SYNOPSIS – PROTOCOL N° UC-0110/1608

A) TRIAL IDENTIFICATION	
SPONSOR – PROTOCOL CODE NUMBER: UCGI 28 VERSION (NR & DATE): V5.0 – SEPTEMBER 7TH 2020	
TRIAL TITLE: Phase II randomized study comparing FOLFIRINOX + Panitumumab versus mFOLFOX6 + Panitumumab in metastatic colorectal cancer patients selected by RAS and B-RAF status from circulating DNA analysis.	
ABBREVIATED TITLE: PANIRINOX	
COORDINATING INVESTIGATOR: Dr. Thibault MAZARD	
NUMBER OF PARTICIPATING CENTERS (ESTIMATE): 20	NUMBER OF PATIENTS: SCREENED: 546 INCLUDED: 209

B) SPONSOR IDENTIFICATION	
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C) TRIAL GENERAL INFORMATION

INDICATION: RAS and B-RAF wild-type metastatic colorectal cancer.
RAS and B-RAF mutation will be determined using circulating cell-free DNA (ccfDNA) by IntPlex method.

METHODOLOGY: National trial, multicenter, randomized, phase II assessing FOLFIRINOX + Panitumumab versus mFOLFOX6 + Panitumumab in metastatic colorectal cancer patients selected by RAS and B-RAF status from circulating DNA analysis.

PRIMARY OBJECTIVE: Evaluation of complete response rate on treatment combining FOLFIRINOX and panitumumab.

SECONDARY OBJECTIVE(S):

- Overall Survival
- Progression free survival
- Secondary resection
- Early tumor shrinkage (ETS)
- Depth of response (DpR)
- Safety profile (NCI CTCAE v 4.03 classification)
- Diagnostic performance of ccfDNA analysis compared to the tumor-tissue analysis (current gold standard)

INCLUSION CRITERIA:

1. Age between 18 and 75 years
2. ECOG PS between 0 and 1
3. Histologically confirmed adenocarcinoma of the colon or rectum
4. Untreated synchronous or metachronous metastatic disease deemed unresectable with curative intent
5. K-Ras (codons 12, 13, 59, 61, 117, 146), N-Ras (codons 12, 13, 59, 61) and B-Raf (codon 600) wild-type tumor status according to plasma analysis of circulating cell free DNA by Intplex technology
6. Measurable disease according to RECIST version 1.1
7. Adequate hematologic, hepatic and renal functions:
    - Absolute neutrophil count (ANC) ≥2 x 10^9/L
    - Haemoglobin ≥9 g/dL
    - Platelets (PTL) ≥100 x 10^9/L
    - AST/ALT ≤5 x ULN
    - Alkaline phosphatase ≤2.5 x ULN
    - Bilirubin ≤1.5 x ULN
    - Creatinine clearance ≥50 mL/min (Cockcroft and Gault formula)
8. Life expectancy of at least 3 months
9. Adequate contraception if applicable
10. Patient affiliated to a social security regimen
11. Patient information and signed written consent form
12. Uracilemia < 16 ng/ml

NON INCLUSION CRITERIA:

1. History of other malignancy within the previous 5 years (except for appropriately treated in-situ cervix carcinoma and non-melanoma skin carcinoma)
2. Adjuvant treatment with oxaliplatin
3. Previous treatment for metastatic disease
4. Patients who received any chemo- and/or radiotherapy within 15 days from the date of blood sampling for the RAS and BRAF test
5. Brain metastases
6. Patients with a history of severe or life-threatening hypersensitivity to the active substances or to any of the excipients delivered in this study
7. Patient with history of pulmonary fibrosis or interstitial pneumonitis
8. Previous organ transplantation, HIV or other immunodeficiency syndromes
9. Concomitant medications/comorbidities that may prevent the patient from receiving study treatment as uncontrolled intercurrent illness (for instance: active infection, active inflammatory disorders, inflammatory bowel disease, intestinal obstruction, symptomatic congestive heart failure, uncontrolled hypertension…)
10. Persistent peripheral neuropathy >grade1 (NCI CT v4.03)
11. Ionic disorders as:
    - Kalemia ≤1 x LLN
    - Magnesemia <0.5mmol/L
    - Calcemia <2mmol/L
12. Patient with known dihydropyrimidine dehydrogenase deficiency
13. QT/QTc>450msec for men and >470msec for women
14. Patient with contraindication for trial drugs (investigators have to refer to SmPC drugs, see Appendix 7)
15. Concomitant intake of St. John's wort
16. Other concomitant cancer
17. Participation in another therapeutic trial
18. Pregnant woman or lactating woman
19. Patients with psychological, familial, sociological or geographical condition hampering compliance with the study protocol and follow-up schedule
20. Legal incapacity or limited legal capacity

PRIMARY ENDPOINT:

Complete response rate where complete response is defined as complete disappearance of metastatic lesions after a maximum of 12 cycles of chemotherapy and tumor marker level normalization (CEA).

Complete disappearance of metastatic lesions will be assessed according to RECIST criteria version 1.1: Disappearance of all target and non-target lesions on the same method of assessment that at baseline (CT Scan or MRI).
Every complete response will have to be confirmed 4 to 6 weeks after the last treatment and by no residual disease activity on PET Scan done 3 months after the end of the last treatment.
It can be reached with chemotherapy only or with a multimodal approach (surgical resection, regional procedures as radiofrequency, cryoablation, radiation therapy).

SECONDARY ENDPOINT(S):

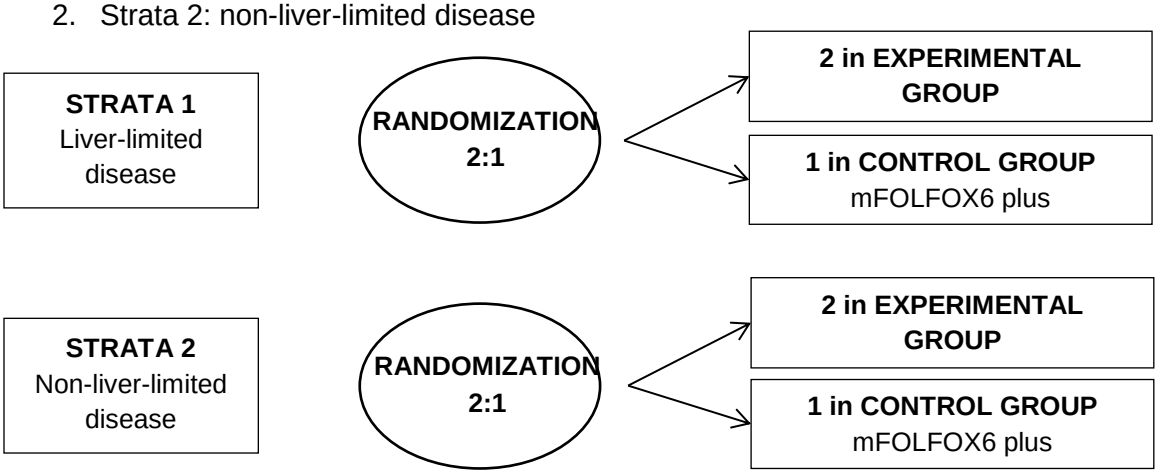
- Overall Survival (OS) is defined as the time from the date of randomization to the date of documented death from any cause.
- Progression-Free Survival (PFS) is defined as the time from the date of randomization to the date of documented progression or any cause of death. Progression will be assessed by CT scan or MRI according to RECIST criteria version 1.1.
- Secondary resection rate is defined as the percentage of patients with initially irresectable metastases who will have a secondary resection R0 or R1 of their metastases.
- Early tumor shrinkage (ETS) is defined as the relative change in the sum of longest diameters of RECIST target lesions after 4 cycles compared to baseline.
- Depth of response (DpR) is defined as the relative change in the sum of longest diameters of RECIST target lesions at the nadir, in the absence of new lesions or progression of non-target lesions, as compared to baseline.
- Adverse events rate will be graded based on NCI CTCAE v4.03 classification.
- Diagnostic performance of ccfDNA analysis compared to the tumor-tissue analysis (current gold standard)

RANDOMIZATION:
Multicenter open-label randomized phase II study

According to a randomization stratified on center and site of primary tumor, patients will be assigned in a 2:1 ratio to receive up to 12 cycles of FOLFIRINOX plus panitumumab (experimental group) or mFOLFOX6 plus panitumumab (control group) in absence of disease progression, occurrence of unacceptable adverse event or withdrawal of consent.

For each arm, there will have two strata according to disease extent:

1. Strata 1: liver-limited disease
2. Strata 2: non-liver-limited disease



D) INVESTIGATIONAL MEDICINAL PRODUCTS

PRODUCT NAMES AND ADMINISTRATION:

Drug name (INN)	Registered name (1)	Pharmaceutical form	Administration route	Posology
Panitumumab	VECTIBIX ®	Concentrate for solution for infusion	IV	**6mg/kg** every 2 weeks
Drug name (INN)	Registered name (1)	Pharmaceutical form	Administration	Posology
Oxaliplatin	Eloxatin® or generic drug	Concentrate for solution for infusion Or powder	IV	**85 mg/m²** IV infusion over 2 hours
Drug name (INN)	Registered name (1)	Pharmaceutical form	Administration	Posology/dosage
Folinic acid	-	Solution for injection	IV	**400 mg/m²** IV infusion over 2 hours (or 200mg/m^2 if L-folinic acid)
Drug name (INN)	Registered name (1)	Pharmaceutical form	Administration	Posology/dosage
5Fluorouracil	-	Concentrate for solution for infusion	IV	**400 mg/m²** IV bolus then 5-FU 2400mg/m² over 46 hours continuous infusion
Drug name (INN)	Registered name (1)	Pharmaceutical form	Administration	Posology/dosage
Irinotecan	Campto® or generic drug	Concentrate for solution for infusion	IV	**150 mg/m²** over 90 minutes to begin 30 min after folinic acid infusion is started

(1) When any generic drug can be is used indicate only the INN name. The choice of the registered name or brand name is left to the decision of the investigation center.

THERAPEUTIC REGIMENS:
Panitumumab will be administered intravenously over 1 hour at 6mg/kg every 2 weeks on day 1 before:

1. In control arm=standard treatment (= Arm B): mFOLFOX6 every 2 weeks: oxaliplatin 85mg/m² IV infusion over 2 hours immediately followed by folinic acid 400mg/m² IV infusion over 2 hours followed by fluorouracil 400mg/m² IV bolus then 5-FU 2400mg/m² over 46 hours continuous infusion.

2. In experimental arm: FOLFIRINOX every 2 weeks (= Arm A): oxaliplatin 85mg/m² IV infusion over 2 hours immediately followed by folinic acid 400mg/m² given as a 2-hour IV infusion with the addition, after 30 minutes of irinotecan 150mg/m² given as a 90-minute intravenous infusion through a Y-connector immediately followed by fluorouracil 400mg/m² IV bolus then 5-FU 2400 mg/m² over 46 hours continuous infusion.

In the experimental arm, prophylactic G-CSF will be systematically given after each course.

E) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE SCREENED / INCLUDED:
The primary objective of this trial is to evaluate complete response rate on treatment combining FOLFIRINOX and panitumumab:

Strata 1 (liver-limited disease): With a one-stage Fleming design, α=5%, β=10%, p0 (the probability of inefficiency maximum)=20% and p1 (the probability of minimum efficiency)=35%, it would be necessary to include 72 evaluable patients (76 patients/ 5% non-evaluable patients).
The association can be considered sufficiently effective if there are at least 20 successes (complete response) out of 72 evaluable patients.

Strata 2 (non-liver-limited disease): With a one-stage Fleming design, α=5%, β=10%, p0 (the probability of inefficiency maximum)=3% and p1 (the probability of minimum efficiency)=12%, it would be necessary to include 60 evaluable patients (63 patients/ 5% non-evaluable patients).
The association can be considered sufficiently effective if there are at least 4 successes (complete response) out of 60 evaluable patients.

A total of 209 patients will be included: 139 patients in the FOLFIRINOX plus panitumumab group (Strata 1 N=76 and Strata 2 N=63) and 70 patients in the mFOLFOX6 plus panitumumab group (Strata 1 N=38 and Strata 2 N=32).

A control group receiving mFOLFOX6 plus panitumumab will be used as an internal control group.

STATISTICAL ANALYSIS:
Descriptive analyses (in each arm) will be performed using median and range for continuous parameters, frequency and percentage for categorical variables.

Baseline characteristics of randomized patients in each arm will be compared by Kruskal-Wallis tests or Wilcoxon for continuous variables, or chi 2 or Fisher exact test for categorical variables.

The primary endpoint, the complete response rate, will be described using percentage and its associated 95% confidence interval.

Incidence rates of adverse events and serious adverse events will be carried using frequencies and percentages.

The median follow-up will be calculated using the reverse Kaplan-Meier method in each arm and overall with its confidence interval of 95%.

All event free survival (PFS, OS) will be estimated using the Kaplan-Meier method, and then described using medians and rates with their associated 95% confidence interval.

F) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

SAMPLE TYPES:
Blood

SAMPLE QUANTITIES:
Blood sample: 3 tubes of peripheral blood (5 mL) at each morphologic assessment (every 4 cycles during the treatment and 4 to 6 weeks after the last treatment if a complete response is reached)

G) TRIAL DURATIONS
INCLUSION PERIOD: 5 years
TREATMENT PERIOD: 24 weeks minimum (12 courses of chemotherapy ± regional procedures ± surgical resection)
FOLLOW-UP: 3 years
DURATION UNTIL PRIMARY ENDPOINT EVALUATION: 12 months
OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP): 8 .5 years