PRODIGE 98 (FFCD 2105) - AMPIRINOX

Randomized, multicenter Phase 3 trial comparing 6 months of adjuvant chemotherapy by modified FOLFIRINOX versus capecitabine or gemcitabine in patients with resected ampullary adenocarcinoma

Phase III randomized - comparative - multicentre

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Intergroup Study FFCD – UNICANCER GI - GERCOR

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SYNOPSIS

Title	**PRODIGE 98 (FFCD 2105) – AMPIRINOX** **Randomized, multicenter Phase 3 trial of adjuvant chemotherapy with modified FOLFIRINOX versus capecitabine or gemcitabine in patients with resected ampullary adenocarcinoma**
Sponsor	Fédération Francophone de Cancérologie Digestive (FFCD)
Design	Phase III randomized study - multicenter
Study objectives	**Main objective:** to assess efficacy of adjuvant mFOLFIRINOX versus single-agent chemotherapy (gemcitabine or capecitabine) in improving disease-free survival (DFS) after surgical resection of an ampullary adenocarcinoma. **Secondary objectives:** • Overall survival (OS) • Rate of patients completing 3 and 6-month chemotherapy schedule according to percentage of administered dose of each product • Assessment of quality of life by EORTC QLQ-C30 and QLQ-PAN26 • Assessment of toxicities according to NCI-CTCAE v5.0 • Subgoup analyses on OS and DFS by prespecified subgroups
Inclusion criteria	• Histologically proven adenocarcinoma on surgical specimen • Macroscopically complete surgical resection of an ampullary adenocarcinoma (R0 or R1) • Adenocarcinoma removed within 12 weeks prior to enrollment • Patients ≥ 18 years of age • Patient without metastatic disease on CT scan < 4 weeks prior to inclusion • WHO performance status 0 or 1 (WHO 0 if age >75) • Normal values of kalemia, magnesemia and calcemia • Patient able to understand and sign the information and informed consent note • Women of childbearing age and men who are sexually active with women of childbearing age must agree to use highly effective contraception during the trial treatment at least until 6 months after the end of the experimental treatment. Women of childbearing potential must use highly effective contraception at least until 9 months after the end of the treatment with oxaliplatin. • Patient affiliated to a social security scheme for France, or equivalents in European countries • CA19.9 level < 180 U/L at inclusion (post-operative level)
Exclusion criteria	• Neoadjuvant systemic chemotherapy • pT1N0M0 tumors • Active infection by HBV, HCV or HIV • Dihydropyrimidine dehydrogenase deficiency (uracilemia ≥ 16 ng/mL) • Pre-existing peripheral neuropathy (grade ≥ 2) • Unresolved or uncontrolled concomitant medical conditions • Neutrophils < 1500/mm^3, platelets < 150 000/mm^3, Haemoglobin < 9 g/dL • Total bilirubin > 1.5x normal, • Creatinine clearance < 50 ml/min according to MDRD • AST or ALT > 2.5 x UNL, alkaline phosphatase > 2.5x normal at least 15 days after resection • Patients with poor nutritional status represented by albuminemia < 30.0g/dl • History of myocardial infarction within the last 6 months, severe coronary artery disease or severe heart failure • Active and/or potentially severe infection • Treatment with a strong cytochrome P450 inhibitor within 4 weeks prior to the

	administration of the protocol treatment (Treatment with Hypericum perforatum) • Patient under treatment by brivudine, or treated by brivudine within 4 weeks prior to beginning of study treatment • Concomitant use with St John's Wort • QT/QTc interval longer than 450msec for men and longer than 470msec for women on the ECG • Hypersensitivity to any of the study products or their excipients • Administration of live vaccines within 28 days prior to randomization • Other cancer treated within the last 5 years except adequately treated, in situ cervical carcinoma or basocellular/spinocellular carcinoma • chronic bowel disease requiring specific treatment and/or intestinal obstruction • Pregnant or breastfeeding woman • Person under guardianship • Inability to undergo the medical follow-up of the trial for geographical, social or psychological reasons
Study treatment	**Arm A (experimental arm): mFOLFIRINOX** every 2 weeks during 12 cycles (24 weeks): ▪ Oxaliplatin 85 mg/m² ▪ Irinotecan 150 mg/m² ▪ Leucovorin 400 mg/m² ▪ Fluorouracil 2400 mg/m² during 46 hours **Arm B (control arm):** investigator's choice**:** ▪ Capecitabine 1250 mg/m² BID, 2 weeks on, 1 week off during 8 cycles (24 weeks) OR ▪ Gemcitabine 1000 mg/m² in 30 min; 3 weeks on, 1 week of, during 6 cycles ((24 weeks)
Randomization	**Randomization (on a 1:1 ratio) of patients will follow the minimization technique and will be stratified by the following factors:** • Center • Stade : I/II versus III • Differentiation grade: well differentiated versus moderately differentiated versus poorly differentiated and undifferentiated • Histological subtype: Intestinal versus pancreatobiliary and mixed/undetermined • CA19.9 <90 vs > or = 90 UI/mL at inclusion
Sample size determination	The hypotheses are: - H_0: Absence of difference between treatment arms on 2-year DFS - H_1: Based on ESPAC3 phase 3 trial and the FFCD Ampullome cohort's data, 2-year DFS rate is expected to be 60% in control arm. An increase of 11% on 2-year DFS is expected in favor of mFOLFIRINOX arm versus control arm (capecitabine or gemcitabine): change from 60% to 71%, HR=0.67 Based on a two-sided α risk of 5% and a power of 80%, using a Schoenfeld method, 203 events are requested. With a follow-up of 48 months, a recruitment of 60 months and considering 5% of patients lost to follow-up or not evaluable, it is necessary to include 294 patients in total (147 patients/arm). Two interim analyses are planned at 33% and 60% of the events for early efficacy or futility. P-values will be calculated with O'Brien-Fleming function according to the real number of events.
Statistical analyses	The main criteria will be analyzed on the intent-to-treat population (ITT). For baseline characteristics, all the statistics will be done by treatment arms and on the overall population. Toxicities and other baseline variables will be described using usual statistics: mean, standard deviation, median, inter-quartile interval and range for quantitative variables, and frequencies and percentages for qualitative variables. Survival analyses will be estimated using Kaplan-Meier method and the two arms will be compared using the log-rank test. Hazard ratios will be calculated using Cox models.

	Comparisons between the two arms will be done using Student t test or Wilcoxon for quantitative variables (depending on the distribution), and Chi² or Fischer Exact test for qualitative variables.
Ancillary study	We will study the prognostic significance of various blood markers in adenocarcinoma of the Ampulla of Vater. - Blood samples (Circulating tumor DNA) will be collected at inclusion, M3, M6 and in case of recurrence - Extracellular vesicles: serum concentration and biomarker assessment will be collected at inclusion, M3, M6 and in case of recurrence ▪ We will study predictive and prognostic markers on tumor material after surgical resection by tumor molecular profiling by DNA NGS and RNA seq, intra tumor microbiota study, multiplex immunohistochemistry (IHC) to characterize subtype and study optimal IHC panel, transcriptomic analyses to determine transcriptomic signatures predictive of response to treatment ▪ Performance of CA19.9 to predict relapse and its relation with survival outcomes (tests performed as part of patient follow-up) ▪ Biobanking of tumour and peripheral blood for tumor and constitutional genetic analyses
Number of subjects needed	294 patients
Study schedule	Planned accrual rate: 5 patients/ month Number of investigational centers: 50 Planned first patient inclusion: May 2025 Planned last patient inclusion: May 2029 End of study (primary and secondary endpoint analysis): December 2035