PRODIGE 86 (FFCD 2103) – FOLFIRINOX SBA

Phase II randomized trial evaluating modified FOLFIRINOX and modified FOLFOX in the treatment of locally advanced or metastatic small bowel adenocarcinoma

Phase II randomized study non-comparative - multicentre

EU Trial number 2023-505486-92-00

Intergroupe Study FFCD – UNICANCER GI – GERCOR- GONO

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SUMMARY

Title	**STUDY PRODIGE 86- (FFCD 2103)– FOLFIRINOX SBA** **Phase II randomized trial evaluating modified FOLFIRINOX and modified FOLFOX in the treatment of locally advanced or metastatic small bowel adenocarcinoma**
Sponsor	CHU Dijon Bourgogne
Operating and Data Center	French Federation of Digestive Oncology (FFCD)
Design	Randomized, non-comparative, open-label, multi-centre Phase II study
Study objectives	**Primary objective:** To assess the percentage of patients alive without progression at 8 months. **Secondary objectives :** • Overall survival • Progression-free survival (PFS) • Time to treatment failure (TTF) • Better response during first line treatment • Treatment tolerance according to NCI-CTC 4.0 • Quality of life during treatment (QLQ-C30) • PFS in 2nd line of the total population and by 2nd line treatment Following the randomization of the first 20 patients in the modified FOLFIRINOX arm who have received at least 2 cycles, toxicities will be reviewed by an independent committee to detect unexpected treatment-related safety issues at an early stage
Inclusion criteria	• Histologically proven adenocarcinoma of the small intestine (duodenum, jejunum, ileum) • Metastatic or locally advanced unresectable tumour with curative intent • Patient who never received first-line chemotherapy • Measurable lesion according to RECIST 1.1 criteria • ECOG status < or = 2 for patients under 70 years, or 0 or 1 for patients over 70 years • Life expectancy estimated at over 3 months • Patient over 18 years of age • Patient able to understand and sign the information and informed consent note • Women of childbearing age and men who have sex with women of childbearing age must agree to use contraception during the trial treatment and for at least 6 months after stopping the experimental treatments.
Exlusion criteria	• MSI/dMMR tumor • Adenocarcinoma of the ampulla of Vater • Neutrophils < 1500/mm^3, platelets < 100 000/mm^3 • Hemoglobin < 9 g/dL, total bilirubin > 1.5x normal, alkaline phosphatase > 2.5x normal (or >5x normal if liver metastases), creatinine clearance > or = 40 ml/min. according to MDRD • Hypokalaemia, hypomagnesaemia and hypocalcaemia below normal, and for • calcaemia, it must be corrected before enrolment. • Adjuvant chemotherapy completed less than 6 months ago • History of myocardial infarction within the last 6 months, severe coronary artery disease or severe heart failure • Severe renal failure • Peripheral sensory neuropathy with functional discomfort • Active and/or potentially severe infection or other uncontrolled conditions • Treatment with a cytochrome P450 inhibitor within 4 weeks prior to the administration of the protocol treatment (refer to paragraph 8.3 "Contraindicated

	treatments" of the protocol) • Patients currently undergoing treatment using St John's Wort • Treatment with brivudine within 4 weeks prior to the administration of protocol treatment • Uncontrolled inflammatory bowel disease and/or unresolved bowel obstruction • Pregnant or breastfeeding woman • Patients with dihydropyrimidine dehydrogenase deficiency (uracilemia ≥ 16 ng/mL) • Hypersensitivity to any of the study products or their excipients. • Administration of live vaccines within 28 days prior to randomization • Other active cancer or history of cancer within 3 years, except for carcinoma *in situ* of the cervix or basal cell or squamous cell skin carcinoma or any other carcinoma *in situ*, considered cured • Person under guardianship • Inability to undergo the medical follow-up of the trial for geographical, social or psychological reasons
Study treatment	**<u>Arm A (experimental arm)</u>:** **Modified FOLFIRINOX regimen D1=D15 (1 course every 14 days)** J1 : ▪ Irinotecan 180 mg/m^2 as a 2-hour IV infusion ▪ Oxaliplatin 85 mg/m^2 as a 2-hour IV infusion ▪ Folinic acid 400 mg/m^2 or 200 mg/m^2 if levorotatory form as a 2-hour IV infusion ▪ 5 FU 2400 mg/m^2 IV infusion over 46 hours. For patients with ECOG=2 or geriatric opinion recommending irinotecan treatment at a reduced dose. Irinotecan should be administered at 150 mg/m^2 for the first two courses and then increased to 180 mg/m^2 from the third course onwards in the absence of > grade 2 toxicity (except alopecia). **<u>Arm B (control arm):</u>** **Modified FOLFOX regimen D1=D15 (1 course every 14 days)** J1: ▪ Oxaliplatin 85 mg/m^2 as a 2-hour IV infusion ▪ Folinic acid: 400 mg/m^2 or 200 mg/m^2 if laevorotatory form as a 2-hour IV infusion ▪ 5FU bolus : 400 mg/m2 as a 10-minute IV infusion ▪ Continuous 5FU: 2400 mg/m2 IV infusion over 46 hours. <u>Patients will receive treatment until progression, patient refusal or unacceptable toxicity</u>
Randomization	**Randomization (1:1) of patients will be done according to the minimization technique and will be stratified according to the following factors** - Centre - Locally advanced tumour versus synchrous metastases versus metachronous metastases - Performance status ECOG 0-1versus 2
Sample size determination	H_0 : 40% of patients alive without progression at 8 months is insufficient. H_1 : A rate of patients alive without progression at 8 months of more than 40% is acceptable. A rate of 55% at 8 months is expected. Alpha = 10% (one-sided). Exact binomial method, power = 85%. 59 patients per arm are required. With 10% of patients not evaluable, 65 patients per arm will be randomized. A total of 130 patients will be randomized. Decision rules in the modified FOLFIRINOX arm: If ≤ 28 out of 59 patients are alive and progression-free at 8 months, the arm will be declared ineffective.

Statistical analyses	- Analyses will be performed on the mITT (modified intention to treat) population, i.e. all randomized patients who received at least one dose of treatment. All statistics will be performed by treatment arm and, for characteristics at randomization, on the whole population. - All quantitative data will be described using the usual statistics: mean, standard deviation, median, interquartile range, minimum and maximum. These variables can also be categorised using clinical thresholds known from the literature. - Categorical variables will be described by their frequency and percentage. - The rate of patients alive without progression at 8 months will be described by treatment arm and a one-sided 90% confidence interval will be calculated. - Survival analyses will be performed using the Kaplan-Meier method (Kaplan and Meier, 1958). Median duration and rates will be presented at different time points with their 95% confidence intervals.
Ancillary study	Planned ancillary studies: 1. **FFPE (**formalin-fixed, paraffin-embedded**) tumour sample:** the archival sample from a primary tumour or metastasis will be collected after enrolment of each patient enrolled in the FOLFIRINOX-SBA study who has given specific informed consent. This collection will allow an extensive and homogeneous analysis to complement the compilation of on-site NGS results already planned to be analysed as secondary endpoints in the main study. The sample will be stored in the EPIGENETEC centre: Centre de Ressources Biologiques FFCD of the Université de Paris Cité, Paris, INSERM U1018, UMR-S1147 (Pr Pierre Laurent-Puig). DNA will be extracted from the samples to allow predictive analysis of molecular alterations. 2. **The ctDNA** will be collected before the first treatment before the 3ème treatment and during the progression. Blood samples will also be stored by EPIGENETEC.
Number of subjects needed	130 patients
Study schedule	Theoretical inclusion rate: 3.6/month Number of centres: 50 Theoretical start of inclusions: June 2023 Theoretical duration of inclusion: 36 months Theoretical end of inclusion: June 2026 End of study (analysis of primary and secondary endpoints): Total duration of the study: 5 years