. Questionnaire QLQ-C30