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

3

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33 **Keywords**

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35 Gastroenteropancreatic

36 Chemotherapy

37 FOLFIRINOX

38 **ABSTRACT**

39

40 **Background**

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

45 **Methods**

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

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

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

58 Recruitment started on October 20, 2020.

59 **1. Rational and aims**

60 Poorly differentiated neuroendocrine carcinomas (NEC) of gastroenteropancreatic
61 (GEP) and unknown origins are rare and heterogeneous diseases. The diagnosis is often done
62 at the metastatic stage and the prognosis is poor. The standard first-line (L1) treatment is
63 platinum-etoposide (PE) combination chemotherapy, mostly based on retrospective studies
64 [1,2]. With this regimen, RR is 40 to 70% but the median PFS is short, between 4 and 9 months
65 [3,4]. Disease progression almost always occurs during or just after treatment and median
66 overall survival (OS) is only about 12-15 months for GEP NEC with similar efficacy of either
67 cisplatin or carboplatin [3,4] and of either oral or intravenous etoposide [5,6]. After progression,
68 only 40 to 45% of patients will receive a second-line (L2) chemotherapy which will include 5-
69 fluoro-uracil (5FU) or capecitabine and irinotecan (FOLFIRI [7]) or oxaliplatin (XELOX,
70 FOLFOX [8]) or dacarbazine/temozolomide [9]. This second-line treatment can provide about
71 30% of RR and a median PFS of 4 months [4,7,8]. Taken together, these data indicate a major
72 medical need for improving NEC treatments.

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

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

88 Although all studies on second-line treatment of metastatic NEC of GEP or unknown
89 origin were retrospective, they have suggested that both irinotecan and oxaliplatin, in
90 combination with 5FU can have anti-tumor effect in NEC [7,8]. In the last decade, the
91 FOLFIRINOX triplet chemotherapy regimen, combining 5FU, oxaliplatin and irinotecan, has
92 shown significant efficacy in several digestive cancers such as pancreas [13] or colorectal
93 adenocarcinoma [14]. Tolerance of this regimen has improved over the years with better
94 tolerability that has led to the development of the mFOLFIRINOX regimen [15]. mFOLFIRINOX
95 could be a good L1 treatment in metastatic GEP NEC because: (i) Oxaliplatin, irinotecan and
96 5FU have anti-tumor effect in metastatic GEP NEC [4,7,8]; (ii) triplet with a potential high RR
97 could be efficient in these chemosensitive cancers; (iii) the degradation of PS following tumor
98 progression during/after L1 treatment makes access to a second-line uncertain which argue
99 for the use of an aggressive L1 treatment; (iiii) administration on a one-day outpatient basis
100 (day hospital), as well as acceptable adverse events, could have an impact on quality of life in
101 these patients with a poor prognosis. With the PRODIGE 69-FOLFIRINEC trial hypothesize
102 that the mFOLFIRINOX triplet may improve the prognosis of patients with metastatic NEC from
103 GEP or unknown primary.

104 Few data are available on predictive factors of L1 chemotherapy efficacy in metastatic
105 NEC which are subdivided in 2 main pathological subtypes; eg. small cell NEC (SCNEC) and
106 large cell NEC (LCNEC). These two subtypes are treated with the same PE regimen, whatever
107 the primary tumour site, although overall response rate (ORR) seem to differ between SCNEC
108 (about 50 to 70%) and LCNEC (about 30-50%) in lung and pancreas NEC retrospective series
109 [16–19]. These data have led to the choice of stratifying the FOLFIRINEC trial according to
110 pathological subtypes. Few studies have reported molecular profiles of NEC with a perspective
111 of personalized treatment. Previous studies have mainly focused on *BRAF* mutation in colon
112 NEC and the efficacy of the dabrafenib-trametinib combination [20–22], contrary to what is
113 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.

124 **2. Study design**

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

129 Eligible patients will be stratified according to ECOG PS (0 vs 1), Ki67 (<55% vs ≥55%)
130 and pathological subtype (small cell vs large cell or unknown) and then randomly assigned
131 (1:1) to either standard regimen arm with platinum (cisplatin 100 mg/m² day 1 or carboplatin
132 AUC 5 day 1, according to physician's choice) and etoposide (100 mg/m² intravenous (IV), day
133 1, 2 and 3) administered every 21 days for 6 to 8 cycles (24 weeks maximum) or experimental
134 treatment arm with mFOLFIRINOX (oxaliplatin 85 mg/m² IV + irinotecan 180 mg/m² IV +
135 LV5FU2 2400 mg/m² without 5 FU bolus) administered every 14 days for 12 cycles (24 weeks
136 maximum).

137 Main inclusion criteria in the PRODIGE 69-FOLFIRINEC trial are patients over 18
138 years, ECOG PS 0 or 1, with a metastatic NEC or high grade MiNEN with a NEC component
139 ≥ 30%, of GEP or unknown origin, whatever the pathological subtype (small cell or large cell
140 or non-small cell or unknown/indetermined) (Table 2). Grade 3 well-differentiated
141 neuroendocrine tumors according to WHO 2017 classification are not eligible. Patient must not
142 have received any prior therapy for metastatic disease. Patient with asymptomatic brain
143 metastases or under stable corticosteroid doses for at least 2 weeks before randomization can
144 be included; otherwise, radiation therapy prior to inclusion is required in case of symptomatic
145 brain metastases. Patient must have adequate haematology parameters (neutrophil count ≥
146 $1.5 \times 10^9/L$, platelet ≥ $100 \times 10^9/L$ and hemoglobin > 8 g/dL), a creatinine clearance above 30
147 ml/min (Cockroft & Gault formula) and adequate liver function (total bilirubin ≤ 1.5N, AST/ALT
148 ≤ 2.5N, or AST/ALT ≤ 5N in case of liver metastases). All patients must undergo
149 dihydropyrimidine dehydrogenase (DPD) deficiency screening and cannot be included in case
150 of uracilemia ≥ 16 ng/mL. Other standard exclusion criteria are applied: pregnancy, history of

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

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

161

162 **2.1. Study endpoints**

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

167 The secondary endpoints are:

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

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

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

184

185 **2.2. Ethical considerations**

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

194

195 **2.3 Statistical methods**

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

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

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

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

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

216

217 **2.4 Biomarker analysis**

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

227

228 **Conclusion**

229 PRODIGE 69 - FOLFIRINEC is designed to challenge the standard platinum-etoposide
230 combination chemotherapy with mFOLFIRINOX for the treatment of patients with NEC of GEP
231 and unknown origin. The associated translational study aims at identifying biomarkers of
232 responses in these patients and to draw the mutational landscape of these tumors with the
233 goal to find targets for personalized medicine. The first patient was included on October 20,
234 2020, the end of inclusion is scheduled for the end of 2024.

235

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245

246 **Conflict of interests:**

247 None

248

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255

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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%)	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	Multicentric retrospective	GEP (69%), UK (31%)	Etoposide/cisplatin	31	4	12
	129			Etoposide/carboplatin	30	4	11
	67						
Yamaguchi et al [27]	258	Multicentric retrospective	GEP (100%)	Irinotecan/cisplatin	50	5.2	13
	160			Etoposide/cisplatin	28	4	7
	46						
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	Monocentric retrospective	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
<ul style="list-style-type: none">• Poorly differentiated neuroendocrine carcinoma or high grade MiNEN with a NEC component $\geq 30\%$• 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 $\geq 1.5 \times 10^9/l$, platelet $\geq 100 \times 10^9/l$ and hemoglobin > 8 g/dl• Total bilirubin $\leq 1.5N$, AST $\leq 2.5N$, ALT $\leq 2.5N$ or AST and ALT $\leq 5N$ in case of liver metastases.
Exclusion criteria
<ul style="list-style-type: none">• 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 Cockcroft and Gault Formula)• QTc interval > 450 msec for male and > 470 msec for female at EKG.• 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

