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**Rationale and Design of the IROCAS Study:  
Multicenter, International, Randomized Phase 3 Trial  
Comparing Adjuvant Modified (m) FOLFIRINOX to  
mFOLFOX6 in Patients With High-Risk Stage III (pT4  
and/or N2) Colon Cancer-A UNICANCER  
GI-PRODIGE Trial**

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## TITLE

**Rational and Design of the IROCAS Study: A multicenter, international, randomized phase III trial comparing adjuvant modified (m)FOLFIRINOX to mFOLFOX6 in patients with high-risk stage III (pT4 and/or N2) colon cancer (A UNICANCER GI-PRODIGE trial).**

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**Short title :** IRinotecan and Oxaliplatin for Colon cancer in Adjuvant Setting

**Keywords:** adjuvant – colon cancer – stage III – irinotecan – oxaliplatin

**Conflict of Interest****Jaafar Bennouna**

Honoraria: Roche, Bristol-Myers Squibb, Astra-Zeneca, Boehringer Ingelheim, MSD, AMGEN

Consulting or Advisory Role: Roche, Bristol-Myers Squibb, Astra-Zeneca, Boehringer Ingelheim, MSD

Travel, Accommodations, Expenses: Roche, Bristol-Myers Squibb

**Thierry André**

Honoraria: Sanofi

Consulting: Roche

**Pascal Artru**

Honoraria: Roche, Merck, Amgen, Eli Lilly, Servier, Bayer

Travel, Accommodations, Expenses: Roche, Merck, Servier

**Olivier Bouché**

Consulting or advisory role: Roche, Merck, AMGEN, Bayer

Speaker's bureau: Eli Lilly, Pierre Fabre, Novartis, Servier

Travel, accommodations, expenses: Eli Lilly, Roche, Merck

**Julien Taïeb**

Honoraria: Merck, Roche, Amgen, Eli Lilly, Sanofi, Sirtex, Servier, Baxalta, Celgene

Consulting or Advisory Role: Roche, Merck KGaA, Amgen, Celgene, Eli Lilly, Shire, Servier, Sirtex

Speakers' Bureau: Servier, Amgen, Shire, Roche, Genentech, Sanofi, Merck, Eli Lilly, Sirtex

**No conflict of interest:** Timothy Asmis, Florence Borde, Loïc Champion, Jean-François Emile, Sandrine Hirt, Claire Jouffroy, Sharlene Gill, Petr Kavan, You-Heng Lam, Laurent Miglianico, Laurent Mineur, Laetitia-Shana Rajpar, Yann Touchefeu.

**Abstract****Background**

According to the IDEA trial, 6-month adjuvant chemotherapy should remain the standard in stage III T4 or N2 colon cancer. The relatively poor survival in this high-risk subgroup (3-year disease-free survival [DFS] rate, 65%) and the potential synergistic efficacy of 5-fluorouracil (5-FU), oxaliplatin, and irinotecan suggest FOLFIRINOX as a regimen of particular interest in this setting.

**Methods**

This multicenter, international, phase III trial (NCT02967289) conducted in 49 centers in France and Canada, plans to randomize (1:1; minimization method) 640 patients, aged 18 to 70 years, ECOG performance status  $\leq 1$ , randomization within 42 days (start treatment, within 56 days) after curative-intent R0 surgical resection of a pT4N1 or pT1-4N2 colon adenocarcinoma, to adjuvant mFOLFIRINOX (oxaliplatin 85 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup>, irinotecan 180 mg/m<sup>2</sup>, and 5-FU 2.4 g/m<sup>2</sup> over 46 h) or mFOLFOX6 (oxaliplatin 85 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup>, 5-FU bolus 400 mg/m<sup>2</sup> then 2.4 g/m<sup>2</sup> over 46 h), every two weeks for 24 weeks (12 cycles). Patients will be followed for 5 years after the end of adjuvant chemotherapy. A gain of 9% in 3-yr DFS (primary endpoint) is expected (74% in the experimental arm vs. 65% in the control arm;  $\alpha$ , 5% [two-sided log-rank test]; 1- $\beta$ , 80%). Secondary endpoints of this study include 2-yr DFS, overall survival, and toxicity.

## **Introduction**

In 1990, Moertel CG et al. validated the use of 5-fluorouracil (5FU) combined with levamisole (LEV), an anti-helminthic drug with immunomodulatory properties, as adjuvant treatment in patients with resected colon cancer classified stage C (lymph nodes involvement) according to the former Dukes' staging system (1). With this regimen, the disease-free survival (DFS) rate at 3 1/2 years was 63% versus 47% in the observation arm with surgery alone ( $P < 0.0001$ ).

Over the past 28 years, the adjuvant treatment for colon cancer has evolved by successive steps, most often slowly, driven by the results of large randomized pivotal phase III trials. Initially, studies focused on different administration schedules of 5-FU. In 2004, the NASBP C-04 randomized phase III trial allowed to abandon LEV for leucovorin (LV) combined with bolus 5-FU (2). The Intergroup 0089 reinforced this data but also added that 6- to 8-month duration of treatment was sufficient and could replace the 12-month previous standard with 5FU + LEV (3). Finally, the GERCOR group performed a randomized phase III trial challenging the semi-monthly regimen for 2 consecutive days (with bolus 5FU and continuous infusion) against the monthly regimen for 5 consecutive days with bolus 5-FU. DFS was similar between the LVFU2 and FULV groups (HR = 1.04;  $P = .74$ ) and between 24 and 36 weeks (HR = 0.94;  $p = 0.63$ ) (4). Toxicities were significantly lower in the LV5FU2 group ( $p < 0.01$ ), promoting this schedule as a new standard.

In 2004, a significant breakthrough deeply modified the adjuvant treatment of stage III resected colon cancer by introducing oxaliplatin in the therapeutic schedule (5). In the MOSAIC trial, for stage III colon cancer, the DFS rate at 3 years was 65.3% and 72.2% [HR 0.76 (0.62 – 0.92)] in the LV5FU2 and FOLFOX4 arms, respectively. Two other trials, the NSABPC-07 and NO16968 (with capecitabine and oxaliplatin), clearly confirmed the gain given by oxaliplatin in adjuvant setting (6, 7). Conversely, Irinotecan is not an approval drug in adjuvant setting. The PETAC-3 and the Accord02/FFCD9802 trials, with LV5FU2 as standard arm, didn't show a statistical significant superiority of the 3-year DFS rate with irinotecan plus LV5FU2, even if the HR was 0.90 (95% CI, 0.79 to 1.02) in favor of the experimental arm in PETAC-3 (8, 9).

Further studies failed to demonstrate an advantage of adding targeted therapies, cetuximab or bevacizumab, to the chemotherapy backbone (10-13). Consequently, six months of FOLFOX or capecitabine plus oxaliplatin (CAPOX) remained the standard treatment regimens for stage III colon cancer until the presentation of the IDEA trial (14). Three months of capecitabine plus oxaliplatin is now the new recommendation for stage T1-T2-T3 and N1 (low-risk group), while 6 months duration of adjuvant chemotherapy is still indicated for stage T4 and/or N2 (high-risk group). For this high-risk group, 6 months is superior to 3 months with a 3-year DFS rate at 64.4% versus 62.7% (HR 1.12; 95% CI, 1.03 – 1.23; p=0.01 for superiority). The French part of the study (IDEA France) yielded a similar conclusion for stage T4 and/or N2 with a 3 year DFS rate at 65% in the 6-month arm (versus 59% in the 3 month arm; HR, 1.38; 95% CI, 1.10 to 1.73) emphasizing the need to improve adjuvant treatment for high-risk III colon cancer (T4 and/or N2) (15).

The present randomized phase III study evaluates the role of mFOLFIRINOX in the adjuvant setting when compared with the standard mFOLFOX6 regimen in high-risk stage III (T4 and/or N2) colon cancer. The rationale for this study is based on the potential synergistic effect of 5FU plus oxaliplatin and irinotecan combination, which was observed in stage IV colon and pancreatic cancers. The relative poor survival of this sub-category of patients could justify the use of this triplet.

## **Discussion**

### *Patients and study design*

IROCAS study is an open-label, randomized (1:1) phase III trial conducted in France and Canada comparing the triplet mFOLFIRINOX (experimental arm) with the standard regimen mFOLFOX6 in patients with high-risk stage III T4 and/or N2 resectable colon cancer. Eligible patients,  $\geq 18$  years and  $< 71$  years, ECOG  $\leq 1$ , have curative R0 surgical resection within 42 days before randomization. Eligibility criteria are shown in Table 1. The randomization is adjusted for the following stratification factors: Perforation or urgent surgery versus no perforation and no urgent surgery; T1-T3N2 versus T4aN1 versus T4bN1 versus T4N2; Right colon (right of splenic flexure) versus left colon and country (France vs Canada). Patients are enrolled in one of the two arms and receive every 14 days their treatment for 12 cycles (Figure 1): mFOLFIRINOX with oxaliplatin 85 mg/m<sup>2</sup>, l-leucovorin 200 mg/m<sup>2</sup>, irinotecan 180 mg/m<sup>2</sup> on day 1 and continuous I.V. 5FU 2400 mg/m<sup>2</sup> for 46 h; or

mFOLOFOX6 with oxaliplatin 85 mg/m<sup>2</sup>, l-leucovorin 200 mg/m<sup>2</sup>, bolus 5FU 400 mg/m<sup>2</sup> on day 1 and continuous I.V. 5FU 2400 mg/m<sup>2</sup> for 46 h.

This study (clinicaltrials.gov NCT02967289) is performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The study was approved by a French ethics committee. All patients provided written informed consent before starting the study.

#### *Endpoints and Assessments*

The primary objective of this study is 3-year DFS defined as the time from the date of randomization up to the date of first local, regional or distant relapse, second colorectal cancer, or death from any cause included treatment-related death. Secondary objectives include DFS at 2 years, overall survival (OS), and toxicities according to the NCI-CTCAE version 4.03. Tumor assessment is recommended to be performed at baseline and every 3 months, with an alternance of abdominal echography and thoraco-abdominal and pelvic CT-scan after surgery for the first 2 years; then every 6 months for the 3 subsequent years. The CEA tumor markers will be assessed according to the same schedule. After 5 years post-surgery, a thoraco-abdominal and pelvic CT-scan is recommended every year.

#### *Statistical analysis plan*

The study will include patients during 48 months and follow-up will continue until 36 months after the last patient was randomly assigned (for evaluation of DFS at 3 years). No interim efficacy analysis is planned. We expect a 9 % gain for DFS at 3-year in the experimental arm (FOLFIRINOX) compared with the reference arm (mFOLFOX6), 74% versus 65%, respectively (delta = 6.8% at 2-year). 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 252 events leading to comparison of two arms with at least 278 evaluable patients in each one. Considering that 15% of patients will be lost to follow up, a total of 320 patients per arm will be included.

#### *Ancillary study: biomarker analysis*

All patients enrolled in this trial will be considered for participation to a biological correlative science study, and informed consent for this translational study will be obtained. Prognostic biomarkers can be studied both on blood and on tumor derived samples. On blood, DNA will be extracted from leucocytes to study polymorphism on genes that could be implicated in

metabolism, transport or target of 5FU (Thymidylate synthase, dihydropyrimidine dehydrogenase), CPT-11 (UDP glucuronosyltransferase), or oxalipatin (ERCC1, XRCC1, Glutathione-S-transferases). Blood samples will be also collected for circulating tumor DNA assessment at day 0, day 28, and at the end of adjuvant therapy (theoretically 6 months +/- 1 month). On tumor tissue, molecular and histological analysis will be performed by the end of inclusion period. Immunohistochemical analysis will define abnormalities in DNA mismatch repair (MMR), P53, SMAD4, PTEN, pERK, pAKT expression, vascular density, density and nature of intratumoral and peritumoral leukocyte infiltration. Molecular analysis will include microsatellite instability (in case of doubtful IHC), search for mutation in KRAS, BRAF, PI3KCA, and SMAD4. Allelotype of the tumors will be investigated by SNP microarrays, validation of available transcriptomic signatures will be done as well as a methylation or a microARN signature.

## **Conclusion**

IROCAS is the first phase III randomized trial evaluating the mFOLFIRINOX regimen in patients with high-risk stage III (pT4 and/or N2) colon cancer. This study plans to include 640 patients, and the first patient was treated in May 2017. Overall, 49 centers are open, 36 in France and 13 in Canada. One hundred and two patients have been enrolled to date as of September 2018. The end of patient enrollment is scheduled for the year 2022.

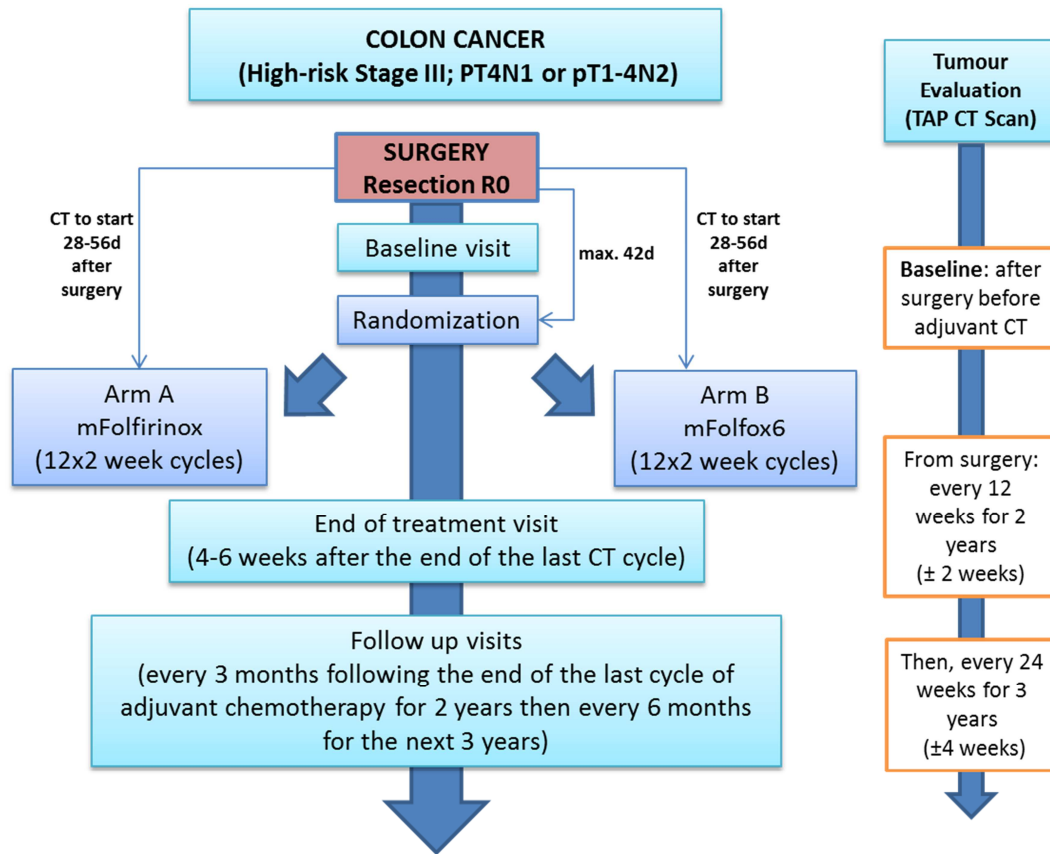
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Figure 1 – Study Design



**Table 1 - Inclusion and exclusion criteria**

Inclusion Criteria
<ol style="list-style-type: none"><li>1. Patient <math>\geq 18</math> years and <math>&lt; 71</math> years</li><li>2. Patient with ECOG <math>\leq 1</math></li><li>3. Pathologically confirmed high-risk stage III colon adenocarcinoma, restricted to pT4N1 or pT1-4N2 tumor.</li><li>4. Curative R0 surgical resection within 42 days before randomization. Patients who have undergone surgery for colon cancer, defined as a tumor location <math>&gt;12</math> 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</li><li>5. Start of study drug treatment has to be performed less than 56 days after surgery.</li><li>6. No prior chemotherapy.</li><li>7. No prior abdominal or pelvic irradiation.</li><li>8. Patient with adequate organ function:<ul style="list-style-type: none"><li>- Absolute neutrophil count (ANC) <math>\geq 2 \times 10^9/L</math></li><li>- Haemoglobin <math>\geq 9g/dL</math></li><li>- Platelets (PTL) <math>\geq 100 \times 10^9/L</math></li><li>- AST/ALT <math>\leq 2.5 \times ULN</math></li><li>- Alkaline phosphatase <math>\leq 2.5 \times ULN</math></li><li>- Total Bilirubin <math>\leq 1.5 \times ULN</math> (Upper Limit of Normal)</li><li>- Creatinine clearance <math>\geq 50</math> mL/min (Cockcroft and Gault formula)</li><li>- Kalemia, magnesemia, calcemia <math>\geq 1</math> LLN (Lower Limit of Normal)</li><li>- Carcinoembryogenic antigen (CEA) <math>\leq 10ng/mL</math> after surgery (during screening period)</li></ul></li><li>9. Adequate contraception if applicable.</li><li>10. Patient able and willing to comply with study procedures as per protocol</li><li>11. 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</li><li>12. Patient affiliated to a social security regimen</li><li>13. Life expectancy <math>\geq</math> at 5 years</li></ol>
Exclusion Criteria
<ol style="list-style-type: none"><li>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</li><li>2. Metastatic disease</li><li>3. Presence of inflammatory bowel disease and/or ileus</li><li>4. Known hypersensitivity reaction to any of the components of study treatments.</li><li>5. Pregnancy (absence to be confirmed by <math>\beta</math>-hCG test) or breast-feeding period</li><li>6. Clinically relevant coronary artery disease or history of myocardial infarction in the last 12 months, or high risk of uncontrolled arrhythmia (for men: QT/QTc <math>\geq 450</math> msec, for women: QT/QTc <math>\geq 470</math> msec)</li><li>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</li><li>8. Medical, geographical, sociological, psychological or legal conditions that would not permit the patient to complete the study or sign informed consent</li><li>9. History or current evidence on physical examination of central nervous system disease or peripheral neuropathy <math>\geq</math> grade 1 Common Toxicity Criteria for Adverse Events (CTCAE) v4.03.</li><li>10. Any significant disease which, in the investigator's opinion, would exclude the patient from the study.</li><li>11. Known Dihydropyrimidine Dehydrogenase deficiency or UGT1A1 homozygous 7/7</li><li>12. Patients already included in another therapeutic trial involving an experimental drug</li></ol>