SYNOPSIS – PROTOCOL PRODIGE 52 - UCGI 29 N° UC-0110/1609

A) TRIAL IDENTIFICATION

SPONSOR – PROTOCOL CODE NUMBER: PRODIGE 52 - UCGI 29 - **IROCAS – n°: UC-0110/1609**

VERSION (NR & DATE): version n°7.0 March 15th 2021

TRIAL TITLE: A Phase III, Randomised, international trial comparing mFOLFIRINOX triplet chemotherapy to mFOLFOX for high-risk stage III colon cancer in adjuvant setting.

ABBREVIATED TITLE: **IROCAS** (IRinotecan and Oxaliplatin for Colon cancer in Adjuvant Setting)

COORDINATING INVESTIGATOR: Prof. Jaafar Bennouna
CO-COORDINATING INVESTIGATOR: Prof. Thierry André, Prof. Julien Taïeb

NUMBER OF PARTICIPATING CENTERS (ESTIMATE): approximately 50 sites in France, 20 sites in Canada and 16 centers in Italy	NUMBER OF PATIENTS: 792

B) SPONSOR IDENTIFICATION

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C) TRIAL GENERAL INFORMATION

INDICATION: High-risk stage III colon cancer

METHODOLOGY: The trial is a phase III, multicenter, open–labeled randomized trial comparing the association 5-fluorouracil, folinic acid, irinotecan and oxaliplatin (mFOLFIRINOX) versus oxaliplatin, folinic acid, 5FU (mFOLFOX 6) chemotherapy protocols in patients with high-risk stage III colon cancer in the adjuvant setting.

PRIMARY OBJECTIVE: The primary objective is the 3-year Disease Free Survival rate.

SECONDARY OBJECTIVE(S):

- Evaluation of Efficacy: Disease-free-Survival at 2 years.
- Overall Survival (OS)
- Evaluation of Toxicity

DIAGNOSIS AND INCLUSION CRITERIA:

1. Patient ≥18 years and < 75 years
2. Patient ≥18 years and <71 years must have an ECOG ≤1 – Patients ≥71 years and < 75 years must have an ECOG = 0
3. Pathologically confirmed high-risk stage III colon adenocarcinoma, restricted to pT4N1 or pT1-4N2 tumor.
4. Curative R0 surgical resection.
5. Patients who have undergone surgery for colon cancer, defined as a tumor location >12 cm from the anal verge by endoscopy and/or above the peritoneal reflection at surgery (high rectum), without gross or microscopic evidence of residual disease after surgery with curative intent
6. Start of study drug treatment has to be performed less than 56 days after surgery.
7. No prior chemotherapy.
8. No prior abdominal or pelvic irradiation.
9. Patient with adequate organ function:
   - ✓ Absolute neutrophil count (ANC) ≥ 2 x 10^9/L
   - ✓ Haemoglobin ≥9 g/dL
   - ✓ Platelets (PTL) ≥100 x 10^9/L
   - ✓ AST/ALT ≤2.5 x ULN
   - ✓ Alkaline phosphatase ≤2.5 x ULN
   - ✓ Total Bilirubin ≤1.5 x ULN (Upper Limit of Normal)
   - ✓ Creatinine clearance ≥50 mL/min (Cockcroft and Gault formula)
   - ✓ Kalemia, magnesemia, calcemia ≥ 1 LLN (Lower Limit of Normal)
   - ✓ Carcinoembryogenic antigen (CEA) ≤10ng/mL after surgery (during screening period)
10. Adequate contraception if applicable.
11. Patient able and willing to comply with study procedures as per protocol
12. Patient able to understand and willing to sign and date the written voluntary informed consent form at screening visit prior to any protocol-specific procedures
13. Public or private health insurance coverage
14. Life expectancy of > or = at 5 years
15. Uracilemia < 16 ng/ml (only for french centers)

NON INCLUSION CRITERIA:

1. Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to study treatment start. Incompletely healed wounds or anticipation of the need for major surgical procedure during the course of the study
2. Metastatic disease
3. Presence of inflammatory bowel disease and/or ileus
4. Known hypersensitivity reaction to any of the components of study treatments.
5. Pregnancy (absence to be confirmed by β-hCG test) or breast-feeding period
6. Clinically relevant coronary artery disease or history of myocardial infarction in the last 12 months, or high risk of uncontrolled arrhythmia (for men: QTc ≥450 msec, for women: QTc ≥470 msec)
7. Previous malignancy in the last 5 years except curative treated basal cell carcinoma of the skin and/or in situ carcinoma of the cervix
8. Medical, geographical, sociological, psychological or legal conditions that would not permit the patient to complete the study or sign informed consent
9. History or current evidence on physical examination of central nervous system disease or peripheral neuropathy ≥ grade 1 Common Toxicity Criteria for Adverse Events (CTCAE) v4.03.
10. Any significant disease which, in the investigator's opinion, would exclude the patient from the study.
11. Patient with a DPD deficiency or UGT1A1 homozygous 7/7; the test should be done for all patients before 5-FU administration, according to ANSM communication regarding recommendation about high risk of no testing DPD in patient before 5-FU administration; (Appendices 8 to 11).
12. Patients already included in another therapeutic trial involving an experimental drug

PRIMARY ENDPOINT:
The primary end-point is the Disease Free Survival (DFS) at 3 years, defined as the time from the date of randomization up to the date of:

- first local, regional or distant relapse;
- second colorectal cancer;
- death from any cause included treatment-related death.

Other primary cancer (except second primary colorectal) will be ignored. Second primary cancer will be recorded to have the opportunity of evaluating other definition of DFS.

SECONDARY ENDPOINT(S):

- *Evaluation of Efficacy:*

The evaluation of efficacy is defined as the Disease Free Survival at 2 years, defined as the time from the date of randomization up to the date of:

- first local, regional or distant relapse
- second colorectal cancer
- death from any cause included treatment-related death.

Other primary cancer (except second primary colorectal) will be ignored. Second primary cancer will be recorded to have the opportunity of evaluating other definition of DFS

- *Overall Survival (OS):* Overall Survival (OS) is defined as the time from the date of randomization to the of documented death from any cause.

- *Evaluation of Toxicity:*

Safety of the study treatment will be assessed on occurrence of Adverse Events (AEs), intake of concomitant treatments, per-treatment arising changes in physical examination, vital signs (blood pressure, pulse rate and body temperature), ECG, and clinical laboratory tests (biochemistry, haematology). Safety parameters will be graded based on NCI CTCAE v4.03 classification.
The following parameters will be particulary followed:

- ✓ The incidence of haematological toxicities (grade 3-4, in particular neutropenia and febrile neutropenia);
- ✓ The incidence of GI toxicities, in particular diarrhea;
- ✓ The incidence of peripheral neuropathy.

D) INVESTIGATIONAL MEDICINAL PRODUCTS

PRODUCT NAMES AND ADMINISTRATION:

Drug name (INN)	Registered name (1)	Pharmaceutical form	Administration route	Posology
Oxaliplatin	--	Powder for solution for injection	IV	85mg/m² IV infusion over 2 hours
Drug name (INN)	Registered name (1)	Pharmaceutical form	Administration	Posology
Folinic acid	--	Solution for injection	IV	400 mg/m² IV infusion over 2 hours (or 200 mg/m² if L-folinic acid)
Drug name (INN)	Registered name (1)	Pharmaceutical form	Administration	Posology/dosage
Irinotecan	--	Concentrate for solution for infusion	IV	180 mg/m² IV infusion over 90 minutes to begin 30 min after folinic acid infusion is started

Drug name (INN)	Registered name [1]	Pharmaceutical form	Administration	Posology/dosage
5-Fluorouracil	--	Concentrate for solution for infusion	IV	2400 mg/m² IV infusion continuous over 46 h

(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:

Arm A: mFOLFIRINOX

mFolfirinox every 14 days, 12 cycles, 24 weeks, new cycle beginning on day 15:

- Oxaliplatin 85 mg/m² on D1, IV infusion over 2 hours, followed by
- Folinic acid 400 mg/m² (racemic mixture) (or 200 mg/m² if L-folinic acid) IV infusion over 2 hours
- Irinotecan 180 mg/m² on D1, IV infusion over 90 minutes to begin 30 min after folinic acid infusion is started;
- 5-Fluorouracil: 2400 mg/m² IV continuous infusion over 46 hours starting at the end of folinic acid infusion

Arm B: mFOLFOX 6

mFOLFOX6 every 14 days, 12 cycles, 24 weeks, new cycle beginning on day 15

- Oxaliplatin 85mg/m², as a 2-hours IV infusion on day 1, immediately followed by
- Folinic acid (FA): 400 mg/m² (racemic mixture) (or 200 mg/m² if L-folinic acid) as a 2-hour IV infusion followed by
- 5-Fluorouracil: 400mg /m² IV bolus then 5-FU 2400 mg/m² over 46 hours continuous infusion.

TREATMENT DURATION:

The patient will be randomized in one of the two treatments arms and will receive every 14 days their treatment for a duration of 12 cycles.

E) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE INCLUDED: 792 PATIENTS

STATISTICAL ANALYSIS:

THE STUDY WILL INCLUDE PATIENTS DURING 72 MONTHS AND FOLLOW-UP WILL CONTINUE UNTIL 24 MONTHS AFTER THE LAST PATIENT WAS RANDOMLY ASSIGNED (FOR EVALUATION OF DFS AT 3 YEARS). NO INTERIM EFFICACY ANALYSIS IS PLANNED. IN THE PETACC8 TRIAL (TAIEB J, ET AL 2012), 1015 PATIENTS WITH PT4 AND/OR N2 DISEASE WERE INCLUDED. FOR THIS SUBGROUP, THE 3-YEAR DFS WAS 65.8% IN THE FOLFOX4 ARM AND 66.7% IN THE FOLFOX4+CETUXIMAB ARM (DATA NOT PUBLISHED).

BASED ON THE RESULTS OF PRODIGE23 NEOFIRINOX (PROF CONROY ET AL- ASCO 2020) WE EXPECT A 8% GAIN FOR DFS AT 3-YEAR IN THE EXPERIMENTAL ARM (FOLFIRINOX) COMPARED WITH THE REFERENCE ARM (MFOLFOX6), 73% VERSUS 65%, RESPECTIVELY (DELTA=6.0% AT 2-YEAR). WITH EXPONENTIAL SURVIVAL HYPOTHESIS COMMONLY USED, THIS 3-YR DIFFERENCE IS EQUIVALENT TO COMPARISON OF DFS MEDIANS AT 58 MONTHS AND 79 MONTHS IN REFERENCE AND EXPERIMENTAL GROUPS RESPECTIVELY (HR=1.369).

IN ORDER TO SIGNIFICANTLY CONCLUDE WITH 80% POWER AND AN ALPHA LEVEL OF 5 % IN A TWO-SIDED LOG-RANK TEST, WE NEED TO OBTAIN DURING THE FOLLOW-UP AT LEAST A TOTAL OF 324 EVENTS LEADING TO COMPARISON OF TWO ARMS WITH AT LEAST 360 EVALUABLE PATIENTS IN EACH ONE.

CONSIDERING THAT 10% OF PATIENTS WILL BE LOST TO FOLLOW UP, 396 PATIENTS PER ARM WILL BE INCLUDED (TOTAL = 792 ABOUT 66/YR/ARM OR 6/MONTH/ARM DURING 6 YEARS).

F) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

SAMPLE TYPES:

Tissues and blood samples

SAMPLE QUANTITIES: TBD

- Tissues: formalin-fixed and paraffin-embedded tissue (FFPE) from primary tumor as well as non-tumor tissue
- Blood: 10 X 10mL

G) TRIAL DURATIONS

INCLUSION PERIOD: 6 YEARS

TREATMENT PERIOD: 24 WEEKS

FOLLOW-UP: 24 MONTHS AFTER THE LAST PATIENT RANDOMIZED

DURATION UNTIL PRIMARY ENDPOINT EVALUATION: 3 YEARS

OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP): 10 YEARS