Phase I-II trial of radiochemotherapy combined with Panitumumab in the treatment of localized squamous cell carcinoma of the anus

FFCD 0904

Statistical Analysis Plan

Final analysis

Phase II

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2 Abbreviations and definitions

CEACarcinoma Epidermoid of the Anus

CRGACentre of Randomization Management Analysis in Dijon

SAESerious adverse event

IMR**T** Intensity Modulated Radiation Therapy

ITTIntention to treat

PTVPlanning Target Volume

PPPer-protocol

ROR Objective response

SPPopulation of Safety (tolerance)

3 Introduction

3.1 Objectives of the trial

3.1.1 Main objective

The primary endpoint of Phase II is the complete response rate 8 weeks after completion of 5FU-panitumumab plus mitomycin and radiotherapy.

3.1.2 Secondary objectives

The secondary objectives of this study are:

- Partial response rate, stabilized and progression 8 weeks after the end of treatment
- Intermediate objective response rate at 6 weeks (prior to adjunctive RTCC)
- 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
- Determination of predictive markers of response or survival

4 Experimental design

4.1 Scheme of the study

This is a multicenter, prospective, single-arm Phase II study.

4.2 Treatment arm

There is a single treatment arm in the study: 5FU-Panitumumab plus mitomycin and radiation. The treatment doses are the tier -1 doses determined by Phase I:

First part of treatment (S1 to S5)

Chemotherapy:

- Panitumumab (3 mg/kg): D1, D15, D29 (S1, S3, S5)
- 5FU continuous infusion (400 mg/m^2/d): D1 to D4 of S1 and D1 to D4 of S5
- Mitomycin C (10 mg/m^2 not to exceed 20 mg/cure): D1 S1 and D1 S5

Radiotherapy:

- 45 Gy in fractions of 1.8 Gy 5 days/week (IMRT)

Additional radiochemotherapy at S6 and S7

Chemotherapy:

- Panitumumab (3 mg/kg): D1 S7

Radiotherapy:

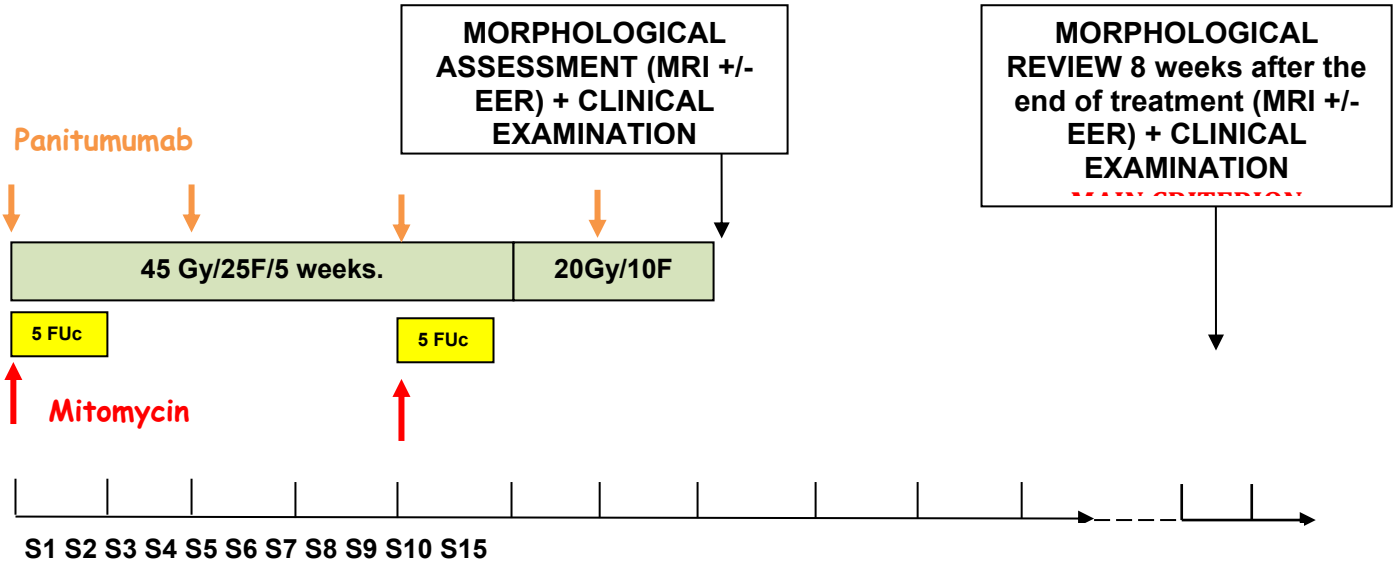
- 20 Gy in 10 fractions over 2 weeks (S6 and S7), 2 Gy per session

4.3 Randomization and blinding

There is no randomization in this trial, it is an open label trial.

4.4 Chronological sequence

Each patient will follow the following therapeutic sequence:



4.5 Justification of the number of subjects needed

The assumptions for calculating the number of subjects needed 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.

Using a 2-step minimax Simon design with a 5% one-sided α risk and a power (1-β) of 90%, a total of **45 patients** are required to be included.

4.6 Steps of the test

4.6.1 First step : intermediate analysis

The interim analysis was performed in July 2017 on the first 26 patients included**.** The independent committee met on 7/24/17 to rule on complete responses at 8 weeks after the end of treatment.

The decision rule was: if 16 or more patients had a complete response 8 weeks after the end of their treatment (61%), the trial was continued with step 2.

17 of 26 patients had a complete response at 8 weeks after the end of treatment, so the trial continued.

4.6.2 Second step: final analysis

This second step will be performed after the inclusion of 19 additional patients (Total number of patients = 26+19 = 45):

- if 32 or fewer patients have a complete response 8 weeks after the end of their treatment (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 8 weeks after the end of their treatment (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.

4.6.3 Transition between steps

Inclusions were suspended at the end of Stage 1 on 09/02/17 pending the results of the interim analysis. Inclusions then resumed on 01/08/17.

4.6.1 Adjustments

Adjustments may be made to this analysis plan in case of amendments to the protocol, or if phenomena not initially foreseen require statistical adaptations. In all cases, these modifications must be made before the database is frozen.

5 Study populations for analysis

The study focuses on patients with localized squamous cell carcinoma of the anus.

5.1 Definition of Analysis Populations

5.1.1 Intent-to-treat (ITT) population

The intention-to-treat (ITT) population is defined as all patients included in the study, regardless of eligibility criteria and treatment received.

5.1.2 Per-protocol (PP) population

The per-protocol (PP) population is defined as the ITT population that received at least one dose of 5FU **and** one dose of mitomycin **and** one dose of panitumumab **and** one radiation session.

5.1.3 Population for Tolerance Analysis (SP)

It is defined as the ITT population that received at least one dose of 5FU or mitomycin or panitumumab or one radiation session.

6 General information about statistical methods

Statistical analyses will be performed by the CRGA.

6.1 Software

Statistical analyses will be performed with SAS software version 9 or later. Some graphs can be made with R software version 2.11 or later.

6.2 Agreements concerning dates and durations

Time since inclusion will be defined as the time since the day of inclusion, with the day of inclusion considered day 1.

The time since the start of treatment will be defined as the time since the day of the first course of treatment, with the day of the first course of treatment being considered as day 1.
Therefore, the durations will be calculated according to the following rule, for example for the duration between death and inclusion: day of death - day of inclusion **+ 1**.
The day before the day of inclusion (resp. the day before the day of treatment) will be considered as day -1 (day 0 does not exist).
The last date of news will be the later of the date of the last examination performed, the last treatment administered, or the last contact.
The following conversion rules will be used to convert the number of days into months or years: 1 month = 30.4375 days; 1 year = 365.25 days.

6.3 Missing Data Conventions

Except in the cases specified, missing data will not be replaced.

6.4 Definition of the baseline

Inclusion measurements will be the last measurements taken before inclusion. In case of missing data, the first measurement performed before the first administration of the treatment will be used.

6.5 Statistics

Quantitative data will be described using the following descriptive statistics: count, mean, standard deviation, median, first and third quartile, and minimum and maximum. These statistics will be considered the usual statistics for the analysis of quantitative variables. Quantitative variables can be categorized using their median or a cut-off known from the medical literature.

Categorical variables will be summarized using the following descriptive statistics: frequencies and percentages for each level of the variable (missing values will not be included in the denominator of the frequency calculation). These statistics will be considered as the usual statistics for the analysis of categorical variables.

When necessary, **confidence intervals** for the proportions will be calculated from the exact binomial distribution.
The confidence intervals provided will be two-sided 95% confidence intervals, except for the primary criterion where a one-sided 95% confidence interval will be given.

Survival data will be estimated and plotted using the Kaplan-Meier method (Kaplan and Meier, 1958).
This will be described by the median and rates calculated at different times. Two-sided 95% confidence intervals will be provided. Confidence intervals for the rates will be constructed from the Greenwood variance calculated using the log-log transformation.
The median follow-up time will be calculated using the reverse Kaplan-Meier method (Shemper, 1996).

7 Statistical analysis

	ITT	SP	PP	Analysis for ASCO 2019	Late analysis at 3 years

Eligibility	X			X	
Characteristics at inclusion	X		X	X	
Main criterion					
CR rate at 8 weeks after the end of treatment	X		X	X	
Secondary criteria					
OR rate at 6 weeks after the start of treatment	X		X	X	
OR rate at 8 weeks after the end of treatment	X		X	X	
OR rate at 16 weeks after the end of treatment	X		X	X	
Overall survival	X		X	X	X
Recurrence-free survival	X		X	X	X
Survival without colostomy	X		X	X	X
Treatment administration		X		X	
NCI-CTC Toxicities		X		X	
Quality of life	X				X

7.1 Patient characteristics at inclusion

7.1.1 Patient Eligibility

Patient eligibility at inclusion will be verified and described by:

- Number and percentage of patients who met all inclusion criteria
- Number and percentage of patients who met all non-inclusion criteria
- Number and percentage of patients who met all criteria (inclusion and non-inclusion)
- Description of the populations

7.1.2 Demographic characteristics

The following characteristics at inclusion will be described:

- Age (years)
- Gender (Male vs Female)
- Inclusion center (number of patients included per center)

7.1.3 Clinical characteristics

The following characteristics at inclusion will be described:

- General status WHO
- TNM Stage T (according to UICC v6 2002)
- TNM Stage N (according to UICC v6 2002)
- Tumor size (mm)

7.1.4 Biological characteristics

The following characteristics at inclusion will be described:

- PNN (/mm^3)
- Wafers (x10^3 /mm^3)
- Hemoglobin (g/dL)
- Leukocytes (/mm^3)
- Creatinine (µmol/L)

- Total bilirubin (≤ N *vs.*]N-2.5N] *vs.*]2.5N-5N] *vs.* > 5N)
- ASAT (≤ N *vs.*]N-2.5N] *vs.*]2.5N-5N] *vs.* > 5N)
- ALAT (≤ N *vs.*]N-2.5N] *vs.*]2.5N-5N] *vs.* > 5N)
- Magnesium (≤ N *vs.*]N-2.5N] *vs.*]2.5N-5N] *vs.* > 5N *vs.*)
- Calcium (≤ N *vs.*]N-2.5N] *vs.*]2.5N-5N] *vs.* > 5N)
- PAL (≤ N *vs.*]N-2.5N] *vs.*]2.5N-5N] *vs.* > 5N *vs.*)
- Albumin level (µmoL/L)
- Potassium (≤ N *vs.*]N-2.5N] *vs.*]2.5N-5N] *vs.* > 5N)
- Sodium (≤ N *vs.*]N-2.5N] *vs.*]2.5N-5N] *vs.* > 5N *vs.*)
- Conjugated bilirubin (≤ N *vs.*]N-2.5N] *vs.*]2.5N-5N] *vs.* > 5N)
- CD4 (/mm^3)
- CSC (≤ N *vs.*]N-2.5N] *vs.*]2.5N-5N] *vs.* > 5N *vs.*)

7.1.5 Characteristics related to the disease

The following characteristics at inclusion will be described:

- HIV test (Done *vs.* Not Done) and if Done, the result (Positive *vs.* Negative)
- HBsAg test (Done *vs.* Not Done) and if Done, the result (Positive *vs.* Negative)

7.2 Monitoring characteristics

The median follow-up time and its 95% confidence interval will be calculated in months.

7.3 Main criterion

7.3.1 Definition of primary efficacy endpoint

Complete response is defined by the complete disappearance of the tumor on proctological examination and morphological examinations (MRI and/or echo-endoscopy) and the absence of secondary lesion appearance. The responses will be validated by an **independent committee**:

- 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;

This endpoint will be assessed 8 weeks after the end of treatment (week 15).

A patient who dies (regardless of cause) is evaluable and considered a failure for the primary endpoint.

7.3.2 Evaluation of the primary endpoint

The rate of patients in complete response 8 weeks after the end of treatment will be calculated on the ITT population and presented using its one-sided 95% confidence interval (exact confidence interval, binomial distribution).

7.4 Secondary efficacy criteria

7.4.1 Response rate

7.4.1.1 Definition

Objective response rates (complete and partial) will be assessed by the ***investigator***:

- 6 weeks after the start of treatment (before the additional radiochemotherapy)
- 8 weeks after the end of the treatment
- 16 weeks after the end of treatment

At 8 weeks, the objective response rate will be evaluated by ***the investigator and the independent committee.***

7.4.1.2 Evaluation

Response rates (CR, PR, S, P, NE) and objective response rates will be described at different time points using frequency and percentage.

7.4.2 Overall survival

7.4.2.1 Definition

It is defined as the time between the date of inclusion and the date of death (regardless of cause). Patients lost to follow-up or alive at the time of analysis will be censored at the date of last news.

7.4.2.2 Evaluation

The time scale considered will be the month.

Overall survival will be plotted using the Kaplan Meier estimator. Median survival and survival rates at 4, 8, 12, 18, 24, 36 months will be calculated along with their 95% confidence intervals.

7.4.3 Survival without colostomy

7.4.3.1 Definition

It is defined as the time from the date of inclusion to the date of colostomy or death (from any cause) in the absence of colostomy. Living patients without a colostomy will be censored at last count. If a patient has a shunt colostomy and continuity is restored, the patient will be counted among the patients without a colostomy.

7.4.3.2 Evaluation

The time scale considered will be the month.

Colostomy-free survival will be plotted using the Kaplan Meier estimator. Median survival and survival rates at 4, 8, 12, 18, 24, 36 months will be calculated along with their 95% confidence intervals.

7.4.4 Recurrence-free survival

7.4.4.1 Definition

It is defined as the time 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.

7.4.4.2 Evaluation

The time scale considered will be the month.

Colostomy-free survival will be plotted using the Kaplan Meier estimator. Median survival and survival rates at 4, 8, 12, 18, 24, 36 months will be calculated along with their 95% confidence intervals.

7.5 Tolerance criteria

7.5.1 Chemotherapy administration

7.5.1.1 Duration of chemotherapy treatment

The duration of chemotherapy treatment (converted to months) will be calculated by the formula:

Start date of last administration - start date of first administration + 1 day

Temporary stoppages and any deferral days during this period will not be subtracted from this duration. It will be described according to the usual descriptive statistics.

7.5.1.2 Doses administered

The number of courses will be reported by treatment type: Panitumumab/5FU/Mitomycin C.

The body surface area used will be the one provided by the investigator on the treatment form, otherwise, if it is not provided, it will be calculated from the formula of Gehan and Georges:

$$0.0235 \times \text{height(cm)}^{0.42246} \times \text{weight(kg)}^{0.51456}$$

The weight used will be the weight indicated at the time of the treatment in question. If the weight is missing, the non-missing weight from the previous treatment will be used instead. If no weight information is available, the weight at inclusion will be used.

The ratios of treatment doses received to theoretical doses will be described by type of treatment according to standard descriptive statistics.

7.5.1.3 Modification of doses and postponement of treatments

The number of patients who had at least one dose modification and the number of patients who had at least one deferral of treatment will be described according to the usual descriptive statistics by type of molecule: Panitumumab/5FU/Mitomycin C and overall.

7.5.1.4 Stop treatment

The number and percentage of patients permanently discontinuing protocol treatment and the reasons for discontinuing protocol treatment (% of the number of patients discontinuing treatment) will be described using standard descriptive statistics.

7.5.2 Administration of radiotherapy

7.5.2.1 Duration of radiotherapy treatment

The duration of radiotherapy treatment (converted to days) will be calculated by the formula:

Start date of last session - start date of first session + 1 day

It will be described according to the usual descriptive statistics.

7.5.2.2 Doses administered

The number of sessions/weeks and the total number of sessions will be reported.

The average dose administered per week and the total dose (over all sessions) will be calculated in Gy.

Treatment interruptions, their duration and reasons will be described

7.5.2.3 Quality criteria for radiotherapy

The quality of radiation therapy will be described by:

- The type of control imaging performed
- The type of radiotherapy (respect of IMRT) and the type of energy used
- The volumes PTV45 and PTV65
- Compliance with dose constraints
-

7.5.3 Duration of the CT+RT sequence

The duration of the total treatment sequence (TC+RT) will also be calculated by the formula (converted to days):

Start date of last CT or RT administration - start date of first CT or RT administration + 1 day

Temporary stoppages and any deferral days during this period will not be subtracted from this duration. It will be described according to the usual descriptive statistics.

7.5.4 Surgery

The number of surgeries, type of surgery and reason for surgery will be described according to standard descriptive statistics.

7.5.5 Toxicities

Toxicities (graded according to NCI-CTC v 4.0) will be described in the same way:

- during treatment (CT+RT),
- 8 weeks after the end of the treatment
- during post-treatment follow-up

By:

- The total number of patients by maximum grade of toxicity by grouping grades (Grade 1-2, Grade 3-4 and Grade 5)
- The number of patients and the maximum grade of toxicity achieved by grouping grades (Grade 1-2, Grade 3-4 and Grade 5) by causality, SOC and type of toxicity

7.5.6 ISG

A summary of the SAEs will be provided by pharmacovigilance.

7.6 Quality of life (Late analysis)

The number of analyzable patients for QoL (having at least one questionnaire) and the percentage (out of the number of patients included) will be described.

Questionnaires will be collected at different times: within 14 days before inclusion, every 6 weeks during treatment, at 8 weeks after the end of treatment and during follow-up every 4 months for 2 years, then every 6 months for 3 years.

The number of patients with a questionnaire available will be described at each measurement time.

Inclusion scores will be calculated and described according to standard statistics.

7.6.1 QLQ-C30

Global quality of life will be assessed using the EORTC QLQ-C30 questionnaire (version 3).

This 30-item scale has 15 dimensions to calculate 15 scores: 5 functional ability scores (physical ability, ability to work or perform any household task, cognitive ability, emotional state, social state), a global quality of life score, a financial problems score, and 8 symptom scores (fatigue, nausea/vomiting, pain, dyspnea, sleep disturbance, loss of appetite, constipation, diarrhea).

In particular, the overall health and fatigue scores will be studied.

A difference of 5 points in these scores will be considered the minimum to define a clinical difference. Quality of life, for overall health and fatigue, will be studied over time until 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 score decrease of more than 5 points (compared to the score at inclusion) without subsequent improvement of more than 5 points or death. Living patients without a decrease in score of more than 5 points will be censored at the last news. It will be plotted using the Kaplan Meier estimator.

7.6.2 Wexner

The impact of incontinence on quality of life will be measured by the Wexner score. A difference of 2 points in this score will be considered the minimum to define a clinical difference. The time to definitive deterioration of this score will be calculated. It will be represented graphically using the Kaplan Meier estimator.