Efficacy of aflibercept with FOLFOX and maintenance with fluoropyrimidine as first-line therapy for metastatic colorectal cancer: GERCOR VELVET phase II study

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Abstract. Aflibercept in combination with 5-fluorouracil (5-FU)/irinotecan improves overall survival in the second-line therapy of patients with metastatic colorectal cancer (mCRC). In this study, we evaluated the effects of aflibercept in first-line therapy with FOLFOX followed by maintenance with fluoropyrimidine. VELVET was a prospective, single-arm multicenter phase II study (completed). Patients with previously untreated, unresectable, evaluable or measurable mCRC, with an age ≥18 years, and an ECOG performance status of 0-2 received 6 cycles of modified FOLFOX7 (5-FU/folinic acid and oxaliplatin) with aflibercept at 4 mg/kg every 2 weeks followed by maintenance therapy with fluoropyrimidine with aflibercept until disease progression or limiting toxicity. The reintroduction of oxaliplatin was performed at first progression. The primary endpoint was progression-free survival (PFS) at 6 months. From May, 2013 to May, 2014, 49 patients were included and 48 were evaluable for response. In total, 33 patients (67.4%) were alive without progression at 6 months. The Kaplan-Meier survival 6-month and 1-year PFS rates were 79.1 and 36.1%, respectively, and the median PFS was 9.3 months (95% CI, 8.3-12.5). The objective response rate was 59.2% (N=29/49). The most common (≥10%) grade 3-4 adverse events were hypertension (23%), fatigue (15%), neutropenia (12%), neuropathy (12%) and stomatitis (10%). Three (6%) treatment-related deaths occurred: One from stroke, one from pulmonary embolism and one from neutropenic sepsis. On the whole, this study demonstrates the efficacy of aflibercept in combination with an oxaliplatin-based regimen in the first-line therapy of patients with mCRC. A strict monitoring of blood pressure and immediate management of hypertension during therapy is mandatory.

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Introduction

Colorectal cancer (CRC) is the third most common type of cancer in western countries and the third most common cause of

cancer-related mortality (1). The median overall survival (OS) of patients with previously untreated with unresectable advanced CRC ranges from 25 to 30 months, when combining molecular targeted therapies and chemotherapy (2).

Standard first-line therapy is doublet or triplet-chemotherapy combined with targeting agents, including either the monoclonal antibody, bevacizumab, that inhibits angiogenesis through vascular endothelial growth factor (VEGF)-A or the monoclonal antibodies, cetuximab and panitumumab, which inhibit the epidermal growth factor receptor (EGFR) pathway (3-7); the latter option is restricted to approximately half the patients harboring wild-type *RAS* in their tumor (8). Oxaliplatin combined with 5-FU (FOLFOX) is one of most commonly used first-line treatment combinations (9). This regimen is optimized with the oxaliplatin stop-and-go strategy (OPTIMOX), which consists of 6 cycles as induction therapy followed by maintenance with fluoropyrimidine without oxaliplatin and later, at progression, reintroduction of the full regimen. Maintenance therapy reduces the frequency and severity of the cumulative neuropathy observed with oxaliplatin (10). Bevacizumab with fluoropyrimidine is considered as a standard for maintenance therapy (11).

Aflibercept is a recombinant fusion protein consisting of the extracellular domains VEGFR1 and VEGFR2 fused to the Fc portion of human immunoglobulin G1. Aflibercept binds VEGF-A and VEGF-B with high affinity (Kd <1 pM) and placental growth factor (PlGF) with lower affinity (Kd 39 pM), leading to the blockade of tumor angiogenesis and vascular permeability. The combination of aflibercept to the standard FOLFIRI regimen in patients with metastatic CRC (mCRC) has been shown to improve OS [primary endpoint, 12.1-13.5 months; hazard ratio (HR), 0.82; P=0.003], progression-free survival (PFS, 4.7-6.9 months; HR, 0.76; P<0.001), and the objective response rate (ORR, 11.1-19.8%; P<0.001) (12). This effect was observed whether or not patients had received prior bevacizumab therapy.

The aim of this study was to evaluate the efficacy and safety of the aflibercept and an oxaliplatin-based chemotherapeutic regimen combination in first-line therapy in order to determine whether aflibercept has the potential to challenge bevacizumab in the first-line treatment of mCRC.

Patients and methods

Study population. The main patient inclusion criteria were as follows: an age ≥18 years, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2, histologically or cytologically confirmed unresectable mCRC and no prior treatment for metastatic disease.

Study design and treatment schedule. This was a prospective, single-arm, multicenter phase II study. All patients provided written inform consent before enrollment. The study was carried out in accordance with the declaration of Helsinki and Good Clinical Practice guidelines. This study was approved by the Ethics Committee (CPP Ile de France VI Groupe Hospitalier Pitié Salpêtrière PARIS) of our institution.

Patients received intravenously modified FOLFOX7 with aflibercept as induction therapy every 2 weeks for 6 cycles as follows: Aflibercept 4 mg/kg, oxaliplatin 100 mg/m^2, folinic acid 400 mg/m^2 and 5-FU 3,000 mg/m^2. In patients without progression or non-amenable to surgery, induction therapy was followed by maintenance therapy with aflibercept and fluoropyrimidine (either 5-FU or capecitabine) until disease progression or limiting toxicity. Dose postponements or reductions were permitted to manage treatment-related adverse events.

Endpoints. The primary endpoint was PFS, defined as the time from the date of inclusion to the date of progression or death (from any cause). Patients alive without documented objective progressive disease (PD) at the time of the final analysis were censored at the date of their final objective tumor assessment. OS was defined as the time from the date of inclusion to the date of patient death (from any cause) or to the last date the patient was known to be alive. Patients still alive at the time of the analysis were censored using the date of final news. The duration of disease control (DDC) was defined as the sum of PFS of each active treatment course (13).

The ORR was defined as the proportion of patients having either complete response (CR) or partial response (PR) according to RECIST version 1.1 (14). The optimal ORR was defined as the optimal response recorded from the beginning of treatment until treatment failure, taking as reference for PD the smallest measurements recorded since the beginning of treatment. The early response rate was evaluated at the first disease evaluation (i.e., 2 months). The disease control rate (DCR) was defined as the percentage of patients who achieved CR, PR, or stable disease (SD).

The reintroduction rate was defined as the number of patients who received reintroduction of oxaliplatin after disease progression during aflibercept-based maintenance therapy. The absolute reintroduction rate was calculated for all included patients and the relative reintroduction rate was calculated for patients eligible to reintroduction, excluding patients having progressed during induction therapy, amenable to surgery or having a residual sensory neuropathy grade >1. The curative surgery rate was assessed globally and per sequence of therapy.

Toxicity was evaluated according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 (15). Health-related quality of life (HRQoL) assessments were performed at baseline, and every 2 months thereafter, using the Quality of Life Questionnaire Core 30 (QLQ-C30) (French version) (16). The survival prognosis was assessed through the GERCOR prognostic model (17), using two-baseline (pre-treatment) parameters: ECOG PS and serum lactate dehydrogenase levels.

Sample size. According to Simon's Minimax two-stage design (18) with a two-sided 5% type I error, a power of 80%, and a 15% improvement in PFS rate at 6-month from 70% (H0, considered as uninteresting to pursue any further investigation) to 85% (H1, considered as promising to warrant further investigation), it was required that we enroll 49 patients, including a 5% drop-out. If >16 patients were free of progression or death at 6 months from inclusion among the first 23 evaluable patients (stage 1), the trial could be pursued to the second stage with further 26 patients. If at least 40 patients were free of progression or death among the

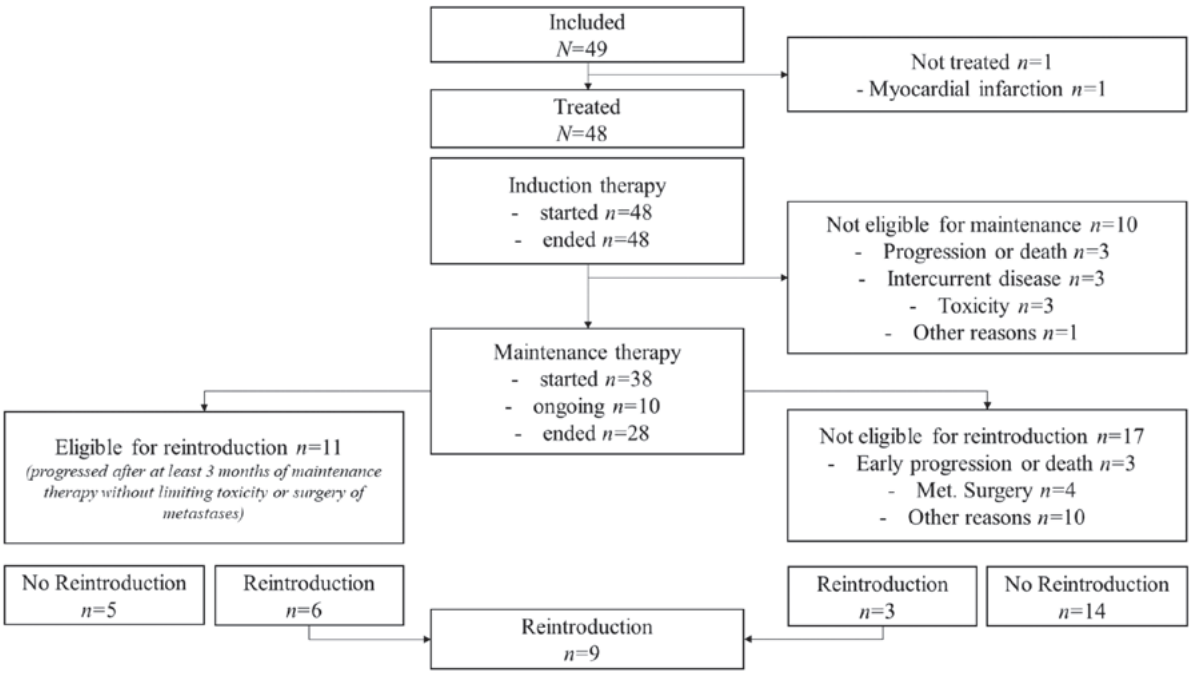

Figure 1. Study flow diagram.

49 included patients (stage 2), treatment could be considered as promising for further evaluation.

Statistical analysis. The primary analysis of efficacy used the intent-to-treat (ITT) population, i.e., including all recruited patients regardless of their eligibility. The confirmative analysis was conducted in the ITT population of eligible patients and in the per-protocol (PP) population comprising all patients who have received at least 2 cycles of the allocated treatment and without any major protocol deviations. The safety analysis included all patients who received at least one dose of any study drug. Follow-up and survival were estimated using the reverse Kaplan-Meier method (19) and Kaplan-Meier method (20), respectively, and were described using median with 95% confidence interval (CI). A linear mixed effects model (repeated measures of variance) was used as to analyze longitudinal changes of HRQoL at baseline, and every 2 months. All patients who completed at least one baseline HRQoL assessment were included. Qualitative variables were described using percentage and means (SD), and continuous variables using medians (minimum-maximum). Fisher's exact test was used for comparison of proportions. The log-rank test was used to compare survival curves, and Cox proportional-hazards regression was used to analyze the effect of several risk factors on survival. The cut-off date for statistical analysis was December, 2015.

Circulating biomarkers. The plasma concentration of 31 biomarkers (3 panels), including cytokines, growth factors, or soluble receptors was determined using multiplexing immunoassays on a Biorad®Bioplex platform. PlGF and neuropillin 1 levels were determined by enzyme-linked immunosorbent assays (ELISA; R&D Systems, Minneapolis, MN, USA). The samples and standards were prepared in duplicate according to the manufacturer's protocol. Plates were incubated for 2 h, washed 4 times, and incubated with enzyme-conjugated antibodies for an additional 2 h at room temperature. The wells were then washed 4 times and substrate was added for 20 min also at room temperature, in the dark. Finally, stop solution was added to each well, and the absorptions at 450 nm were determined using a luminometer plate reader. Plasma markers were evaluated at baseline, and before each induction therapy infusion, for a total of 7 time points.

Results

Study conduct. From May, 2013 to May, 2014, 49 patients were included in 9 French centers (Fig. 1). In total, 23 (46.9%) and 26 (53.1%) patients were included in the Simon's stage 1 and stage 2, respectively.

Patient characteristics. The patient and tumor baseline characteristics are presented in Table I. The median age was 62.9 years, ranging from 32 to 86 years. In total, 20 (40.8%) patients were 70 years or older, 19 (38.8%) had a medical history of hypertension, and 18 (36.7%) had liver-limited metastatic disease. According to the GERCOR prognostic model, 13 (26.5%) patients were at high-risk for death at study entry.

Treatment administration. One patient did not receive study treatment due to myocardial infarction.

Induction therapy. A total of 48 (97.9%) patients received at least one treatment dose, and 46 (93.8%) received at least 2 cycles of the full therapy. A total of 268 cycles of induction therapy were administered with a mean number of 5.6 cycles per patient. In total, 19/268 (7.1%) cycles were postponed.

Maintenance therapy. Following induction therapy, 10 (20.8%) patients did not receive the planned maintenance therapy with fluoropyrimidine and aflibercept due to limiting toxicity (n=4), progression or death (n=3), or interrupted

Table I. Patient and tumor baseline characteristics.

Baseline characteristics	No. of patients (n=49)	%
Sex		
Male	26	53.1
Female	23	46.9
Age, years		
<70	30	61.2
≥70	19	38.8
ECOG performance status		
0	23	46.9
1	22	44.9
2	4	8.2
Number of metastatic organ sites		
1	26	53.1
≥2	23	46.9
Metastatic disease		
Liver	37	75.5
Lung	16	32.6
Node	15	30.6
Peritoneal	8	16.3
Primary tumor sidedness		
Right	20	40.8
Left	29	59.2
Initial disease stage		
I-III (metachronous)	6	12.2
IV (synchronous)	43	87.8
Prior primary tumor resection		
Yes	20	40.8
No	29	59.2
Prior adjuvant chemotherapy		
Yes	5	10.2
No	44	89.8
RAS mutational status		
Wild-type	18	36.7
Mutated	27	55.1
Unknown	4	8.2
White blood cell count		
<10,000/mm^3	38	77.5
≥10,000/mm^3	11	22.5
Platelet count		
≤1 x ULN	39	79.6
>1 x ULN	10	20.4
Lactate dehydrogenase level		
≤1 x ULN	19	38.8
>1 x ULN	26	53.1
Missing data	4	8.2
Alkaline phosphatase level		
≤1xULN	31	63.3
>1xULN	18	36.7
Carcinoembryonic antigen level		
≤1 x ULN	10	20.4
>1 x ULN	28	57.1
Missing data	1	2.0
GERCOR prognostic score		
Low-risk	8	16.3
Intermediate-risk	24	49.0
High-risk	13	26.5
Missing data	4	8.2

ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal.

administration of aflibercept for >21 days (n=2), or investigator decision (n=1). Among the 38 (79.2%) patients who received maintenance therapy (fluorouracile-based, n=37; capecitabine-based, n=1), 10 (26.3%) patients were still on maintenance therapy. A total of 415 cycles of maintenance therapy were administered, with a mean number of 10.9 cycles per patient. In total, 48/415 (11.6%) cycles were postponed. The median duration of maintenance therapy was 5.5 months (95% CI, 3.7-9.9).

Reintroduction. At the time of analysis, 11 patients were eligible for oxaliplatin reintroduction and 6 patients received an oxaliplatin reintroduction. Three other patients had an unplanned reintroduction of FOLFOX-aflibercept after surgery of metastasis (n=2) or an early progression (n=1).

Efficacy

Progression-free survival. At Simon's stage 1 (n=23), 17 (73.9%; 95% CI, 56.0-91.9) patients were alive without disease progression at 6 months. In the ITT population (n=49), 33 (67.4%; 95% CI, 54.2-80.5) patients were alive without disease progression at 6 months, 12 (24.5%) patients were considered as failure (5 patients had RECIST progression, 4 patients had clinical progression, and 3 patients died), and 4 (8.2%) patients were not evaluated for other reasons (no tumor measure, patient decision, surgery of the primary tumor and investigator's decision). Following a median follow-up of 22.5 months (95% CI, 20.9-24.5), the median PFS was 9.3 months (95% CI, 8.3-12.5). The 6-month and 1-year PFS rates were 79.1 and 36.1%, respectively. The median PFS from the beginning of maintenance therapy (n=38) was 7.4 months (95% CI, 5.9-9.5). Patients with prior hypertension or high systolic blood pressure (≥140 mmHg) at study entry had a significantly shorter PFS (HR, 2.37 and 2.61, respectively) than the other subgroups (Table II).

Overall survival. At the time of analysis, 26 (53.1%) patients were alive. The median follow-up was 10.9 months (95% CI, 9.9-12.0). The median OS was 22.2 months (95% CI, 18.2-24.7). The 6-month and 1-year survival rates were 91.8 and 79.6%, respectively.

Tumor response. A total of 45/49 (91.8%) patients were evaluated, and 4 (8.2%) patients were not evaluable for tumor response (2 patients with early death, 1 with gastrointestinal perforation, and 1 patient was not treated). The ORR (CR or PR) was observed in 29 (59.2%) of the 49 patients in the ITT population, and in 28 (60.9%) of the 46 patients in the PP population (Table III).

Table II. Progression-free survival in the ITT population.

Parameter	No.	Events	Median (months)	95% CI	Hazard ratio	95% CI	P-value
All patients	49	23	9.5	8.7-12.6			
Age (years)							
<65	25	9	11.9	9.3-12.6	ref		
≥65	24	14	8.8	7.0-9.9	1.86	0.82-4.21	0.136
Tumor response							
CR or PR	29	13	9.9	8.8-12.6	ref		
SD or PD	20	10	9.5	5.0-11.0	1.71	0.71-4.15	0.191
Body mass index (kg/m^2)							
<25	29	12	9.5	8.7-11.9	ref		
≥25	20	11	9.1	7.0-11.0	1.81	0.76-4.29	0.148
Systolic blood pressure (mmHg)							
<140	34	13	12.6	8.7-12.6	ref		
≥140	13	8	8.7	5.7-11.0	2.61	0.87-7.74	0.023
Diastolic blood pressure (mmHg)							
<90	40	18	9.1	8.3-12.6	ref		
≥90	7	3	11.0	5.7-11.0	0.90	0.28-2.93	0.866
Prior hypertension							
No	30	10	11.9	9.3-12.6	ref		
Yes	19	13	8.8	6.8-9.9	2.37	1.00-5.56	0.033
Number of metastatic sites							
1	26	12	9.5	8.7-12.6	ref		
>1	23	11	8.8	6.4-9.9	1.36	0.59-3.15	0.455
Liver involvement							
No	12	3	-	-	ref		
Yes	37	20	9.3	8.7-12.6	2.86	1.17-6.97	0.074
ECOG PS							
0	23	10	11.0	7.6-12.6	ref		
1-2	26	13	9.5	8.7-11.9	1.26	0.56-2.86	0.562
Sex							
Male	23	11	9.1	7.7-12.6	ref		
Female	26	12	9.5	8.3-11.9	0.96	0.42-2.18	0.922
KRAS exon 2 mutation status							
Mutated	25	10	9.9	8.7-11.0	ref		
Wild-type	20	11	9.5	7.7-12.6	1.12	0.48-2.65	0.784
Weight (kg)							
<70	27	10	9.5	8.7-9.5	ref		
≥70	22	13	9.9	6.4-11.9	1.41	0.62-3.19	0.406

'ref' indicates the reference group for comparison. ITT, intent-to-treat; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal.

Salvage surgery. A total of 6 (8.4%) patients had liver surgery during maintenance therapy for the resection of 2 to 7 lesions per patient with a maximum tumor size of 15 to 55 mm. The percentage of necrosis ranged between 50 and 100%. Of the 4 patients who underwent salvage surgery, 1 patient had a complete pathological response and 1 patient had <1% viable residual tumor cells. A R0 resection was achieved in 1 patient and R1 in 3 patients.

Safety. The most common (≥10%) treatment-related grade 3-4 adverse events were hypertension (23%), fatigue (15%), neutropenia (12%), neuropathy (12%) and stomatitis (10%; Table IV).

Table III. Tumor response in the ITT and PP populations.

Response	Intent-to-treat population (n=49), no. (%)	Per protocol population (n=46), no. (%)
Optimal response rate		
Complete response	2 (4.1)	2 (4.3)
Partial response	27 (55.1)	26 (56.5)
Stable disease	15 (30.6)	15 (30.4)
Progressive disease	1 (2.0)	1 (2.2)
Not evaluable	4 (8.2)	2 (4.3)
Objective response rate	29 (59.2)	28 (60.9)
Disease control rate	44 (89.8)	43 (93.5)

ITT, intent-to-treat; PP, per-protocol.

The majority of events occurred during induction therapy and decreased following the termination of oxaliplatin, apart from fatigue and stomatitis. Severe (grade 3 or 4) hypertension occurred in 11 (22.9%) patients, mainly during induction therapy (n=10/11, 90.9%), and was reversed in most cases before maintenance therapy. In total, 26 (54.2%) and 22 (45.8%) patients had treatment-related hypertension grade 0-1 and 2-4, respectively (Table V). Patients with grade 2-4 hypertension were more frequently women (P=0.081), had more frequently high systolic blood pressure at study entry (P=0.001), had a higher number of metastatic sites involved (P=0.008), and had more treatment-induced proteinuria (P=0.016). There were 3 (6.1%; 95% CI, -0.6-12.8) treatment-related deaths due to stroke in the context of hypertension (n=1), pulmonary embolism (n=1) and neutropenic sepsis (n=1).

Health-related quality of life. A total of 47 (95.9%) patients filled the baseline HRQoL questionnaire. In total, 10 patients with no follow-up measure had a lower baseline HRQoL level than other patients. The median time until definitive deterioration or death varied from 5.6 months (99% CI, 2.0-10.3) for physical functioning to 8.9 months (99% CI, 3.9-14.1) for emotional functioning. For sensitivity analysis, all medians for targeted dimensions were <5 months. An abnormal monocyte level was associated with a shorter time until the definitive deterioration of emotional functioning or death (HR=3.7; 99% CI, 1.1-12.0).

Circulating biomarkers. The exposure to aflibercept with FOLFOX was associated with an increase in the levels of soluble (s)VEGFR1 and PlGF after the first infusion. High baseline levels of sVEGFR2, sEGFR, G-CSF, prolactin and low baseline levels of VEGFA and migration inhibitory factor (MIF) were associated with a higher response rate. High baseline levels of PlGF predict a poor PFS and OS

Table IV. A summary of the adverse events by System Organ Class.

	Whole strategy[a] (n=48)		Induction (n=48)		Maintenance (n=28)	
NCI CTCAE	Any grade no. (%)	Grade 3-4 no. (%)	Any grade no. (%)	Grade 3-4 no. (%)	Any grade no. (%)	Grade 3-4 no. (%)
Neutrophil count decreased	18 (37)	6 (12)	18 (37)	5 (10)	3 (11)	1 (4)
Platelet count decreased	21 (44)	2 (4)	19 (40)	2 (4)	7 (25)	0 (0)
Anemia	29 (60)	1 (2)	27 (56)	1 (2)	11 (39)	0 (0)
Febrile neutropenia	1 (6)	1 (6)	1 (6)	1 (6)	0 (0)	0 (0)
Nausea	35 (73)	0 (0)	32 (67)	0 (0)	14 (50)	0 (0)
Vomiting	20 (42)	1 (2)	18 (37)	1 (2)	2 (7)	0 (0)
Mucositis oral	35 (73)	5 (10)	29 (60)	2 (4)	16 (57)	3 (11)
Diarrhea	27 (56)	2 (4)	23 (48)	2 (4)	10 (36)	0 (0)
Peripheral sensory neuropathy	43 (90)	6 (12)	43 (90)	4 (8)	20 (71)	2 (7)
Palmar-plantar erythrodysesthesia syndrome	17 (35)	4 (8)	11 (23)	1 (2)	13 (46)	4 (14)
Alopecia	11 (23)	5 (10)[b]	7 (15)	3 (6)[b]	7 (25)	2 (7)[b]
Fatigue	33 (69)	7 (15)	30 (62)	5 (10)	15 (31)	3 (11)
Hypertension	26 (54)	11 (23)	26 (54)	10 (21)	14 (50)	2 (7)
Venous thromboembolic event	1 (2)	1 (2)	1 (2)	1 (2)	0 (0)	0 (0)
Arterial thromboembolic event	2 (4)	2 (4)	2 (4)	2 (4)	0 (0)	0 (0)
Proteinuria	17 (35)	3 (6)	9 (19)	1 (2)	11 (29)	2 (7)
Gastrointestinal perforation	2 (4)	2 (4)	1 (2)	1 (2)	1 (4)	1 (4)
Hemorrhage	9 (19)	1 (2)	5 (10)	1 (2)	5 (18)	0 (0)
Fistula	1 (2)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)

[a]Whole strategy includes induction, maintenance, reintroduction, and maintenance following reintroduction. [b]Alopecia grade 2. NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Table V. Patient baseline characteristics and clinical outcomes according to the occurrence of hypertension during study treatment.

Characteristic	Grade 0-1 hypertension (n=26), no. (%)	Grade 2-4 hypertension (n=22), no. (%)	P-value
Sex			
Male	17 (65.4)	8 (36.4)	0.081
Female	9 (34.6)	14 (63.6)	
Age (years)			
<70	15 (57.7)	14 (63.6)	0.771
≥70	11 (42.3)	8 (36.4)	
Prior history of hypertension			
No	18 (69.2)	12 (54.5)	0.375
Yes	8 (30.8)	10 (45.5)	
Prior history of arterial TEE			
No	26 (100.0)	20 (90.0)	0.205
Yes	0 (0.0)	2 (9.1)	
Prior history of venous TEE			
No	26 (100.0)	22 (100.0)	1.000
Yes	0 (0.0)	0 (0.0)	
Baseline systolic blood pressure (mmHg)			
<120	8 (30.8)	3 (13.6)	0.001[a]
120-139	15 (57.7)	7 (31.8)	
140-159	2 (7.7)	9 (40.9)	
>160	0 (0.0)	2 (9.1)	
Missing	1 (3.8)	1 (4.5)	
Baseline diastolic blood pressure (mmHg)			
<80	12 (46.2)	13 (59.1)	0.686[a]
80-89	10 (38.5)	4 (18.2)	
90-99	3 (11.5)	2 (9.1)	
≥100	0 (0.0)	2 (9.1)	
Missing	1 (3.8)	1 (4.5)	
Weight (kg)			
<70	16 (61.5)	11 (50.0)	0.561
≥70	10 (38.5)	11 (50.0)	
Body mass index (kg/m^2)			
<25	18 (69.2)	11 (50.0)	0.239
≥25	8 (30.8)	11 (50.0)	
Number of metastatic sites			
1	19 (73.1)	7 (31.8)	0.008
>1	7 (26.9)	15 (68.2)	
Liver involvement			
No	7 (26.9)	5 (22.7)	1.000
Yes	19 (73.1)	17 (77.3)	
KRAS exon 2 mutation status			
Wild-type	10 (38.5)	9 (40.9)	1.000
Mutated	13 (50.0)	12 (54.5)	
Unknown	3 (11.5)	1 (4.5)	
Time to metastasis			
Metachronous	3 (11.5)	3 (13.6)	1.000
Synchronous	23 (88.5)	19 (86.4)	
ECOG performance status			
0	11 (42.3)	11 (50.0)	0.772
1	13 (50.0)	9 (40.0)	
2	2 (7.7)	2 (9.1)	

Table V. Continued.

Characteristic	Grade 0-1 hypertension (n=26), no. (%)	Grade 2-4 hypertension (n=22), no. (%)	P-value
Symptoms			
No	16 (61.5)	17 (77.3)	0.351
Yes	10 (38.5)	5 (22.7)	
Creatinine level			
≤1 x ULN	25 (96.2)	20 (90.9)	0.587
>1 x ULN	1 (3.8)	2 (9.1)	
Clearance of creatinine (ml/min/m^2)			
≥90	14 (53.8)	10 45.5)	0.147
<90	12 (46.2)	12 (54.5)	
Aspartate aminotransferase level			
≤1 x ULN	15 (57.7)	18 (81.8)	0.241
>1 x ULN	11 (42.3)	6 (27.3)	
Alanine aminotransferase level			
≤1xULN	20 (76.9)	17 (77.3)	1.000
>1xULN	6 (23.1)	5 (22.7)	
Lactate dehydrogenase level			
≤1 x ULN	10 (38.5)	9 (40.9)	1.000
>1 x ULN	13 (50.0)	12 (54.5)	
Missing	1 (3.8)	1 (4.5)	
Carcinoembryonic antigen level			
≤1 x ULN	6 (23.1)	5 (22.7)	1.000
>1 x ULN	20 (76.9)	17 (77.3)	
Placenta growth factor level			
Low	11 (36.7)	9 (62.3)	0.256
High	19 (63.3)	5 (35.7)	
Treatment outcomes, efficacy			
Tumor response (CR or PR)			
No	12 (46.2)	7 (31.8)	0.382
Yes	14 (53.8)	15 (68.2)	
Treatment outcomes, safety			
Arterial TEE			
No	25 (96.2)	21 (95.5)	1.000
Yes	1 (3.8)	1 (4.5)	
Hemorrhage			
No	23 (88.5)	16 (72.7)	0.267
Yes	3 (11.5)	6 (27.3)	
Proteinuria			
No	21 (80.8)	10 (45.5)	0.016
Yes	5 (19.2)	12 (54.5)	
On treatment death			
No	24 (92.3)	22 (100.0)	0.493
Yes	2 (7.7)	0 (0.0)	
Serious adverse events reported			
No	12 (46.2)	7 (31.8)	0.382
Yes, treatment-related	8 (30.8)	8 (36.4)	
Yes, non-treatment-related	6 (23.1)	7 (31.8)	

[a]Comparison of groups 0-1 versus 2-4. TEE, thromboembolic event; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal; CR, complete response; PR, partial response.

Table VI. Association between baseline circulating biomarker levels and progression-free survival and overall survival.

Biomarker	Cut-off (pg/ml)	No.	HR PFS	95% CI	P-value	HR OS	95% CI	P-value
Angiopoietin 1	>7,000	21						
	<7,000	23	0.73	0.38-1.43	0.361	1.32	0.54-3.24	0.547
Angiopoietin 2	>2,700	22						
	<2,700	23	1.39	0.72-2.70	0.319	1.47	0.60-3.60	0.403
Eotaxin	>120	23						
	<120	21	0.94	0.48-1.82	0.851	0.66	0.27-1.63	0.378
FGF	>800	21						
	<800	23	1.40	0.71-2.73	0.332	1.47	0.60-3.61	0.403
Follistatin	>800	20						
	<800	24	0.90	0.46-1.77	0.778	0.68	0.27-1.68	0.392
G-CSF	>250	22						
	<250	22	1.20	0.62-2.33	0.584	0.99	0.40-2.44	0.991
HER1 (EGFR)	>28,000	22						
	<28,000	22	0.76	0.39-1.49	0.427	0.96	0.38-2.37	0.925
HER2	>7,300	22						
	<7,300	22	0.47	0.23-0.94	0.019	0.53	0.21-1.36	0.195
HGF	>1,700	22						
	<1,700	22	0.64	0.33-1.26	0.192	0.42	0.17-1.07	0.074
ICAM1 (CD54)	>115,000	23						
	<115,000	22	1.60	0.82-3.11	0.159	0.78	0.31-1.91	0.579
IL6Rα	>24,000	22						
	<24,000	21	0.50	0.25-0.98	0.034	0.53	0.21-1.34	0.194
IL8	>30	21						
	<30	23	0.88	0.45-1.72	0.710	1.77	0.72-4.34	0.220
Leptin	>5,900	22						
	<5,900	22	0.98	0.50-1.89	0.950	1.06	0.43-2.62	0.890
MIF	>6,000	22						
	<6,000	22	0.71	0.36-1.39	0.289	0.58	0.23-1.44	0.233
NRP1	>500,000	22						
	<500,000	21	1.02	0.52-2.00	0.953	0.59	0.23-1.48	0.264
Osteopontin	>145,000	20						
	<145,000	23	0.66	0.33-1.32	0.194	0.99	0.39-2.49	0.977
PDGF	>1,000	21						
	<1,000	22	0.66	0.33-1.31	0.221	0.57	0.22-1.43	0.233
PECAM1	>7,300	21						
	<7,300	23	0.63	0.32-1.22	0.160	0.41	0.16-1.00	0.058
PlGF	>20	4						
	<20	40	0.32	0.06-1.74	0.021	0.31	0.04-2.23	0.044
Prolactin	>7,000	23						
	<7,000	20	0.93	0.48-1.83	0.840	0.62	0.25-1.57	0.322
SCF	>400	22						
	<400	21	1.12	0.57-2.22	0.740	0.82	0.32-2.07	0.668
SDF1α	>135	20						
(CXCL12)	<135	24	0.84	0.43-1.63	0.598	0.80	0.32-1.97	0.625
SPD	>9,600	22						
	<9,600	22	1.69	0.86-3.31	0.106	2.10	0.85-5.19	0.106
Tenascin C	>10,000	22						
	<10,000	22	0.62	0.32-1.23	0.152	0.40	0.16-1.00	0.047

Table VI. Continued.

Biomarker	Cut-off (pg/ml)	No.	HR PFS	95% CI	P-value	HR OS	95% CI	P-value
TIE2	>20,000	16						
	<20,000	27	0.70	0.34-1.46	0.299	0.49	0.19-1.28	0.129
VCAM1	>1,300,000	23						
	<1,300,000	21	0.92	0.48-1.79	0.812	0.70	0.28-1.72	0.438
VEGF-A	>0	17						
	0	27	0.66	0.32-1.39	0.232	0.67	0.26-1.74	0.379
VEGF-C	>800	18						
	<800	26	1.72	0.89-3.35	0.098	1.41	0.57-3.47	0.469
VEGFR1	>1,300	22						
	<1,300	21	0.98	0.50-1.92	0.957	1.06	0.42-2.67	0.901
VEGFR2	>7,000	22						
	<7,000	21	0.96	0.49-1.89	0.905	1.10	0.43-2.80	0.840
VEGFR3	>2,250	21						
	<2,250	23	1.74	0.89-3.40	0.093	1.52	0.62-3.74	0.361

FGF, fibroblast growth factor; G-CSF, granulocyte colony-stimulating factor; HER/EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HGF, hepatocyte growth factor; ICAM1, intercellular adhesion molecule 1 (also known as CD54); IL8, interleukin 8; MIF, migration inhibitory factor; NRP1, neuropilin-1; PDGF, platelet-derived growth factor; PlGF, placental growth factor; SCF, stem cell factor; SDF1α, stromal cell-derived factor 1 α; SPD, spindle-defective protein; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor.

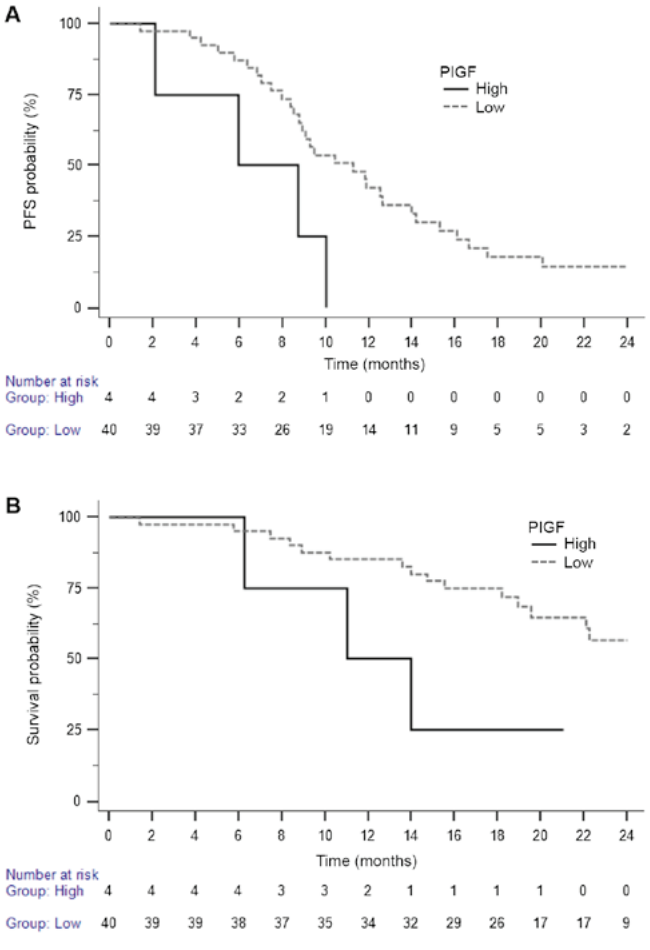

Figure 2. (A) Progression-free survival (PFS); and (B) overall survival curves according to baseline placental growth factor (PlGF) levels.

(Table VI and Fig. 2). There was a trend for an association between the high on-treatment PlGF level and the occurrence of grade 2-4 diarrhea (P=0.086), but not with hypertension (P=0.256).

Discussion

VELVET was the first phase II study evaluating aflibercept with an oxaliplatin stop-and-go strategy in patients with previously untreated and unresectable mCRC. The targeted 85% 6-month PFS rate was not reached in the ITT population: The absolute rate and the Kaplan-Meier estimates of 6-month PFS were 67 and 79%, respectively. The ORR was 59% and median PFS and OS were 9.3 months and 22.2 months, respectively. The maintenance rate (79%) was higher than in previous oxaliplatin stop-and-go studies (10,21,27).

In the OPTIMOX1 and OPTIMOX2 studies (10,21) a similar oxaliplatin stop-and-go strategy without anti-angiogenic agent led to a response rate of 59.2% and median PFS <9 months. In the AFFIRM randomized phase II study (22), 236 patients with unresectable mCRC were randomized between first-line FOLFOX (n=117) and FOLFOX-aflibercept (n=119) until progression. That study was conducted in Europe, Asia and Australia, regions with different clinical guidelines for the treatment of mCRC. The 1-year PFS rate (primary endpoint) was similar in both groups (21.2 versus 25.8%). There was no significant improvement in efficacy endpoints with the addition of aflibercept to chemotherapy (ORR, 45.9 versus 49.1%; median PFS, 8.8 versus 8.5 months; and median OS, 22.3 versus 19.5 months) and in salvage surgery rate (5.1 versus 5.0%). In the NO16966 study (4) the addition of

Table VII. Summary of treatment regimens and outcomes of studies evaluating FOLFOX with or without antiangiogenic agent.

Antiangiogenic agent	None				Bevacizumab			Aflibercept	
Study (ref.)	NO16966 (4)	OPTIMOX1 (10)	OPTIMOX1 (10)	OPTIMOX2 (21)	NO16966 (4)	HORIZON III (30)	DREAM[a] (28)	AFFIRM (22)	VELVET (29)
No. of patients	351	309	311	98	699	713	429	119	49
Administration	Continuously	Continuously	Stop-and-go	Stop-and-go (maintenance)	Continuously	Continuously	Stop-and-go	Continuously	Stop-and-go
Chemotherapeutic regimen	FOLFOX4	FOLFOX4	FOLFOX7	mFOLFOX7	FOLFOX4	mFOLFOX6	mFOLFOX7	mFOLFOX6	mFOLFOX7
Oxaliplatin dose (mg/m^2)	85	85	130	100	85	85	100	85	100
5-FU infusion dose (mg/m^2)	2,400	2,400	2,400	3,000	2,400	2,400	2,400	2,400	3,000
5-FU bolus	Yes	Yes	No	No	Yes	Yes	No	Yes	No
Objective response rate (%)	49.0[a]	58.5	59.2	59.2	47.0[a]	47.3	52.2	49.1	59.2
PFS (months)	8.6	9.0	8.7	8.6	9.4	10.3	9.4	8.5	9.5
OS (months)	20.3	19.3	21.2	23.8	21.2	21.3	25.6	19.5	22.2

[a]Including XELOX-bevacizumab. 5-FU, 5-fluorouracil; PFS, progression-free survival; OS, overall survival.

bevacizumab to an oxaliplatin-based chemotherapy (FOLFOX or XELOX) led to an improvement in PFS (primary endpoint) from 8.0 to 9.5 months (HR, 0.83; P=0.002). This benefit was greater when patients were censored at the time of drug discontinuation ('on-treatment PFS'; HR, 0.63). The median PFS in patients who received FOLFOX4-bevacizumab was 9.4 months. The ORR was similar whether patients received chemotherapy with (47%) or without (49%) bevacizumab. The oxaliplatin-based stop-and-go strategy with bevacizumab was previously evaluated in several randomized phase III trials (11,23-26). Among 700 patients enrolled in the DREAM study (27), 429 (61.3%) received an induction therapy with modified FOLFOX7 plus bevacizumab, using the same dose of oxaliplatin (100 mg/m^2) than in the present study, although a lower dose of 5-FU infusion. In those patients, the ORR was 52.2% and the median PFS was 9.4 months (28). Thus, the addition of aflibercept to an oxaliplatin stop-and-go strategy in patients with unresectable mCRC seems to increase PFS to the same degree as bevacizumab (from <9 to 9.5 months) and to slightly increase the tumor ORR (Table VII). This effect may also be associated with higher doses of 5-FU infusion.

In the present study, the frequency of severe (grade 3 or 4) hypertension (23%) was similar to that reported in the VELOUR trial (19%) (29), although lower than described in the AFFIRM study (36%) (22). When adding bevacizumab to an oxaliplatin-based chemotherapy in patients with advanced mCRC, the incidence of grade 3-4 hypertension ranges between 4 and 6% (4,30-32). In this study, this adverse event occurred mainly during induction therapy, and was reversed in most cases before maintenance therapy. Of note, a high systolic blood pressure (≥140 mmHg) at study entry was associated with shorter PFS and a higher frequency of treatment induced grade 2-4 hypertension.

The exposure to aflibercept with FOLFOX was associated with an increase in PlGF levels after the first infusion. When trapping circulating PlGF, aflibercept inhibits the binding to VEGF receptors 1 and 2, thus increasing the circulating PlGF level.

Despite the statistically negative result of this study, but given the high response rate, OPTIMOX-aflibercept may be an active first-line treatment strategy in patients with previously untreated and unresectable mCRC, providing strict monitoring of blood pressure and immediate management of hypertension during therapy. Further trials evaluating this combination should provide early safety analysis.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on request.

Authors' contributions

BC and ADG were responsible for the conception and design of the study. CT, BC, TA, WS, and ADG recruited the patients. BC, JBB, TA, DA, JDe, GD, CLe, CLo, CT, VL, JDa, GL, MLG, OD, NBH, AM, AKL, and ATR collected the data. BC, FB, and AdG analyzed the data. CT and AdG interpreted the data. BC and AdG wrote the manuscript. All authors have edited, read and approved the final manuscript.

Ethics approval and consent to participate

The study was carried out in accordance with the declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. This study was approved by the Ethics Committee of our institution (CPP Ile de France VI Groupe Hospitalier Pitié Salpêtrière PARIS).

Patient consent for publication

Not applicable.

Competing interests

BC reported personal fees from Roche Pharma AG, Amgen, Sanofi and Menarini. JBB reported personal fees from Amgen, Bayer, Celgène, Merck Serono, Roche, Sanofi and Roche. TA reported personal fees from BMS, Roche, MSD Oncology, Sanofi, Novartis, Servier, Amgen, Lilly, Xbiotec, Mundipharma and Yacult. All remaining authors have declared no competing interests.

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