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FFCD 0904

PHASE I-II TRIAL OF RADIOCHIMIOTHERAPY WITH PANITUMUMAB FOR THE TREATMENT OF LOCAL EPIDERMOID CARCINOMAS OF THE ANUS

EudraCT N°: 2011-005436-26

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PROTOCOL AGREEMENT AND BPC

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EudraCT N°: 2011-005436-26
Version 2.1 of 11.12.2017

This version of the protocol is approved by :

The Promoter : Ms. Cecile GIRAULT Date: 14.08.2015 Signature:

The Coordinator : Dr Véronique VENDRELY Date: 14.08.2015Signature :

I, the undersigned, Doctor : .....

After having read the requirements of this research, the protocol and its appendices, I hereby certify that I will conduct this trial in compliance with Good Clinical Practice and in accordance with the applicable provisions of the Public Health Code.
In particular, I agree to:

- comply with the protocol and any modifications notified to it by the promoter
- agree to supervise the research in the center and to train collaborators in the conduct of the research and provide a list of names
- have each patient sign a written consent after having read the information note intended for him/her, before any research is carried out
- Report serious adverse events or developments within 24 hours of learning of them, and as specified in the research protocol
- respect the inclusion and non-inclusion criteria, as well as the start and end dates of the study
- participate in the translational part of the study subject to the patient's signature of the specific consent and to send the samples according to the recommendations,
- complete all the items in the observation book, ensure the quality of the data collection and the proper management of the products
- retain research data and documents until notified by the sponsor that they are no longer required
- inform the sponsor of any conflict of interest situation that may affect its scientific independence in the context of the research
- inform the sponsor without delay of any action, whether amicable or contentious, brought by a person involved in the research or his or her beneficiaries, which may call into question the sponsor's liability
- accept periodic visits from the sponsor's representatives, and make available to them all the source documents and materials relating to the research in order to ensure quality control of the data recorded in the case report book. The investigator accepts control in the form of an audit by the sponsor and/or inspection by the health authorities.
- respond by phone or mail to requests for corrections or clarifications regarding the observation book,
- Allow time for the ARC FFCD to sign the forms, answer any questions and take action

Date: **Signature:**

STAMP of the CENTER :

Send the original to the CRGA of the FFCD - 7 bd Jeanne d'Arc - BP 87900 - 21079 Dijon Cedex

SUMMARY

<table>
<tr><td>TITLE</td><td>FFCD 0904

Multicenter, prospective phase I-II trial of radiochemotherapy combined with panitumumab in the treatment of localized squamous cell carcinoma of the anus</td></tr>
<tr><td>OBJECTIVES</td><td>Phase I:
Primary Objective:
To determine the limiting dose (DLT) and maximum tolerated dose (MTD) of 5 FU-Panitumumab combined with mitomycin and radiotherapy in patients with localized squamous cell carcinoma of the anus.
Phase II
Primary Objective:
To assess the complete response rate 8 weeks after completion of 5 FU-panitumumab plus mitomycin and radiation therapy in patients with localized squamous cell carcinoma of the anus.
Secondary objectives, assess:
- Intermediate objective response rate (complete and partial) at week 6,
- Partial response rate, stability and progression, 8 weeks after the end of treatment
- Objective response rate 16 weeks after the end of treatment
- Toxicity of 5FU + mitomycin C + panitumumab + radiotherapy
- Colostomy-free survival at 3 years
- 3-year recurrence-free survival
- Overall survival at 3 years
- Quality of life (EORTC QLQ-C30 + Jorge and Wexner questionnaire)
- Determination of predictive markers of response or survival</td></tr>
<tr><td>TREATMENT</td><td>Phase I: n=6 to 24 patients
6 patients treated at the recommended dose
Panitumumab: D1, D15, D29,
5FU continuous infusion: D1 to D4 (S1) and D29 to D32 (S5)
Mitomycin C at 10 mg/m^2 : D1
Radiotherapy: 45 Gy in 1.8 Gy fractions 5 days/week (IMRT mandatory) in 5 weeks

<table><tr><th>LANDSCAPE</th><th>5FU mg/m²/d</th><th>Panitumumab mg/kg</th></tr><tr><td>-1</td><td>400</td><td>3</td></tr><tr><td>0</td><td>600</td><td>3</td></tr><tr><td>1</td><td>600</td><td>6</td></tr><tr><td>2</td><td>800</td><td>6</td></tr><tr><td>3</td><td>1000</td><td>6</td></tr></table>
Complementary radiochemotherapy:
Radiotherapy: 20 Gy in 10 fractions of 2 Gy over 2 weeks (S6 and S7)
+ panitumumab at D1 of S7)

Phase II: n=45 patients
The treatment will be identical to phase I but using the maximum tolerated dose determined in phase I. In view of the latest advances in treatment and in order to follow current standards, the elimination of the free interval between the two radiotherapy sequences, and consequently the elimination of a course of 5FU + Panitumumab, do not allow the integration of the 6 patients from Phase I at the selected level (level -1) in the analysis of Phase II.
The dosage of 5 FU and panitumumab will be as determined by phase I (tier -1).</td></tr>
<tr><td>ANCILLARY STUDY</td><td>Three optional ancillary biological studies:
1. Search for known mutations in receptor tyrosine kinase signaling pathways and viral oncogenic factors. Formalin fixed and kerosene embedded biopsies: KRAS, BRAF, PI3K, NRAS. Study of HPV subtypes by PCR. Study of EGFR signaling pathways
2. Immuno-monitoring of myeloid and lymphocyte suppressive populations
(circulating cells), blood samples at different stages of treatment</td></tr>
</table>

	3. **Pharmacokinetic study of panitumumab**. Blood samples at different time points during treatment
POPULATION	**1- <u>Inclusion criteria</u>** - Histologically proven squamous cell carcinoma of the anus - Locally advanced tumor without metastasis - Stage T2> 3 cm or T3 or T4 - N1-N3 stage regardless of T stage (T1 to T4) - General status WHO 0-1 - Life expectancy > 3 months - Signed informed consent - Age ≥ 18 years - Effective contraception in women and/or men of childbearing potential during treatment and up to 6 months after the end of treatment - CD4 ≥ 400 / mm^3 (only for HIV+ patients) - Measurable tumor on at least one of the following tests: MRI, echo-endoscopy, clinical examination **2- <u>Non-inclusion criteria</u>** - Presence of metastases - Previous treatment with anti-EGFR - Stage T1N0 or T2< 3 cm N0 - History of pelvic radiotherapy - At least one of the following laboratory findings: PNN < 1500/mm^3 , platelets < 100,000/mm^3 , hb < 9 g/dl, WBC < 3000/mm^3 , bilirubin > 1.5 times the upper limit of normal, transaminase (AST and ALT) > 2.5 times the upper limit of normal creatinine clearance < 50 mL/min (Cockcroft formula), Mg^{2+} < lower limit of normal, Ca^{2+} < lower limit of normal - Significant coronary artery disease or myocardial infarction within one year - History of interstitial lung disease or pulmonary fibrosis - History of malignancy within the last five years except for properly treated basal cell skin carcinoma or carcinoma in situ of the uterine cervix - Impossible to follow up for psychological or geographical reasons - Pregnant or breastfeeding women, women of childbearing age who have not taken a pregnancy test. **Positive HIV status is not a criterion for non-inclusion**
STATISTICS	**Phase I** A minimum of 6 patients and a maximum of 24 patients will be included, corresponding to a minimum of 3 patients per dose level (and 6 at the maximum tolerated dose). A minimum of 9 patients will be required to proceed to Phase II. **Phase II** Primary endpoint: Complete response rate 8 weeks after the end of treatment, as determined by morphological and clinical examinations. The Phase II study will be conducted at the maximum tolerated dose level determined in Phase I (Level -1). The 6 patients from Phase I treated at the recommended tier (tier -1) will not be eligible for inclusion in Phase II. The number of subjects required for the recommended tier is 45. A 2-step minimax Simon plan will be used. The assumptions are: H0: A complete response rate 8 weeks after the end of treatment of 60% is considered unattractive; H1: A complete response rate of 80% at 8 weeks after the end of treatment is expected. With an alpha risk of 5%, a power of 90%, the number of subjects needed for phase II is 45. An independent committee is formed. The theoretical duration of inclusion for phase II is 24 months The total duration of the phase II study is 72 months (3 years of minimum follow-up for the last patient included + 1 year of analysis)

SCHEDULE OF THE STUDY

	Before the start of treatment		During treatment			Evaluations		Follow-up of patients after discontinuation of the protocol treatment	
	Within 21 days prior to treatment	Within 14 days prior to inclusion	Before each course of chemotherapy	Before each administration of panitumumab	Every week during radiation therapy	At 6 weeks	8 weeks after the end of the treatment	Every 4 months after the end of treatment for 2 years	Every 6 months for the next 3 years
CLINICAL STUDY									
Informed consent		X							
Clinical examination		X	X			X	X	X	X
Proctological examination	X	X	X			X	X		
Weight		X	X		X	X	X	X	X
General status WHO		X	X		X	X	X	X	X
Smoking/non-smoking character		X							
QoL Questionnaire (QLQ-C30 + Jorge and Wexner)		X				X	X	X	X
HIV and HBV serology [1]		X							
Biological check-up		X[2]	X[4]	X[3]		X[2]	X[2]	X	X
CD4 count (if HIV+)		X							
Blood ionogram + electrolyte (K^+ , Na^{2+} , Ca^{2+} , Mg^{2+})		X	X[5]	X		X	X		
SCC marker		X				X	X	X	X
Pregnancy test within 72 hours before C1			X						
ECG		X							
Thoracic and abdominal-pelvic CT	X[6]						X[6]	X	X
Pelvic MRI	X[6]					X[6]	X[6]	X	X
Rectal echo-endoscopy	X[6]						X[6]	X	X
PET-Scan	X[6]							X (6 months after the end of treatment)	
Assessment of treatment toxicity			X	X	X	X	X	X	X

1. Less than 1 year old
2. CBC/platelets, creatinine, albumin, AST, ALT, alkaline phosphatase, total and conjugated bilirubin, GGT
3. NFS-platelets
4. CBC/platelets, creatinemia, AST, ALT, alkaline phosphatases
5. To be performed if panitumumab is discontinued
6. Make a copy on CD-ROM to be retrieved by the FFCD CRAs for the independent committee if necessary

BIOLOGICAL STUDY SCHEDULE

WEEKS	DAYS	Admi Panitumumab	PHARMACOKINETIC STUDY Phase II (1 dry tube)	CIRCULATING CELLS Phase II (5 ADC tubes)	SIGNALING PATHWAYS
Inclusion report				T0	4 biopsies
S1	J1	X (1ière)			
	J2				
	J3				
	J4				
	J5				
	J6				
	J7				
S2	J8				
	J9				
	J10				
	J11				
	J12				
	J13				
	J14				
S3	J15	X (2ième)			
	J16				
	J17				
	J18				
	J19				
	J20				
	J21				
S4	J22				
	J23				
	J24				
	J25				
	J26				
	J27				
	J28				
S5	J29	X (3ième)	Before the 3ième infusion		
	J30				
	J31				
	J32				
	J33				
	J34				
	J35				
S6	J36				
	J37				
	J38				
	J39				
	J40				
	J41				
	J42				
S7	J43	X (4ième)			
	J44				
	J45				
	J46				
	J47				
	J48				
	J49				
S8 to S14	D50 to D98				
S15	J99			T end of treatment	

LIST OF ABBREVIATIONS

LDT :	Toxic limiting dose
MTD :	Maximum tolerated dose
QLQ-C30:	Quality of Life Questionnary Cancer
IMRT:	Intensity-Modulated Radiation Therapy
5FU :	5 Fluorouracil
ASAT :	Aspartate amino transferase
ALAT :	Alanine amino transferase
PAL :	Alkaline phosphatase
SCC :	Squamous cell carcinoma
MRI :	Magnetic Resonance Imaging
CT :	Computed tomography
TAP:	Thoracoabdomino-pelvic
WHO:	World Health Organization
CBC:	Blood count
CRGA:	Center for Randomized Management and Analysis
SP :	Safety Population

I. RESEARCH OBJECTIVES

1. Main objective

The primary objective of the **phase I trial** is to determine the limiting dose (LDT) of 5FU and panitumumab in combination with radiation therapy and mitomycin, and to derive the maximum tolerated dose (MTD) in patients with localized squamous cell carcinoma of the anus.

The main objective of the **phase II study** is to determine the complete response rate 8 weeks after the end of the protocol treatment with radiochemotherapy (theoretically in week 15) in patients with localized squamous cell carcinoma of the anus, defined on MRI, endorectal echo-endoscopy if necessary and proctological examination.

2. Secondary objectives

The secondary objectives of **Phase II** will be to evaluate:
- Intermediate objective response rate (complete and partial) at week 6
- Partial response rate, stability and progression 8 weeks after the end of treatment
- Objective response rate 16 weeks after the end of treatment
- Toxicity of 5FU + mitomycin C + panitumumab + radiotherapy
- Colostomy-free survival at 3 years
- 3-year recurrence-free survival
- Overall survival at 3 years
- Quality of life (EORTC QLQ-C30 and Jorge and Wexner questionnaire)
- Determination of predictive markers of response and/or survival

II. SELECTION CRITERIA

1. Inclusion criteria

- Histologically proven squamous cell carcinoma of the anus
- Locally advanced tumor without metastasis
- Stage T2> 3 cm or T3 or T4, regardless of N
- N1-N3 stage regardless of T stage (T1 to T4)
- General status WHO 0-1
- Life expectancy > 3 months
- Signed informed consent
- Age > 18 years
- Effective contraception in women and/or men of childbearing potential during treatment and up to 6 months after the end of treatment
- CD4 $\geq$ 400 / mm^3 (only for HIV+ patients)
- Measurable tumor on at least one of the following tests: MRI, echo-endoscopy, clinical examination

2. Criteria for non-inclusion

- Presence of metastases
- Previous treatment with anti-EGFR
- Stage T1N0 or T2 $\leq$ 3 cm N0
- History of pelvic radiotherapy
- At least one of the following laboratory findings: PNN < 1500/mm^3 , platelets < 100,000/mm^3 , Hb < 9 g/dl, WBC < 3000/mm^3 , bilirubinemia > 1.5 times the upper limit of normal, transaminase (AST and ALT) > 2.5 times the upper limit of normal creatinine clearance < 50

mL/min (Cockcroft formula appendix 5), Mg^{2+} < lower limit of normal, Ca^{2+} < lower limit of normal
- Significant coronary artery disease or myocardial infarction within one year
- History of interstitial lung disease or pulmonary fibrosis
- History of malignant pathologies in the last 5 years except for basal cell skin carcinoma or carcinoma *in situ* of the uterine cervix properly treated
- Impossible to follow up for psychological or geographical reasons
- Pregnant or breastfeeding women, women of childbearing age who have not taken a pregnancy test.

Positive HIV status is not a criterion for non-inclusion

III. INCLUSION

Inclusion will be carried out, after the eligibility check-up and the signature of the informed consent, from MONDAY to FRIDAY from 9 am to 6 pm at the Randomization-Management-Analysis Center of the French-speaking Federation of Digestive Oncology (CRGA of the FFCD) by faxing the inclusion form to : **03 80 38 18 41**
For further information, please call 03 80 66 80 13.

A registration number will be provided by the CRGA.
Treatment will be started within 2 weeks.

IV. INCLUSION ASSESSMENT

The inclusion assessment is identical for phase I and phase II.

In order to evaluate the efficacy of the treatment, it is essential that the same technique**, MRI +/- rectal echo-endoscopy +/- clinical examination** (if performed at the time of the inclusion assessment)**,** be used for the three assessments of the same patient (inclusion, assessment at 6 weeks and assessment at 8 weeks after the end of the treatment)

- **Within 14 days prior to inclusion:**
  - Clinical examination, weight, height
  - ECG
  - WHO General Status Estimate (Appendix 5)
  - Completion of the QLQ-C30 + Jorge and Wexner questionnaire (Appendix 6)
  - Biological workup including:
    - CBC-platelets
    - Blood ionogram and electrolyte (Mg^{2+} , Ca^{2+} , $Na^{2+,}$ K^{+}), albumin, creatinemia
    - AST, ALT, PAL, GGT, total and conjugated bilirubin, CD4 for HIV+ patients
  - HIV and HBV serology less than one year old
  - Marker: squamous cell carcinoma (SCC)
  - Non-smoker/smoker status of the patient

- **Within 21 days before the first treatment**
  - Thoraco-abdominal CT scan to ensure the absence of distant lesions
  - Pelvic MRI **and/or** rectal echo-endoscopy with measurement of tumor and adenopathy
  - Optional PET-scan

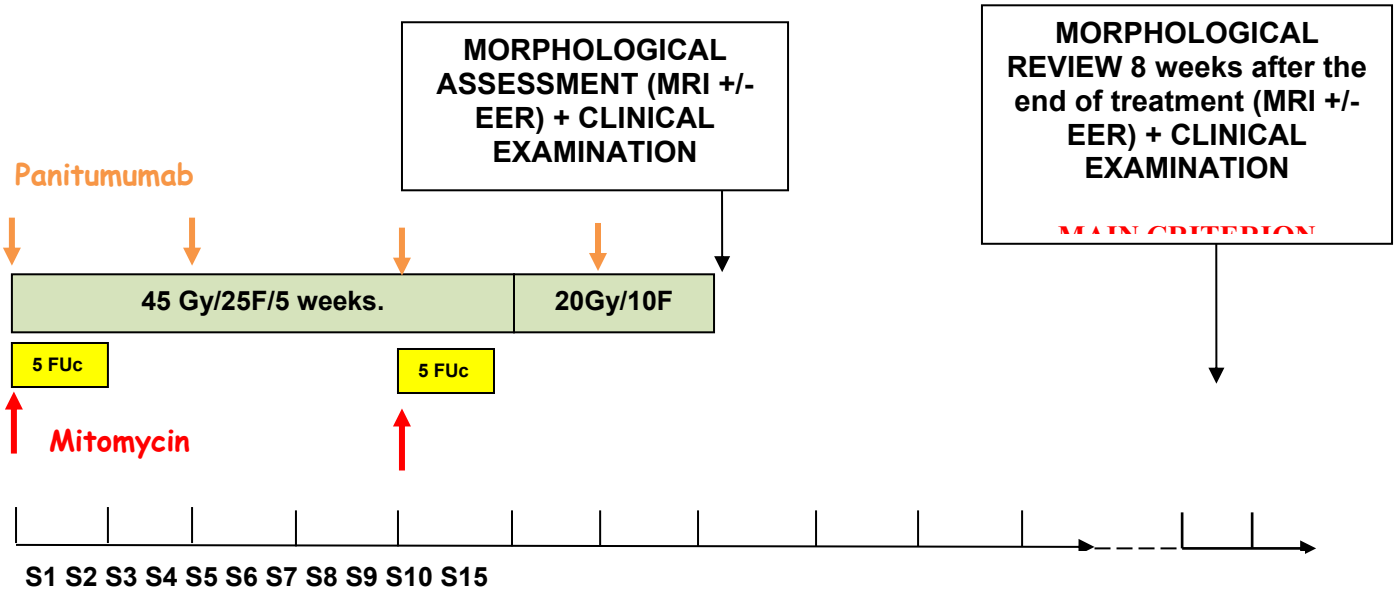
  Make a CD-ROM copy of the images that will be retrieved by the FFCD in order to transmit them to the independent committee if needed.

- **Within 72 hours before the first treatment:**

- For women of childbearing age, a blood pregnancy test and effective contraception throughout the study

V. TREATMENT

1. Scheme of the study



First part of treatment (S1 to S5)

Chemotherapy:

- Panitumumab (3 or 6 mg/kg depending on the dose level). As the dose level chosen by Phase I is -1, the dose of panitumumab will be 3 mg/kg at D1 and D15, D29 (S1, S3, S5)
- 5FU as a continuous infusion (400-600-800 or 1000 mg/m²/d depending on the dose level). The dose level chosen by phase I being -1, 5FU will be at 400 mg/m² from D1 to D4 of week 1 and D1 to D4 of week 5.
- Mitomycin C (10 mg/m² regardless of dose level not to exceed 20 mg/cure): D1 week 1 and D1 week 5

Radiotherapy:

- 45 Gy in 1.8 Gy fraction 5 days/week in IMRT. Considering the suppression of the free interval week 6 and 7, it is requested that the radiotherapy technique be IMRT.

Additional radiochemotherapy at S6 and S7

Chemotherapy:

-

Panitumumab (3 or 6 mg/kg depending on dose tier) Since the dose tier selected by Phase I is -1, the panitumumab dose will be 3 mg/kg at: D1 week 7 Radiotherapy :

- 20 Gy in 10 fractions over 2 weeks (S6 and S7), 2 Gy per session

a. PHASE I: estimation of the maximum tolerated dose

Dose levels

Five dose levels, corresponding to different 5FU and panitumumab dose combinations, will potentially be analyzed.

LANDSCAPE	5FU mg/m²/d	Panitumumab mg/kg
-1	400	3

0	600	3
1	600	6
2	800	6
3	1000	6

Definition of the maximum tolerated dose (MTD)
The maximum tolerated dose (MTD) is defined as the dose level before the dose level defining the limiting dose (LDT). It is also the recommended dose.

Definition of the limiting toxic dose (LDT)
The limiting toxic dose is defined by the occurrence of specific toxicity during treatment at this dose up to 30 days after the end of S9 or after treatment discontinuation (Pre-Amendment 5 scheme).

Specific toxicities are:

Hematological Toxicities (according to NCI-CT v4.0)

- Febrile neutropenia (A disorder characterized by a decrease in neutrophils associated with fever)
- Neutropenic infection
- Neutropenia grade 4 for more than 7 days
- Thrombocytopenia ≥ grade 3 for more than 7 days
- Thrombocytopenia grade 4

Non-hematological toxicities

- Nausea grade ≥ 3, vomiting or diarrhea despite optimal medical treatment
- Grade 3 fatigue for more than 7 days or grade 4 fatigue
- Dermal toxicity > 3
- Any other toxicity grade ≥ 3 (except alopecia)
- First part of treatment incomplete (75% of planned doses)
- Any toxicity that delays the next course of treatment or radiation therapy by more than 7 days should be reviewed by the independent committee. Based on the opinion of the independent committee, this toxicity may be considered dose-limiting; if this toxicity is not related to the study treatments, the patient will be removed from the study and an additional patient will be included at the same dose level.

In the case of patients who did not receive the full course of treatment for reasons other than specific toxicity, the independent committee may discuss the possibility of including additional patients as a replacement.

Determination of the MTD

MTD determination will be performed using the dose escalation method in groups of 3 patients, starting at step 0.
The rules of evolution from one level to another are described in the following table:

If toxicity in	So	If toxicity in	So
0/3 patients	move to the next dose level		
1/3 patients	add 3 patients at this dose level	1 or 2/6 patients	move to the next dose level

2/3 patients	add 3 patients at this dose level	2/6 patients	move to the next dose level
		more than 2/6 patients	STOP Previous level = LMD[1]
3/3 patients	STOP Previous level = LMD[1]		

Except for the case where the previousstep is the -1 step.

At a given level :

- if none of the 3 patients show toxicity, go to the next level;
- if 1 out of 3 patients has toxicity, include 3 additional patients at that same tier:
  - if 1 or 2 of the 6 patients in this tier show toxicity, move to the next tier;
  - if 3 or more of the 6 patients in that tier have toxicity, the dose associated with the lower tier is the MTD[1] ;
- if 2 out of 3 patients show toxicity, include 3 additional patients at that same tier:
  - if 2 out of 6 patients in this tier show toxicity, move to the next tier;
  - if 3 or more of the 6 patients in that tier have toxicity, the dose associated with the lower tier is the MTD[1] ;
- if 3 out of 3 patients show toxicity, the dose associated with the lower tier is the MTD[1] ;

If 3 or more out of 6 patients have toxicity in Tier 0, include 3 patients in Tier - 1 :

- if fewer than 3 patients have toxicity, include 3 additional patients at that tier; if fewer than 3 of the 6 patients have toxicity, then the dose associated with the -1 tier is the MTD;
- if 3 out of 3 patients, or at least 3 out of 6 patients show toxicity, then there is no MTD.

A total of six patients should be included at the LMD level, even in the absence of a DLT. In the absence of a DLT, Tier 3 will be used for Phase II.

If no DMT is identified, then the protocol is not continued in Phase II.

Following Phase I, the dose level selected is level -1.

b. PHASE II: estimation of efficacy and tolerance

It will be performed at the maximum tolerated dose of 5FU and panitumumab determined in Phase I. Patients who were treated at this dose in Phase I will not be retained for Phase II due to the deletion of the free interval at S6 and S7.
An interim safety analysis will be performed after the inclusion of the first 12 new patients in Phase II to ensure the validity of the MTD estimated in Phase I.

2. Experimental treatment

a. Panitumumab

Panitumumab will be supplied in a vial containing a 20 mg/ml solution of panitumumab. One vial is used for a single course of panitumumab. Vials should be stored at 2-8°C and protected from light until use.

For administration, panitumumab should be diluted in 100 ml of saline (concentration should not exceed 10mg/ml). The diluted solution should be infused within 6 hours if stored at room temperature or within 24 hours if stored at 2-8°C.

The dose of Panitumumab is **3 mg/kg** (according to the -1 tier retained by Phase I) and to be administered every 2 weeks (14 days) starting at D1 of S1, i.e. at **D1, D15, D29, and then at D1 week 7.**

Administration is done before chemotherapy, intravenously in an infusion equipped with a filter (filter pore size = 0.2 or 0.22 µm) and connected to a pump.

The recommended infusion time is 60 minutes. If the first infusion is well tolerated, subsequent infusions can be given over 30 to 60 minutes. Doses above 1000 mg should be administered over 90 minutes.

If the total infusion volume exceeds 150 ml, the treatment can be administered over 90 +/-15 minutes.
Caution: Panitumumab should not be administered as a bolus, mixed or infused simultaneously with any other product. The infusion should be flushed with saline before and after administration of panitumumab.

Reduce the infusion rate in patients with mild to moderate infusion-related reactions (CTCAE v4.0 grades 1 and 2) for the duration of this infusion. Maintain this reduced infusion rate for all subsequent infusions.
If a severe or life-threatening reaction occurs during an infusion or at any time after an infusion, panitumumab should be permanently stopped.
.

Anti-allergic premedication is not necessary for the administration of panitumumab. In case of a reaction, pre-medication with an anti-histamine may be introduced for subsequent infusions.
Prophylactic treatment of acne may be proposed (see treatments associated with panitumumab, paragraph VI).

Empty and expired vials will be kept by the center's pharmacy. The green light for the destruction of empty and/or expired vials will be given by the Sponsor.

For further information on panitumumab, please refer to the product's SPC (Appendix 7).

b. Chemotherapy 5FU + mitomycin

Two concomitant treatments with radiotherapy (treatment 1 from D1 to D4 of week 1 and treatment 2 from D1 to D4 of week 5 according to the following modalities:

- Mitomycin C (on Day 1 of the 2 courses): 10 mg/m² in bolus, not exceeding 20 mg per course
- 5FU: 400 mg/m²/d (dose retained at stage -1 of phase I) whatever the body surface and according to the dose stage determined in phase I, in continuous infusion over 4 days in G5% (QSP portable diffuser or syringe pump)

Systemic prophylaxis with growth factors (G-CSF or others) is strongly recommended to reduce the risk of neutropenia.

c. Radiotherapy

Radiation therapy should be performed with intensity modulation (either conformal radiation therapy with intensity modulation or tomotherapy), using photons of energy greater than or equal to 6 MV.

Radiation therapy will consist of two parts:

- A 1ère part will deliver a dose of 45 Gy in 25 fractions of 1.8 Gy, (at a rate of one session per day, 5 days/7, over 5 weeks) in a volume including the tumor and the lymph node drainage areas

- A 2ème part, will deliver a complement of 20 Gy in 10 fractions of 2 Gy in a volume including the tumor and the initially invaded lymph nodes.

Treatment position:

The patient will be treated in the supine position. A restraint system is desirable to ensure better reproducibility of patient positioning.

Centering Scanner:

The CT scan will be performed without and with injection of contrast medium at the arterial time, and in the treatment position, in contiguous sections of 3 to 5 mm maximum.

The acquisition volume of the scanner will start above L3 and end below the lesser trochanters.

Margin marking with a wire or a lead ball may be useful, as well as in case of skin extension of the tumor beyond the anal margin.

The centering scan as well as the treatment sessions will be performed with a full bladder, asking the patient to drink 500 ml of water, 30 minutes before the scan or the irradiation session.

Contouring of target volumes and critical organs:

The contouring will be performed taking into account the data of the clinical examination and the paraclinical examinations (echo-endoscopy, pelvic MRI, PET scan if performed outside the trial). A fusion of the PET scan or even the pelvic MRI with the centring scan is recommended to help delineate the tumour and lymph node volume.

The **GTV (Gross Tumor Volume)** includes the primary tumor and the lymph nodes considered pathological at the initial workup.

The **CTV (Clinical Target Volume)** includes the GTV as well as areas at risk of microscopic invasion:

- bilateral inguinal chains-external iliac ganglion chains
- obturator and internal iliac chains (these chains will be outlined with a 7 mm margin around the arteriovenous axes of the same name, excluding muscular and bony structures)
- ischio-rectal fossae
- mesorectum and presacral space
- anal canal and anal margin

The **PTV1 (Planning Target Volume)** includes the CTV + a margin of 8 mm

The PTV2 (corresponding to the volume irradiated during the second part of the irradiation) includes the GTV + a margin of 8 mm.

Critical organs:

- Bladder
- Right and left femoral heads: from the upper end to the upper part of the lesser trochanter
- External genitalia: penis and scrotum in men, vulva in women
- Iliac crests: from the upper end to the acetabulum
- Small intestine and colon will be outlined in the same block called digestive volume

Dose prescription and constraints:

They will be validated by the realization of dose-volume histograms.

Intensity modulation :

The prescription of the dose will be done according to the ICRU 62 criteria:

- The dose is prescribed at the median of the PTV

- 95% of the volume must receive 95% of the dose
- 98% of the volume must receive at least 90% of the dose
- 3% of the volume should not receive more than 107% of the dose.

Dose constraints:

The proposed dose constraints serve as a basis for optimization in IMRT. The priority remains the coverage of the PTV :

From this point of view, the creation of "OAR - PTV" type structures helps in the optimization, as well as phantom structures (or dummies) can be designed with the objective of conforming the dose to the volume of the PTV.

Volume	Prescription	Isodose of prescription
PTV 45		- The dose is prescribed at the median of the PTV - 95% of the volume must receive 95% of the dose, i.e. 42.75 Gy - 98% of the volume must receive at least 90% of the dose, i.e. 40.5 Gy - 3% of the volume must not receive more than 107% of the dose, i.e. 48.15 Gy
PTV 65	**45 Gy/1.8 + 20 Gy/2**	- The dose is prescribed at the median of the PTV - 95% of the volume must receive 95% of the dose, i.e. 61.75 Gy - 98% of the volume must receive at least 90% of the dose, i.e. 58.5 Gy - 3% of the volume should not receive more than 107% of the dose, i.e. 69.55 Gy

SRO	TOLERANCES
	Constraints
Digestive - PTV	**V30Gy** < 400 cc/ 40
	V35Gy < 300 cc/30
	V45Gy < 200 cc/20%.
Vessie-PTV	**V50 Gy<** 5% (1)
	V40 Gy < 35
	V35 Gy < 50
EMB	**V50 Gy** < 5
	V40 Gy < 60
Iliac crests	**V10 Gy** < 45
	V20 Gy < 30
Femoral heads	**V44 Gy** < 5
	V40 Gy < 35
	V30 Gy < 30

Treatment quality control:
A verification of the treatment isocenter and the shape of the beams by portal imaging or gammagraphy will be performed during the first two sessions and then once a week.

In addition, the patient will be seen weekly by the radiotherapist to evaluate the tolerance of the treatment (NCI-CTC-AE toxicity scale version 4.0 (Appendix 8)).

VI. DISCONTINUATION CRITERIA - DOSE ADJUSTMENT - TREATMENT OF TOXIC EFFECTS

Toxicities will be evaluated before each treatment by questioning, clinical examination and biology, and graded according to the NCI version 4.0 criteria (Appendix 8). Toxicities observed during the treatment will be reported in the observation book.
Dose adjustments are planned in case of toxicity observed 48 hours before the treatment or on the day of the treatment.

Doses that have been reduced for toxicity should not be increased again.

1. Deferral and dose adjustment for 5FU

Type of toxicity	Toxicity grade (NCI-CTC v4.0) on day of treatment	Adjustment of 5FU dosage
Non-hematological toxicity	0-1	No change
	2	Decrease daily dose by 25
	3-4	Delay treatment until toxicity is reduced to a grade $\leq$ 1. Resume with a 25% decrease in daily dose. The reduction in dosage is maintained for the current course and the remainder of the treatment.
Hematological toxicity	0-1	No change.
	2-4	Postponement of treatment until grade $\leq$ 1 then Resumption with a 25% reduction of 5 FU for the current treatment and the rest of the treatment.
Toxicity after initial dose adjustment	0-2	No change
	3-4	Stopping chemotherapy

2. Deferral and dose adjustment for mitomycin C

Type of toxicity	Toxicity grade (NCI-CTC v4.0) on day of treatment	Adjustment of mitomycin dosage
Non-hematological toxicity (except Panitumumab-related skin toxicity)	0-2	No change
	3-4	Postponement of treatment until grade $\leq$ 1. Resume at 8 mg/m^2
Hematological toxicity	0-1	No change.
	2	Postponement of treatment until grade $\leq$ 1 then 100% recovery
	3-4	Postponement of treatment until grade $\leq$ 1. Resume at 8 mg/m^2
Toxicity after initial dose adjustment	0-2	No change.
	3-4	Stopping chemotherapy

Chemotherapy is permanently discontinued when there is a recurrence of grade 3-4 toxicity after an initial dose adjustment. Systemic prophylaxis with growth factors (G-CSF or others) is recommended to reduce the risk of neutropenia.

3. Deferral and dose adjustment for Panitumumab

Panitumumab treatment may be delayed for up to 2 weeks. Panitumumab may be restarted at 100% or reduced dose based on observed toxicities.
Panitumumab treatment should be permanently discontinued in cases where more than 2 consecutive infusions have not been administered at any dose.

Skin and Nail Toxicity (NCI CTC version 3.0 with modifications)

Relative skin and nail toxicities will be graded according to the modified NCI-CTC Version 3 scale:

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Nail modification	Discoloration, wrink (koilonychia) paronychia: unnecessary treatment	Complete or partial loss of nails, nail pain, paronychia: necessary treatment	Difficulty in the gestures of daily living (ADL)	___
Erythema	Erythema without pain	Painful erythema	Erythema with desquamation*.	Vital prognosis engaged
Pruritus/itching	Moderate or localized	Intense or generalized	Intense or generalized disturbance of the gestures of daily life	___
Acneiform rash	Unnecessary treatment	Treatment required	Associated with pain requiring morphine analgesics, ulceration, or desquamation*.	___
Skin rash/desquamation	Asymptomatic maculopapular or erythematous rash	Asymptomatic maculopapular or erythematous rash with pruritus or other associated symptoms; localized scaling or other lesions covering less than 50% of the body surface (BSA)	Severe, generalized erythroderma or rash, vesicular scaling * covering more than 50% of the body surface (BSA)	Generalized ulceration or bullous dermatosis
Ulceration	___	superficial ulceration < 2 cm, local treatments, requiring	Ulceration≥ 2 cm, surgical debridement, primary closure or other invasive procedure required (e.g. hyperbaric chamber)	Vital prognosis; major intervention required (e.g. complete tissue resection, reconstruction, grafting)

*Desquamation is defined as skin peeling and not skin detachment.

Type of toxicity (NCI-CTC v4.0)	
skin and nail (V3.0)	non-cutaneous and non-nail (V4.0)

Grade 1 or 2 - initiation of anti-acne treatment ⇨ no panitumumab dose offset or reduction	**Grade 1 or** 2 - treatment of symptoms ⇨ no panitumumab dose offset or reduction
Grade 3 or 4 - symptoms requiring corticosteroids or intolerable for the patient, - infection requiring antibiotics or antifungals, - need for surgical debridement ⇨ cancel the treatment and start the next treatment Secondary effect returned to a **grade≤ 2** - patients who have regained tolerable skin or nail symptoms and no longer require systemic treatment with corticosteroids, antibiotics or antifungals. A dermatological opinion is required ⇨ resumption of 100% panitumumab after 1 or 2 weeks of deferral	**Any grade 3 or 4 toxicity including** - symptomatic hypomagnesemia and/or hypocalcemia persisting despite supplementation - nausea, diarrhea or grade 3 or 4 vomiting despite maximum symptomatic treatment, - anemia and/or thrombocytopenia grade 3 or 4 despite transfusions ⇨ delay panitumumab administration until grade ≤ 1 Secondary effect returned to a **grade≤ 1** ⇨ resumption of treatment at : 100% at 1er episode. 80% at 2ème episode 60% at 3ème episode Final stop at 4ème episode Once the panitumumab dosage is reduced, it will be saved for subsequent infusions.

No discontinuation of CT (5 FU + mito) and RT in case of Panitumumab-related skin toxicities. Panitumumab should be withheld or discontinued if dermatologic or soft tissue toxicity occurs with severe or life-threatening inflammatory or infectious complications.

4. Deferral and dose adjustment of radiation therapy

Type of toxicity	Toxicity grade (NCI-CTC v4.0)	Adaptation of radiotherapy
Digestive toxicity: diarrhea	0	No change
	1-2	Prescription of transit slowers, continuation of radiotherapy
	3-4	Stopping radiation therapy sessions, resuming from a grade < 2
Hematological toxicity	0-2	No change.
	3-4	Stopping the sessions until grade ≤ 2

5. Associated treatments

With chemotherapy

- Anti-emetic treatment with metoclopropamide or setron if necessary
- If chest pain: stop 5 FU; do ECG and cardiac enzymes
- If hand-foot syndrome: moisturizing lotion, greasy creams
- If severe mucositis: mouthwash with bicarbonate at 14^0 /$_{00}$, fungizone oral suspension, Xylocaine® viscous if pain and acyclovir if history of herpes.

- If diarrhea: loperamide at first loose stool take loperamide 2 capsules after each loose stool. If diarrhea persists after 48 hours despite treatment or in case of concomitant vomiting, fever or neutropenia, rapid hospitalization is necessary.
- Corticosteroids are authorized on an occasional basis, for anti-emetic purposes, but are not recommended for long-term use.
- The use of a cooling helmet is allowed
- All other anti-cancer treatments are prohibited
- Contraindicated with 5FU and Mitomycin C: Phenytoin, yellow fever vaccine, live attenuated vaccines
- Systemic prophylaxis with growth factors (G-CSF or others) is recommended to reduce the risk of neutropenia.

With panitumumab

Preventive and active treatment for skin toxicities such as acneiform rash:
To be started 24 hours before the start of panitumumab treatment and continued for at least 6 weeks depending on the patient and the type of skin toxicity:
- In case of skin dryness, the use of emollient creams is beneficial. To be applied to the face, hands, feet, neck, back and chest

CAUTION: CREAM APPLICATIONS in the irradiated area (pelvis) MUST NOT BE DONE BEFORE RADIOTHERAPY SESSIONS

- Skin cracks may occur in case of dryness; they can be treated with dressings
- A local anti-acne treatment (e.g. benzoyl peroxide, erythromycin) or systemic antibiotic therapy (e.g. tetracycline such as doxycycline 200 mg/day) may be considered. The patient should then avoid sun exposure.
- Anti-UV creams are recommended.
- In case of pruritus, oral treatment with antihistamines is recommended.

Preventive treatment of nail lesions:
- A consultation with a pedicurist is recommended.

In case of skin lesions, refer to the recommendations of the national digestive cancer thesaurus (www.tncd.org) in the chapter on metastatic colon cancer.

With radiotherapy

- A residue-free diet will be recommended from the beginning of the radiotherapy treatment and throughout its duration.
- The main digestive toxicity expected is the occurrence of diarrhea, justifying, as of grade 1, the prescription of transit slowing agents to which intestinal dressings may be associated. Compliance with the residue-free diet should also be checked. If diarrhea persists after 48 hours despite treatment or in the event of concomitant vomiting, fever or neutropenia, rapid hospitalization is necessary
- Radioepithelitis (inguinal folds in particular) may appear from the third week of radiotherapy treatment: applications of biafine-type cream may be suggested after the radiotherapy session.
- If there is a reaction at the anal margin, sitz baths can be offered.
- Any application of alcoholic lotions, irritating products, at the level of the irradiated zone is disadvised
- Sitz baths may be suggested, as well as applications of biafine after the radiotherapy session **(any application of cream to the treated area before the radiotherapy session is to be avoided**).

VII. DURATION OF TREATMENT

The treatment consists of two sequences. The initial treatment lasts 5 weeks, followed by an additional 2 weeks of radiochemotherapy.
An evaluation is performed at week 6. If there is no response or progression, surgical resection may be decided. Treatment may be stopped prematurely for the following reasons

- Toxicity
- Progression of the disease
- Refusal to continue the trial
- Lost to view

Whenever possible, patients who have stopped their treatment prematurely will be followed up in the same way as other patients.

VIII. FOLLOW-UP OF PATIENTS DURING AND AFTER TREATMENT DISCONTINUATION

1. Before each course of chemotherapy

Within 48 hours before the treatment:

- Assessment of tolerance to chemotherapy and radiotherapy (NCI-CTC criteria version 4.0 - appendix 8)
- Proctological examination, weight, general condition WHO
- CBC/platelets, creatinine, transaminases (AST and ALT), alkaline phosphatases
- If Panitumumab is discontinued, electrolyte levels (K^+ , Na^{2+} , Ca^{2+} , Mg^{2+})

2. Once a week during radiation therapy

- Weight,
- General status WHO
- Toxicity assessment: NCI-CTC-AE version 4.0 toxicity scale (Appendix 8)

3. Before each administration of Panitumumab

- CBC-platelets
- Blood ionogram and electrolytes (K^+ , Na^{2+} , Ca^{2+} , Mg^{2+})

4. Assessment at 6 weeks

- Proctological examination, weight, general condition WHO
- CBC/platelets, blood ionogram + electrolyte (K^+ , Na^{2+} , Ca^{2+} , Mg^{2+}), creatinine, albumin, AST, ALT, alkaline phosphatases, GGT, total and conjugated bilirubin, SCC marker.
- Pelvic MRI **and/or** rectal echo-endoscopy. **Use the same technique as for the initial evaluation**.
- Quality of life assessment (QLQC30 + JORGE and WEXNER questionnaire)

Make a CD-ROM copy of the images that will be retrieved by the FFCD in order to transmit them to the independent committee if needed.

5. Assessment 8 weeks after the end of the treatment if no deferral

- Proctological examination, weight, general condition WHO
- CBC-platelets, blood ionogram + electrolyte (K^+ , Na^{2+} , Ca^{2+} , Mg^{2+}), creatinine, albumin, AST, ALT, alkaline phosphatases, GGT, total and conjugated bilirubin, CSC
- Abdominal-pelvic MRI **and/or** rectal echo-endoscopy. **Use the same technique as for the initial evaluation**
- Thoracic-abdominal-pelvic CT
- Quality of life assessment (QLQ-C30 + JORGE and WEXNER questionnaire)

- Effective contraception in women and/or men of childbearing age for up to 6 months after the end of treatment

Make a CD-ROM copy of the images that will be retrieved by the FFCD in order to transmit them to the independent committee if needed.

6. Check-ups every 4 months for 2 years after the end of treatment

- NFS-Plates
- Proctological examination, weight, general condition WHO
- SCC
- Pelvic MRI and/or rectal echo-endoscopy. **Use the same technique as for the** initial **evaluation**
- Thoracic-abdominal-pelvic CT
- Optional PET scan 6 months after the end of treatment
- Quality of life assessment (QLQC30 + JORGE and WEXNER questionnaire)
- Effective contraception in women and/or men of childbearing age for up to 6 months after the end of treatment

7. Check-ups every 6 months for 3 years

- NFS-Plates
- Proctological examination, weight, general condition WHO
- SCC
- Pelvic MRI and/or rectal echo-endoscopy. **Use the same technique as for the** initial **evaluation**
- Thoracic-abdominal-pelvic CT
- Quality of life assessment (QLQC30 + JORGE and WEXNER questionnaire)

Protocol monitoring will be discontinued in case of tumor recurrence

IX. ANCILLARY RESEARCH

There are 3 translational biology studies performed on 3 different biological collections (Appendix 1).
Participation in ancillary research is optional.
For details of these 3 studies, please refer to Appendix 1 of the protocol.

1. Analysis of signaling pathways (Phase I and II)

Samples: 4 biopsy specimens obtained at diagnosis, from tumor tissue fixed in formalin and embedded in kerosene.

Sending: The blocks will be sent to the PRODIGE Biological Resource Center (45 rue des saints pères 75006 Paris) (Pr Pierre Laurent-Puig).

2. Study of local and peripheral anti-tumor immune response as a predictor of overall response (circulating immunocompetent cells) (Phase II only)

This study will be implemented for Phase II.
Samples: Collection of 5 ACD tubes (7 ml)

Sampling schedule :

- before the start of treatment (D0 or T0), before the panitumumab infusion
- 8 weeks after the end of the treatment (S15 if no postponement of treatment)

That is a total of 2 samples (10 tubes) for each patient.

Shipment of samples: Blood samples will be sent at room temperature by DHL to the Biological Resource Center (BRC) of PRODIGE (45 rue des Saints Pères 75006 Paris) (Pr Pierre Laurent-Puig).
PBMCs will be isolated, frozen and stored on site; RNAs will be extracted extemporaneously and stored on site.

3. Sampling for pharmacokinetic study (mandatory for Phase I and optional for Phase II)

The pharmacokinetic study is mandatory for Phase I and optional for Phase II.

Samples: Collect one dry tube (5 ml) for measurement of serum panitumumab concentrations. Complete the sample identification form

Tube preparation and shipping:
At each sampling :

- Identify the tube (patient initials + inclusion number + sampling time).
- Put the blood tube + the pharmacokinetic sheet* corresponding to the sample(s) in the DHL box.
- Call DHL within 24 hours for collection (delivery within 48 hours after collection). If there is a delay between collection and pick-up, keep the tube at 4°C.
- At the same time, notify the CRB of Tours of the shipment:
  Contact : Mrs Ludivine Diot or Mrs Coraline Gadras
  Phone : 02.47.36.01.73
  Opening hours: Monday to Friday from 9:30 am to 5 pm
  Address : CRB de Tours, EFS - Hôpital Bretonneau, 2 boulevard Tonnellé, 37044 Tours cedex 9

*Note on the PK sheet the exact dates and times of the start and duration of the panitumumab infusion corresponding to the sample(s) as well as the dates and times of the PK sample(s).

At the end of the study, the tubes will be sent in a group to the pharmacology-toxicology laboratory of the CHRU of Tours (Pr Gilles PAINTAUD) where the panitumumab assays will be performed by ELISA technique.

Sampling schedule PHASE I:

- before each panitumumab infusion at weeks 3, 5, 8 and 10 [PaniT0].
- 2 hours after completion of panitumumab infusion at weeks 1, 3 and 8 [PaniT2h].
- 24 hours after the end of the panitumumab infusion at week 3 (in practice when the patient comes to the radiotherapy session the day after the panitumumab infusion) [PaniT1j]
- 7 days after the 2ème panitumumab infusion, i.e. beginning of week 4 [PaniT7j].
- After 5FU in weeks 1 and 8 (weekend)

That is a total of 11 samples for each patient in Phase I.

Sampling schedule PHASE II :

- before the 3ième panitumumab infusion

That is a total of 1 sample for each patient in Phase II.

X. SAFETY ASSESSMENT

1. Security assessment parameters

Safety will be assessed by evaluating the general, clinical and biological status of patients at the time of scheduled visits and by collecting events occurring between visits. Toxicities will be assessed using the NCI-CTC-AE version 4.0 toxicity scale (Appendix 8).
In case of an emergency, the patient, his family or his physician should call the investigator to inform him of an event.

2. Definitions

a. Adverse Event (AE)

An adverse event is a harmful occurrence in a person who is a subject of biomedical research, whether or not the occurrence is related to the research or the product being investigated.

All adverse events will be recorded in the observation book on the pages provided.

b. Serious Adverse Event (SAE)

A serious adverse event is any event that meets at least one of the following criteria:

- Resulting in death,
- Life-threatening,
- Leading to hospitalization or prolonged hospitalization,
- Causing permanent disability or severe temporary incapacity,
- Causing a birth defect, fetal malformation or abortion,
- Medically significant (examples: overdoses, second cancers, pregnancies and new developments may be considered medically significant)

The terms disability and incapacity correspond to any temporary or permanent physical or psychological handicap, clinically significant and affecting the physical activity and/or quality of life of the patient.
Any clinical event or laboratory result considered serious by the investigator and not corresponding to the severity criteria defined above is considered medically significant. They may put the patient at risk and require medical intervention to prevent an outcome corresponding to one of the above mentioned severity criteria (e.g. overdose, second cancers, pregnancies and new events may be considered as medically significant).
Pregnancy is an exclusion criterion in this trial. However, if a pregnancy is discovered after inclusion, the patient must be excluded from the trial. The sponsor should be informed without delay via the serious adverse event reporting form (no severity criteria should be checked). The patient should be followed until the outcome of the pregnancy and this outcome, whatever it may be, should be reported to the sponsor.

Disease progression should not be considered as an SAE. Events that are potentially related to progression but may also be secondary to treatment will continue to be reported (e.g. thromboembolic events, perforations, etc.)
Due to the severity of the disease in this study, certain conditions defined as SAEs will be excluded from the SAE reporting procedure, namely:
- Hospitalization as per protocol
- Hospitalization or surgery specifically related to the treatment of the disease
- Hospitalization performed to simplify study treatments or procedures

c. Undesirable Effect

Any noxious and unintended response to an investigational drug at any dose or to any investigational component. An adverse reaction is serious if it meets the severity criteria (see above).

d. Unexpected Serious Adverse Effect

A serious unexpected adverse reaction is an event that is not mentioned, or is different in nature, intensity, or evolution compared to the product reference document

In this essay the reference documents will be:

- For panitumumab, the Investigator's Brochure version 14.0 or its latest update

- For 5-fluorouracil, the Summary of Product Characteristics for **FLUOROURACILE EBEWE** (Appendix 7)
- For mitomycin C, the Summary of Product Characteristics for Ametycin® (Appendix 7)

The versions of the PCRs used for the definition of expected or unexpected will be the latest available on the anniversary date of the start of the trial.

3. Course of action

The investigator informs the sponsor of all Serious Adverse Events (Expected and Unexpected), whether or not attributable to the research, that occur during treatment and within 30 days of the last treatment administration.

All Delayed Serious Adverse Events (occurring after this 30-day period) considered reasonably related to the protocol treatment(s) or research should be reported without time limitation.

The report is made by faxing the "notification of a serious adverse event" form (Appendix 9), documented as precisely as possible, dated and signed, within 24 working hours of their discovery to the **FFCD's Randomization Management Analysis Center (CRGA): by fax to 03 80 38 18 41**

Modalities and duration of follow-up of individuals following the occurrence of adverse events
The investigator is responsible for appropriate medical follow-up of patients until resolution or stabilization of the effect or until the patient's death. This may sometimes mean that this follow-up extends beyond the patient's discharge from the trial.

He/she transmits the additional information to the sponsor using an SAE reporting form (checking the Follow-up No. X box to specify that it is a follow-up report and not an initial report) within 24 hours of obtaining it. It also forwards the last follow-up to the resolution or stabilization of the SAE. Responds to requests for additional information to document the initial observation.
He keeps the documents concerning the suspected adverse reaction in order to allow, if necessary, to complete the information previously transmitted.

The sponsor is responsible, upon receipt of the investigator's report of the serious adverse event, for issuing an opinion on the causal relationship between the serious adverse event and the study product(s).
If the serious adverse event is linked by the investigator and/or sponsor to one of the study products (i.e., it is a serious adverse event), the investigator and/or sponsor must establish the expected or unexpected nature of the event.
If it is a serious unexpected adverse reaction, or if it is a new fact, the sponsor writes an initial report which will be transmitted to the ANSM, the CPP and the EMA (via EudraVigilance) within 7 days in case of death or life-threatening situation, otherwise within 15 days.
If it is an expected serious adverse event, it will be collected for the semi-annual and annual safety reports.

XI. JUDGING CRITERIA, DATA MANAGEMENT AND STATISTICS

1. Response criteria

Response criteria will be defined based on clinical and morphological examinations performed at patient inclusion, at 6 weeks, 8 weeks after the end of treatment (week 15) and 24 weeks (6 months) after the end of treatment.
These criteria are detailed in the table below:

Response to treatment	Criterion
Full answer	Disappearance of all lesions on all examinations

Partial response	Tumor shrinkage of at least 30% on imaging or significant shrinkage on clinical examination*.
Progressive disease	Increase of at least 20% on imaging or significant on clinical examination*.
Stable disease	No progression, no complete response, no partial response

* Tumor size will be measured in the largest dimension on any imaging

2. Primary endpoint: complete response rate 8 weeks after the end of treatment

It is defined by the complete disappearance of the tumor on proctological examination and morphological examinations (MRI and/or echo-endoscopy) and the absence of the appearance of a secondary lesion, a response validated by an independent committee (see paragraph XI.8)

3. Secondary criteria

- Intermediate objective response rate (complete and partial) at 6 weeks. The rate of 80% decrease in the largest tumor diameter will also be recorded.

- Objective response rate 16 weeks after the end of treatment

- Partial response rate, stability and progression 8 weeks after the end of treatment

- Survival without colostomy: analysis of time interval from date of inclusion to date of colostomy or death if no colostomy. Patients alive without a colostomy will be censored at the last count. Colostomy-free survival will be estimated at 3 years. If a patient has a bypass colostomy and continuity is restored at 3 years, the patient will be counted as a colostomy-free patient.

- Recurrence-free survival: analysis of the time interval from the date of inclusion to the date of first recurrence (local, regional, metastatic and second anal cancer) or death in the absence of recurrence. Living patients without recurrence will be censored at last count. Second cancers other than anal will be censored. Recurrence-free survival will be estimated at 3 years.

- Overall survival: analysis of the time interval between the date of inclusion and the date of death (regardless of cause). Living patients will be censored at last count. Overall survival will be estimated at 3 years.

- Quality of life (EORTC QLQ-C30 + Jorge and Wexner questionnaire): the global quality of life will be assessed using the EORTC QLQ-C30 questionnaire (version 3). In particular, the evolution of the global health score and the fatigue score will be described. A difference of 5 points in these scores will be considered as the minimum to define a clinical difference. A sensitivity analysis will be performed using a difference of 10 points as the minimum difference. Quality of life, for global health and fatigue, will be characterized by the rates of patients with an improved, deteriorated or stabilized score, as well as by the time to definitive deterioration of the score.
Time to definitive deterioration of a score will be defined as the time interval between the date of inclusion and the first date of a score decrease of more than 5 points with no subsequent improvement of more than 5 points or with no subsequent available score. Patients alive or deceased without a score decrease of more than 5 points or with a score decrease of more than 5 points with a subsequent improvement of more than 5 points will be censored at the latest. A sensitivity analysis will be performed using a minimum difference of 10 points.
The impact of incontinence on quality of life will be measured by the Jorge and Wexner score. A difference of 2 points in this score will be considered the minimum to define a clinical difference.

The rates of patients with an improved, deteriorated or stabilized score will be calculated, as well as the time to final deterioration of this score.

4. Management

The CRGA in Dijon (Tel: 03 80 66 80 13; Fax: 03 80 38 18 41) will be responsible for data management and analysis.
A clinical research associate (CRA), designated by the FFCD, may complete the case report forms under the supervision of the center's investigator. A copy of the case report forms will be sent to the CRGA in Dijon by the investigator. The CRGA will validate the data and send correction requests to the investigator in case of errors or incomplete data.

5. Statistical methodology

The study is a Phase I-II trial evaluating the safety and efficacy of the Panitumumab - RTCT combination.

Three populations are defined according to the criterion studied:

- the strict intention-to-treat (ITT) population, corresponding to all patients included regardless of their eligibility criteria and the treatment received;
- the per-protocol (PP) population, corresponding to the ITT population without major protocol deviations;
- the population for the phase II safety analysis (SP), corresponding to all ITT patients who received at least one dose of 5FU + mitomycin + panitumumab and one radiation session.

The primary analysis of the Phase II trial will be done on a strict intention-to-treat (ITT) basis. A secondary analysis will be performed on the per-protocol population.

6. Number of subjects needed

Phase I
A minimum of 6 and a maximum of 24 patients will be included, corresponding to a minimum of 3 patients per dose level (and 6 at the maximum tolerated dose).
The 6 patients treated at the maximum tolerated dose will be included in the Phase II trial.
A minimum of 9 patients will be required to proceed to Phase II.
Based on the Phase I results, the -1 dose level was selected for the transition to Phase II. In order to follow as closely as possible the treatment practices that have evolved since the launch of Phase I, an amendment to the treatment schedule was made. As a result, patients in the -1 dose level of Phase I will not be analyzed in Phase II.

A suspension of inclusions will be made between each tier and between Phase I and Phase II.

Phase II
The Phase II study will be conducted with the maximum tolerated dose determined in Phase I (=Tier -1).
A 2-step minimax Simon design will be used, with a one-sided α risk of 5% and a power (1-β) of 90%.
The assumptions are:

- H0: A complete response rate 8 weeks after the end of treatment of 60% is considered unattractive;
- H1: A complete response rate of 80% is expected 8 weeks after the end of treatment.

Total number of patients required for Phase II: 45.

Step 1
Include 26 patients (the 6 patients from Phase I - 1 cannot be included in Phase II due to amendment #5). The analysis of step 1 will be performed once complete responses have been determined for each of these 26 patients 8 weeks after the end of their treatment.
During analysis:

- if 15 or fewer patients have a complete response at 8 weeks (58%), then the trial is stopped, as the response rate is not significantly higher than 60%;
- if 16 or more patients have a complete response at 8 weeks (61%), the trial is continued with step 2.

Step 2
Include 19 additional patients. Stage 2 analysis includes the 26 patients from stage 1 and the 19 patients from stage 2.
During analysis:

- if 32 or fewer patients have a complete response at 8 weeks (71%), the complete response rate cannot be considered significantly higher than 60%, no Phase III study is considered.
- if 33 or more patients have a complete response at 8 weeks (73%), the complete response rate is significantly higher than 60%.

The probability of stopping the study at the end of step 1 if H0 cannot be rejected is 48%; the average number of patients included to show that H0 cannot be rejected is 35.9.

Statistical analysis

Continuous variables will be described using means, standard deviations, medians, minimum, and maximum. Categorical variables will be described using frequencies and percentages. Percentages will be calculated with or without the missing modality.

A detailed analysis plan will be defined before the base is frozen.

Analysis of the judging criteria

Response rates will be reported using percentages and numbers with their 95% confidence intervals.
Survival and time estimates will be made by the Kaplan Meier (KM) method. They will be described by median survival times and survival rates at different time points, and their 95% confidence intervals.
Analysis of prognostic factors for complete response will be performed using univariate and multivariate Cox models.
Quality of life scores will be generated according to the algorithms in the EORTC QLQ-C30 manual. These scores will be described at each measurement time.
For overall health, fatigue, and incontinence scores, the rates of patients whose scores improved, deteriorated, or stabilized will be reported by frequencies and percentages.
The times to final deterioration of global health, fatigue, and incontinence scores will also be estimated by the Kaplan Meier method; the median time and rates at different time points, along with their 95% confidence intervals, will be reported.

7. Tolerance analysis

Tolerance analyses will be performed on the SP population.
Adverse events will be reported using frequencies and percentages for all grades, grades 3-4, and by relationship to treatment.
The incidence of SAEs will be described.
Changes in biological values and vital signs will be described using mean (standard deviation),

median, minimum, and maximum.
The dose intensity will be calculated and the changes in the general WHO status will be described.
Deaths related to toxicities and unexpected serious side effects after discontinuation of treatment will be described.

A safety analysis, based on toxicities and SAEs collected during treatment and the first 30 days following its administration, will be performed after the inclusion of the first 12 patients in phase II to ensure the validity of the MTD estimated in phase I and the change in the radiation therapy administration scheme.

8. Independent Committee

An independent committee is set up and includes two physicians (a radiotherapist and an oncologist), and a pharmacovigilance expert.

For Phase I, the independent committee met, among others:

- to review the AEs reported during Phase I;
- after each level to validate the DLTs and determine the passage to the next or next lower level;
- to determine, in view of the toxicities observed during phase I, the passage to phase II, and to confirm the choice of doses according to the definition of the DLT and DMT noted in the protocol.

For Phase II, the independent committee will meet, among others:

- to validate the complete responses to the treatment, based on the reports of the various examinations (clinical and morphological);
  - In the event of a discrepancy between the investigator and the independent committee, the independent committee's response will be used;
  - in case of uncertainty of the investigator on the response, the committee will decide on the response in view of the clinical and morphological data;
  - the Promoter undertakes to provide, at the request of the committee, all additional information necessary for the validation of these answers
- to review the SAEs and serious toxicities reported in Phase II

In Phase II, the committee will meet at the end of Stage 1 and 2.
Advancement to Step 2 will require approval by the Efficacy and Tolerability Data Committee.

The independent committee may also meet at any time during the course of the protocol when deemed necessary by the Sponsor.

XII. INTRODUCTION - RATIONALE OF THE STUDY

1. Treatment of squamous cell carcinoma of the anus

Squamous cell carcinoma of the anus (SCC) accounts for 4% of cancers of the lower digestive tract. Squamous cell carcinoma of the anal canal accounts for 95% of anal canal cancers. Only 5% are metastatic at diagnosis. In addition to female gender and age, homosexuality, HPV infection and smoking are risk factors. Its incidence is increasing and varies by country ($2/10^5$ inhabitants in the United States *vs.* 0.5 to $1.2/10^5$ inhabitants in Switzerland). The incidence has particularly increased in male homosexuals in the last 30 years, with an even more marked increase in HIV-positive male homosexuals in whom anal cancer is twice as frequent as in HIV-negative male homosexuals. In a recent French study, cancer of the duct ranks 4th among cancers in HIV-infected patients (ONCOVIH cohort, provisional results). With the progress of antiretroviral treatments, the prognosis of AECs has improved in HIV-infected patients to reach the prognosis of non-infected patients (1).

Treatment is based on radiochemotherapy for locally advanced tumors. The objective of the treatment is to allow a cure without recourse to abdomino-perineal amputation and with preservation of sphincter function.

The prognosis is essentially related to tumor size and lymph node involvement. The vast majority of patients do not have distant spread of their tumor at the time of diagnosis (2).

Recurrences are essentially loco-regional and require abdominoperineal amputation. This operation is not always possible or not always complete, which then exposes the patient to a particularly painful local evolution with a 3-year survival rate of about 30%. (3).

It is therefore very important to obtain a complete and definitive tumor response from the initial treatment with radiochemotherapy

Radiation therapy techniques have evolved with the development of Intensity Modulated Conformal Radiation Therapy (IMCR), which allows the dose to be tailored to the complex shaped volume to be treated with better homogeneity and coverage while decreasing the dose received by healthy organs (9-10).

2. Treatment by radiotherapy

These dosimetric advantages translate into a reduction in acute toxicities during treatment, which allowed a reduction in the total treatment spread by eliminating or reducing the planned therapeutic pause at the end of the first treatment phase (11-12). The RTOG 0529 trial showed a significant reduction in acute gastrointestinal and hematological toxicities, while reducing the total treatment duration to 43 days (median) compared with 49 days for RTOG 98-11 (11;14). This break (or free interval) was necessary with non-intensity-modulated conformal radiotherapy techniques because of the acute toxicity of the treatment, and was routinely planned in phase 1 of the study. Nevertheless, recent studies with intensity modulation have shown that a short spread (total treatment time) was significantly associated with tumor response and survival: current recommendations are to eliminate the break between the first and second phase of treatment (15-16). Rationale for radiochemotherapy with 5FU + mitomycin

Non-surgical treatment of localized AECs initially relied on radiotherapy alone (4). However, the local control rate of large tumors was insufficient. It was then demonstrated that the combination of radiotherapy + chemotherapy with 5FU-mitomycin improved local control and survival (5; 6). The combination of 5FU + mitomycin + radiotherapy provides better local control than the combination of 5FU + radiotherapy (7). Finally, a recent randomized trial showed that the combination of chemotherapy with radiotherapy 5FU + cisplatin was not superior to the combination of 5FU + mitomycin and that there was no benefit to perform induction chemotherapy before radiotherapy. (8). The data from the ACCORD 03 trial coordinated by D. Peiffert confirm the absence of benefit of induction treatment (17). Finally, the long-term results of the RTOG 9811 trial confirm the superiority of the combination of mitomycin and 5FU over the combination of platinum and 5FU, both in terms of overall survival and recurrence-free survival (14)

With the combination of radiotherapy + 5FU + mitomycin, the complete response rate is about 80% and the 3-year recurrence-free survival is 67%. (6) and the recurrence-free survival at 3 years is 67% and the colostomy rate at 3 years is 10%. (8).

3. Rationale for combining radiochemotherapy with anti-EGFR therapy

EGFR receptor expression increases progressively in preneoplastic lesions of the anus, depending on their grade, up to cancer (18-20) which makes it possible to consider the EGFR receptor as a therapeutic target. There are currently no results from studies that have combined radiotherapy, chemotherapy and anti-EGFR targeted therapy in anal cancers.

The use of a monoclonal antibody directed against the EGF receptor results in an increased response to radiotherapy of tumour lines both in vitro and in vivo (21). In ENT squamous cell carcinoma, the addition of an anti-EGFR antibody to cisplatin has been shown to significantly increase the response rate to local and/or metastatic recurrence compared to cisplatin alone (22). In addition, the use of an anti-EGFR antibody in combination with exclusive radiotherapy in ENT cancers increased the recurrence-free survival and overall survival of these

patients (23). These data support the use of a combination of chemotherapy and anti-EGFR antibody in anal squamous cell carcinoma.

The combination of panitumumab with radio-chemotherapy has never been tested. In the study by Ajani et al, the grade 4 toxicity rate of the combination of 5FU + mitomycin + radiotherapy reached 34%. (8).

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XIII. LEGAL AND ETHICAL ASPECTS ADMINISTRATIVE CONSIDERATIONS

1. Study sponsor

The sponsor of the study is the Fédération Francophone de Cancérologie Digestive (FFCD). The study was registered under the number EudraCT 2011-005436-26.

2. Reminder of the texts in force

This test will be carried out according to the new European Directive 2001/20/EC.

3. Public liability insurance

Insurance was purchased by the sponsor on 10/26/2011 from SHAM insurance under number 137681, in accordance with Article L 1121-10 of the Public Health Code (Appendix 11).

4. Application for authorization to the CPP and AFSSAPS

This protocol was authorized by the CPP (Committee for the Protection of Individuals) ILE DE FRANCE X on 09/02/2012 (appendix 12).
This protocol received a favorable opinion from the AFSSAPS (French Agency for the Safety of Health Products) on 12/03/2012 (appendix 13).

5. Collection of the patient's consent

The investigator undertakes to collect, after information, the clinical and biological consents of the patient in writing (information sheets and consent forms in appendices 2 and 3). A copy of these consents must be kept by the investigator for 15 years, to be presented to the supervisory authorities in case of inspection. The original must be given to the patient.

6. Hospital management information and research agreement

Prior to the implementation of the study, the hospital management will be informed by the sponsor of the investigator's interest in participating in this trial.
A no-cost research agreement will be established between the investigating center administrator and the sponsor.
Data archiving
The files will remain confidential and can only be consulted under the responsibility of the doctors in charge of the patients. The sponsor and the health authorities in case of inspection will have direct access to these documents.
At the end of the trial, the observation book will be kept for 15 years by the investigator.

7. Computer support

In accordance with the text of the law n° 78-17 of January 6, 1978 modified by the law of August 9, 2004, relating to data processing, files and freedoms, the data of the trial will be recorded in a data bank of the Center of Randomization and Management Analysis of the FFCD, with the exception of the elements relating to the identity of the patients.

8. Data processing

The FFCD's Center for Randomization Management and Analysis (CRGA) will be responsible for data management and analysis.

9. Monitoring, quality assurance and inspections by authorities

The investigator agrees in advance that the records of the patients included in the trial may be consulted by a person mandated by the FFCD and/or by the health authorities to conduct an audit. On-site visits to the files, scheduled after agreement by the investigator, may take place during or after the period of inclusion in the trial
This protocol will be monitored by the FFCD's mobile ARCs.

XIV. PUBLICATION

The current FFCD publication rules will be applied (Appendix 10)

XV. APPENDICES