PRODIGE 86 (FFCD 2103 – GONO – ENGIC-02) – FOLFIRINOX SBA: Phase II randomized trial to evaluate mFOLFIRINOX and mFOLFOX for locally advanced or metastatic small bowel adenocarcinoma

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Background

- Small bowel adenocarcinoma (SBA) is rare.
- Palliative chemotherapy was evaluated mainly in retrospective studies and the fluoropyrimidine + oxaliplatin combination regimen appears to be the best option.
- No randomized trial has been previously performed to evaluate front line chemotherapy in advanced SBA.
- In metastatic colorectal adenocarcinoma, the **triplet 5FU + oxaliplatin + irinotecan** showed better efficacy than doublet chemotherapy
- The aim of PRODIGE 86 study is to assess the efficacy of modified FOLFIRINOX in metastatic SBA

Objectives

Primary endpoint:

Rate of patients alive without progression at 8 months.

Secondary endpoints:

- Overall Survival, progression-free survival (PFS), time to treatment failure, tumor response rate, tolerance, quality of life and PFS in 2nd line.

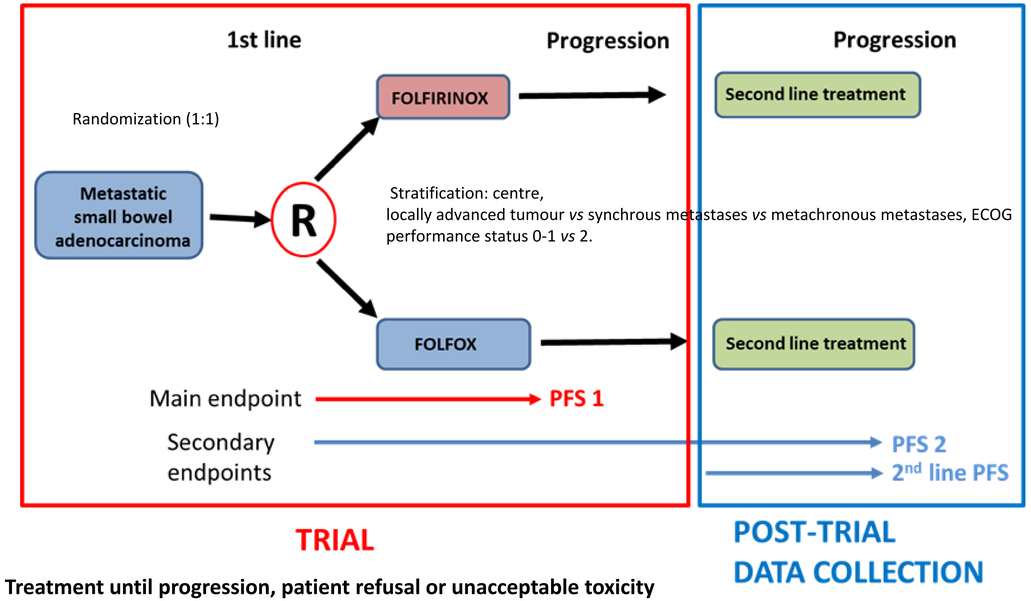
Statistical methods

The clinical hypotheses are:

- H0: <40% of patients alive without progression at 8 months is insufficient, a rate of 55% is expected.
- Alpha=10% (one-sided), power=85%.
- 65 patients per arm will be randomized. A total of 130 patients will be randomized.
- **Decision rules in the mFOLFIRINOX arm: If ≤28 of 59 patients are alive and progression-free at 8 months, the arm will be declared ineffective.**

Trial design

Randomised, non-comparative, open-label, multi-centre phase II study



Treatment until progression, patient refusal or unacceptable toxicity

mFOLFOX regimen D1=D15: oxaliplatin 85 mg/m2, folinic acid: 400 mg/m2, 5FU bolus: 400 mg/m2 followed by 5FU: 2400 mg/m2 IV infusion over 46 hours.

mFOLFIRINOX regimen: mFOLFOX plus irinotecan 180 mg/m2, without 5FU bolus

Ancillary study

- FFPE tumor sample will be collected to perform an extensive NGS analysis to decipher prognostic and predictive factors for tumor progression and overall survival.
- The ctDNA will be collected before the first treatment before the 3ème treatment and at progression to evaluate prognostic value of ctDNA and decipher change of mutation profile during treatment.

Sponsor: CHU Dijon
Grant: PHRC from INCa
EU clinical trial registry number: 2023-505486-92

Disclosure T. APARICIO: MSD, BMS, Pierre Fabre, Bayer, Servier

Main inclusion criteria

- Histologically proven adenocarcinoma SBA (duodenum, jejunum, ileum)
- Metastatic or locally advanced unresectable tumor with curative intent
- No previous chemotherapy for metastatic disease
- Measurable lesion according to RECIST 1.1 criteria
- ECOG status ≤2 for patients <70 years, or 0-1 for patients ≥70 years
- Life expectancy estimated at over 3 months
- Patient over 18 years of age

Main exclusion criteria

- MSI-H/dMMR tumor
- Adenocarcinoma of the Vater ampulla
- Biologic contra-indication for chemotherapy
- Adjuvant chemotherapy completed less than 6 months ago
- Recent severe cardiovascular co-morbidity
- Significant peripheral sensory neuropathy
- Active or potentially severe infection or other uncontrolled conditions
- Patients with known dihydropyrimidine dehydrogenase deficiency
- Other active cancer or history of cancer within 3 years

Perspectives

- Inclusion start in 2024. 3 patients are already enrolled.
- The post-trial data collection of second line treatment will allow the exploratory evaluation of different treatment in second line including off label prescription of specific targeted therapy in small cohorts.
- Another trial with the same design will start in Germany in 2025 and another similar trial is submitted for grant in United Kingdom. A pooled analysis of these 3 trials is planed (**ENGIC 02**) to assess a difference in PFS (H0=7 months, H1=10 months, HR=0.7, 248 events are needed)

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