FOLFIRINEC: a randomized phase II trial of mFOLFIRINOX vs platinum-etoposide for metastatic neuroendocrine carcinoma of gastroenteropancreatic or unknown origin

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ABSTRACT

Background

Poorly differentiated neuroendocrine carcinomas (NEC) are rare diseases with a poor prognosis. Platinum-etoposide (PE) has been the recommended first-line treatment for decades. FOLFIRINEC (NCT04325425) is a national multicenter randomized phase II study which aims to challenge this standard regimen.

Methods

The primary objective is to compare the median progression-free survival (PFS) under mFOLFIRINOX versus PE. The secondary objectives are to evaluate the objective response rates (ORR), median overall survival (OS), safety and quality of life. The associated real-time translational study will establish a molecular profile for each patient enrolled.

Main inclusion criteria are: NEC of gastroenteropancreatic (GEP) or unknown origin, metastatic and RECIST 1.1 evaluable disease, tumor sample available and no contraindication to chemotherapy. Patients will be randomized 1:1 between PE every 21 days for 6-8 cycles and mFOLFIRINOX every 14 days for up to 12 cycles and stratified according to center, performance status, Ki67 and pathological subtype.

This trial will randomize 218 patients (24 months of follow-up) to have 80% power to detect an improvement of the median PFS from 5 months under PE to 7.5 months under mFOLFIRINOX (HR of 0.67, α =5%, two-sided). An intermediate analysis is planned at 50% of events.

Recruitment started on October 20, 2020.

1. Rational and aims

Poorly differentiated neuroendocrine carcinomas (NEC) of gastroenteropancreatic (GEP) and unknown origins are rare and heterogeneous diseases. The diagnosis is often done at the metastatic stage and the prognosis is poor. The standard first-line (L1) treatment is platinum-etoposide (PE) combination chemotherapy, mostly based on retrospective studies [1,2]. With this regimen, RR is 40 to 70% but the median PFS is short, between 4 and 9 months [3,4]. Disease progression almost always occurs during or just after treatment and median overall survival (OS) is only about 12-15 months for GEP NEC with similar efficacy of either cisplatin or carboplatin [3,4] and of either oral or intravenous etoposide [5,6]. After progression, only 40 to 45% of patients will receive a second-line (L2) chemotherapy which will include 5-fluoro-uracil (5FU) or capecitabine and irinotecan (FOLFIRI [7]) or oxaliplatin (XELOX, FOLFOX [8]) or dacarbazine/temozolomide [9]. This second-line treatment can provide about 30% of RR and a median PFS of 4 months [4,7,8]. Taken together, these data indicate a major medical need for improving NEC treatments.

Since the first description, thirty years ago, of the PE combination efficacy for what was called “anaplastic neuroendocrine carcinomas” and referred nowadays to NEC by Moertel and collaborators, no change has been made to this standard of care [10]. Only one randomized phase II trial have compared the efficacy of the cisplatin - irinotecan (PI) combination to the standard PE regimen. This phase II enrolled 66 patients and was terminated prematurely following interim analysis showing equivalent efficacy. Indeed, the objective RR were similar in both arm (42.4%), the median PFS was 6.4 months in the PE arm and 5.8 months in the PI arm, respectively (p=0.81), and the median OS was 11.3 months and 10.2 months, respectively, (p=0.37) [11]. A single arm phase II study evaluated PE intensification with the addition of paclitaxel and found an objective RR of 53%, a median PFS of 7.5 months and a median OS of 14.5 months which led the authors to conclude to the absence of higher efficacy as compared to the standard PE regimen [12]. Other studies are almost all retrospective and have reported equivalent efficacies of either PE or PI, except the Yamaguchi *et al.* study

suggesting higher efficacy of PI regimen but this study was not randomized, the studies of first-line chemotherapy in NEC are summarized in Table 1.

Although all studies on second-line treatment of metastatic NEC of GEP or unknown origin were retrospective, they have suggested that both irinotecan and oxaliplatin, in combination with 5FU can have anti-tumor effect in NEC [7,8]. In the last decade, the FOLFIRINOX triplet chemotherapy regimen, combining 5FU, oxaliplatin and irinotecan, has shown significant efficacy in several digestive cancers such as pancreas [13] or colorectal adenocarcinoma [14]. Tolerance of this regimen has improved over the years with better tolerability that has led to the development of the mFOLFIRINOX regimen [15]. mFOLFIRINOX could be a good L1 treatment in metastatic GEP NEC because: (i) Oxaliplatin, irinotecan and 5FU have anti-tumor effect in metastatic GEP NEC [4,7,8]; (ii) triplet with a potential high RR could be efficient in these chemosensitive cancers; (iii) the degradation of PS following tumor progression during/after L1 treatment makes access to a second-line uncertain which argue for the use of an aggressive L1 treatment; (iiii) administration on a one-day outpatient basis (day hospital), as well as acceptable adverse events, could have an impact on quality of life in these patients with a poor prognosis. With the PRODIGE 69-FOLFIRINEC trial hypothesize that the mFOLFIRINOX triplet may improve the prognosis of patients with metastatic NEC from GEP or unknown primary.

Few data are available on predictive factors of L1 chemotherapy efficacy in metastatic NEC which are subdivided in 2 main pathological subtypes; eg. small cell NEC (SCNEC) and large cell NEC (LCNEC). These two subtypes are treated with the same PE regimen, whatever the primary tumour site, although overall response rate (ORR) seem to differ between SCNEC (about 50 to 70%) and LCNEC (about 30-50%) in lung and pancreas NEC retrospective series [16–19]. These data have led to the choice of stratifying the FOLFIRNIEC trial according to pathological subtypes. Few studies have reported molecular profiles of NEC with a perspective of personalized treatment. Previous studies have mainly focused on *BRAF* mutation in colon NEC and the efficacy of the dabrafenib-trametinib combination [20–22], contrary to what is observed in colon adenocarcinoma, which has been suggested to be related to an epigenetic

114 silencing of the epidermal growth factor receptor in colon NEC [21]. Moreover, little is known
115 on the putative predictive biomarkers to immunotherapy efficacy in NEC of GEP and unknown
116 origin. Tumour mutational burden (TMB) is between 8.6 and 10.5 mutations/megabase in NEC
117 of the lung [23,24] but no data exist for GEP and unknown origin NEC. In addition MLH1 and
118 PMS2 loss of expression by immunohistochemistry mostly due to *MLH1* promoter methylation
119 (dMMR phenotype) have been reported in 12.4% tumoral samples of a series of 89 GEP NEC
120 and mixed neuroendocrine neoplasms [25]. In an attempt to expand knowledge on molecular
121 alterations in NEC of GEP and unknown origin, the FOLFIRINEC-PRODIGE 69 phase II trial
122 is associated with a “real time” translational study which will establish the tumor molecular
123 profile of each participating patients for whom tumoral sample is available.

2. Study design

The PRODIGE 69-FOLFIRINEC study is a national, multicentre, prospective, open-label, randomized and trial comparing the efficacy of mFOLFIRINOX versus PE regimen for the treatment of patients with metastatic NEC of GEP and unknown origin associated with a molecular profiling for therapeutic targets and biomarkers identification (Figure 1).

Eligible patients will be stratified according to ECOG PS (0 vs 1), Ki67 (<55% vs ≥55%) and pathological subtype (small cell vs large cell or unknown) and then randomly assigned (1:1) to either standard regimen arm with platinum (cisplatin 100 mg/m² day 1 or carboplatin AUC 5 day 1, according to physician's choice) and etoposide (100 mg/m² intravenous (IV), day 1, 2 and 3) administered every 21 days for 6 to 8 cycles (24 weeks maximum) or experimental treatment arm with mFOLFIRINOX (oxaliplatin 85 mg/m² IV + irinotecan 180 mg/m² IV + LV5FU2 2400 mg/m² without 5 FU bolus) administered every 14 days for 12 cycles (24 weeks maximum).

Main inclusion criteria in the PRODIGE 69-FOLFIRINEC trial are patients over 18 years, ECOG PS 0 or 1, with a metastatic NEC or high grade MiNEN with a NEC component ≥ 30%, of GEP or unknown origin, whatever the pathological subtype (small cell or large cell or non-small cell or unknown/indetermined) (Table 2). Grade 3 well-differentiated neuroendocrine tumors according to WHO 2017 classification are not eligible. Patient must not have received any prior therapy for metastatic disease. Patient with asymptomatic brain metastases or under stable corticosteroid doses for at least 2 weeks before randomization can be included; otherwise, radiation therapy prior to inclusion is required in case of symptomatic brain metastases. Patient must have adequate haematology parameters (neutrophil count ≥ $1.5x10^9$/L, platelet ≥ $100x10^9$/L and hemoglobin > 8 g/dL), a creatinine clearance above 30 ml/min (Cockroft & Gault formula) and adequate liver function (total bilirubin ≤ 1.5N, AST/ALT ≤ 2.5N, or AST/ALT ≤ 5N in case of liver metastases). All patients must undergo dihydropyrimidine dehydrogenase (DPD) deficiency screening and cannot be included in case of uracilemia ≥ 16 ng/mL. Other standard exclusion criteria are applied: pregnancy, history of

recent malignancy, active HIV or viral hepatitis and any active or suspected acute or chronic uncontrolled disease that would impair study participation.

The radiological assessment will be performed at baseline (within a maximum of 3 weeks before inclusion) using a TAP computed tomography (CT) scan (or magnetic resonance imaging (MRI) of the abdomen plus chest CT-scan in case of contrast medium allergy), and the same procedure (CT and/or MRI) will be repeated every 8 weeks until tumor progression or death. Radiological tumor assessment will be performed according to the RECIST v1.1 criteria. Brain imaging is required at baseline either by CT-scan and/or MRI. Imaging of brain lesions by CT-scan and/or MRI is required every 8 weeks (+/- 1 week) during treatment and follow-up if present at baseline.

2.1. Study endpoints

The primary endpoint is the median PFS. PFS is defined as the time interval between date of randomization and date of the first radiological progression (according to RECIST 1.1) or death due to any cause, whichever occurs first, according to the investigator. Patient alive without progression will be censored at date of last follow-up visit.

The secondary endpoints are:

- centralized PFS by independent reviewed
- OS which is defined as the time between date of randomization and date of death (whatever the cause). Patients alive will be censored at date of last news.
- Best objective RR which is defined as the proportion of patients with an objective response (complete response (CR) + partial response (PR)) at any evaluation during the treatment, according to RECIST 1.1 and centralized review.
- Safety which is defined as the percentage of patients who experienced toxicities and grading of these toxicities according to NCI-CTC V4. Toxicities will be presented as the number of patients presenting at least one toxicity by maximum grade.
- Dose reductions and dose intensity which are defined as the number of treatment cycles, the dose received and the percentages of actual dose received as compared to the

theoretical dose will be described, as well as the percentage of patients with at least one dose modification/reduction or at least one postponement of chemotherapy.

- Quality of life assessed by the EORTC QLQ-C30 and EQ-5D-5L questionnaires.
- Exploratory analyses (see “biomarkers analyses”). The predictive value of each molecular alterations will be evaluated using correlation with objective RR, PFS and OS, in both arms.

2.2. Ethical considerations

This study is sponsored by the *Fédération Francophone de Cancérologie D*igestive (FFCD) and Dijon University hospital. PRODIGE 69-FOLFIRINEC has been authorized by the French medicines agency (*Agence Nationale de Sécurité du Médicament et des produits de santé*, ANSM) on March 23, 2020. It was submitted and approved (July 20, 2020) by the ethics committee (*Comité de protection des personnes*, CPP). This trial is registered on the European Union Clinical Trials Register (EudraCT no. 2019-001013-16) and on the clinicaltrials.gov website (NCT04325425). The study complies with the Declaration of Helsinki and the principles of Good Clinical Practice guidelines.

2.3 Statistical methods

For the primary endpoint, the median PFS will be calculated among patients who have received at least one dose of chemotherapy, whatever the dose and the treatment (modified intent-to-treat). Median PFS will be given for each treatment arm with their two-sided 95% confidence interval. The Kaplan-Meier method (Kaplan and Meier, 1958) will be used to estimate median and curves will be plotted. Log-rank test will be used to compare the 2 treatment arms. Hazard ratios will be calculated using Cox proportional model (Cox, 1984). Proportionality (Schoenfeld residual methods) and linearity (Martingale residuals) hypotheses will be checked.

The hypothesis of the PRODIGE 69-FOLFIRINEC trial is that mFOLFIRINOX could increase median PFS from 5 months in the control arm (PE) to 7.5 months in the experimental arm (H1).

With a two-sided risk alpha of 5% and a power of 80%, 203 events (radiographic progression or death) are required to demonstrate a median PFS difference of 2.5 months (HR=0.67). With 24 months of follow-up, an inclusion rate of 5 patients/month and a lost-to-follow-up rate of 5%, 218 patients will be randomized.

An intermediate analysis is planned at 50% of events (102 radiographic progression or death). The intermediate analysis is planned in order to show efficacy at an early stage (rejection of H0) or futility (accept H0). The p-values will be calculated using the O'Brien-Fleming function based on the real number of events.

As G3 NEC is a rare disease, 48 centers will be open to recruitment throughout France.

2.4 Biomarker analysis

This study includes a real-time, centralized molecular profiling of the tumor consisting of immunohistochemistry (IHC) markers (PD-L1 (Programmed death-ligand 1), Rb (retinoblastoma protein), TP53, MLH1 (MutL Homolog 1)) and a targeted next generation sequencing (NGS) panel of 161 genes (Oncomine Comprehensive assay V3, ThermoFisher©, Waltham, Massachusetts, US) associated with the determination of mutational tumor burden (TMB) and microsatellite instability status (MSI). This molecular profile will be reviewed by a molecular tumor board and the report will be sent to the investigator, together with the molecular profile results, within 2 months of tumor sample submission for informing further line treatment-decision making in the case of targetable alterations.

Conclusion

PRODIGE 69 - FOLFIRINEC is designed to challenge the standard platinum-etoposide combination chemotherapy with mFOLFIRINOX for the treatment of patients with NEC of GEP and unknown origin. The associated translational study aims at identifying biomarkers of responses in these patients and to draw the mutational landscape of these tumors with the goal to find targets for personalized medicine. The first patient was included on October 20, 2020, the end of inclusion is scheduled for the end of 2024.

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Conflict of interests:

None

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Table 1: First-line chemotherapy results in gastroenteropancreatic poorly differentiated neuroendocrine carcinoma

Authors	n patients	Study design	Primary	Chemotherapy regimen	response rate (%)	median PFS (months)	median OS (months)
Zhang et al [11]	66	Monocentric randomized phase II	GEP(88%), UK(12%)				
	33			Etoposide/cisplatin	44	6.4	11.3
	33			Irinotecan/cisplatin	44	5.8	10.2
Hainsworth et al [12]	78	Multicentric monoarm Phase II	UK(62%), GEP(19%), lung(9%)	Etoposide/carboplatin/paclitaxel	53	7.5	14.5
Kulke et al [26]	4	Monocentric phase II	GEP (84%), UK (11%), lung (5%)	Irinotecan/cisplatin	25	4.5	11.4
Sørbye et al & ali et al [3,6]	252						
	129	Multicentric retrospective	GEP (69%), UK (31%)	Etoposide/cisplatin	31	4	12
	67			Etoposide/carboplatin	30	4	11
Yamaguchi et al [27]	258						
	160	Multicentric retrospective	GEP (100%)	Irinotecan/cisplatin	50	5.2	13
	46			Etoposide/cisplatin	28	4	7
Walter et al [4]	253	Multicentric retrospective	GEP (80%) UK (20%)	Etoposide/platinum	50	6.2	11.6
Frizziero et al [5]	98	Bicentric retrospective	GEP (54%), UK (23%), GU (21%)	Etoposide/carboplatin	48	5.8	11.6
Ramella et al [28]	27	Bicentric retrospective	GEP(64%), UK(21%)	Irinotecan/cisplatin	46.4	3.7	11.7
Lokesh et al [29]	114	Monocentric retrospective	GEP (33%), lung(26%), GU (15%), HN (14%), UK(9%)	Etoposide/platinum	24	NR	11
Yoon et al [30]	64	Monocentric retrospective	GEP (87,5%), UK(12,5%)	Etoposide/cisplatin	28	3.5	NR

Bukhari et al [31]	58	Monocentricretrospective	GEP (100%)	Etoposide/platinum	NR	NR	85% at 1 year
Mitry et al [32]	41	Monocentric retrospective	GEP (20), lung (10), HN (4), UK (7)	Etoposide/cisplatin	41.5	8.9	15
Iwasa et al [33]	21	Monocentric retrospective	Pancreas & biliary (100%)	Etoposide/cisplatin	14	1,8	5.8
Moertel et al [10]	18	Monocentric retrospective	GEP (14), lung (1), UK (3)	Etoposide/cisplatin	67	11	19
Deutschbein et al [34]	18	Monocentric retrospective	GEP (60%), UK (30%), other (10%)	Etoposide/cisplatin or carboplatin	17	6.3	NR
Patta et al [35]	8	Monocentric retrospective	Colo-rectal (100%)	Etoposide/cisplatin	62.5	4.5	9.5
Nakano et al [36]	30	Monocentric retrospective	HN (41%), UK (28%), GEP (20%), GU (9%)	Irinotecan/cisplatin	46	4.5	14.3
Lu et al [37]	16	Monocentric retrospective	GEP (94%), UK (6%)	Irinotecan/cisplatin	57	5.5	10.6
Okita et al [38]	12	Monocentric retrospective	stomach (100%)	Irinotecan/cisplatin	75	7	10.4
Okuma et al [39]	12	Monocentric retrospective	oesophagus (100%)	Irinotecan/cisplatin	50	4	12.6

Legend: GEP = gastroenteropancreatic, UK = unknown primary, HN = Head and neck primary, GU = Genitourinary primary, PFS = progression-free survival, OS = overall survival, NR = Not reported

Table 2: Main inclusion and exclusion criteria

Inclusion criteria
• Poorly differentiated neuroendocrine carcinoma or high grade MiNEN with a NEC component ≥30% • Small cell or large cell or non-small cell or unknown/undetermined subtype • gastro-entero-pancreatic or unknown origin • Metastatic disease • First-line treatment • At least one measurable lesion according to RECIST 1.1 guidelines (CT-scan) • Age ≥ 18 years • ECOG Performance Status ≤ 1 (Appendix 4) • Available tumor block • Absolute neutrophil count ≥ $1.5x10^9$/l, platelet ≥ $100x10^9$/l and hemoglobin > 8 g/dl • Total bilirubin ≤ 1.5N, AST ≤ 2.5N, ALT≤ 2.5N or AST and ALT ≤ 5N in case of liver metastases.
Exclusion criteria
• Grade 3 well differentiated neuroendocrine tumor according to WHO 2017 classification • Symptomatic brain metastases*. • Previously treated by chemotherapy or targeted therapy • History or know hypersensitivity to any of the study chemotherapy agents, or their excipients. • Known or historical active infection with HIV, or known active viral hepatitis • Pre-existing permanent neuropathy (NCI CTC V4.0 grade ≥2) • Known Gilbert's syndrome • Pregnant women or breastfeeding mother • History of prior malignancy, in the three years before randomization except for cured non-melanoma skin cancer and cured in situ cervical carcinoma • Active or suspected acute or chronic uncontrolled disease that would induce excess risk associated with study participation. • Patient under guardianship and/or deprived of his/her freedom • Partial or complete Dihydropyrimidine Dehydrogenase deficiency (uracilemia ≥ 16 ng/mL) • Severe renal impairment (creatinine clearance less than 30 mL/min,according to Cockroft and Gault Formula) • QTc interval > 450 msec for male and > 470 msec for female at EKC. • K+ <lower limit of normal (LLN), Mg^{2+} < LLN, Ca^{2+} < LLN

**Patient with asymptomatic brain metastases or under stable corticosteroid doses for at least 2 weeks before randomization can be included.*

Figure 1: FOLFIRINEC study design