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Progress Report

Nal-IRI/LV5-FU versus paclitaxel as second-line therapy in patients with metastatic esophageal squamous cell carcinoma (OESIRI)-PRODIGE 62: A multicentre, randomised, non-comparative phase II study

Violaine Randrian[a], Antoine Adenis[b], Jérôme Desrame[c], Emilie Barbier[d], Frédéric Di Fiore[e], Astrid Lièvre[f], Laetitia Dahan[g], Pierre Laurent-Puig[h], Laurent Mineur[i], Gilles Breysacher[j], Guillaume Roquin[k], Samy Louafi[l,m], Anthony Lopez[n], Christophe Louvet[o], Christophe Borg[p], Jean Philippe Metges[q], Roger Faroux[r], Lila Gaba[d], Sylvain Manfredi[s], David Tougeron[a,*]

[a] *Gastroenterology Department, Centre Hospitalo-Universitaire de Poitiers, University of Poitiers, Poitiers, France*
[b] *Medical Oncology Department, Institut Régional Du Cancer de Montpellier (ICM), Université de Montpellier, France*
[c] *Medical Oncology Department, Hôpital Privé Jean du Cancer de Mermoz, Lyon, France*
[d] *FFCD EPICAD INSERM LNC-UMR 1231, University of Burgundy and Franche-Comté, Dijon, France*
[e] *Medical Oncology Department, Centre Henri Becquerel, Rouen, France*
[f] *Gastroenterology Department, Centre Hospitalo-Universitaire Pontchaillou, Rennes 1 University, Rennes, France*
[g] *Digestive Oncology Department, AP-HM, La Timone Hospital, Aix-Marseille Université, Marseille, France*
[h] *Biology Department, Assistance Publique-Hôpitaux de Paris, European Georges Pompidou Hospital, Paris, France*
[i] *Digestive Oncology Department, Institut Sainte Catherine, Avignon, France*
[j] *Gastroenterology Department, Hôpitaux Civils, Colmar, France*
[k] *Gastroenterology & Digestive Oncology Department, Centre Hospitalo-Universitaire d'Angers, Angers, France*
[l] *Gastroenterology Department, Centre Hospitalier Sud Francilien, Corbeil-Essonnes, France*
[m] *Gastroenterology Department, Groupe Hospitalier Nord Essonne, Longjumeau, France*
[n] *Gastroenterology and Hepatology Department, Centre Hospitalo-Universitaire de Nancy, Vandoeuvre-lès-Nancy, France*
[o] *Medical Oncology Department, Institut Mutualiste Montsouris, Paris, France*
[p] *Medical Oncology Department, Centre Hospitalo-Universitaire de Besançon, Besançon, France*
[q] *Medical Oncology Department, Centre Hospitalier Régional Universitaire de Brest-Hôpital Morvan, Brest, France*
[r] *Gastroenterology Department, Centre Hospitalier de La Roche-sur-Yon, La Roche-sur-Yon, France*
[s] *Gastroenterology Department, Centre Hospitalo-Universitaire de Dijon, EPICAD INSERM LNC-UMR 1231, University of Bourgogne-Franche Comté, Dijon, France*

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ABSTRACT

Half of patients newly diagnosed with esophageal squamous cell cancer (ESCC) have metastatic disease (mESCC) and therefore a poor prognosis. Furthermore, half of patients with initial loco-regional disease present disease recurrence after surgery and/or chemoradiation. In mESCC, the recommended first-line treatment combines 5-fluorouracil and cisplatin, although this has not been validated by a phase III trial. Patients with disease progression or recurrence after platinum-based chemotherapy and good performance status probably benefit from second-line chemotherapy. Several molecules have been evaluated in phase I/II trials or retrospective studies (docetaxel, paclitaxel and irinotecan) but no randomised studies are available.

OESIRI is a multicentre, randomised, open-label phase II trial designed to evaluate efficacy and safety of liposomal irinotecan (nal-IRI) plus 5-FU versus paclitaxel as second-line therapy in patients with mESCC. The main inclusion criteria are histologically proven mESCC in progression after first-line platinum-based chemotherapy. Patients with initial resectable disease can be included if recurrence occurred within 6 months.

The primary objective is to evaluate the percentage of patients alive 9 months after randomisation. Secondary endpoints are progression-free survival, overall survival, response rate, safety and

* Corresponding author at: Department of Gastroenterology, Centre Hospitalo-Universitaire de Poitiers, Poitiers, 2 rue de la Milétrie, Poitiers Cedex, 86021, France.
E-mail address: david.tougeron@chu-poitiers.fr (D. Tougeron).

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quality of life. In addition, circulating tumour DNA will be monitored to assess its prognostic value.

1. Rationale and aims

Esophageal cancer has a poor prognosis, partly explained by a delayed diagnosis as about 50% of patients are diagnosed with metastasis. In the remaining 50% of patients with loco-regional disease at first, systemic metastatic disease will occur in the vast majority [1–3]. Esophageal cancer prognosis is poor at metastatic stages with an overall survival (OS) rate at 5 years of 3% [4]. Esophageal cancers equally subdivide in esophageal squamous cell carcinomas (ESCC) and adenocarcinomas in western countries [5].

The treatment of metastatic ESCC (mESCC) is palliative. Continuation of chemotherapy seems efficient because it provides longer and better control of disease symptoms [6]. A Cochrane meta-analysis suggests that second-line chemotherapies probably increase OS as compared to best supportive care alone, without any decrease in quality of life [7]. All international guidelines, based on phase II trials and a meta-analysis, recommend combination of platinum salt (oxaliplatin or cisplatin) with fluoropyrimidine (5-fluoro-pyrimidine - FU - or capecitabine) as first-line treatment [8–10]. Patients with advanced ESCC treated with the most common regimen, cisplatin combined with 5FU, have a response rate of 35%, a median OS duration of 7.6 months and a l-year OS of 34% [9].

There is no standard second-line treatment in mESCC. The association of irinotecan plus docetaxel allowed 2 months progression-free survival (PFS), 6 months OS whereas the paclitaxel plus capecitabine regimen allowed 5.2 months PFS, 8.4 months OS [11,12]. In France, the most commonly used regimens in second-line setting of mESCC are 5FU plus irinotecan (FOLFIRI) and paclitaxel monotherapy [12].

Research in mESCC focuses on new drug combinations to improve their efficacy and tolerance [13,14]. MM-398, or nal-IRI, is a nanoliposomal irinotecan. Loading irinotecan on liposomes maintains it in the blood circulation, increasing and prolonging intratumoral levels of both irinotecan and its active metabolite (SN-38). In patients with metastatic pancreatic adenocarcinoma after first line of gemcitabine-based therapy nal-IRI combined with 5FU increased OS versus 5FU alone [15]. A phase II trial comparing nal-IRI in second-line treatment of advanced esophago-gastric adenocarcinomas to irinotecan and docetaxel showed 13.6% of objective response in the nal-IRI arm, 6.8% in the irinotecan arm and 15.9% in the docetaxel arm with no difference in median PFS and OS between the 3 arms [16]. There is no data about efficacy of nal-IRI in ESCC.

The aim of OESIRI study is to evaluate the efficacy and safety of nal-IRI plus 5FU versus paclitaxel as a second-line therapy in patients with mESCC who failed first-line platinum-based chemotherapy.

2. Study design

OESIRI - PRODIGE 62 is a multicentre, randomised, open label phase II cooperative trial of PRODIGE French group (FFCD, UNICANCER GI and GERCOR groups) assessing the efficacy of nal-IRI plus 5FU as second-line treatment of mESCC.

Trial starts in March 2019. Theoretical end of recruitment is March 2022 and primary endpoint analysis is March 2023.

2.1. Inclusion and non-inclusion criteria

Inclusion criteria are: ≥18 years, histologically proven mESCC, failure after first-line platinum-based chemotherapy. Patients with resectable disease treated by surgery with or without platinum-based chemotherapy (or radiotherapy) can be included if a metastatic recurrence occurs within 6 months after the end of treatment. Disease must be considered unresectable but patients with measurable disease or not, according to RECIST 1.1 criteria, are eligible. WHO performance status should be ≤2. Biological parameters must meet the following criteria: neutrophils ≥1500/mm^3, platelets ≥100 000/mm^3, haemoglobin ≥9 g/dl, total bilirubin ≤2 × ULN, albumin ≥25 g/l, AST and ALT ≤ 2.5 × ULN (≤5 × ULN in case of hepatic metastases) and creatinine clearance ≥50 ml/min according to MDRD formula.

Non-inclusion criteria are: brain metastases if symptomatic or untreated, malignancy during the previous 3 years, serious arterial thromboembolic events during the previous 3 months, New York Heart Association (NYHA) class III or IV congestive heart failure, uncontrolled high blood pressure, ventricular arrhythmia, clinically significant gastro-intestinal disorders, peripheral neuropathy ≥grade 2 according to National Cancer Institute — Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria v.4.0, known hypersensitivity or allergy to one of the drug administered in the study, Gilbert's syndrome or any known counter indication to irinotecan, known complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency (defined by an uracilemia ≥16 ng/ml) and use of potent CYP3A4 enzyme inhibitors or inducers.

Patients will be randomised in a 1:1 ratio using the minimisation technique. Randomisation will be stratified based on: center and WHO performance status (0/1 versus 2).

2.2. Study treatments

In the experimental arm (arm A), every 14 days patients will receive intravenous (IV) infusion of nanoliposomal irinotecan (80 mg/m^2) followed by folinic acid (400 mg/m^2) or L-folinic acid (200 mg/m^2) and then 5FU (2400 mg/m^2 over 46 h). In the control arm (arm B), patients will receive an IV infusion of paclitaxel (80 mg/m^2) at Day 1, Day 8 and Day 14 of a 28 days-cycle (Fig. 1).

Cycles will be repeated in the two treatment arms until disease progression, unacceptable toxicity (grade 4 toxicity or grade 3 toxicity after the dose has been adjusted twice), patient refusal or upon investigator decision. If the reason for treatment discontinuation is not disease progression and third-line treatment has not started, the treatment can be reintroduced after either maintenance therapy with 5FU (arm A) or pause (arm A or B).

All toxicities requiring dose adjustment will be evaluated according to the NCI-CTCAE v4.0 criteria and managed as usually recommended for nal-IRI, 5FU and paclitaxel.

2.3. Trial objectives and endpoints

The main objective is to evaluate survival at 9 months in patients with mESCC treated with nal-IRI/5FU versus paclitaxel. The primary endpoint is the percentage of patients alive at 9 months after randomisation.

The secondary endpoints are PFS, OS, best response rate (complete response or partial response according to RECIST 1.1 criteria), toxicities (according NCI-CTCAE v4.0 criteria) and quality of life using EORTC QLQ-C30 and OES18 questionnaires.

2.4. Monitoring of the patients

The initial biological and clinical assessments and morphological examinations should take place within 2 and 4 weeks prior

to randomisation, respectively. The initial assessment includes clinical examination (medical history, weight, height and body surface area, WHO performance status, QLQ-C30 and OES18 questionnaires) and biological evaluation: complete blood count, UDP-glycosyltransferase 1 A1 peptide (UGT1A1*28) and dihydropyrimidine dehydrogenase (DPD) testing, creatinine clearance (MDRD formula), liver function tests, lactate dehydrogenase (LDH), albumin and pre-albumin, SCC tumour marker). Within 4 weeks prior to randomisation a CT-scan of neck-thorax-abdomen-pelvis should be performed measuring the target lesions according to RECIST criteria version 1.1.

Evaluation will be performed every 8 weeks until progression. These evaluations include clinical examination, biological tests, quality of life questionnaires and the radiological exams performed at initial assessment.

2.5. Calculation of sample size and statistical methods

This is a non-comparative trial. The clinical hypotheses are to extend the 9-months survival rate from 40% (H0: the percentage of patients alive at 9 months of 40% is not useful) to 60% (H1: the percentage of patients alive at 9 months of 60% is expected). Drugs used in second-line treatment, irinotecan, docetaxel or paclitaxel, allow a 9-months survival rate between 30 to 50% [16]. With a one-sided type 1 error α of 5% and a power of 85%, using an exact binomial method, it is necessary to randomise 50 patients per arm. Taking into account a 5% rate of patients lost to follow-up, 53 patients will be randomised per arm (for a total of 106 patients).

The study conclusions will be based solely on arm A (experimental arm), according to the following rule: out of 50 evaluable patients, if 27 patients or more are still alive 9 months after randomisation, then the treatment will be considered effective.

Best response rate, 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).

For the primary evaluation endpoint, a one-sided 95% confidence interval (CI) will be calculated in the experimental arm. Survival criteria (OS and PFS) will be estimated using the Kaplan-Meier method and described by medians and their 95% CI. Follow-up will be estimated by the reversed Kaplan–Meier method.

2.6. Administrative and ethical considerations

The trial sponsor is the Fédération Francophone de Cancérologie Digestive (FFCD). The trial is registered under the EudraCT number 2017-004730-28. This protocol was authorized by the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM), on August 14, 2018. The trial is registered on the clinicaltrials.gov website with the number NCT03719924. This protocol received approval from an Institutional Review Board, Comité de Protection des Personnes SUD EST IV (CCP) on 15 October, 2018.

This trial will be conducted in accordance with current French law, with the ethical principles of the Declaration of Helsinki of 1964 and with the International Conference on Harmonization Good Clinical Practice Guideline (ICH–E6, 17/07/96)

2.7. Ancillary study

Circulating tumor DNA (ctDNA) is a potential surrogate of solid biopsy for detecting important theranostic genetic alterations [17]. ctDNA helps to envision the spatial and temporal heterogeneity of tumors [18,19], and their evolution during treatment [20]. Preliminary results in lung, colon and pancreatic cancers show that the normalisation of ctDNA after 4 weeks of treatment is highly predictive of PFS and OS [21–23]. Very few data are available on ctDNA in ESCC [24] and the OESIRI trial represents an opportunity to study ctDNA in mESCC.

Detection of ctDNA will first be based on a massive parallel sequencing method combined with a specific pipeline analysis named base PER-sequencing which allows small fractions of

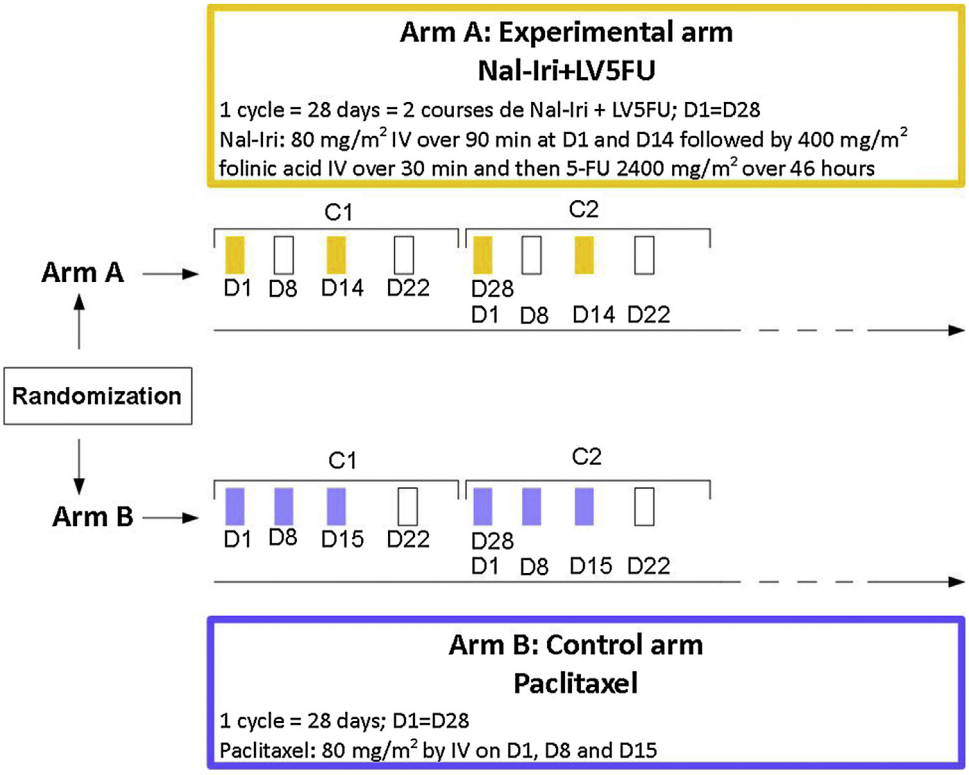

Fig. 1. Design of OESIRI trial.

mutated alleles (0.1%) to be detected [25]. The second method is based on the detection by digital droplet PCR of specific methylated regions in the enhancer region of some genes, which are specifically methylated in tumor DNA [26].

In the OESIRI trial, we investigate the prognostic value of the detection and quantification of ctDNA at the time of inclusion in the trial, and also to test the prognostic impact of an early decrease in the amount of ctDNA. An analysis of ctDNA will be performed before the first cycle of treatment and at Day 28. This will provide the prognostic value of the detection and amount of ctDNA at the time of inclusion and of the decrease or normalisation of ctDNA at Day 28. Analyses of these same biomarkers will be performed on tumour tissue. All analyses will be conducted in a centralized manner.

3. Discussion

There is no standard second-line treatment in mESCC. As some drugs are already used in routine clinical practice [8–10], it would be difficult to perform a randomised study versus best supportive care alone. Immune checkpoint inhibitors (ICI) emerge as potential therapies in eso-gastric tumors. Unfortunately, most studies mix both esophageal tumors and gastric tumors and/or both esophageal squamous cell carcinomas and adenocarcinomas. Nivolumab, an anti-programmed cell death-1 (anti-PD1), in 65 patients with chemoresistant esophageal cancer has demonstrated a disease control rate of 42% and 10.8 months of OS [27]. Similar results are observed with pembrolizumab (anti-PD1) [28]. The phase III KEYNOTE-181, presented at ASCO 2019, compared pembrolizumab versus investigator's choice chemotherapy as second-line therapy for patients with advanced/metastatic squamous cell carcinoma and adenocarcinoma of the esophagus or eso-gastric junction [29]. Median OS in both arms was 7.1 months but pembrolizumab is superior to chemotherapy in the subgroup of mESCC (8.2 months). Available evidences for efficacy of ICI alone remain limited in esophageal tumors. The evaluation of a new chemotherapy regimen as a second-line treatment for mESCC is a major issue to determine the best backbone chemotherapy to combine with ICI.

Conflicts of interest

None declared.

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