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Progress Report

Modified FOLFIRINOX versus CisGem first-line chemotherapy for locally advanced non resectable or metastatic biliary tract cancer (AMEBICA)-PRODIGE 38: Study protocol for a randomized controlled multicenter phase II/III study

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ABSTRACT

Introduction: Combination of cisplatine and Gemcitabine (CisGem) is the reference 1st line Chemotherapy in patients with advanced biliary cancer. FOLFIRINOX demonstrated an overall survival superiority when compared to gemcitabine in 1st line for patients with metastatic pancreatic adenocarcinoma. Because of similarities between pancreatic and biliary cancers, we proposed a randomized trial comparing mFOLFIRINOX and CisGEm.
Aim: PRODIGE38-AMEBICA is a phase II/III trial evaluating efficacy of modifed FOLFIRINOX (D1 bolus removed) or CisGEm on patients with locally advanced non resectable or metastatic biliary tract cancer.
Patients and methods: Main inclusion criteria are histologically or cytologically proven biliary tract tumor (intra or extra hepatic or hilar or gallbladder carcinoma), measurable disease (metastases and/or primary tumor), Bilirubin <1,5 N and transaminases <5 N. The randomization (ratio 1:1) will be stratified on center, stage of the disease, tumor localization and previous adjuvant treatment. The Phase II trial has an objective of 73% patients alive and without progression at 6 months for Folfirinox (versus 59% for Gemcis). 128 additional patients should be added in the phase III trial with an objective of overall survival improvement of 4 months in favor of mFOLFIRINOX.
Conclusion: The study is opened in France (EudraCT no.: 2015-002282-35). All the patients (188) of the phase II part are currently randomized.

1. Rational and aims

Although of low incidence (2000 new cases/year in France), biliary tract cancers (BTC) (adenocarcinoma in more than 90% of cases) are the second primary liver tumor in incidence after hepatocellular carcinoma [1]. They are classified into four subtypes based on anatomic location: intrahepatic or peripheral cholangiocarcinoma (CCA) developed within the hepatic parenchyma, proximal or extra-hepatic CCA between the second-order bile ducts and the cystic duct including Klatskin tumors, distal extra-hepatic CCA located on the main bile duct below the bifurcation of the cystic duct and gallbladder carcinoma. Their prognosis is poor, mainly because of late diagnosis, frequently at an advanced stage not amenable to

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curative surgery. The relative 5-year overall survival (OS) for all stages taken together is only 10% in France (1).

5FU plus cisplatin combination enabled a tumor control in 50% of the patients, with a median OS of 10 months (2). Gemcitabine combined with oxaliplatin or cisplatin had the same response rate with a more prolonged median OS reaching 12 months (3).

In 2010, the CisGem doublet (gemcitabine 1000 mg/m^2 plus cisplatin 25 mg/m^2 on day 1 and day 8, every 3 weeks) became the first-line reference chemotherapy in advanced BTC based on the ABC-02 phase III trial (4). This study showed the superiority of CisGem over gemcitabine monotherapy in terms of OS (median: 11.7 vs. 8.1 months, $p < 0.001$) and progression-free survival (PFS, median: 8.0 vs 5.0 months, $p < 0.001$) in 410 patients with locally advanced unresectable or metastatic BTC and performance status (PS) ≤ 2 (4). This was also supported by a Japanese randomized phase II trial in 84 patients with PS 0-1 (BT22) (Okusaka, BJC 2010), and a meta-analysis pooling the results from these two randomized trials The majority of French centers as well as many foreign centers use the GEMOX (gemcitabine plus oxaliplatin) doublet, considered as a standard equivalent to CisGem and achieving a median SG of 10–12 months [4]. Since the ABC-02 results, and taking into account the scarcity of these tumors, no other randomized phase III trial has been launched to improve this first-line standard and no other international project is planned to our knowledge.

In patients with metastatic pancreatic adenocarcinoma, the FOLFIRINOX regimen (5FU, folinic acid, oxaliplatin and irinotecan) showed a significant OS improvement compared to gemcitabine alone (median OS: 11.1 vs. 6.8 months, $p < 0.0001$) in a randomized phase III trial (5). Mainly hematological and digestive toxicities were increased in the FOLFIRINOX arm, with grade 3–4 neutropenia occurring in 45.7% in the FOLFIRINOX arm vs. 18.7% in gemcitabine arm ($p = 0.0001$), and vomiting in 14.5% in vs. 4.7%, respectively ($p = 0.002$). Of note, modified FOLFIRINOX (no bolus 5FU) was reported to have an improved safety profile and maintained efficacy in retrospective studies in this setting [5].

Following these results in pancreatic cancer (5), and because of the histological, biological and therapeutic (sensitivity to 5FU, platinum, and gemcitabine) similarities between pancreatic and biliary cancers, it appeared relevant to assess the FOLFIRINOX regimen in comparison to standard CisGem chemotherapy as first-line treatment in advanced in BTC. Because of the well-known limiting toxicity (mainly, hematologic and digestive) of this triplet chemotherapy, we proposed to use modified FOLFIRINOX (mFOLFIRINOX), i.e. without bolus 5FU on day 1 of each cycle.

The aim of the AMEBICA-PRODIGE 38 phase II/III trial is to evaluate the safety and efficacy of the FOLFIRINOX combination as first-line chemotherapy in patients with locally advanced or metastatic BTC, which could improve OS without compromising the health-related quality of life (HRQoL) and become a new reference treatment in this setting. Given the relative scarcity of these tumors, the implementation of such trial necessarily relies on the participation of a national network of centers to recruit the patients. The French Federation of Digestive Cancerology (FFCD), which is the sponsor of this study, provides logistics with a network of private, public, university or non-university structures to ensure the feasibility of this project, in collaboration with other French collaborative groups (UNICANCER GI and GERCOR), within the PRODIGE intergroup.

2. Study design

AMEBICA-PRODIGE 38 is a multicenter, open label phase II–III cooperative (FFCD-UNICANCER GI-GERCOR, PRODIGE French group) randomized trial, which aims to evaluate the efficacy of mFOLFIRINOX regimen vs. CisGem (gemcitabine plus cisplatin) standard in metastatic or locally advanced BTC.

Inclusion criteria are WHO PS of 0 or 1, age >18 years histopathologically- (or cytologically) proven (from metastase(s) or primary site) BTC (intra- or extra-hepatic CCA or gallbladder carcinoma), visceral measurable metastases (at least one lesion >10 mm) and/or measurable and non-resectable primary tumor. In the absence of visceral metastasis, non-resectability should be confirmed in a multi-disciplinary meeting involving an expert hepato-biliary surgeon. Biological parameters must fulfill the following criteria: bilirubin level <1.5 fold the upper limit of normal (ULN) (after optimal endoscopic or trans-hepatic biliary drainage if required), transaminases (AST and ALT) <5 ULN, neutrophil count $\geq 1500/mm^3$, platelet count $\geq 75{,}000/mm^3$, creatinine <130 μmol/l and creatinine clearance >60 ml/min, prothrombin rate >70%, albumin >25 g/l. Signed and dated informed consent document must be obtained, and patients must be registered in a national health care system (CMU included), and willing and able to comply with protocol requirements and follow-up.

Non-inclusion criteria are non-measurable disease, ampullary carcinoma or pancreatic cancer with infiltration of biliary tract, end of adjuvant chemotherapy or chemo-radiotherapy less than 6 months before the inclusion visit, history of other malignant disease (with the exception of basal cell skin carcinoma or in situ carcinoma of the cervix), major uncontrolled co-morbidities factors (unstable angina, recent (<6 months) or symptomatic congestive heart failure with NYHA >2, uncontrolled arterial hypertension), pregnancy or lactation, uncontrolled biliary obstruction with bilirubin >1.5 ULN despite optimal biliary drainage.

Biological and clinical exams should be performed within 30 days prior to randomization, as well as a baseline tumor assessment (thoraco-abdominal pelvic CT-scan with or without contrast injection).

2.1. Study treatment

Two chemotherapy regimens will be compared (Fig. 1):

- Arm A: CisGem: cisplatin 25 mg/m^2 intravenously (IV) over 1 h on day 1 and day 8 followed by gemcitabine 1000 mg/m^2 IV over 30 min on D1 and D8, every 3 weeks
- Arm B: mFOLFIRINOX: on day 1 of each cycle, oxaliplatin 85 mg/m^2 (IV, 120 min), irinotecan 180 mg/m^2 (IV, 90 min), folinic acid 400 mg/m^2 (or 200 mg/m^2 Elvorine) (IV, 2 h, at the same time as irinotecan), 5FU 2400 mg/m^2 (IV for 46 h), every 2 weeks.

Treatment duration is planned for at least 6 months. Treatment will be permanently stopped in case of disease progression, severe grade 4 hematological adverse events or persistent grade 3 toxicity despite 2 dosage adjustments and/or patient refusal.

2.2. Randomization

The randomization (ratio 1:1) will be performed using minimisation procedure and will be stratified according to center, tumor stage (locally advanced vs metastatic) and primary site location (gallbladder vs intra-hepatic vs extra-hepatic) and previous treatment (surgery alone vs. surgery plus (radio) chemotherapy vs. no previous treatment).

2.3. Study objectives

The primary objective for the phase II study is the rate of patients alive and free of progression at 6 months. The secondary objectives are OS, best response according RECIST1.1 criteria, toxicities

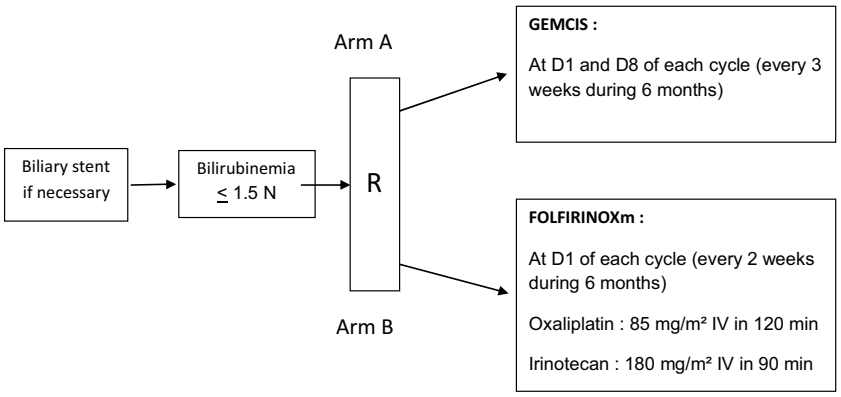

Fig. 1. Experimental schedule.

according to the NCI-CTC version 4.0, and biliary complications (angiocholangitis, biliary obstruction).

The primary objective for the phase III study is the OS. The secondary objectives are PFS, best response according RECIST1.1 criteria, toxicities according to the NCI-CTC version 4.0, biliary complications (angiocholangitis, biliary obstruction), and HRQoL according to the EORTC QLQ-C30 questionnaire.

2.4. Ancillary research

Ancillary biological research will carried out to explore prognosis and/or treatment response predictive factors. A FFPE tumor sample from the initial diagnostic biopsy will be sent to PRODIGE-EPIGENETEC biological resource center (EPIGENETEC – Unité INSERM U775 45 rue des Saints Pères 75006 PARIS). It will be used to determine the biological profile (DNA) of each tumor and to search biomarkers predictive of the outcome and the tumor response (RECIST1.1). In addition, blood sample (2 tubes STRECK of 5 ml) will be taken at baseline and sent to EPIGENETEC for assessment of circulating tumor DNA. A correlation analysis between the circulating mutational tumor DNA profile and the tissue molecular profile will be for each patient.

2.5. Statistical methods

For the Phase II: to assess the rate of patients and free of progression at 6 month. The following hypotheses will be considered:

- H_0 (null): a PFS rate at 6 months of 59% (uninteresting to pursue any further investigation).
- H_1 (alternative): a PFS rate at 6 months of 73% (warrants further investigation in a comparative phase III trial).

According to exact binomial design with a one-sided 5% type I error and power of 85%, 89 patients will need to be randomized in order to test the previous hypotheses. In parallel, 89 patients will be included in the control arm.

For Phase III: to compare OS; an increase in median OS from 11 months with CisGem to 15 months with mFOLFIRINOX is expected (two-sided alpha risk = 5% and power = 80%)

The study will randomize 316 patients in total (188 in the Phase II plus additional 128 patients in phase III). The estimated recruitment duration for phase II is 18 months and the estimated recruitment duration for phase III is 13 months. The minimal duration of participation of each patient is 24 months.

The rules to continue in Phase III study will be only applicable on mFOLFIRINOX arm and will be calculated on the 89 evaluable patients: if 61 patients or more are alive and progression-free at 6 months, then mFOLFIRINOX will be declared as efficient and will be compared to CisGem in the Phase III.

All the analysis will be performed on the intent-to-treat patient population. All the patients will be followed-up on a regular basis until the end of the study. Baseline characteristics will be described on the overall population and by treatment arms.

Tumor response, toxicities and other baseline variables will be reported using usual descriptive statistics: for quantitative variables: mean, standard deviation, median, inter-quartile interval and range and for qualitative variables frequencies and percentages.

The phase II recruitment is stopped (191 patients randomized by 43 centers), results are expected for June 2019.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.11.018.

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