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Original Article

Clinico-biological factors predicting the benefit of the LV5FU2 maintenance strategy as a first-line therapy in patients with metastatic pancreatic cancer

Emeric Boisteau[*,1], Laetitia Dahan[2], Nicolas Williet[3], Karine Le Malicot[4], Jérôme Desramé[5], Olivier Bouché[6], Caroline Petorin[7], David Malka[8], Christine Rebischung[9], Thomas Aparicio[10], Cédric Lecaille[11], Yves Rinaldi[12], Anthony Turpin[13], Anne-Laure Bignon[14], Jean-Baptiste Bachet[15], Côme Lepage[16], Victoire Granger[17], Jean-Louis Legoux[18], Gaël Deplanque[19], Mathieu Baconnier[20], Thierry Lecomte[21], Isabelle Bonnet[22], Jean-François Seitz[2], Eric François[23], Astrid Lièvre[1], For the PRODIGE 35 Investigator/Collaborators[†]

[1]Department of Gastroenterology, University Hospital Pontchaillou, Rennes 1 University, INSERM U1242 "Chemistry Oncogenesis Stress Signalling," Rennes, France
[2]Department of Digestive Oncology, La Timone, AMU, Marseille, France
[3]Hepatogastroenterology Department, University Hospital of Saint-Etienne, Saint-Etienne, France
[4]Biostatistics Department, Francophone Federation of Digestive Cancerology, EPICAD INSERM LNC-UMR 1231 University of Burgundy and Franche Comté, Dijon, France
[5]Jean Mermoz Private Hospital, Lyon, France
[6]Department of Digestive Oncology, CHU Reims, Reims, France
[7]Department of Digestive Oncology, University Hospital d'Estaing, Clermont-Ferrand, France
[8]Department of Hepato-Gastroenterology, Gustave Roussy Cancer Campus, Villejuif, France
[9]Savoie Medipole, Challes-Les-Eaux, France
[10]Department of Gastroenterology, Saint Louis Hospital, APHP, Université de Paris, Paris, France
[11]Oncology Department, Polyclinique Nord, Bordeaux, France,
[12]Department of Hepato-gastroenterology, European Hospital, Marseille, France,
[13]Univ. Lille, CNRS UMR9020, Inserm UMR-S 1277, Canther, Cancer Heterogeneity, Plasticity and Resistance to Therapies, CHU Lille, Department of Medical Oncology, Lille, France,
[14]Department of Digestive Oncology, University Hospital Côte de Nacre, Caen, France,
[15]Department of Hepato-gastroenterology, Pitié-Salpêtrière Hospital, Paris, France,
[16]Department of Hepato-gastroenterology, University hospital of Dijon, EPICAD INSERM LNC-UMR 1231, University of Burgundy and Franche Comté, Dijon, France,
[17]Department of Hepato-gastroenterology and Digestive Oncology, University Hospital of Grenoble Alpes, Grenoble, France,
[18]Department of Hepato-gastroenterology and Digestive Oncology, Orléans Regional Hospital, Orléans, France,
[19]Department of Hepato-Gastroenterology, Saint-Joseph Hospital, Paris, France,
[20]Department of Hepato-Gastroenterology, Annecy-Genevois Hospital Center, Epagny Metz-Tessy, France,
[21]Department of Hepato-Gastroenterology and Digestive Oncology, University Hospital of Tours; UMR INSERM 1069 Nutrition, Croissance et Cancer, University of Tours, Tours, France,
[22]Department of Oncology, Valenciennes, France,
[23]Antoine Lacassagne Center, Oncology Department, Nice, France

[*]Corresponding author: Emeric Boisteau, MD, Digestive Disease Department, Rennes University Hospital, 2, Street Henri Le Guilloux, 35033 RENNES Cedex 9, France (emeric.boisteau@chu-rennes.fr).
[†]A list of the members of the PRODIGE 35 Investigator/Collaborators is provided in the Appendix.

Abstract

Introduction: Predictive markers of LV5FU2 maintenance benefit after first-line induction with FOLFIRINOX in patients with metastatic pancreatic cancer are necessary to select patients who will not be harmed by this strategy.

Patients and Methods: We focused on patients who received 12 cycles of FOLFIRINOX (arm A, $N = 88$) or 8 cycles of FOLFIRINOX followed by LV5FU2 maintenance in controlled patients (arm B, $N = 91$) from the PRODIGE-35 trial. Prognostic factors and predictors of efficiency were identified by using Cox regression. Median progression-free survival (PFS), overall survival (OS), and time to deterioration of quality of life (TTD-QoL) were evaluated.

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Results: Poor independent prognostic factors were primary tumor in place, age <65 years and the presence of liver metastases for PFS, a baseline neutrophil/lymphocyte ratio (NLR) ≥5 and CA19.9 ≥500 UI/L for OS, independent of the treatment arm. Patients with one metastatic site had a longer PFS in arm A, whereas patients with ≥2 metastatic sites had a longer PFS in arm B. We also identified predictors of OS and TTD-QoL in arm B but these differences were not statistically significant.

Conclusion: Except for patients with one metastatic site who benefited more from 12 cycles of FOLFIRINOX, a maintenance strategy with LV5FU2 should be widely offered to mPC patients whose survival and QoL are preserved after 4 months of FOLFIRINOX. (ClinicalTrials.gov: NCT02352337).

Key words: pancreatic neoplasm; metastases; chemotherapy; maintenance.

Implications for practice

In this retrospective analysis of the PRODIGE-35 trial, we showed that LV5FU2 maintenance after 8 cycles of FOLFIRINOX is feasible in patients treated first line for a metastatic pancreatic cancer. Importantly for these patients, having more than one metastatic site is predictive of LV5FU2 maintenance, while patients with only one metastatic site benefit more from 12 cycles of FOLFIRINOX. Thus, the number of metastatic sites can be easily used in routine as a clinical marker to help clinicians choose a maintenance strategy with or without LV5FU2 after 8 cycles of FOLFIRINOX.

Introduction

Pancreatic ductal adenocarcinoma has become the second most common digestive cancer in France after colorectal cancer (CRC),[1] with 13 346 new cases in 2014.[2] Its incidence has been increasing continuously for the last 40 years, as has its mortality, and it will become the second highest cause of cancer-related death in the US[3] and the third in Europe.[4] The prognosis is poor, with <10% of patients alive at 5 years, and all stages confounded.[1,5] Gemcitabine has long been the only treatment approved for metastatic patients,[6] improving quality of life (QoL) with a moderate effect on overall survival (OS). Since 2011, compared with gemcitabine, FOLFIRINOX has become a standard first-line treatment for patients with metastatic pancreatic cancer (mPC) with good performance status (PS) (0 or 1), improving patient OS, progression-free survival (PFS) and the objective response rate (ORR).[5] However, it is associated with substantial toxicity,[5] which raises the question of whether a less toxic maintenance chemotherapeutic regimen could improve patient QoL. In metastatic CRC, a maintenance strategy involving 5-FU after induction with FOLFOX or FOLFOXIRI has been shown to reduce neurotoxicity without deleterious effects on OS.[7]

The PANOPTIMOX-PRODIGE-35 phase II randomized trial[8] recently showed that a maintenance strategy with LV5FU2 after 8 cycles of FOLFIRINOX did not impact the PFS rate at 6 months (42.9% vs. 47.1%) nor the median OS (11.2 months vs. 10.1 months) compared to 12 cycles of FOLFIRINOX and was associated with a greater median survival without deterioration in QoL scores and a later occurrence of severe neurotoxicity. If this trial shows that maintenance with LV5FU2 is feasible and effective in patients with mPC controlled after 4 months of FOLFIRINOX, there is still no certainty this strategy is beneficial for all patients. Therefore, it is necessary to identify predictive factors of the efficacy of such a maintenance strategy to better select patients who could truly benefit from it.

The aim of the present study was to identify clinical and biological factors that could predict the prognosis and predict the benefit of a maintenance strategy with LV5FU2 from the analysis of patients included in the PANOPTIMOX-PRODIGE 35 trial.

Materials and methods

Patients and trial design

The inclusion and exclusion criteria of the phase II French, multicenter, randomized clinical trial, PANOPTIMOX-PRODIGE-35, were previously described.[8] Patients were randomly assigned (1:1:1) to receive 12 cycles of FOLFIRINOX chemotherapy or less in the case of progression in arm A, FOLFIRINOX for 8 cycles then LV5FU2 for control patients in arm B, and FIRGEM, a sequential treatment with FOLFIRI.3, in arm C as previously described.[8] Analyses in the present study focused on patients from arms A and B.

Clinical and biological parameters studied

We retrospectively planned an ancillary analysis to evaluate the factors that could predict prognosis and those that could predict the benefit of a maintenance strategy by LV5FU2 after 8 cycles of FOLFIRINOX on the basis of prospective clinico-biological parameters collected during the PANOPTIMOX-PRODIGE 35 study.[8]

The evaluated variables were those usually described in the literature as prognostic factors in mPC.[9-12] The following baseline factors were analyzed for PFS, OS, and TTD-QoL: treatment arm (for prognosis only), age (< or ≥65 years), sex (female vs male), body mass index (BMI) (with classes ranging from <18.5, [18.5-25[, [25-30[, ≥30), Eastern Cooperative Oncology Group (ECOG) score (PS 0 or 1), primary tumor resection, number of metastatic sites (1 or ≥2 sites), presence of liver or peritoneal metastases, neutrophil/lymphocyte ratio (NLR) (< or ≥5), platelet count (< or ≥300 G/L), hemoglobin level (< or ≥12 g/dL), leucocyte count (< or ≥10 000/mm^3), alkaline phosphatase (ALP) level (< or ≥300 UI/L), total bilirubin (< or ≥1,5 the normal), albumin serum level (< or ≥28 g/L), and CA19.9 serum level (< or ≥500 UI/L). The predictive value of biological factors at 4 months was also evaluated.

Outcomes

The primary endpoint was the median PFS.[13] Living patients free of progression were censored at the date of the last follow-up visit. The secondary endpoints were median OS and median time to definitive deterioration of the global health score (TTD-GHS). This TTD-GHS was defined as the time between the date of randomization and the date when the score was reduced by ≥5 points compared to baseline, without any improvement after, death, or date of last news. Patients without a reduction of more than 5 points were censored to last news.

Statistical analysis

All analyses were performed in the predefined modified intent-to-treat (mITT) population, ie, on randomized patients

receiving at least one dose of treatment and considering the real treatment intake in arms A and B. Qualitative variables are reported as frequencies and percentages, and continuous variables are reported as the means (SD) and medians (range). PFS, OS, and time to deterioration of QoL (TTD-QoL) were estimated using the Kaplan-Meier method and are described as the median values and rates at specific times with the corresponding 95% confidence intervals (CIs). Factors associated with survival and TTD-QoL were tested via univariate and multivariate analyses using a Cox regression model. HR and 95% CI were determined for exploratory purposes. To be included in the multivariate model, the *P*-value of each factor was required to be ≤ .10. For each endpoint (PFS, OS, and TTD-GHS), the interaction between treatment and these parameters was studied using the Cox model. If an interaction was found with a *P*-value <0.16, then the 2 arms of treatment were compared within each category using a Cox model. All the statistical analyses were performed using SAS software version 9.4.

Results

Population study

Between January 2015 and November 2016, 276 patients from 53 French centers were randomly assigned to one of the 3 arms of the PANOPTIMOX-PRODIGE-35 trial.[8] The mITT population was 87 in arm A and 91 in arm B as previously described.[8] One patient randomized to the FIRGEM arm received FOLFIRINOX. Therefore, 88 patients were treated according to arm A, and 91 were treated according to arm B (Supplementary Figure S1).[8]

The clinicobiological characteristics of the patients were well balanced between arm A and arm B (Table 1).

Prognostic factors associated with survival and quality of life

In univariate analysis, age <65 years, PS 1 vs. 0, ≥2 metastatic sites, presence of liver metastases, no primary tumor resection, baseline platelet levels ≥300 G/L, baseline ALP ≥300 UI/L, and CA19.9 ≥500 UI/L were associated with a shorter median PFS (Table 2). According to the multivariate analysis, age <65 years (*P* = .013), no primary tumor resection (*P* = .02), and the presence of liver metastases (*P* = .05) remained independent factors for poor PFS (Table 2).

According to the univariate analysis, a PS of 1, no primary tumor resection, the presence of liver metastases, ≥2 metastatic sites, an NLR ≥5, a baseline platelet count ≥300 G/L, a leucocyte count ≥10 000/mm^3, an ALP concentration ≥300 UI/L and CA19.9 concentration ≥500 UI/L were associated with shorter OS (Table 3). According to the multivariate analysis, a baseline NLR ≥5 (*P* = .008) and CA19.9 level ≥500 UI/L (*P* = .03) remained independent factors for poor OS (Table 3).

According to the univariate analysis, an intensive strategy involving 12 cycles of FOLFIRINOX, age <65 years, the presence of liver metastases, no primary tumor resection and an NLR ≥5 were associated with a shorter TTD-GHS (Supplementary Table S1). According to multivariate analysis, all of them, except liver metastases, remained significantly associated with a shorter time before deterioration of GHS.

Predictive factors of the benefit of maintenance strategy

A significant interaction (*P* < .16) between the treatment arm and the following factors was found for PFS: age, number of metastatic sites, baseline NLR, leucocyte count, ALP and CA19.9 levels. For all these parameters, the 2 arms of treatment (arm A and B) were compared within each category (Supplementary Table S2). Except for the group of patients with one metastatic site who had a longer PFS in the FOLFIRINOX arm than in the maintenance arm (9.0 months vs. 5.6 months; HR = 1.66, 95% CI [1.11; 2.49], *P* = .01), there was no statistically significant difference between the 2 arms in any of the other groups of patients (Supplementary Table S2, Figures 1 and 2). PFS was even longer in the maintenance arm than in the FOLFIRINOX arm in patients with ≥2 metastatic sites (6.1 months vs. 4.1 months, HR = 0.51, 95% CI [0.31; 0.84], *P* = .009) (Figure 2).

Similarly, significant interactions between the treatment arm and the following factors were found for OS: age, ECOG PS, BMI, number of metastatic sites, baseline NLR, leucocytes, CA 19.9, and hemoglobin at 4 months. We compared the 2 arms of treatment within each category for all (Supplementary Table S3). OS was longer in the maintenance arm than in the FOLFIRINOX arm in patients aged <65 years (*P* = .048), those with ≥2 metastatic sites (*P* = .04) and those with an NLR ≥5 (*P* = .05) (Figure 3; Supplementary Table S3).

For TTD-GHS, the interaction effects were significant between the treatment arm and sex, ECOG PS, primary tumor resection, and leucocyte count at 4 months. The 2 arms of treatment were compared within each category for all these parameters (Supplementary Table S4). TTD-GHS was longer in the maintenance arm than in the FOLFIRINOX arm in men (*P* = .007), patients with an ECOG PS of 0 (*P* = .011), patients who underwent primary tumor resection (*P* = .02) and patients whose leucocyte count was ≥10 000/mm^3 at 4 months (*P* = .008; Supplementary Figure S2 and Table S4).

Discussion

In the present study, the poor prognostic factors for PFS were age <65 years, no primary tumor resection and the presence of liver metastases, while the poor prognostic factors for OS were a baseline NLR ≥5 and CA19.9 level ≥500 UI/L. These parameters, regardless of the treatment received, are known to be linked to more aggressive disease, especially the presence of liver metastases, a baseline CA19.9 level ≥500 UI/L and an NLR ≥5, and poor patient general conditions.[5,9,14] Other poor prognostic factors have been described in the literature, such as serum CRP ≥5 mg/dL and the absolute neutrophil count.[9,14] Interestingly, in our study, primary tumor resection was a good prognostic factor as it was already suggested in other digestive malignancies, such as metastatic colorectal cancers or advanced biliary tract cancers.[15,16]

The PANOPTIMOX-PRODIGE-35 trial opened the way for a maintenance strategy in patients with controlled mPC.[8] Following these results, LV5FU2 maintenance is now frequently offered to patients who have a controlled disease after 4 months of FOLFIRINOX treatment in daily practice, and in France, it is now recommended as an option in national pancreatic cancer guidelines.[17-19]

In the present ancillary study, we evaluated the predictors of survival associated with LV5FU2 maintenance to help clinicians better select patients who would benefit from this strategy. Hence, apart from those with only one metastatic site, all patients seem to benefit from a maintenance strategy. Our data even suggest that a maintenance strategy may be more beneficial than 12 cycles of FOLFIRINOX until

Table 1. Characteristics of patients in the modified intention-to-treat analysis.

Characteristics	FOLFIRINOX (*N* = 88)	LV5FU2 maintenance (*N* = 91)	Total (*N* = 179)
Age—*N.* (%)			
Median (years)	64.4	64.2	64.3
<65 y.o.	45 (51.1)	50 (54.9)	95 (53.1)
> 65 y.o.	43 (48.9)	41 (45.1)	84 (46.9)
Sex—*N.* (%)			
Male	54 (61.4)	58 (63.7)	112 (62.6)
Female	34 (38.6)	33 (36.3)	67 (37.4)
BMI—*N.* (%)			
<18.5	5 (5.7)	6 (6.6)	11 (6.1)
[18.5-25[	47 (53.4)	53 (58.2)	100 (55.9)
[25-30[	29 (33)	26 (28.6)	55 (30.7)
≥30	7 (7.9)	6 (6.6)	13 (7.3)
ECOG PS—*N.* (%)			
0	36 (40.9)	44 (48.4)	80 (44.7)
1	52 (59.1)	47 (51.6)	99 (55.3)
Primary tumor resection—*N.* (%)			
Yes	15 (17.1)	10 (11.0)	25 (14.0)
No	73 (82.9)	81 (89.0)	154 (86.0)
Number of metastatic sites—*N.* (%)			
1	47 (53.4)	58 (63.7)	105 (58.7)
≥ 2	41 (46.6)	33 (36.3)	74 (41.3)
Liver metastases—*N.* (%)			
Yes	72 (81.8)	70 (76.9)	142 (79.3)
No	16 (18.2)	21 (23.1)	37 (20.7)
Peritoneal metastases—*N.* (%)			
Yes	20 (22.7)	17 (18.7)	37 (20.7)
No	68 (77.3)	74 (81.3)	142 (79.3)
Hemoglobin at baseline—*N.* (%)			
Median (g/dL)	13.1	13.1	13.1
<12	25 (28.4)	18 (19.8)	43 (24.0)
≥12	63 (71.6)	73 (80.2)	136 (76.0)
Platelet at baseline—*N.* (%)			
Median (G/L)	244	267	261
<300	61 (69.3)	62 (68.1)	123 (68.7)
≥300	27 (30.7)	29 (31.9)	56 (31.3)
Leucocytes at baseline—*N.* (%)			
Median (/mm^3)	7827	8420	8120
<10 000	68 (77.3)	64 (70.3)	132 (73.7)
≥10 000	20 (22.7)	27 (29.7)	47 (26.3)
Neutrophil/lymphocytes ratio—*N.* (%)			
<5	72 (81.8)	73 (80.2)	145 (81.0)
≥5	16 (18.2)	18 (19.8)	34 (19.0)
ALP at baseline—*N.* (%)	*N = 86*	*N = 90*	*N = 176*
<300 UI/L	64 (72.2)	77 (84.6)	141 (78.8)
≥300 UI/L	22 (25)	13 (14.3)	35 (19.6)
Total bilirubin at baseline—*N.* (%)			
<1.5 ULN	86 (97.7)	86 (94.5)	172 (96.1)
≥1.5 ULN	2 (2.3)	5 (5.5)	7 (3.9)
Albumin at baseline—*N.* (%)	*N = 82*	*N = 78*	*N = 160*
<28 g/L	6 (6.8)	2 (2.2)	8 (4.5)
≥28 g/L	76 (86.4)	76 (83.5)	152 (84.9)
CA19.9 at baseline—*N.* (%)	*N = 69*	*N = 74*	*N = 143*
<500 UI/L	35 (39.8)	35 (38.5)	70 (39.1)
≥500 UI/L	34 (38.6)	39 (42.9)	73 (40.8)

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *N*, number; ULN, upper limit normal.

Table 2. Univariate and multivariate analyses of prognostic factors associated with progression-free survival.

			Univariate analysis			Multivariate analysis	
		No. of patients	No. of Events	HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
Parameters							
Strategy arm	FOLFIRINOX vs. maintenance	179	170	1.05 [0.78; 1.42]	.75		
Sex	Female vs. Male	179	170	1.06 [0.78; 1.45]	.71		
Age (years)	< 65 vs. ≥65	179	170	**1.29 [0.95;1.75]**	**.010**	**1.59 [1.10; 2.28]**	**.013**
ECOG PS	1 vs. 0	179	170	**1.30 [0.96; 1.77]**	**.09**	1.19 [0.82; 1.71]	.35
BMI	<18.5 vs. [18.5; 25[[25; 30[vs. [18.5; 25[≥ 30 vs. [18.5; 25[	179	170	1.04 [0.54; 2.00] 0.81 [0.58; 1.14] 0.75 [0.40; 1.41]	.90 .23 .37		
Liver metastases	Yes vs. No	179	170	**2.08 [1.41; 3.08]**	**<.001**	**1.56 [1.00; 2.45]**	**.05**
Peritoneal carcinosis	Yes vs. No	179	170	1.04 [0.72; 1.51]	.83		
Primary tumor resection	No vs. Yes	179	170	**2.22 [1.38; 3.55]**	**.001**	**1.92 [1.10; 3.35]**	**.02**
Number of metastatic sites	≥2 vs. 1	179	170	**1.31 [0.96; 1.77]**	**.09**	1.08 [0.75; 1.57]	.66
NLR	≥5 vs. <5	179	170	1.10 [0.75; 1.60]	.64		
Platelets	≥300 vs. <300	179	170	**1.37 [0.99; 1.90]**	**.05**	1.24 [0.85; 1.81]	.27
Hemoglobin (g/dL)	<12 vs. ≥12	179	170	1.25 [0.88; 1.77]	.21		
Leucocytes (/mm^3)	≥10 000 vs. <10 000	179	170	1.20 [0.85; 1.69]	.29		
Albumin (g/L)	<28 vs. ≥28	160	152	1.71 [0.84; 3.51]	.14*		
ALP (UI/L)	≥300 vs. <300	176	170	**1.40 [0.95; 2.05]**	**.09**	1.00 [0.60; 1.66]	.99
Total bilirubin (Nl)	≥1.5 vs. <1.5	179	170	1.89 [0.88; 4.06]	.10*		
CA 19.9 (UI/L)	≥500 vs. <500	143	134	**1.55 [1.10; 2.19]**	**.01**	1.34 [0.93; 1.93]	.11

*No multivariate analysis because of the low number of patients.
Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; N, number; Nl, normal; NLR, neutrophil/lymphocyte ratio.

Table 3. Univariate and multivariate analyses of prognostic factors associated with overall survival.

			Univariate analysis			Multivariate analysis	
		No. of patients	No. of events	HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
Parameters							
Treatment arm	FOLFIRINOX vs. maintenance	179	158	1.14 [0.83; 1.56]	.41		
Sex	Female vs. male	179	158	1.12 [0.81; 1.54]	.51		
Age (years)	<65 vs. ≥65	179	158	1.14 [0.83; 1.56]	.42		
ECOG PS	1 vs. 0	179	158	**1.58 [1.14; 2.18]**	**.005**	1.35 [0.91; 2.00]	.14
BMI	<18.5 vs. [18.5; 25[[25; 30[vs. [18.5; 25[≥ 30 vs. [18.5; 25[	179	158	1.08 [0.56; 2.09] 0.97 [0.69; 1.38] 1.13 [0.60; 2.12]	.81 .88 .71		
Liver metastases	Yes vs. No	179	158	**2.22 [1.45; 3.40]**	**<.001**	1.54 [0.95; 2.49]	.08
Peritoneal carcinosis	Yes vs. No	179	158	1.14 [0.78; 1.68]	.51		
Primary tumor resection	No vs. yes	179	158	**2.44 [1.45; 4.11]**	**<.001**	1.65 [0.90; 3.02]	.11
Number of metastatic sites	≥ 2 vs. 1	179	158	**1.39 [1.01; 1.91]**	**.04**	0.90 [0.60; 1.36]	.61
NLR	≥5 vs. <5	179	158	**1.71 [1.15; 2.54]**	**.008**	**2.18 [1.23; 3.86]**	**.008**
Platelets (G/L)	≥300 vs. <300	179	158	**1.42 [1.02; 1.98]**	**.04**	1.43 [0.94; 2.18]	.09
Hemoglobin (g/dL)	<12 vs. ≥12	179	158	1.25 [0.87; 1.79]	.22		
Leucocytes (/mm^3)	≥10 000 vs. <10 000	179	158	**1.65 [1.16; 2.35]**	**.005**	1.06 [0.61; 1.84]	.83
Albumin (g/L)	<28 vs. ≥28	160	140	1.97 [0.96; 4.04]	.065*		
ALP (UI/L)	≥300 vs. <300	176	155	**1.74 [1.18; 2.57]**	**.005**	0.72 [0.41; 1.26]	.25
Total bilirubin (Nl)	≥1.5 vs. <1.5	179	158	1.63 [0.76; 3.48]	.21		
CA 19.9 (UI/L)	≥500 vs. <500	143	124	**1.75 [1.22; 2.51]**	**.0025**	**1.53 [1.04; 2.23]**	**.03**

*No multivariate analysis because of the poor number of patients.
Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; *N*, number; Nl, normal; NLR, neutrophil/lymphocyte ratio.

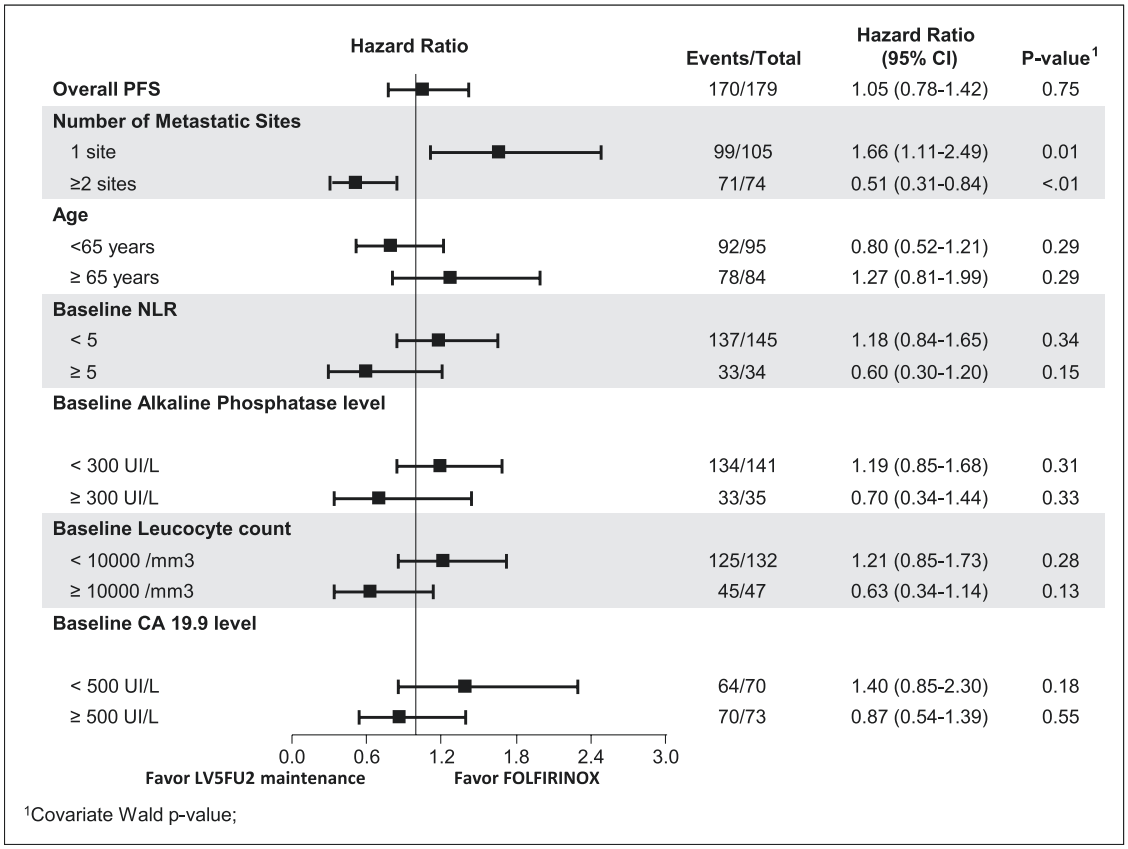

Figure 1. Forest plots of predictive factors of the benefit of maintenance therapy associated with progression-free survival. CI, confidence interval; HR, hazard ratio; NLR, neutrophil/lymphocytes ratio, PFS, progression-free survival.

progression in patients with ≥2 metastatic sites, as their PFS and OS were significantly longer in the maintenance arm. The number of metastatic sites is a marker of tumor burden and aggressiveness. This would mean that a maintenance strategy would be more adaptable to patients with more aggressive disease, whereas those with a low tumor burden and a more limited disease would be better controlled with 12 cycles of FOLFIRINOX. This result is somewhat surprising as we could believe that an intensive strategy is not necessary for patients with a less severe disease. However, one possible explanation is that an intensive strategy would lead to a greater and more durable tumor response in patients with a limited disease and good performance status, allowing longer PFS and OS. Conversely, a more extensive disease, generally associated with poorer general conditions, malnutrition, and more frailty, can lead to more toxicity, less response and impaired quality of life. This result is all the more important, as maintenance with LV5FU2 was found in our study to be a factor associated with a better preservation of QoL, with a longer time without GHS deterioration observed in this treatment arm. Therefore, our results suggest that the number of metastatic sites may help clinicians choose the best strategy: patients with only one metastatic site should be treated with 12 cycles of FOLFIRINOX, whereas those with at least 2 metastatic sites should receive a maintenance strategy. The number of metastatic sites is an easy parameter to collect by clinicians, which makes this parameter applicable in daily practice.

Similarly, our results also suggest that patients with other clinicobiological factors related to poor prognosis, reflecting a more aggressive tumor disease, may benefit more from maintenance. Indeed, patients with a baseline NLR ≥5 had a significantly longer OS and tended to have a longer PFS with a maintenance strategy than FOLFIRINOX patients did until progression, similar to patients with a baseline leucocyte count ≥10 000/mm^3 who tended to have both longer PFS and longer OS with maintenance therapy.

The maintenance strategy was developed to improve or, at least, to preserve patients' QoL as long as possible. In the present study, maintenance strategy was an independent factor significantly associated with a longer TTD-GHS, while no deleterious effects were observed on QoL in any subgroup of patients. In contrast, the maintenance strategy was even associated with an increased TTD-GHS in male patients, those with an ECOG PS of 0, those with baseline leucocyte count ≥10 000/mm^3 and patients who underwent primary tumor resection. Such a result is rare enough in the oncology literature, especially in gastrointestinal cancers, that it deserves to be highlighted and it completely validates maintenance treatment of mPC.

Recently, the POLO trial demonstrated the benefit of maintenance therapy with olaparib in patients with germline *BRCA*-mutated mPC who did not progress during first-line platinum-based chemotherapy.[20,21] PFS was longer in patients treated with olaparib than in those treated with placebo. If OS did not differ between the 2 treatment groups, a subgroup of patients treated with olaparib were considered long responders and long survivors. If this PARP inhibitor may be an alternative to LV5FU2 as a maintenance treatment after induction with FOLFIRINOX, it is reserved for

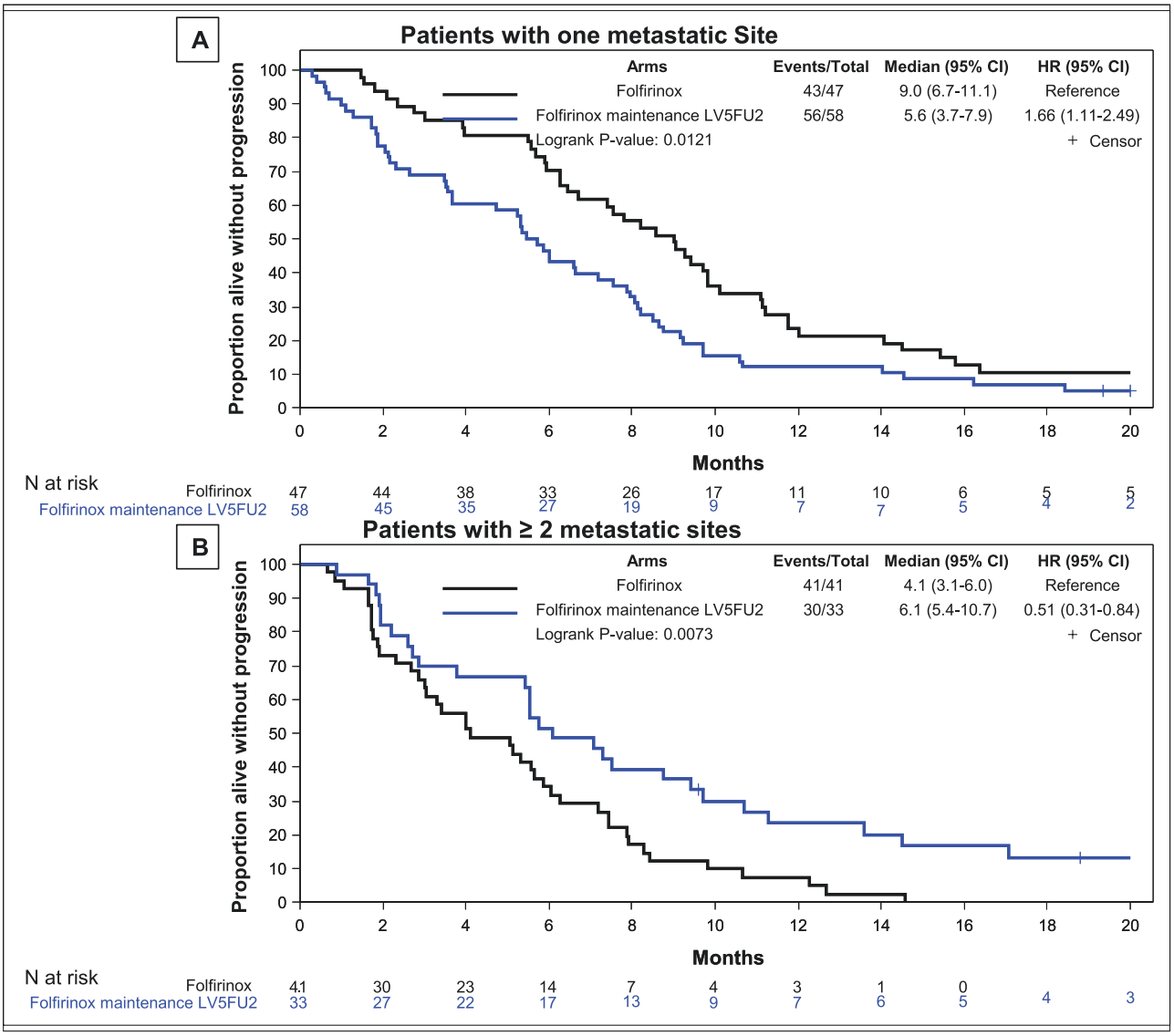

Figure 2. Progression-free survival according to treatment arm in patients with (A) 1 metastatic site and (B) ≥2 metastatic sites. *N* = number.

a very selected population, as germline *BRCA* mutations are present in <5% of all patients with mPC. Moreover, no data on predictive factors of the benefit of olaparib maintenance therapy have been published to date that would help clinicians choose maintenance treatment in this small subgroup of patients. Finally, FOLFIRI maintenance is still often used, but a retrospective French analysis of practice showed that the de-escalation of FOLFIRINOX with 5-FU was as effective as FOLFIRI de-escalation, suggesting that LV5FU2 maintenance is likely the most interesting and acceptable maintenance strategy.[17]

Our study has several limitations. Our results should be interpreted with caution owing to the retrospective nature of the study, although the data were collected prospectively as part of a randomized trial. Furthermore, this analysis of prognostic and predictive factors was not initially planned. Another limitation is the small number of patients analyzed, which resulted in a lack of power that prevented us from identifying other potential prognostic and predictive factors associated with the benefit of maintenance strategy.

Conclusion

Based on the data of the PANOPTIMOX-PRODIGE-35 trial, the number of metastatic sites is a predictor of the benefit of a maintenance strategy with LV5FU2 in first-line treatment of mPC patients. Other clinicobiological parameters, linked to a more aggressive tumor disease, also seem to be associated with a greater survival benefit with maintenance therapy compared with the continuation of FOLFIRINOX until progression. These factors are easily evaluated routinely and could help clinicians better select patients likely to benefit the most from a maintenance strategy. However, their predictive value needs to be confirmed prospectively in a randomized phase III trial with a larger number of patients.

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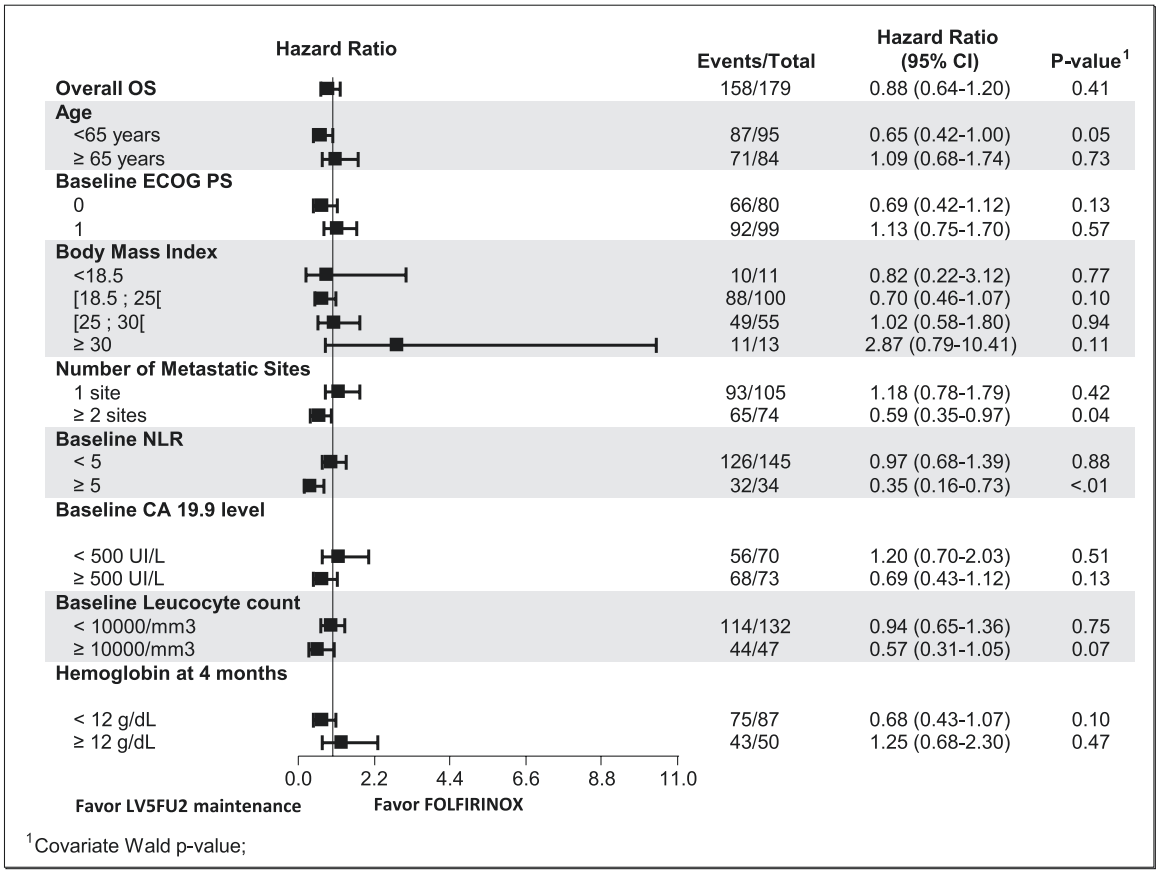

Figure 3. Forest plots of predictive factors of the benefit of maintenance therapy associated with overall survival. CI, confidence interval; HR, hazard ratio; NLR, neutrophil/lymphocytes ratio; ECOG PS, Eastern Cooperative Oncology Group Performance Status; OS, overall survival.

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Ethics approval and consent to participate

Written informed consent from all patients before study entry was obtained. The PRODIGE 35 trial was approved by the Agence Nationale de Sécurité du Médicament and by Human Ethic Committee Sud Mediterranée II. The study was performed in accordance with the Declaration of Helsinki.

Conflict of interest

Nicolas Williet reported financial relationships with Sanofi, Servier, and Ispen. Thomas Aparicio declared conferences for Roche, Ipsen, Amgen, Servier, Sanofi, and AstraZeneca; financial support to congress from Roche and Bayer; and advisory roles for Biogen and Servier. Yves Rinaldi reported financial relationships with Sanofi, Merck, Servier, Amgen, Roche and Bayer. Victoire Granger declared financial support for research from Sanofi-Genzyme, Roche, Servier, and Astellas; consultancy from Amgen, Lilly, Roche, Sanofi-Genzyme, Servier, and Pierre Fabre; and financial support for congresses from Amgen, Ipsen, Lilly, Roche, and Sanofi-Genzyme. Jean-Louis Legoux declared consulting and advisory fees from Novartis, research funding fees from Sanofi, Keocyt, Novartis, Pfizer, and honoraria from Ipsen, Merck-Serono. Thierry Lecomte declared consulting fees, lecture fees and travel accommodations from IPSEN; lecture fees from AstraZeneca. Emeric Boisteau, Laetitia Dahan, Karine Le Malicot, Jerome Desramé, Olivier Bouché, Caroline Petorin, David Malka, Christine Rebischung, Cédric Lecaille, Anthony Turpin, Anne-Laure Bignon, Jean-Baptiste Bachet, Côme Lepage, Gael Deplanque, Mathieu Baconnier, Isabelle Bonnet, Jean-François Seitz, Eric François, and Astrid Lièvre declared no potential conflicts of interest.

Author contributions

Conception/design: E.B., L.D., K.L.M., A.L. Provision of study material or patients: L.D., N.W., J.D., O.B., C.P., D.M., C.R., T.A., C.L., Y.R., A.T., A.-L.B., J.-B.B., C.L., V.G., J.-L.L., G.D., M.B., T.L., I.B., J.-F.S., E.F., A.L. Collection and/or assembly of data: All authors. Data analysis and interpretation: E.B., K.L.M., A.L. Manuscript writing: E.B., A.L., K.L.M., N.W., O.B., T.A., A.T., J.-L.L., T.L. Final approval of manuscript: All authors.

Data availability

Data are property of the Fédération Française de Cancérologie Digestive. They are available on request.

Appendix: FFCD Investigators/Collaborators: PRODIGE 35

Dr Anna PIGUI (Centre Hospitalier de Béziers, service d' HGE, 2 rue Valentin Hauy, 34525 Béziers). Dr Anne

ESCANDE (Clinique Sainte Anne, département d'hématologie et d'oncologie, 184 route La Wantzenau, 67085 Strasbourg). Pr Denis PEZET (service de chirurgie digestive, 1 place Lucie Aubrac, 63003 Clermond Ferrand). Dr Muriel DULUC (CHU La Timone, service d'oncologie digestive, 264 Rue Saint Pierre, 13385 Marseille). Dr Nicolas BARRIERE (Hôpital Européen, service d'HGE, 26 boulevard Louvain, 13285 Marseille). Dr Isabelle MOULLET Clinique de la Sauvegarde, centre de cancérologie médicale et d'hématologie, 480 Avenue Ben Gourion, 69009 Lyon). Dr Franck AUDEMAR (Centre Hospitalier de la Côte Basque, service d'HGE, 13 Av Interne Jacques Loeb, 64109 Bayonne). Dr Vincent BOURGEOIS (Hôpital Duchenne, service d'oncologie Digestive, Allée Jacques Monod, 62321 Boulogne Sur Mer). Dr Agnès VIMAL-BAGUET (service d'oncologie digestive, 1 place Lucie Aubrac, 63003 Clermond Ferrand). Dr Emmanuelle NORGUET (CHU La Timone, service d'oncologie digestive, 264 Rue Saint Pierre, 13385 Marseille). Dr Jean-Paul LAGASSE (Hôpital de La Source, service d'HGE, 14 Avenue de l'Hôpital, 45067 Orléans). Dr Jean-Christophe DUCHMANN (Centre Hospitalier de Compiègne, Service d'HGE, 8 Avenue Henri Adnot 60321 Compiègne). Dr Marielle GUILLET (Hôpital de la Croix Rousse, service d'HGE—CCC, 103 Grande Rue de la Croix Rousse, 69317 Lyon). Dr Stéphane BERDAH (Clinique Sainte Marguerite, service d'oncologie, avenue Alexis Godillot, 83400 Hyères). Dr Robert SVERDLIN (Groupe Hospitalier Saint Joseph, service d'oncologie, 185 rue Raymond Losserand, 75014 Paris). Pr Julien TAIEB (Hôpital Européen Georges Pompidou, service d'HGE, 20 rue Leblanc, 75015 Paris). Dr Stéphane CORBINAIS, Service de Médecine II A, 1 rue de la Marne, 35403 Saint Malo). Dr Gérard LLEDO (Hôpital Privé Jean Mermoz, Institut de Cancérologie, 55 Avenue Jean Mermoz, 69008 Lyon). Pr Laurent BEDENNE (Centre hospitalier universitaire F. Mitterrand Dijon-Bourgogne, service d'HGE et de cancérologie digestive, 14 Rue Paul Gaffarel, 21000 Dijon). Pr Mohamed HEBBAR (Hôpital Claude Huriez, service Maladies Appareil Digestif, 1 place de Verdun 59037 Lille). Dr Karine BOUHIER-LEPORRIER (CHU Côte de Nacre, service d'HGE, avenue Côte de Nacre, 14033 Caen). Dr Charles FERTE (Institut Gustave Roussy, département de médecine, 114 rue Edouard Vaillant, 94805 Villejuif). Dr Lionel STAUDACHER (Groupe Hospitalier Saint Joseph, service de Pneumologie, 185 rue Raymond Losserand, 75014 Paris). Dr Ludovic EVESQUE (Centre Antoine Lacassagne, service d'oncologie, 33 Avenue Valombrose, 06189 Nice). Dr Stéphane REMY (Centre d'Oncologie et de radiothérapie du Pays-Basque, service d'oncologie 14 allées Paulmy, 64100 Bayonne). Dr Thierry CHARLOIS (Centre Hospitalier Départemental de Vendée, service d'HGE, boulevard Stéphane Moreau, 85925 La Roche sur Yon). Dr Catherine LOMBARD-BOHAS (Hôpital Edouard Herriot, service d'Oncologie, 5 Place Arsonval, 69437 Lyon). Dr Aziz ZAANAN (Hôpital Européen Georges Pompidou, service d'HGE, 20 rue Leblanc, 75015 Paris). Dr Corina CORNILA (Hôpital de La Source, service d'oncologie, 14 Avenue de l'Hôpital, 45067 Orléans). Dr Antoine HOLLEBECQUE (Institut Gustave Roussy, service d'HGE, 114 rue Edouard Vaillant, 94805 Villejuif). Dr Pascal ARTRU (Hôpital Privé Jean Mermoz, Institut de Cancérologie, 55 Avenue Jean Mermoz, 69008 Lyon). Dr Laure DUPONT KAZMA (Polyclinique Bordeaux Nord, service d'HGE, 15-33 rue Claude Boucher, 33300 Bordeaux). Pr Thomas WALTER (Hôpital Edouard Herriot, service d'Oncologie, 5 Place Arsonval, 69437 Lyon). Dr Iris DEVAURE (Polyclinique Bordeaux Nord, service d'HGE, 15-33 rue Claude Boucher, 33300 Bordeaux). Dr Julie GIGOUT (Hôpital Européen, service d'HGE, 26 boulevard Louvain, 13285 Marseille). Dr DESAUW (Hôpital Claude Huriez, service d'oncologie médicale, 1 place de Verdun 59037 Lille). Dr Anne GUILNGAR (Centre d'Oncologie et de radiothérapie du Pays-Basque, service d'oncologie 14 allées Paulmy, 64100 Bayonne). Dr Christophe LOCHER (GHI de l'Est Francilien, service de gastroentérologie, 6-8 Rue Saint Fiacre, 77100 Meaux). Dr Joël EZENFIS (Centre Hospitalier Sud Francilien, service d'Oncologie, 40 av. Serge Dassault, 91106 Corbeil-Essonnes). Dr BELLETIER (Institut de Cancérologie de Strasbourg Europe, service d'HGE, 17 rue Albert Calmette, 67200 Strasbourg). Dr Valérie BOIGE (Institut Gustave Roussy, service de Cancérologie Digestive, 114 rue Edouard Vaillant, 94805 Villejuif). Dr Stéphane CATTAN (Hôpital Claude Huriez, Service Maladies Appareil Digestif, 1 place de Verdun 59037 Lille). Dr Caroline COUFON (Hôpital du Scorff -Groupe Hospitalier Bretagne Sud - Lorient, service d'HGE, 5 Avenue de Choiseul, 56322 Lorient). Dr Camille SIBERTIN-BLANC (CHU La Timone, service d'oncologie digestive, 264 Rue Saint Pierre, 13385 Marseille). Dr Anne-Laure VILLING (Centre Hospitalier d'Auxerre, service d'Oncologie, 2 boulevard de Verdun, 89000 Auxerre). Dr Pascal BURTIN (Institut Gustave Roussy, service de Cancérologie Digestive, 114 rue Edouard Vaillant, 94805 Villejuif). Dr BOULAT (Hôpital Henri Duffaut, service Médecine Interne, 305 Rue Raoul Follereau, 84902 Avignon). Dr Pierre ANDRAU (Centre Hospitalier de Bigorre, service d'HE, Bd Mal de Lattre de Tassigny, 65013 Tarbes). Dr Jérôme MEUNIER (Hôpital de La Source, Service d'Onco/Hématologie, 14 Avenue de l'Hôpital, 45067 Orléans). Dr Christine LE FOLL, CH Marne La Vallée-Jossigny, service d'oncologie médicale, 2-4 cours de la Gondoire, 77600 Jossigny). Pr Michel DUCREUX (Institut Gustave Roussy, service de Cancérologie Digestive, 114 rue Edouard Vaillant, 94805 Villejuif). Dr Laurianne PLASTARAS, Hôpitaux Civils de Colmar, service de Médecine A, 39 Avenue de la Liberté, 68024 Colmar). Dr Gilles BREYSACHER, Hôpitaux Civils de Colmar, service de Médecine A, 39 Avenue de la Liberté, 68024 Colmar). Dr Philippe BERNARD (Clinique Sainte Marguerite, service d'oncologie, avenue Alexis Godillot, 83400 Hyères). Dr Aurelie DURAND (GHM Institut Daniel Hollard, service d'oncologie, 8 rue du Dr Calmette, 38028 Grenoble). Dr Olivier ROMANO (Institut Cancérologie Lille Métropole, 20 avenue de la Reconnaissance, 59657 Villeneuve d'Ascq). Dr Delphine FARNETI (Hôpital Nord Michallon, oncologie médicale, Bd de la Chantourne, 38700 La Tronche). Dr Mireille SIMON (Centre Hospitalier de Pau, service d'HGE, 4 Boulevard de Hauterive, 64046 Pau). Dr Marie TALARMIN (Centre Eugène Marquis, service d'oncologie, avenue de la Bataille Flandre Dunkerque, 35000 Rennes). Dr Anne -Claire DUPONT GOSSART (Centre hospitalier universitaire Jean-Minjoz, service d'HGE, 3 Boulevard Alexandre Fleming, 25030 Besançon). Dr Samuel LE SOURD (Centre Eugène Marquis, service d'oncologie médicale, avenue de la Bataille Flandre Dunkerque, 35000 Rennes). Dr Fayçal HOCINE (Centre Hospitalier de Beauvais, service d'oncologie, 40 Avenue Léon Blum, 60021 Beauvais). Dr David SEFRIOUI (CHU Charles Nicolle, service d'HGE, 1 rue de Germont, 76031 Rouen). Dr Florence LE ROY (Institut Gustave Roussy, Département de médecine, 114 rue Edouard

Vaillant, 94805 Villejuif). Dr Romain DESGRIPPES, service Hépato-gastro-entérologie, 1 rue de la Marne, 35403 Saint Malo). Dr Amalia TOPOLSKI, Hôpitaux Civils de Colmar, service de Médecine A, 39 Avenue de la Liberté, 68024 Colmar). Dr Florence MARY (Hôpital Avicenne, service d'HGE, 125 rue de Stalingrad, 93000 Bobigny). Pr Pierre MICHEL (CHU Charles Nicolle, service d'HGE, 1 rue de Germont, 76031 Rouen). Pr Thomas APARICIO (Hôpital Avicenne, service d'HGE, 125 rue de Stalingrad, 93000 Bobigny). Dr Gérard CAVAGLIONE (Centre Antoine Lacassagne, service d'oncologie, 33 Avenue Valombrose, 06189 Nice). Dr Nabil BABA-HAMED (Groupe Hospitalier Saint Joseph, service d'oncologie, 185 rue Raymond Losserand, 75014 Paris). Dr Philippe FOLLANA (Centre Antoine Lacassagne, service d'oncologie, 33 Avenue Valombrose, 06189 Nice). Dr Isabelle CUMIN (Hôpital du Scorff -Groupe Hospitalier Bretagne Sud - Lorient, service d'HGE, 5 Avenue de Choiseul, 56322 Lorient). Dr Laurence THOMAS MARQUES (GHI de l'Est Francilien, service de gastroentérologie, 6-8 Rue Saint Fiacre, 77100 Meaux). Dr Nathalie BAIZE (Centre hospitalier universitaire d'Angers, service d'HGE, 4 rue Larrey, 49933 Angers). Dr Nicolae ARSENII (Centre hospitalier universitaire de Reims, service d'HGE, avenue du Général Koenig, 51100 Reims). Dr Tatiana CEBAN (Centre hospitalier de Dunkerque, service d'oncologie, 130 avenue Louis Herbeaux, 59385 DUNKERQUE). Dr Jean-Louis JOUVE (Centre hospitalier universitaire F. Mitterrand Dijon-Bourgogne, service d'HGE et de cancérologie digestive, 14 Rue Paul Gaffarel, 21000 Dijon). Dr Yann MOLIN (Clinique de la Sauvegarde, centre de cancérologie médicale et d'hématologie, 480 Avenue Ben Gourion, 69009 Lyon). Dr Marc PRACHT (Centre Eugène Marquis, service d'oncologie médicale, avenue de la Bataille Flandre Dunkerque, 35000 Rennes).

Supplementary material

Supplementary material is available at *The Oncologist* online.

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