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Original Research

Oxaliplatin, 5-Fluorouracil and Nab-paclitaxel as perioperative regimen in patients with resectable gastric adenocarcinoma: A GERCOR phase II study (FOXAGAST)

S. Watson [a], C. de la Fouchardière [b], S. Kim [c], R. Cohen [d], J.B. Bachet [e], C. Tournigand [f], J.M. Ferraz [g], M. Lefevre [h], D. Colin [h], M. Svrcek [i], A. Meurisse [j], C. Louvet [a,*]

[a] *Medical Oncology Department, Institut Mutualiste Montsouris, Paris, France*
[b] *Medical Oncology Department, Centre Léon Bérard, Lyon, France*
[c] *Medical Oncology Department, Centre Hospitalier Régional Universitaire, Besançon, France*
[d] *Sorbonne Université, Medical Oncology Department, AP-HP, hôpital Saint-Antoine, F-75012 Paris, France*
[e] *Sorbonne Universités, UPMC, Gastro-enterology Department, Hôpital de la Pitié-Salpétrière, Assistance Publique - Hôpitaux de Paris, Paris, France*
[f] *Medical Oncology Department, Hôpital Henri Mondor, Assistance Publique - Hôpitaux de Paris, UPEC, Créteil, France*
[g] *Surgical Department, Institut Mutualiste Montsouris, Paris, France*
[h] *Pathology Department, Institut Mutualiste Montsouris, Paris, France*
[i] *Sorbonne Université, UPMC, Pathology Department, Hôpital Saint-Antoine, Assistance Publique - Hôpitaux de Paris, Paris, France*
[j] *Methodological and Quality of Life in Oncology Unit, Centre Hospitalier Régional Universitaire, Besançon, France*

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Abstract ***Background:*** 5-Fluorouracil (5-FU) and platinum-based perioperative chemotherapy is standard of care for resectable gastric adenocarcinoma (RGA). Nanoparticle albumin-bound (Nab-) paclitaxel is active in advanced disease but has never been evaluated in the perioperative setting. The objective was to evaluate the efficacy of Nab-paclitaxel in combination with FOLFOX for RGA patients.
Methods: We performed a non-randomised, open-label, phase II study. RGA patients were assigned to receive neoadjuvant Nab-paclitaxel (150 mg/m^2) and FOLFOX q2w for six cycles. Six additional post-operative cycles were kept at the investigator's discretion. The primary end-point was complete pathological response (tumour regression grade [TRG1]) rate.

* *Corresponding author*: Prof. Christophe Louvet, Medical Oncology Department, Institut Mutualiste Montsouris, 42 Boulevard Jourdan, 75014, Paris, France. Fax: + 33 1 56 61 61 70.
E-mail address: christophe.louvet@imm.fr (C. Louvet).

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According to Fleming design, 49 patients were required to test H_0 (10% TRG1) and H_1 (25% TRG1). To reject H_0, TRG1 had to be achieved in 8 patients.

Results: Forty-nine patients were included. Median number of neoadjuvant chemotherapy cycles was 6 (range, 3–6). Median dose intensity for Nab-paclitaxel, oxaliplatin and 5-FU was 96% (38–103%), 97% (47–103%) and 99% (50–112%), respectively. Surgery could not be performed in 5 (10.2%) patients. Tumour resection was R0 for 42 of 44 (95.5%) patients. Pathological review classified tumours as TRG1 to TRG5 for 8 (16.3%), 11 (22.5%), 4 (8.2%), 18 (36.7%) and 3 (6.1%) patients, respectively. Grade 3 or worse toxicities during neoadjuvant chemotherapy were non-febrile neutropenia (20.4%), nausea (8.2%), diarrhoea (8.2%) and neuropathy (6.1%). Of 44 patients, 14 (31.8%) experienced surgery-related complications and three (6.8%) died of surgical complications.

Conclusion: This regimen shows promising activity. Toxicity is manageable but a meaningful rate of surgical complications was observed. This strategy deserves investigation in phase III studies.

1. Introduction

Gastric adenocarcinoma is characterised by a poor prognosis, with 5-year survival rate below 30% when all stages taken together. Perioperative chemotherapy significantly improves survival in patients with resectable tumour [1,2]; however, approximately 60% of them will ultimately relapse underlying the urge for alternative therapeutic options. Several chemotherapy regimens have proved their efficacy in the perioperative setting, all of them containing antimetabolites and platinum [3–6]. Although FOLFOX (oxaliplatin, 5-Fluorouraciul and leucovorin) was not used in the pivotal phase III studies that established the beneficial role of perioperative chemotherapy (POC), this regimen is widely used routinely. During the last 12 months, combining docetaxel to 5-FU and platinum has shown to improve efficacy but significantly increases toxicity [7–9]. Thus, following the results of the randomised FLOT4-AIO trial, FLOT (5-FU, leucovorin, oxaliplatin and docetaxel) is becoming one of the new standards of care in this setting.

Nanoparticle albumin-bound paclitaxel (Nab-paclitaxel) uses albumin as an alternative paclitaxel-delivery agent compared to the standard solvent-delivery method, thus facilitating its administration [10]. It is approved for the treatment of several cancer types, including metastatic breast, non–small-cell lung and pancreatic carcinomas. Nab-paclitaxel has also shown to be active in advanced gastro-oesophageal junction and gastric adenocarcinoma patients either in monotherapy [11–13] or in combination [14–16]. However, its activity in the perioperative setting has never been investigated.

The tumour regression grade (TRG) on resected specimens is an objective parameter for assessing the efficacy of neoadjuvant chemotherapy in resectable gastric adenocarcinoma (RGA). The most commonly used TRG classification is Mandard-TRG grading scale [17], which classifies tumours from TRG1 to TRG5 according to the number of residual tumour cells and fibrosis [18]. TRG provides important prognostic information because complete or subtotal tumour regression has shown to be associated with better patient outcome [19–21].

The objective of this phase II study was to evaluate the efficacy of Nab-paclitaxel combined with 5-FU and oxaliplatin (FOLFOX) in terms of TRG as perioperative regimen in patients with resectable gastro-oesophageal junction or gastric adenocarcinoma.

2. Patients and methods

FOXAGAST is a single-arm, open-label, multicentre, phase II study. The protocol was approved by independent ethics committee. All patients provided written informed consent for participation. This study has been registered as ClinicalTrials.gov number NCT02486601.

2.1. Patient's eligibility

Patients with previously untreated, pathologically confirmed, HER2-negative localised adenocarcinoma of the stomach or the low oesophagus were eligible. All tumours had to be resectable according to standard surgical practice (stage I-III). Eligibility criteria also included the following: age $\geq$18 years; Eastern Cooperative Oncology Group performance status of zero to two; normal haematopoietic, hepatic and renal functions; serum albumin $\geq$25 g/l; adequate contraceptive method; and registration in the national healthcare system.

Main exclusion criteria were: metastatic disease or non-resectable primary tumour; concomitant unplanned antitumour therapy; other serious and uncontrolled non-malignant disease (active infection; coronary stenting, myocardial infarction or stroke in the past 6

months); pre-existing permanent neuropathy (National Cancer Institute grade $\geq$ 2).

2.2. Treatment

Neoadjuvant chemotherapy consisted in Nab-paclitaxel (150 mg/m^2) and FOLFOX (oxaliplatin: 85 mg/m^2; 5-FU: 2400 mg/m^2 over 48 h, and leucovorin; 400 mg/m^2) q2w for six cycles. Computed tomography scan restaging was performed after 4 cycles of chemotherapy and before surgery. Surgery was performed according to French standard procedures: Lewis-Santy procedure for oesogastric junction tumours, total or subtotal gastrectomy for gastric cancer. Modified D2 lymphadenectomy was recommended. Following surgery, completion of six additional chemotherapy cycles was kept at the investigator's discretion. Granulocyte-colony stimulating factor prevention for febrile neutropenia could be used either as primary prophylaxis or as secondary prophylaxis after a first episode of grade 3–4 neutropenia.

2.3. Evaluation of efficacy

The primary end-point for efficacy was the rate of complete pathological response (cPR) assessed on resected specimens. Centralised pathological evaluation of resected specimens was performed by two independent pathologists, and tumours were classified according to Mandard TRG classification, with TRG1 corresponding to cPR, TRG2 major pathological response with few residual tumour cells, TRG3 fibrosis and tumour cells with a dominance of fibrosis, TRG4 fibrosis and tumour cells with a dominance of tumour cells, and TRG5 tumour without evidence of regression. The histological tumour type was determined according to Lauren's classification [22].

Secondary end-points were progression-free survival (PFS), overall survival (OS), health-related quality of life, safety and biomarker analysis. PFS was defined as the time from inclusion up to the date of first documented disease progression or death from any cause. OS was defined as the time from inclusion to the date of death from any cause. Survival data were evaluated using the Kaplan–Meier method. Data cut-off was 25th June 2018.

2.4. Toxicity

Toxicity was graded according to the National Cancer Institute's Common Toxicity Criteria, version 4.03. Post-operative morbidity and mortality were recorded.

2.5. Statistical analysis

The study was designed to test an increase in cPR (TRG1) from 10% (H_0) to 25% (H_1). According to Fleming design, 49 patients had to be included with unilateral α of 5% and β of 10%. To reject H_0, TRG1 had to be achieved in at least 8 patients.

3. Results

From June 2015 to March 2017, 60 patients were enrolled from six different institutions in France. Fifty-five patients were considered as eligible, and six patients were next excluded for consent withdrawal (n = 2), refusal to participate to translational analyses (n = 2) and absence of available pathological material (n = 2). The characteristics of the 49 evaluable patients are detailed in Table 1.

3.1. Neoadjuvant chemotherapy

The median number of neoadjuvant chemotherapy cycles was six (range, 3–6). The median dose intensity for

Table 1
Patients demographics at baseline.

Patient characteristics	All patients N = 49 (%)
Age: median (range)	63.7 (54.9–80.8)
Gender	
- Male	36 (73.5)
- Female	13 (26.5)
Performance status	
- 0	27 (55.1)
- 1	22 (44.9)
Dysphagia at baseline	
- Yes	21 (43.7)
- No	27 (56.3)
- Missing	1
Tumour location	
- Low oesophagus	11 (22.4)
- Cardia	17 (34.7)
- Body	18 (36.7)
- Pylorus	3 (6.2)
Histological type	
- Intestinal	33 (80.5)
- Diffuse	6 (14.7)
- Mixed	1 (2.4)
- Not applicable	1 (2.4)
- Missing	8
Grade	
- Well differentiated	14 (31.1)
- Moderately differentiated	12 (26.7)
- Poorly differentiated	16 (35.6)
- Undifferentiated	2 (4.4)
- Not applicable	1 (2.2)
- Missing	4
Depth of tumour invasion	
- T1	1 (2)
- T2	10 (20.4)
- T3	19 (38.8)
- T4	0 (0)
- Unknown	19 (38.8)
Lymph node involvement	
- Yes	26 (53)
- No	23 (47)

Nab-paclitaxel, oxaliplatin and 5-FU was 96% (38–103%), 97% (47–103%) and 99% (50–112%), respectively.

3.2. Surgery

Surgery could not be performed in 5 patients (10.2%), due to local tumour progression (n = 3) or altered performance status (n = 2). Seventeen patients (38.6%) underwent a Lewis-Santy procedure, 15 (34.1%) a total gastrectomy, and 12 (27.3%) a partial gastrectomy. Lymph node dissection was classified as D1, D2 and D2 plus splenectomy in 7 (15.9%), 33 (75.0%) and 4 (9.1%) patients, respectively.

Tumour resection was microscopically complete (R0) in 42 patients (95.5%) and macroscopically complete with invaded margins (R1) in 2 patients (4.5%).

3.3. Adjuvant chemotherapy

Twenty-two of the 44 patients (50%) who underwent surgery resumed FOXAGAST treatment according to the study protocol. Eight (18.2%) patients received alternative adjuvant chemotherapy regimens including LV5FU2 (n = 6), FOLFOX (n = 1) and FOLFIRI (n = 1), and 14 (31.8%) patients did not receive any post-operative chemotherapy. Reasons for discontinuing FOXAGAST were unacceptable tolerance, altered performance status and insufficient response to neo-adjuvant chemotherapy.

3.4. Outcomes

Pathological outcomes are described in Table 2. cPR (TRG1) was observed in eight (16.3%; 95% confidence interval [CI], 5.8–26.8) patients, and near-complete pathological response (TRG2) in 11 (22.5%; 95% CI, 10.6–34.4) patients. The TRG1 plus TRG2 rate was 38.8% (95% CI, 24.9–52.7).

With a median follow-up of 22.9 months (95% CI, 18.2–25.6), 12-month PFS was 87.0% (95% CI, 73.4–94.0; Fig. 1a). The median PFS was not reached. And 24-month OS was 87.1% (95% CI, 73.5–94.0; Fig. 1b).

3.5. Adverse events

Forty-nine patients were assessable for treatment-related adverse events (AEs). Grade 3 and 4 treatment AEs are listed in Table 3. Overall, 21 (42.9%) and 27 (55.1%) patients experienced at least one grade 3–4 AE during the neoadjuvant and overall treatment period, respectively. The most frequent toxicities were neutropenia (22.4%), nausea (10.2%), vomiting (10.2%), diarrhoea (8.2%) and neuropathy (12.2%). Granulocyte-colony stimulating factor was used in 26 patients (53.1%), either as primary prophylaxis (n = 17) or as secondary prophylaxis (n = 9). No febrile neutropenia occurred.

Table 2
Pathological tumour stage, nodal status and outcome.

Patient characteristics	All patients
Pathological T stage (N = 44)	
- ypT0	8 (18.2)
- ypT1	6 (13.6)
- ypT2	7 (15.9)
- ypT3	19 (43.2)
- ypT4	3 (6.8)
- Unknown	1 (2.3)
Pathological N stage (N = 44)	
- ypN0 (0)	29 (65.9)
- ypN1 (1–6)	11 (25.0)
- ypN2 (7–15)	3 (6.8)
- ypN3 (>15)	1 (2.3)
Pathological response (N = 49)	
- TRG1	8 (16.3)
- TRG2	11 (22.5)
- TRG3	4 (8.2)
- TRG4	18 (36.7)
- TRG5	3 (6.1)
- Not applicable[a]	5 (10.2)

[a] Five patients did not undergo surgery due to tumour progression or altered performance status, but TRG1 rate was assessed on the overall intent-to-treat population.

The operative mortality was 6.8% (n = 3). Post-operative complications occurred in 14 patients (31.8%). These complications were fistulas (n = 5), ischemic complications (n = 4), infections (n = 3) and anaesthesia-related complications (n = 2).

4. Discussion

Since 2006 and the MAGIC trial, POC has become the standard of care for RGA patients, with benefits in terms of OS while not influencing perioperative morbidity and mortality. In the MAGIC trial, the combination of perioperative epirubicin, cisplatin and 5-FU was shown to be superior to surgery alone in terms of OS. If the benefit of epirubicin has proven to be controversial, 5-FU and platinum (cisplatin or oxaliplatin)-based POC has remained standard of care. Several studies have failed to show any benefit for adding targeted therapies such as panitumumab [23] or bevacizumab [24] to conventional chemotherapy regimens.

Nab-paclitaxel has shown activity in patients with advanced gastric cancer, with response rates varying from 20% to 55% [13,14], but had never been evaluated in the perioperative setting. With 16% of cPR (TRG1), our study meets its primary end-point and shows that the combination of Nab-paclitaxel and FOLFOX represents an effective regimen for patients with RGA. More importantly, 38.8% of major PR (TRG1 + TRG2) were observed in our study, a promising result because

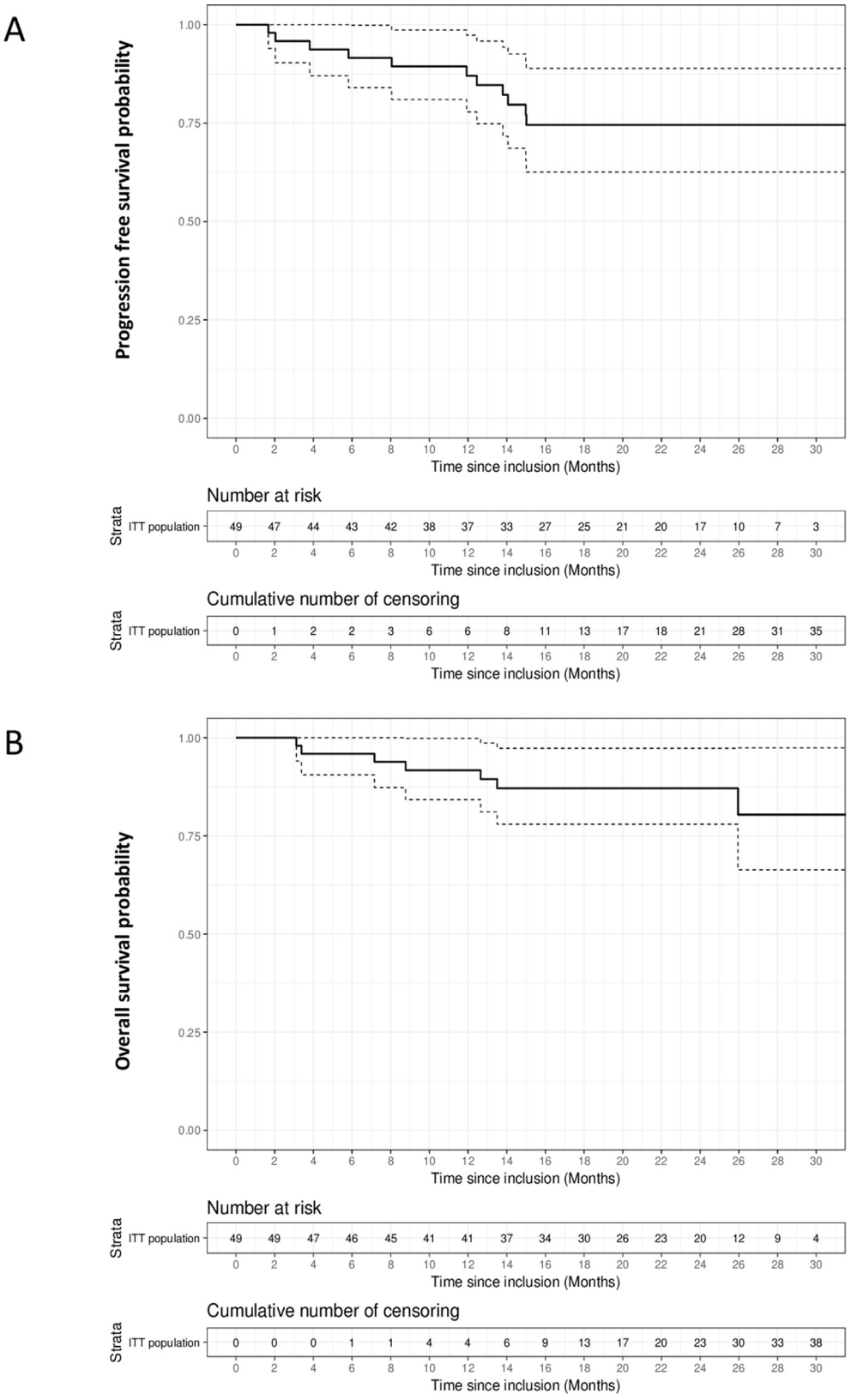

Fig. 1. Survival data in the intent-to-treat population. (a) Progression-free survival. (b) Overall survival. Kaplan–Meier estimation (black line) and 95% confidence interval (dot lines) are indicated.

Table 3
Grade 3–4 treatment-related adverse events.

Patient characteristics	All patients Neoadjuvant phase N = 49 (%)	All patients Overall N = 49 (%)
Haemoglobin	1 (2)	1 (2)
Neutrophils	10 (20.4)	11 (22.4)
Febrile neutropenia	0 (0)	0 (0)
Platelets	1 (2)	1 (2)
Haematological toxicity, overall*	12 (24.5)	13 (26.5)
Nausea	4 (8.2)	5 (10.2)
Vomiting	3 (6.1)	5 (10.2)
Diarrhoea	4 (8.2)	4 (8.2)
Mucositis	1 (2)	2 (4)
Neuropathy	3 (6.1)	6 (12.2)
Fatigue	1 (2)	2 (4.1)
Non-haematological toxicity, overall**	13 (26.5)	21 (42.9)

The adverse events observed during the neoadjuvant phase (left column) and during the overall trial (neoadjuvant and adjuvant phases) are listed. * At least one grade 3 or 4 haematological toxicity. ** At least one grade 3 or 4 non-haematological toxicity.

major PR has proven to be associated with increased OS. The results of the randomised phase II part of the FLOT4-AIO trial showed that neoadjuvant docetaxel, oxaliplatin, 5-FU and leucovorin (FLOT) chemotherapy was superior to epirubicin, cisplatin and 5-FU in terms of cPR, with 16% of cPR in patients treated with FLOT versus 6% in the control arm [7]. Those results were then confirmed in the following randomised FLOT4-AIO phase III [25]. Similarly, docetaxel, cisplatin and 5-FU (DCF) regimen was associated with increased OS compared to standard chemotherapy in a large retrospective study [9]. As a result, DCF or FLOT are being increasingly used as new POC regimens.

In the original phase II study evaluating FLOT as perioperative regimen [26], the authors reported comparable cPR (20%) and major PR (40%) rates, with the majority of very good responses being observed in patients with intestinal-type tumours. In the following FLOT4-AIO phase III study, the benefit of POC was confirmed in both intestinal and diffuse tumours [25]. The identification of patients that are most likely to benefit from POC intensification remains necessary, and a biomarker analysis is currently ongoing for patients included in the FOXAGAST study.

With a median follow-up of 22.9 months, median PFS and OS are still not reached in the FOXAGAST study. Additional follow-up of patients will be required to compare its efficacy with the FLOT4-AIO study in terms of survival, but early results are promising.

The toxicity profile of this regimen was manageable, with the most frequent grade 3–4 AEs being non-febrile neutropenia, nausea, diarrhoea and neuropathy. However, a meaningful rate of post-operative complications and deaths was observed. Similar rates of post-operative complications were observed in the FLOT4-AIO trial [7], and increased post-operative morbidity with FLOT has already been observed in fragile and elderly patients [27]. In the FOXAGAST study, the median age of patients was 63.7 years, and post-operative complications were not correlated with older age. The identification of patients at risk remains to be further studied, but this suggests that POC intensification should be proposed to selected patients. Health-related quality of life analysis for patients included in FOXAGAST is ongoing.

Taken together, this study shows that perioperative Nab-paclitaxel and FOLFOX is an effective and promising regimen for patients with RGA. The final results of PFS and OS will show whether it deserves evaluation in phase III trials and further comparison with FLOT regimen.

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Conflicts of interest

R.C.: Amgen, Sanofi; J.B.B.: Amgen, Bayer, Celgene, Merck, Roche, Sanofi, Servier and Shire; C.T.: BMS, Lilly, Roche and Sanofi; C.L.: Celgene, MSD and Roche. The other authors have no COI to disclose.

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