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Progress Report

Phase III randomized trial comparing systemic versus intra-arterial oxaliplatin, combined with LV5FU2 +/- irinotecan and a targeted therapy, in the first-line treatment of metastatic colorectal cancer restricted to the liver (OSCAR): PRODIGE 49 ☆

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ABSTRACT

Introduction: In patients with unresectable liver metastases from colorectal cancer (CRCLM), systemic doublet or triplet chemotherapy and targeted therapy is considered a standard first-line treatment. Hepatic arterial infusion of oxaliplatin (HAI-ox) generates a high response rate, but this still needs to be confirmed in a randomized trial. We incorporated HAI-ox in doublet or triplet + targeted therapy to validate its efficacy.

Aim: The OSCAR study is an ongoing randomized phase III trial comparing FOLFOX + targeted therapy according to *RAS* status, or FOLFOXIRI + bevacizumab in patients eligible for triplet therapy, with the same regimen but with HAI-ox instead of IV-ox as the first-line treatment for CRCLM.

Materials and methods: Main eligibility criteria are colorectal cancer, unresectable liver metastasis, no extra-hepatic metastases except pulmonary nodules if ≤3 and <10 mm, ECOG performance status 0 or 1.

Endpoint: The primary endpoint is progression-free survival (PFS). A difference of 4 months for the median PFS in favor of HAI-ox is expected (HR = 0.73). Secondary endpoints include overall survival, overall response rate, secondary liver resection, safety, and quality of life.

Conclusion: This study is planned to include 348 patients to demonstrate the superiority of HAI-ox over systemic oxaliplatin in first-line CRCLM treatment (NCT02885753).

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1. Background

Around 60% of patients with colorectal cancer (CRC) tumors develop liver metastases (LM) during the course of the disease. Fifteen percent of these patients have resectable LM at diagnosis and will be treated with curative intent, while the vast majority will be managed with palliative intent [1].

In some patients with liver-limited disease (LLD) initially considered unresectable, an aggressive first-line therapeutic regimen can lead to long-lasting survival and potentially curative secondary resection of the metastases [2–5]. However, in the current literature, only 36% at most of such patients undergo curative surgery, and many of these will experience liver recurrence [6,7]. Overall, CRCLM progression leads to death in more than 50% of patients with metastatic CRC (mCRC), justifying an aggressive locoregional treatment when possible [8], even in patients for whom potentially curative intent is not being considered. It is therefore important to develop new therapeutic strategies in this specific population with LLD.

Since liver metastases mainly receive blood supply from the hepatic artery whereas normal liver tissue is mainly supplied by the portal vein, hepatic arterial infusion (HAI) has been used to increase the local concentration of cytotoxic agents to liver metastases, while sparing the healthy liver parenchyma. For more than 30 years, HAI chemotherapy has been considered an effective alternative to systemic chemotherapy in patients with LLD [9]. Floxuridine (FUDR) and more recently oxaliplatin have been the two most tested drugs in this setting, with high tumor response rates and secondary liver metastases resection rates ranging from 20 to 66% [10–13]. A meta-analysis of 10 trials using HAI with FUDR or Fluorouracil in a total of 461 patients showed a large benefit for intra-arterial hepatic chemotherapy, with a risk ratio of 2.26 for the response rate ($p<0.05$). However, this meta-analysis failed to show an improvement in overall survival (HR: 0.90 95% CI (0.76–1.07)) [13]. However, there is a clear lack of standardization concerning the therapeutic protocol for IA administration, and these trials were mostly conducted before the arrival of modern chemotherapy regimens and the use of targeted agents. Thus, the majority of the studies did not use concomitant active systemic chemotherapy. Moreover, a large majority allowed a crossover, leading to difficulties in the interpretation of overall survival. Oxaliplatin therapy may be better standardized and easier to use than FUDR or 5FU in terms of the technical approach (no need for an implantable pump, which are not available in Europe) and toxicities (FUDR seems to cause significant biliary toxicity, especially when combined with bevacizumab) [14]. No randomized trials have validated the use of oxaliplatin in daily practice.

The rebirth of intra-arterial therapies has been promoted by recent advances in interventional radiology and the use of less toxic drugs that are easier to use than FUDR. Interventional radiology has made it simpler and safer to place an intra-arterial catheter in the hepatic artery, dramatically reducing the complications of HAI procedures [15]. Moreover, catheters implanted using interventional radiology have an increased lifetime and allow the use of effective intra-arterial treatments for more relevant periods of time [16]. Thanks to these improvements, HAI has become a new treatment option for patients with LLD [17], and may increase survival and resection rates of LM of CRC, decrease the risk of relapse after liver surgery, and help to spare liver parenchyma [10,11,18,19].

HAI Oxaliplatin (HAI-ox) is usually administered after the failure of multiple systemic chemotherapies and biotherapy in mCRC with liver-exclusive or liver-dominant metastatic disease. In parallel, huge progress has been made in systemic chemotherapy, with the use of targeted therapies according to the *RAS* mutation status.

The combination of a highly effective systemic approach and HAI-ox could not only improve the response rate, but also lead to a deeper response and early tumor shrinkage, which is, known to correlate with progression free survival (PFS) and overall survival (OS) in mCRC patients [20,21]. It may also lead to increased secondary resection rates of liver metastases with curative intent.

The combination of an anti-EGFR therapy with oxaliplatin-based HAI has already been evaluated in two different phase II trials. In the OPTILIV-07 trial, patients who did not respond to systemic chemotherapy were treated with Cetuximab IV plus oxaliplatin, irinotecan and 5FU HAI. This combination led to an impressive secondary resection rate of 31% in heavily pretreated patients [22]. In a first-line setting, the CHOICE trial tested the combination of cetuximab plus LV5FU2 IV and HAI-ox in patients with unresectable CRCLM. The objective response rate was 96% with a disease control rate of 100%, and a resection rate of 66% in patients with *KRAS*/*BRAF* wild-type CRCLMs [23]. The combination of bevacizumab with HAI-ox has not yet been fully evaluated. Some pilot studies showed a good safety profile of HAI-ox combined with bevacizumab [24], whereas the combination of FUDR + bevacizumab seems to cause some toxicity [14].

Despite these promising results, there have been no randomized trials to assess HAI versus modern systemic treatments in mCRC patients with LLD. In addition, intensive systemic chemotherapy protocols have been successfully developed during the last decade and a triplet regimen combining 5FU+irinotecan+oxaliplatin together with bevacizumab has been shown to improve all oncologic outcomes including OS in patients with mCRC [3,4]. Some trials have also suggested the efficacy of the triplet combined with panitumumab or cetuximab, with encouraging response rates. However, in the absence of randomized trials, and given that previous studies involved populations highly selected according to both the molecular profile and clinical status, the triplet + anti-EGFR combination cannot be considered a standard at this time [25]. However, not all patients are eligible for such an intensive systemic regimen due to its associated toxicities. A doublet regimen with a targeted agent corresponding to the tumor *RAS* status, bevacizumab in RAS mutant and cetuximab or panitumumab in *RAS* wild type, is preferred in elderly patients or in patients unfit for a triplet regimen.

We have thus designed a study to evaluate the efficacy of an intensification strategy based on oxaliplatin HAI in patients with unresectable CRCLM as compared with standard systemic treatment. The OSCAR study is a randomized phase III trial, comparing FOLFOX plus targeted therapy according to the *RAS* status, or FOLFOXIRI plus bevacizumab in patients eligible for a triplet upfront treatment, versus the same regimen with oxaliplatin administered intra-arterially in the first-line treatment for CRCLM.

2. Methods

This study is designed as a multicenter, randomized, open-label, comparative phase III trial. Informed consent is being obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee (Comité de Protection des Personnes (CPP) Ile-de France 8 and the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)). The clinical trial has been registered in European (EudraCT n°2016–002,393–12) and international registries (NCT02885753).

The study flow-chart is detailed in Fig. 1. The first included patient was randomized on December 23, 2016, and as of September 9, 2021, 193 patients have been included.

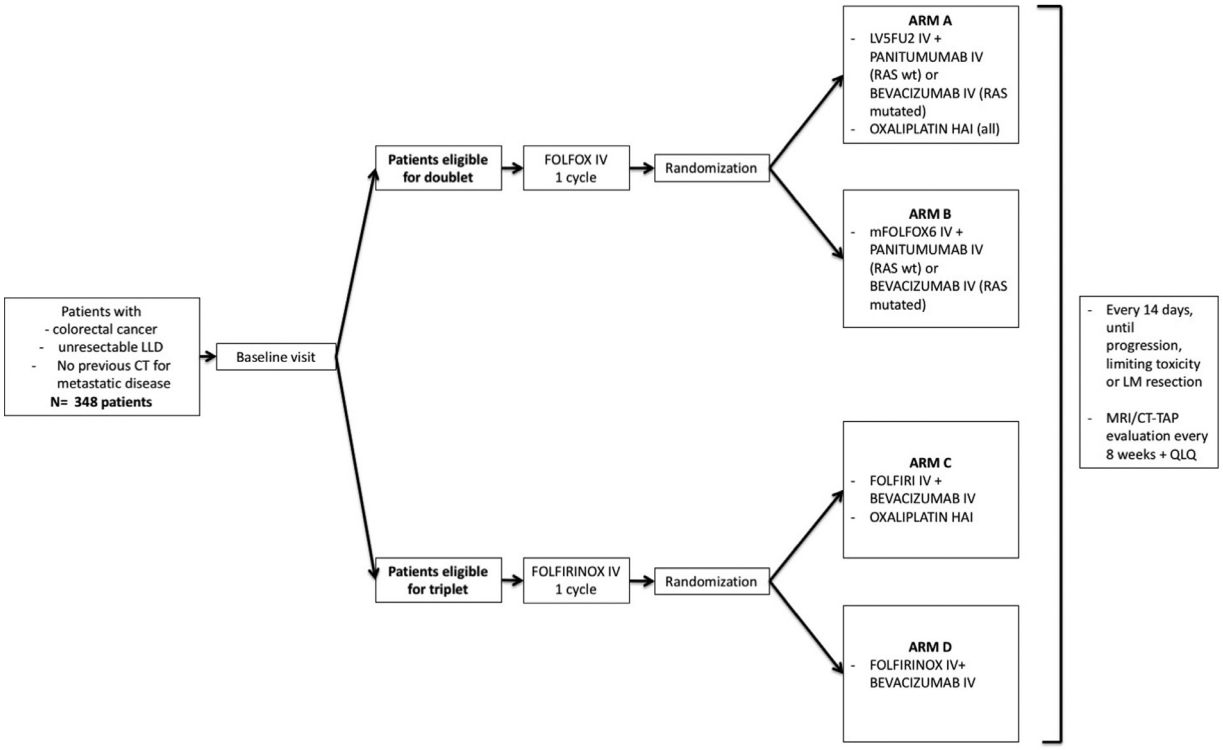

Fig. 1. Flowchart of the OSCAR trial. IV: intravenous; HAI: hepatic arterial infusion; LLD: liver limited disease; LM: liver metastases; MRI: Magnetic resonance imaging; CT-TAP: computed tomography of the thorax, abdomen and pelvis; QLQ: quality of life questionnaire.

2.1. Study objectives and endpoints

2.1.1. Primary objective

The primary objective is to assess the efficacy of first-line HAI-ox compared with IV-ox incorporated in a doublet plus targeted therapy or a triplet plus bevacizumab regimen, in terms of progression-free survival (PFS), in patients with LLD from mCRC. Progression is defined as radiological progression, evaluated according to RECIST v1.1 criteria evaluated by the investigator, or clinical progression.

Considering the growing evidence in favor of triplet + bevacizumab [4], FOLFOXIRI + bevacizumab is now considered a standard first-line regimen, especially when tumor shrinkage is necessary (aggressive disease or to obtain metastases resection). We therefore amended the protocol in March 2021 after the inclusion of 174 patients to allow triplet chemotherapy + bevacizumab as a treatment possibility. Following this amendment, and according to investigators' assessments, patients are now classified as "eligible for triplet" or "eligible for doublet" before randomization.

Randomized patients eligible for triplet therapy receive either HAI oxaliplatin plus the systemic FOLFIRI and bevacizumab combination, or IV oxaliplatin plus the systemic FOLFIRI and bevacizumab combination.

Randomized patients eligible for doublet therapy receive either HAI oxaliplatin plus systemic LV5FU2 and a targeted agent according to tumor RAS status (i.e. panitumumab in RAS wild-type or bevacizumab in RAS mutant) or IV oxaliplatin plus systemic LV5FU2 (FOLFOX 4 regimen) and a targeted agent according to tumor RAS status (i.e. panitumumab in RAS wild-type or bevacizumab in RAS mutant).

2.1.2. Secondary objectives

The secondary objectives include overall survival (OS), hepatic PFS, objective response rate (ORR), depth of response (DpR), early tumor shrinkage (ETS) according to the investigator's evaluation, rate of secondary liver resection, and PFS under active treatment. A post-hoc centralized evaluation of PFS and ORR is also planned.

OS is defined as the time between the beginning of treatment and the occurrence of death due to any cause. Patients alive or lost to follow-up are censored at the date of the last news.

Radiological and/or clinical PFS is defined as the time between the beginning of treatment and the occurrence of the first progression, whatever the time of occurrence or death, or the date of last follow-up in patients alive without progression. Radiological progression is defined according to response evaluation criteria in solid tumors (RECIST) v1.1. For hepatic PFS, only hepatic progressions are taken into account. Patients with extra-hepatic progression are therefore followed till hepatic progression, death or the date of last news in patients alive without hepatic progression. ORR is defined as the best objective (complete or partial response) response according to RECIST v1.1 evaluated by a computed tomography scan of the thorax, abdomen and pelvis (CT-TAP) or magnetic resonance imaging (MRI) every 8 weeks. DpR is defined as the relative change in the sum of the longest diameters of RECIST1.1 target lesions at the nadir, in the absence of new lesions or progression of non-target lesions, as compared to baseline. ETS is defined as a relative change in the sum of the longest diameters of RECIST1.1 target lesions >20% at 8 weeks. The resection rate considers all macroscopically complete surgical resections (R0, R1), percutaneous destruction and/or stereotaxic body radiation therapy (SBRT) of all liver metastases. PFS under active treatment is defined as the time between the start of treatment and the date of progression under treatment (excluding breaks) or death. The dose-intensity of oxaliplatin and other systemic cytotoxic/targeted agents received will be analyzed.

Quality of life will be assessed using the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) v3 every two months. Finally, safety will be carefully considered using the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 to evaluate

the toxicity of HAI and systemic CT. HAI efficacy and tolerability will also be assessed independently for patients receiving a triplet or doublet therapy.

2.1.3. Ancillary objectives

The ancillary studies will include an optional biological study and a radiological study.

The biological study will dynamically investigate circulating tumor DNA (ctDNA). The objectives of the biological study are

- to determine the prognostic value on survival of the ctDNA level before the start of treatment, and of the rapid decrease in ctDNA (at 28 days as compared to baseline)
- to compare the mechanisms of resistance to panitumumab between patients treated with intra-arterial or intravenous oxaliplatin

For this purpose, blood from patients included in the biological study is being collected in STRECK tubes to determine the presence of ctDNA before the first chemotherapy, then before the third cycle, and finally at disease progression. Tumor DNA is characterized using the NGS technique and the following gene panel: KRAS NRAS BRAF RAF1 ERBB2 ERBB3 ERBB4 EGFR MET PIK3CA AKT1 PTEN MTOR MAP2K1MAP2K2 MAP2K4 MAP3K13 MAPK3 MAPK4 APC TP53.

A radiological study is also planned, to determine radiological parameters associated with the effectiveness of intra-arterial treatment.

2.2. Study population

2.2.1. Inclusion criteria

Eligible patients must have histologically confirmed colorectal adenocarcinoma, with at least one measurable liver metastasis according to RECIST v1.1 criteria. Patients should have no extrahepatic disease, except pulmonary nodules if $\leq$3 and $<$10 mm, and the primary tumor. They should have received no prior chemotherapy for metastatic disease (except perioperative chemotherapy for previously resected metastases and/or if last cycle was administered at least 12 months before randomization). Adjuvant chemotherapy after primary resection is also allowed if the last cycle was administered at least 12 months before randomization. Tumor *RAS* mutation status must be available.

Patients must be 18 years or older, have a good general health status, normal liver, kidney, cardiac, hematologic, and coagulation functions. Patients also need to agree to have an efficient contraceptive method, to be affiliated to a social security system, and to provide a signed informed consent form before study entry.

2.2.2. Non-inclusion criteria

Patients with liver metastases eligible for up-front curative treatment (i.e. resection and/or radiofrequency ablation) are ineligible for the study. Curative treatment feasibility has to be assessed by the local multidisciplinary committee with at least one surgeon and one interventional radiologist experienced in liver metastases treatment.

Specific contraindications to the placement of an HAI catheter are exclusion criteria (thrombosis of hepatic artery, or arterial anatomy compromising catheter placement).

Specific contraindications to the administration of bevacizumab or panitumumab are also exclusion criteria. Patients with sensory neuropathy $\geq$grade 2 (NCI-CTAE v.4.0), significant chronic liver disease, history of cancer within 5 years prior to entry into the study (other than adequately treated basal-cell skin cancer or in situ carcinoma of the cervix), clinically significant active heart disease or myocardial infarction in the last 6 months, risk of developing ventricular arrhythmia, previous organ transplantation, HIV or other immunodeficiency syndromes, or partial or complete dihydropyrimidine deshydrogenase deficiency are not eligible for the study.

Patients should not be pregnant or breast-feeding, already included in another clinical study with an experimental molecule, deprived of liberty or under guardianship, or unable to undergo medical monitoring tests for geographical, social or psychological reasons.

2.2.3. Randomization

After validation of inclusion/non-inclusion criteria and signature of informed consent form patients are randomized.

Once the *RAS* status is determined, and once the investigator has judged the patient eligible for triplet or doublet chemotherapy, patients are randomized by the centre de randomisation – Gestion – analyse (CRGA) of the Féderation Française de Cancérologie Digestive (FFCD).

Randomization is stratified using a minimization method according to the following factors:

- Center
- Number of liver metastases: $<$5 vs. $>$ 5
- Age: $\leq$70 years vs. $>$ 70 years
- *RAS* status: RAS wild type vs RAS mutated tumor

2.2.4. Treatment schedule

Patients are randomly assigned in a 1:1 ratio to the experimental arm (Arm A or C) or the control arm (Arm B or D). All patients receive 1 cycle of IV FOLFOX without targeted therapy before randomization. This cycle has been allowed to take into account the time needed to determine the *RAS* mutation status, and to organize placement of the HAI catheter before the second cycle.

Arm A or C (experimental arm): HAI oxaliplatin combined with systemic chemotherapy plus targeted therapy every 2 weeks.

Patients eligible for doublet chemotherapy (Arm A): patients receive 2-h HAI oxaliplatin 85 mg/m^2, combined with a systemic modified LV5FU2 regimen (leucovorin 400 mg/m^2 as a 120-minute infusion at day 1 (or 200 mg/m^2 in 2 h for a racemic mixture if L-folinic acid) followed by 5FU 400 mg/m^2 bolus at day 1, followed by 46-h IV 5-FU 2400 mg/m^2 plus targeted therapy. Targeted therapy is determined according to the RAS status: 1-h IV panitumumab 6 mg/kg in patient with an RAS wild-type tumor, or 30-min IV bevacizumab 5 mg/kg in patients with an RAS-mutated tumor.

Patients eligible for triplet chemotherapy (Arm C): Patients receive 2-h HAI oxaliplatin 85 mg/m^2, combined with systemic FOLFIRI-bevacizumab regimen (leucovorin 400 mg/m^2 as a 120-minute infusion at day 1 (or 200 mg/m^2 in 2 h for a racemic mixture if L-folinic acid) followed by Irinotecan (150 mg/m^2) then 5FU 400 mg/m^2 bolus at day 1, followed by 46-h IV 5-FU 2400 mg/m^2), plus 30-min IV bevacizumab 5 mg/kg, whatever the *RAS* status.

Arm B or D (control arm): IV FOLFOX plus targeted therapy or FOLFIRINOX plus bevacizumab every 2 weeks.

Patients eligible for doublet chemotherapy (Arm B) receive 2-h IV oxaliplatin 85 mg/m^2, combined with systemic modified LV5FU2 plus targeted therapy, according to the RAS mutation status.

Patients eligible for triplet chemotherapy (Arm D) receive 2-h IV oxaliplatin 85 mg/m^2, combined with leucovorin or L-folinic acid, followed by Irinotecan (150 mg/m^2), followed by 46-h IV 5-FU 2400 mg/m^2, plus IV bevacizumab 5 mg/kg, whatever the RAS status.

In both arms, treatment is administered until disease progression, limiting toxicity, or LM surgery. Three-month adjuvant systemic chemotherapy with LV5FU2 or FOLFOX (according to patients' residual neuropathy) is recommended in cases of curative intent LM resection.

The HAI catheter is placed before starting treatment, percutaneously by an interventional radiologist under fluoroscopic monitoring in order to allow perfusion of the whole liver volume through a single catheter linked to an implantable port, or surgically in cases of planned laparotomy, according to methods previously described [26,27]. Digital subtracted angiography during injection of contrast medium through the HAI catheter port is systematically obtained before treatment initiation, and then every two courses of HAI during the first four months of treatment, and then according to the investigator's discretion. HAI is delivered if the control angiogram confirms the patency of the catheter and perfusion of the entire liver without extrahepatic perfusion or leaks [28]. Only physicians and nurses familiar with the HAI technique administer the HAI chemotherapy.

2.2.5. Assessments and follow-up

Clinical, biological, and para-clinical examinations are performed every 2 weeks (Fig. 1).

Efficacy is assessed with a CT-scan performed every 8 weeks, until progression, whatever the site. In cases of extrahepatic progression, follow-up is continued until hepatic progression, in order to document hepatic PFS. Quality of life is assessed at the same time points.

If the treatment is stopped without documented progression, patients are evaluated every 8 weeks.

After progression, patients are followed up every 6 months, and post-progression treatments, including locoregional treatments, and survival data are monitored.

2.3. Statistical considerations

2.3.1. Required number of patients

The analysis will compare HAI oxaliplatin (arms A and C) with IV oxaliplatin (arms B and D). The required number of patients is based on the following hypothesis:

H0: No difference in the median PFS between the two types of oxaliplatin administration;
H1: An improvement in the median PFS of 4 months with the experimental arms A and C (from 11 months to 15 months) is expected (HR = 0.73).

With a risk α of 5% (two-sided) and a power of 80%, 318 events (progression or death) are necessary (Schoenfeld method). With a 36-month follow-up, an inclusion rate of six patients per month and taking into account a rate of non-evaluable patients or lost to follow-up by 5%, we will have to randomize 348 patients.

2.3.2. Statistical analysis plan

All analyses will be performed using SAS software version 9.4 or higher. A statistical analysis plan will be drawn up before the database is frozen.

The modified intention to treat population, defined by all patients randomized, whatever their eligibility and who have received at least one dose of treatment (whatever the dose and the treatment), will be used for the description of the population, and the main analysis of primary and secondary efficacy criteria. Additionally, an analysis of the primary criteria (PFS) in the ITT and per protocol population (patients receiving at least 6 months of treatment, and four consecutive cycles of HAI-oxaliplatin in arm A and C) is planned.

Subgroup analyses are planned, including analysis according to the RAS status (wild type vs. mutated), age (< 70 vs. ≥ 70), doublet or triplet treatment, the number of liver metastases (≤ 5 vs. > 5), the presence of extra-hepatic metastases (liver dominant vs. liver only disease), and primary tumor sideness (right vs. left). Such analysis may be completed by multivariate analyses using logistic regression (in particular for the primary endpoint) or Cox model, as appropriate, and adjusted for other prognostic factors in case of imbalance between arms.

Safety will be analyzed in the safety population, defined as patients receiving at least one dose of treatment, whatever the dose and the treatment.

Continuous variables will be described using means, standard deviations, medians, inter-quartile intervals, minimum and maximum. Qualitative variables will be described using frequencies and percentages. Efficacy and safety analyses will be presented by treatment arm. The median follow-up will be calculated using the reverse Kaplan-Meier method. The best response under treatment will be reported using percentages and numbers. The two types of oxaliplatin administration (Arms A + C versus Arms $B + D$) will be compared using a $\chi 2$ test or a Fischer test, as appropriate.

2.3.3. Serious adverse events (SAE) and toxicity monitoring

The investigator is responsible for ensuring that all adverse events (AEs) are properly captured in the Case Report Forms (CRFs). It is left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study.

All SAE occurring during the study treatment period must be reported within 24 h.

SAE analysis will be carried out by the Pharmacovigilance department of the FFCD.

An independent committee will include at least two gastrointestinal oncologists, a statistician / methodologist, and a pharmacovigilance expert. The committee will meet at least once a year or more if the Promoter deems it necessary for the analysis of SAEs. The committee will rule on all tolerance data sent by the centers to the Promoter (SAE +/- adverse events). The FFCD is responsible for the medical review of all SAEs and for their notification to the appropriate Ethics Committees, Competent Authorities and participating Investigators. All patients included in the study will be evaluated up to 2 months before the date of the independent committee meeting.

3. Discussion

OSCAR is the first randomized phase III trial to assess the efficacy of oxaliplatin HAI in the 1st-line treatment of patients with LLD from mCRC. Currently, HAI is cited as an option in many guidelines [17,29]. Validation of HAI-ox efficacy in a randomized trial would allow the practice of HAI to be extended to a larger number of centers and included in our LLD mCRC therapeutic strategies.

During the study, growing evidence showed that triplet chemotherapy + bevacizumab leads to improved ORR, PFS and OS. We thus amended the trial recently to allow this possibility for patients eligible for an aggressive first-line treatment regimen, i.e. FOLFOXIRI+bevacizumab. Indeed, although ESMO guidelines cited this regimen only as an alternative option in 2014 [30], it became a front-line standard in BRAF mutant mCRC in 2016 and in selected fit patients where tumor shrinkage is the goal. [17] It is now a routine standard first-line option for fit patients with mCRC. It thus seemed to be of most importance to demonstrate the potential added value of HAI-ox, not only in patients treated with a standard doublet regimen but also in those eligible for a triplet regimen.

We choose PFS as the primary endpoint. Indeed, although OS remains a major endpoint in oncology, it did not seem to us to be the most suitable criterion for evaluating the efficacy of HAI-ox in this population, and PFS has been validated as a surrogate marker of OS in mCRC [31]. On the one hand, there is a risk of frequent crossover in patients with liver-limited metastasis treated in centers with access to intra-arterial chemotherapy, since HAI is

also an option in pre-treated patients. On the other hand, long-term therapeutic strategies are complex and multimodal in these patients with exclusive and non-resectable LMCRC, with therapeutic histories mixing locoregional treatment, such as thermoablation or surgery, with other intra-arterial treatments (selective internal radiotherapy, chemoembolization). We considered that this complexity of global management could make it more difficult to assess the effect of HAI by using OS as the primary endpoint in the OSCAR trial. Finally, the long survival times in these patients would have required prolonged follow-up. The secondary resection rate was also not selected as a primary endpoint for several reasons. First, the assessment of resectability can be partly subjective [5,32], and this may bias the assessment of the efficacy of HAI-ox. Moreover, the centers performing HAI-ox are generally expert centers in liver surgery, and secondary resectability in these centers would have lacked reproducibility. Finally, secondary resectability is not a goal for all unresectable patients, and increased treatment efficacy also prolongs survival and reduces symptoms in patients who will never undergo surgery.

By the 9 September 2021, 193 patients had been included in 30 centers, with a rate of recruitment of five patients per month over the last 6 months.

Conflict of interest

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Simon Pernot has received honoraria as a speaker and/or in an advisory role from Merck KGaA, Sanofi, Astra Zeneca, Servier, Pierre Fabre, and Amgen

David Tougeron has received honoraria as a speaker and/or in an advisory role from Merck KGaA, Sanofi, Roche Genentech, MSD, BMS, Astra Zeneca, Servier, Pierre Fabre, Sandoz and Amgen

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Faiza Khemissa has received honoraria as a speaker and/or in an advisory role from Sanofi, Bayer

Michel Ducreux has received honoraria as a speaker and/or in an advisory role from Merck KGaA, Sanofi, Roche Genentech, MSD, BMS, Astra Zeneca, Servier, Pierre Fabre, Sandoz and Amgen

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Other authors didn't declare any conflict of interest.

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