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Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: Prespecified subgroup analyses from the VELOUR trial

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Abstract ***Purpose:*** The antiangiogenic agent aflibercept (ziv-aflibercept in the United States) in combination with 5-fluorouracil, leucovorin and irinotecan (FOLFIRI) significantly improved survival in a phase III study of patients with metastatic colorectal cancer (mCRC) previously treated with an oxaliplatin-based regimen. In the present analysis, outcomes were evaluated in prespecified subgroups to assess the consistency of the treatment effect.

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Subgroup analysis

Methods: Patients were randomised to receive FOLFIRI plus aflibercept or placebo every 2 weeks until disease progression or unacceptable toxicity occurred. Efficacy and safety outcomes were analysed with respect to demographic and baseline characteristics, and stratification factors (prior bevacizumab treatment and Eastern Cooperative Oncology Group performance status).

Results: Median overall survival (OS, months [95.34% confidence interval (CI)]) for aflibercept versus placebo was 12.5 (10.8–15.5) versus 11.7 (9.8–13.8) in patients with prior bevacizumab treatment and 13.9 (12.7–15.6) versus 12.4 (11.2–13.5) in patients with no prior bevacizumab treatment. The p value for interaction was 0.5668, indicating there was no heterogeneity in these subgroups. For OS and progression-free survival (PFS), there was a significantly greater benefit (at the 2-sided 10% level) of treatment for patients with liver only metastases versus patients with no liver metastases/liver metastases with other organ involvement (p value for interaction: 0.0899 [OS]; 0.0076 [PFS]). There was no evidence of heterogeneity in treatment effect in any of the other subgroups examined.

Conclusions: The benefits of aflibercept in combination with FOLFIRI in patients with mCRC previously treated with oxaliplatin were maintained across the specified patient subgroups, including in patients with or without prior bevacizumab treatment.

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1. Introduction

The majority of patients (60%) with colorectal cancer (CRC) have locally advanced or metastatic disease at the time of diagnosis [1]. Prognosis for these patients is poor, with a 5-year survival rate of approximately 12% [1]. However, the administration of molecularly targeted agents in combination with standard chemotherapy regimens has improved the outlook for patients with metastatic CRC (mCRC).

Aflibercept (known as ziv-aflibercept in the U.S., and also known as VEGF Trap or AVE0005) is a recombinant fusion protein containing vascular endothelial growth factor (VEGF)-binding portions from the extracellular domains of human VEGF receptors 1 and 2, fused to the Fc portion of human immunoglobulin (Ig)G1. Aflibercept blocks the activity of VEGFA, VEGFB and placental growth factor (PlGF), by acting as a high-affinity ligand trap to prevent these ligands from binding to their endogenous receptors [2,3].

Aflibercept is the first targeted therapy to demonstrate a statistically significant and clinically meaningful survival benefit in patients previously treated with an oxaliplatin-based regimen and receiving the irinotecan-containing regimen FOLFIRI (5-fluorouracil, leucovorin and irinotecan) for the treatment of metastatic disease [4]. The VELOUR (VEGF Trap (aflibercept) with irinotecan in colorectal cancer after failure of oxaliplatin regimen) trial evaluated the efficacy and safety of the combination of aflibercept and FOLFIRI in patients with mCRC, following disease progression while on or after completion of treatment with an oxaliplatin-based regimen. Adding aflibercept to FOLFIRI significantly improved overall survival (OS) relative to placebo plus FOLFIRI (hazard ratio [HR], 0.817; 95.34% confidence interval [CI], 0.713–0.937; $p = 0.0032$), with median survival times of 13.50 versus 12.06 months, respectively. Aflibercept also significantly improved progression-free survival (PFS; HR, 0.758; 95% CI, 0.661–0.869; $p = 0.00007$). Median PFS was 6.90 months for aflibercept plus FOLFIRI and 4.67 months for placebo plus FOLFIRI. The response rate in VELOUR was 19.8% (95% CI, 16.4–23.2%) for aflibercept plus FOLFIRI and 11.1% (95% CI, 8.5–13.8%) for placebo plus FOLFIRI ($p = 0.0001$). No unexpected toxicities were observed in the aflibercept plus FOLFIRI treatment arm. As a consequence aflibercept was approved by the U.S. Food and Drug Administration (FDA) in August 2012 and by the European Medicines Agency (EMA) in February 2013 for use in combination with FOLFIRI in the treatment of patients with mCRC who were resistant to or progressed following an oxaliplatin-based regimen.

The purpose of this analysis of data from the VELOUR trial was to assess the consistency of the benefit of aflibercept on OS and PFS by evaluating its effect in prespecified subgroups. Of particular interest was the analysis of outcomes in patients stratified by prior bevacizumab treatment. In addition, the relationship between patient demographics and baseline characteristics and outcome was investigated.

2. Materials and methods

2.1. Patients and study design

Details of patient eligibility and the design of the VELOUR study (a prospective multinational, randomised, double-blind, parallel-arm, phase III study [ClinicalTrials.gov number, NCT00561470]) have been reported previously [4]. Eligible patients were aged at least 18 years; with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2.

Eligible patients had histologically- or cytologically-proven colorectal adenocarcinoma with metastatic disease not amenable to potentially curative treatment. Patients were required to have undergone a single prior oxaliplatin-containing chemotherapy regimen for metastatic disease, with documented evidence of disease progression during or after treatment completion. Patients who relapsed within 6 months of completion of oxaliplatin-based adjuvant therapy were also eligible for inclusion. Prior bevacizumab was permitted, but not prior irinotecan.

Eligible patients were randomised 1:1 to receive FOLFIRI plus either aflibercept 4 mg/kg (aflibercept arm) or placebo (control arm) every 2 weeks, with stratification according to prior bevacizumab treatment (yes/no) and ECOG PS (0/1/2). Aflibercept or placebo was administered intravenously (IV) over 1 h on day 1 of each cycle, followed immediately by the FOLFIRI regimen (irinotecan 180 mg/m^2 IV over 90 min, with leucovorin 400 mg/m^2 IV over 2 h, followed by 5-FU 400 mg/m^2 bolus and 5-FU 2400 mg/m^2 continuous infusion over 46 h). Premedication with atropine and anti-emetics was permitted. Granulocyte-colony stimulating factor (G-CSF) was used according to the American Society of Clinical Oncology guidelines [5]. Dose adjustments for each study treatment component individually and/or cycle delays (up to 2 weeks) were permitted in the event of toxicity. Patients were treated until the occurrence of disease progression or unacceptable toxicity as judged by the physician. If FOLFIRI was permanently discontinued, patients could continue to receive aflibercept/placebo; if aflibercept/placebo was permanently discontinued, patients could continue to receive FOLFIRI. No crossover to aflibercept was permitted after progression was documented in the control arm.

At each treatment cycle, patients underwent clinical examination and laboratory assessments (including urinalysis) before receiving study treatment. Adverse events (AEs) coded using The Medical Dictionary for Regulatory Activities (MedDRA) version 13.1, to provide a system organ class (SOC) and preferred term (PT) for each event and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v3.0, were recorded. Concomitant medications were also recorded. Disease assessment was performed every 6 weeks until documented progression. Response was assessed according to Response Evaluation Criteria In Solid Tumors (v1.0) [6] by a third party (independent review committee, IRC), blinded to patient treatment.

2.2. Statistical analysis

The primary end-point of the study was OS, defined as the time interval from randomisation to death from any cause. The cutoff date for OS was the date of the 863rd event (7th February 2011). Secondary end-points included PFS, cutoff date 6th May 2010, defined as the interval from randomisation to the first observation of disease progression according to IRC review, or death from any cause; objective response (complete response and partial response), and treatment-emergent adverse events (TEAEs) and laboratory abnormalities.

Prespecified subgroups were defined according to demographic variables (age, gender, race, geographic region), baseline characteristics (prior hypertension, number of metastatic sites [IRC evaluation], liver metastasis [IRC evaluation], location of primary tumour) and stratification factors at randomisation (ECOG PS, prior bevacizumab treatment).

HRs and CI estimates for OS and PFS in the intention-to-treat (ITT) population (all randomised patients) and within each subgroup were estimated by a Cox proportional hazards model [4]. Interactions between treatment and each subgroup were tested at the 2-sided 10% level (i.e. a p-value >0.1 indicates no evidence of heterogeneity of treatment effect across the subgroups for each factor).

Descriptive analysis of adverse events by treatment arm was performed within each subgroup in the safety population (patients who received at least one dose of study treatment).

All final analyses were conducted by Sanofi personnel.

3. Results

Between November 2007 and March 2010, 1226 patients were randomised to receive, in combination with FOLFIRI, either aflibercept (612 patients) or placebo (614 patients). Five patients in each treatment arm were not treated and four patients randomised to placebo received at least one administration of aflibercept, therefore the safety population included 611 patients in the aflibercept arm and 605 in the control arm (Fig. 1). At the cutoff date for survival analysis (7th February 2011), the median follow-up was 22.28 months.

3.1. Efficacy in demographic subgroups

OS and PFS in patients grouped by age, gender, race and geographic region are shown in Figs. 2A and 3A. For both efficacy end-points, there was no significant treatment interaction between treatment groups and factors for any of the demographic subgroups examined. In all subgroups, a treatment effect in favour of the aflibercept arm over the control arm (HR < 1.0) was seen for both OS and PFS.

3.2. Efficacy in baseline characteristic subgroups

As shown in Figs. 2B and 3B, there was a significantly greater benefit of treatment for patients with metastases

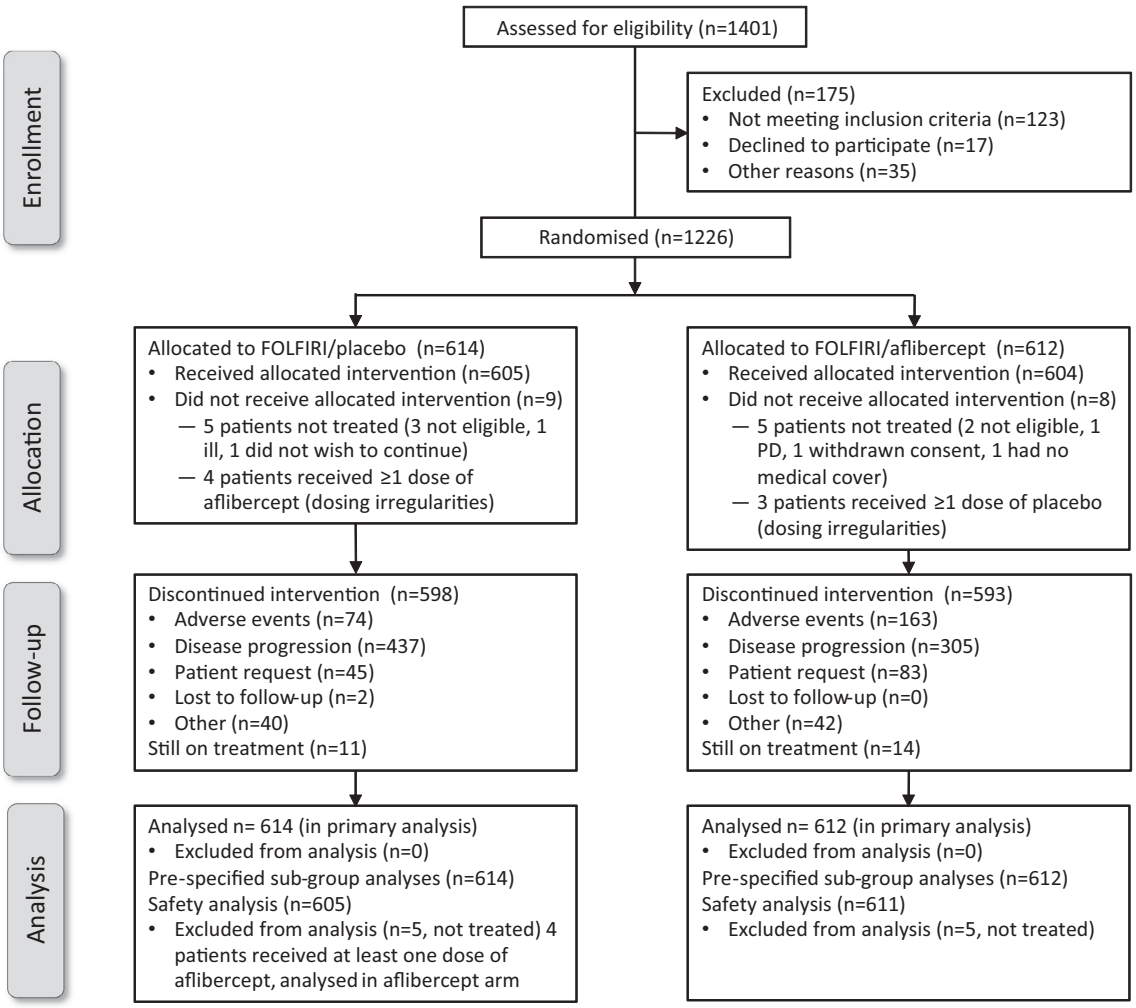


Fig. 1. CONSORT diagram.

confined to the liver versus patients with no liver metastases or liver and metastases at other sites (OS: $p = 0.090$; PFS: $p = 0.008$). A consistent treatment effect in favour of the aflibercept arm was seen for OS and PFS for all subgroups (Figs. 2B and 3B). Of note a revised classification was used for the primary tumour location (colon/rectosigmoid/other versus rectum). In the previous presentations and using the three prespecified primary tumour location categories of colon, rectosigmoid/other and rectum, patients with the location rectosigmoid/other had a less favourable outcome for OS with aflibercept (HR: 1.039 [0.7702, 1.4]).

3.3. Efficacy by baseline stratification factors (prior bevacizumab treatment and ECOG PS)

Baseline characteristics for patients stratified by prior bevacizumab treatment are shown in Table 1. Patients with prior bevacizumab treatment comprised 30% of the ITT population and the duration of bevacizumab use as well as the antiangiogenic-free period were well balanced between the control and aflibercept treatment arms. For OS, there was no significant interaction at the 2-sided 10% level between treatment and stratification levels for prior bevacizumab treatment (yes versus no; $p = 0.5668$) or ECOG PS (0 versus 1 versus 2; $p = 0.7231$), and thus no evidence of heterogeneity in treatment effect (Table 2). A difference in favour of aflibercept over placebo was observed in each stratification subgroup.

Survival outcomes by stratification level of prior bevacizumab treatment are shown in Fig. 4. For patients previously treated with bevacizumab, median OS was 12.5 months in the aflibercept arm and 11.7 months in the control arm. Median OS in patients without prior exposure to bevacizumab was 13.9 months in the aflibercept arm and 12.4 months in the control arm.

The analysis of PFS by stratification level also indicated that there was no significant interaction at the 2-sided 10% level between treatment and stratification levels for prior bevacizumab treatment (yes versus no; $p = 0.1958$) or ECOG PS (0 versus 1 versus 2; $p = 0.6954$) (Table 2). For patients who had received prior bevacizumab, median PFS was 6.7 months in the

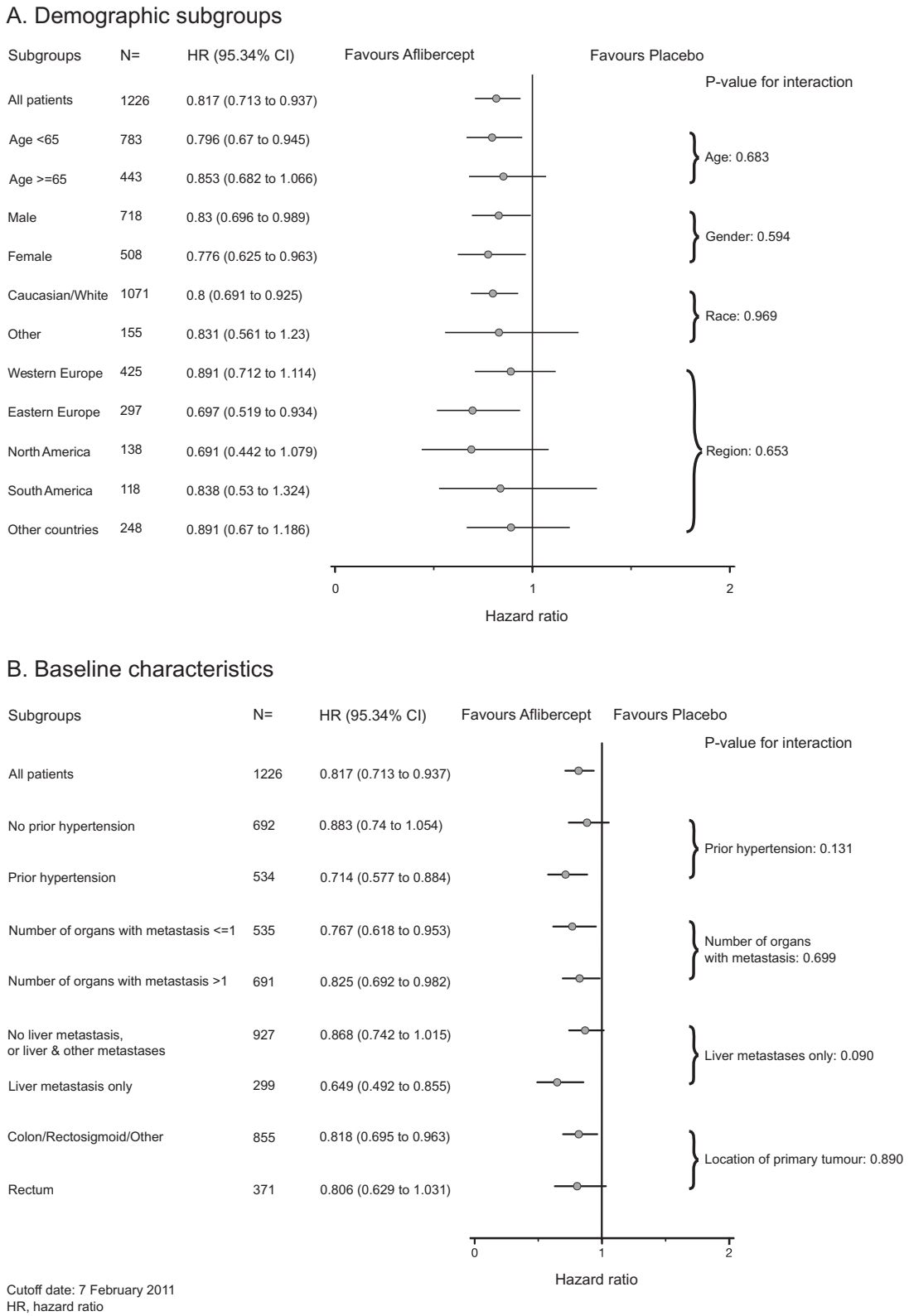


Fig. 2. Forest plots for overall survival in planned subgroup analyses by patient demographic (Panel A) and baseline characteristics (Panel B). *p* values ⩽0.1 indicate a significant interaction between treatment and demographic subgroup factors at the 2-sided 10% level (Cox proportional hazard model). HR, hazard ratio.

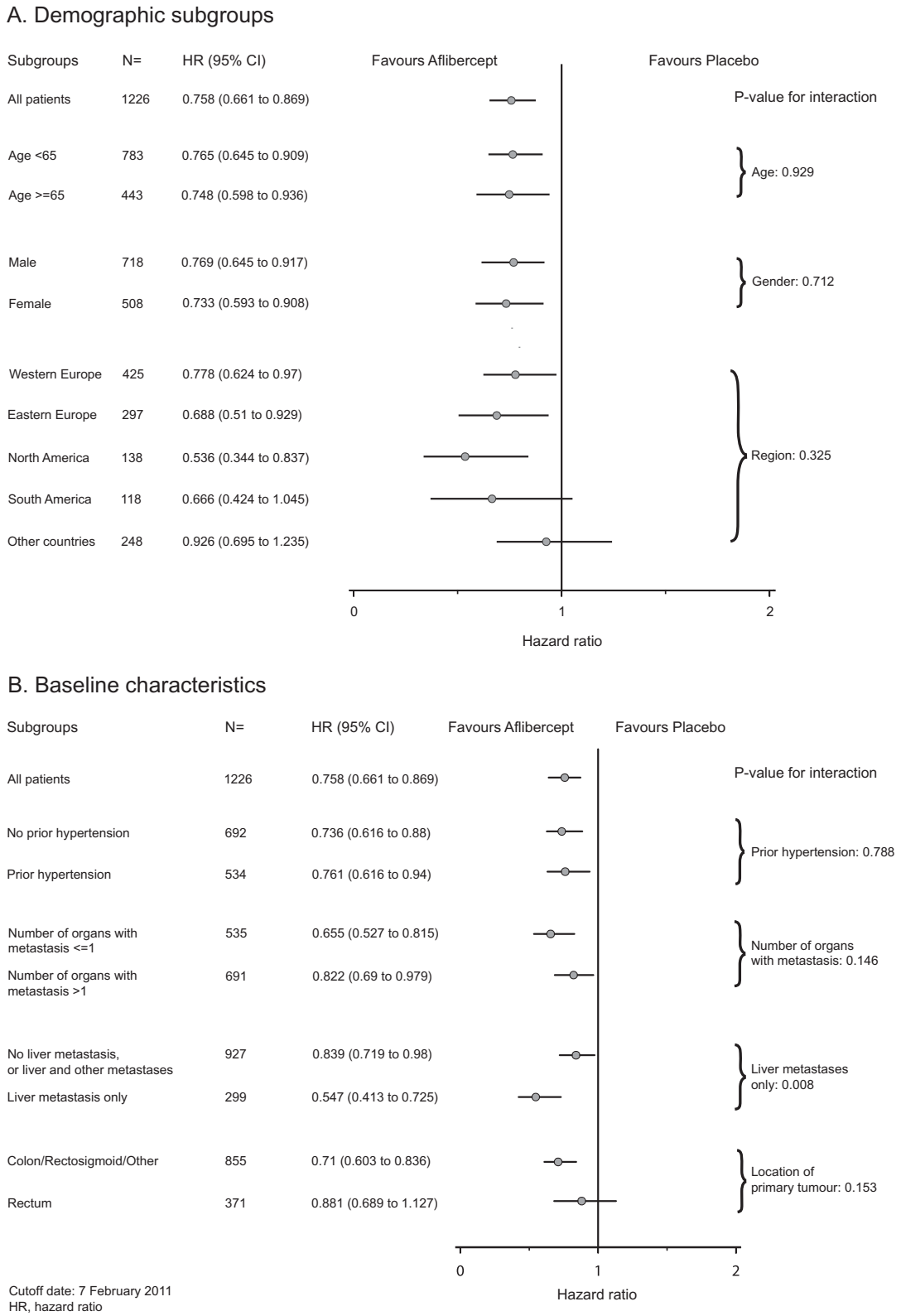


Fig. 3. Forest plots for progression-free survival in planned subgroup analyses by patient demographic (Panel A) and baseline characteristics (Panel B). p values $\leqslant 0.1$ indicate a significant interaction between treatment and baseline characteristic subgroup factors at the 2-sided 10% level (Cox proportional hazard model). HR, hazard ratio.

Table 1
Baseline characteristics in patients stratified by prior bevacizumab treatment.

Parameter	Prior bevacizumab		No bevacizumab	
	Placebo/FOLFIRI ($n = 187$)	Aflibercept/FOLFIRI ($n = 186$)	Placebo/FOLFIRI ($n = 427$)	Aflibercept/FOLFIRI ($n = 426$)
Eastern Cooperative Oncology Group performance status, *n* (%)				
0	107 (57.2)	107 (57.5)	243 (56.9)	242 (56.8)
1	74 (39.6)	74 (39.8)	176 (41.2)	176 (41.3)
2	6 (3.2)	5 (2.7)	8 (1.9)	8 (1.9)
Male, *n* (%)	105 (56.1)	110 (59.1)	248 (58.1)	255 (59.9)
Age, y, median (range)	60.0 (27–86)	59.0 (32–81)	61.0 (19–84)	61.0 (21–82)
Prior hypertension, *n* (%)	97 (51.9)	92 (49.5)	171 (40.0)	174 (40.8)
Region, *n* (%)				
Western Europe	70 (37.4)	54 (29.0)	147 (34.4)	154 (36.2)
Eastern Europe	34 (18.2)	47 (25.3)	102 (23.9)	114 (26.8)
North America	53 (28.3)	49 (26.3)	22 (5.2)	14 (3.3)
South America	8 (4.3)	8 (4.3)	48 (11.2)	54 (12.7)
Other countries	22 (11.8)	28 (15.1)	108 (25.3)	90 (21.1)
Race, *n* (%)				
Caucasian/White	166 (88.8)	172 (92.5)	357 (83.6)	376 (88.3)
Black	7 (3.7)	5 (2.7)	20 (4.7)	11 (2.6)
Asian/Oriental	6 (3.2)	4 (2.2)	45 (10.5)	31 (7.3)
Other	8 (4.3)	5 (2.7)	5 (1.2)	8 (1.9)
Primary tumour location				
Colon/rectosigmoid/other	141 (75.4)	140 (75.3)	299 (70.0)	275 (64.6)
Rectum	46 (24.6)	46 (24.7)	128 (30.0)	151 (35.4)
No. of metastatic organs involved at baseline, *n* (%)				
0	1 (0.5)	1 (0.5)	5 (1.2)	1 (0.2)
1	86 (46.0)	80 (43.0)	185 (43.3)	176 (41.3)
>1	100 (53.5)	105 (56.5)	237 (55.5)	249 (58.5)
Metastatic organs involved at baseline, *n* (%)				
Any site	186 (99.5)	185 (99.5)	422 (98.8)	425 (99.8)
Liver	146 (78.1)	146 (78.5)	285 (66.7)	313 (73.5)
Lung	74 (39.6)	87 (46.8)	203 (47.5)	184 (43.2)
Lymph nodes	49 (26.2)	46 (24.7)	132 (30.9)	127 (29.8)
Peritoneum	23 (12.3)	24 (12.9)	65 (15.2)	44 (10.3)
Liver metastasis, *n* (%)				
None, or liver and other metastases	131 (70.1)	134 (72.0)	337 (78.9)	325 (76.3)
Liver metastasis only	56 (29.9)	52 (28.0)	90 (21.1)	101 (23.7)
Duration of bevacizumab use, months, median (range)	6 (0–28)	6 (0–29)	–	–
Antiangiogenic-free period, months, median (range)	2 (1–21)	2 (1–33)	–	–

Abbreviation: FOLFIRI, 5-fluorouracil, leucovorin and irinotecan.

aflibercept arm and 3.9 months in the control arm. Median PFS in patients without prior exposure to bevacizumab was 6.9 months in the aflibercept arm and 5.4 months in the control arm (Fig. 5).

3.4. Adverse events in patient subgroups

The frequency of TEAEs was generally consistent across patient subgroups. Table 3 summarises the most frequently reported grade 3 and grade 4 adverse events (including those leading to treatment discontinuation), as well as events typically associated with anti-VEGF therapy, in patients stratified by prior bevacizumab treatment. As previously reported, the use of aflibercept increased the chemotherapy-related toxicities associated with FOLFIRI [4]. There was no evidence of greater toxicity in patients previously treated with bevacizumab compared with those not previously treated with bevacizumab. Furthermore, the previous use of bevacizumab did not increase the rate of anti-VEGF-associated events.

4. Discussion

Patients with mCRC comprise a heterogeneous population as represented by differences in variables such as age, co-morbidities, primary tumour site, extent and location of metastases, ECOG PS and prior treatment

Table 2
Median overall survival (months) and median progression-free survival (months) and hazard ratio estimates by stratification factors.

Overall survival	*n*	Placebo/FOLFIRI median (95.34% CI)	Aflibercept/FOLFIRI median (95.34% CI)	Hazard ratio (95.34% CI)	*p* Value for interaction
All patients	1226	12.1 (11.07–13.11)	13.5 (12.52–14.95)	0.817 (0.713–0.937)	
Prior bevacizumab					
No	853	12.4 (11.17–13.54)	13.9 (12.71–15.64)	0.788 (0.669–0.927)	0.5668
Yes	373	11.7 (9.82–13.77)	12.5 (10.78–15.51)	0.862 (0.673–1.104)	
ECOG PS					
0	699	14.1 (12.88–16.62)	16.9 (14.78–18.79)	0.768 (0.635–0.928)	0.7231
1	500	10.1 (9.20–11.53)	10.7 (9.36–12.35)	0.869 (0.71–1.063)	
2	27	4.4 (1.97–10.02)	2.8 (0.92–9.82)	0.978 (0.43–2.221)	
Progression-free survival		(95% CI)	(95% CI)	(95% CI)	
All patients	1226	4.7 (4.21–5.36)	6.9 (6.51–7.20)	0.758 (0.661–0.869)	
Prior bevacizumab					
No	853	5.4 (4.53–5.68)	6.9 (6.37–7.20)	0.797 (0.679–0.936)	0.1958
Yes	373	3.9 (3.02–4.30)	6.7 (5.75–8.21)	0.661 (0.512–0.852)	
ECOG PS					
0	699	5.4 (4.70–5.82)	7.2 (6.87–8.31)	0.761 (0.633–0.913)	0.6954
1	500	4.1 (3.06–4.47)	5.6 (5.06–6.90)	0.749 (0.607–0.923)	
2	27	2.0 (1.51–4.76)	2.7 (0.92–12.88)	0.618 (0.259–1.475)	

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan.

with bevacizumab. The present analysis has established that the benefit of adding aflibercept to FOLFIRI in patients with mCRC demonstrated in the overall (ITT) population in the VELOUR study [4] is consistently observed across a range of prespecified patient subgroups based on demographic variables and baseline clinical characteristics including stratification factors at randomisation (prior bevacizumab treatment and ECOG PS).

For OS and PFS, there was no significant interaction at the 10% level between treatment arms and demographic factors, indicating a consistent benefit of aflibercept across age, gender, race and geographical region subgroups (Figs. 2 and 3). Similarly, there was no significant interaction between treatment arms and stratification by prior exposure to bevacizumab or by ECOG PS (Table 1; Figs. 4 and 5). However, no conclusions can be drawn from the HR in patients with an ECOG PS of 2, because of the small sample size for this stratum (27 patients).

Conducting subgroup analyses based on patients' baseline characteristics showed a significant interaction between treatment arms and factors only in patients grouped according to liver metastases (Figs. 2B and 3B). There was a greater aflibercept treatment effect in patients with liver-only metastases at baseline than in patients with either no liver metastases or liver metastases plus other organ involvement. The same effect has been seen in another trial in the second-line setting evaluating the role of adding an anti-epidermal growth factor receptor (EGFR) agent, panitumumab, to FOLFIRI, this suggesting that this patient population may derive more benefit from a more intensive treatment [7]. No significant heterogeneity in treatment effect was detected in patients classified according to prior hypertension, the number of metastatic organs involved and location of the primary tumour.

For the end-points of OS and PFS, all prespecified subgroup analyses showed a consistent treatment effect favouring aflibercept over placebo (HR, <1.0).

Since bevacizumab in combination with chemotherapy is approved for first-line treatment for mCRC, it is important to establish whether exposure to this agent compromises the efficacy of subsequent therapies that also target the angiogenic pathway, such as aflibercept. Although the present study was not powered to show differences between treatment arms for OS within specific subgroups, the absence of a significant interaction between treatment arm and prior bevacizumab treatment (yes or no) showed that the efficacy of aflibercept was not diminished by prior bevacizumab treatment. It is unknown whether these results reflect the broad anti-angiogenic effect of aflibercept, which targets VEGFB and PIGF in addition to VEGFA. Nevertheless, this is an encouraging observation and potentially broadens the options for those patients surviving first-line regimens that include bevacizumab and who are eligible for further treatment. Further evidence that patients treated first-line with bevacizumab can benefit from subsequent therapies that target VEGF is provided by the results from the TML study. In this study, patients who had progressed on bevacizumab in combination with chemotherapy as first-line treatment demonstrated a significant prolongation of OS and PFS when

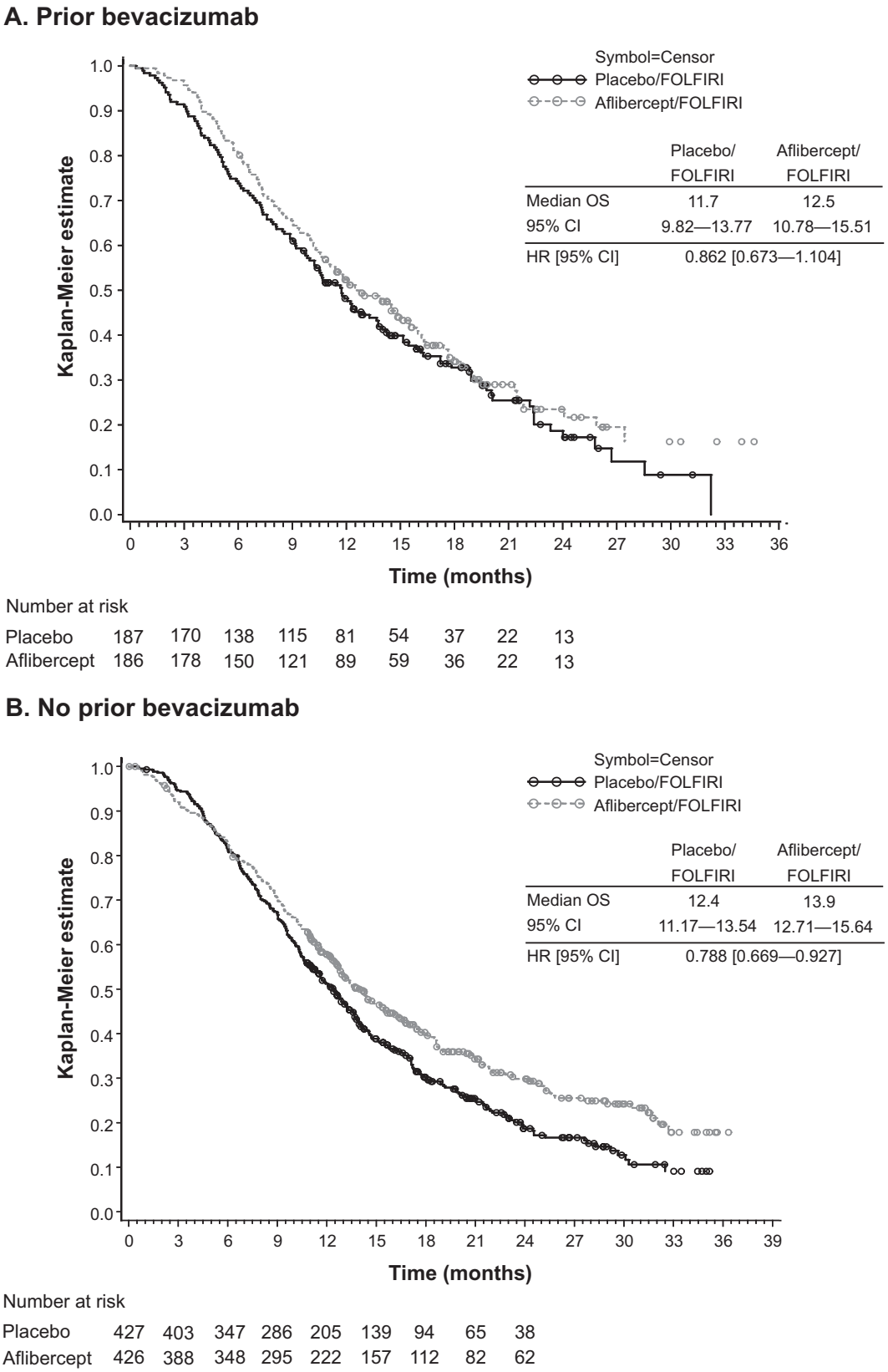
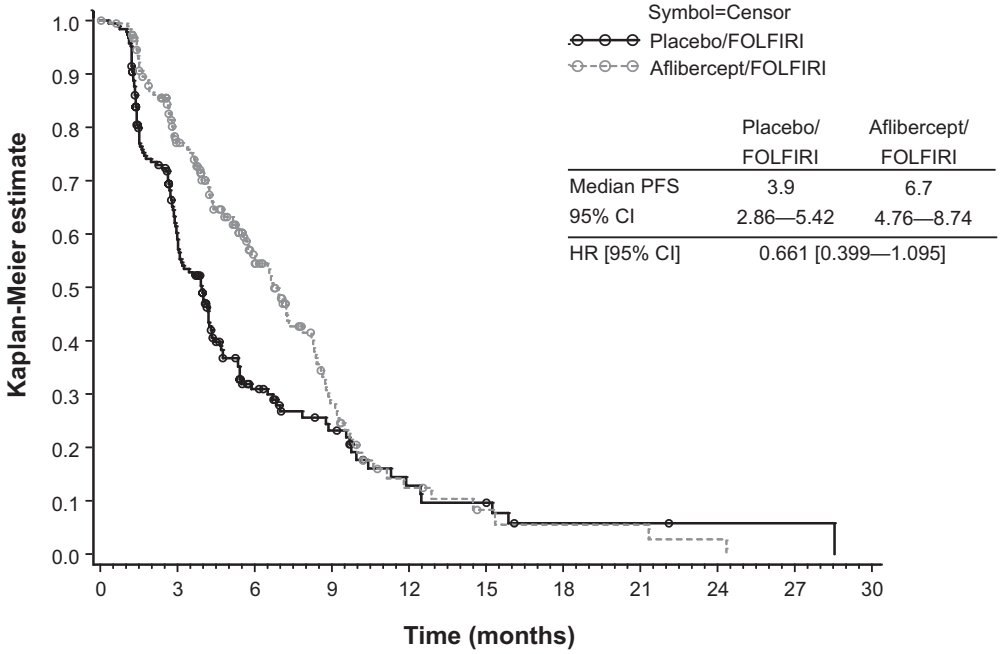


Fig. 4. Kaplan–Meier curves for overall survival stratified by prior bevacizumab. HRs are placebo/FOLFIRI versus aflibercept/FOLFIRI. FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; OS, overall survival; HR, hazard ratio.

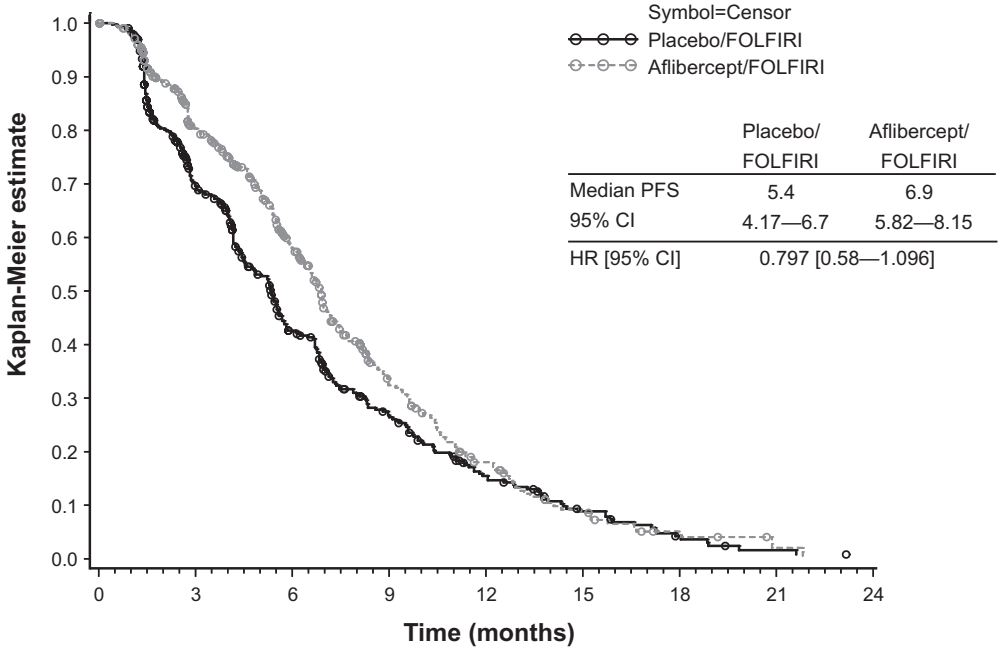
A. Prior bevacizumab



Number at risk

Placebo	187	96	33	19	8	6	2
Aflibercept	186	124	66	23	7	3	2

B. No prior bevacizumab



Number at risk

Placebo	427	259	138	75	38	18	7
Aflibercept	426	296	181	76	36	14	5

Fig. 5. Kaplan–Meier curves for progression-free survival stratified by prior bevacizumab. HRs are placebo/FOLFIRI versus aflibercept/FOLFIRI. FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; OS, overall survival; HR, hazard ratio.

Table 3
Adverse events in patients stratified by prior bevacizumab status according to e-CRFs (safety population).

Adverse events[a], % patients	Prior bevacizumab				No bevacizumab			
	Placebo/FOLFIRI ($n = 172$)		Aflibercept/FOLFIRI ($n = 171$)		Placebo/FOLFIRI ($n = 433$)		Aflibercept/FOLFIRI ($n = 440$)	
Serious AEs	32		52		33		47	
Fatal AE [b] due to PD	3		2		2		2	
Fatal AE [b] in other context than PD	2		2		1		3	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Grade 3/4 AEs in >10% of patients in any treatment group								
Neutropenia (PT)	9.3	4.1	13.5	6.4	17.1	8.3	18.0	9.1
Diarrhoea (PT)	8.1	0.6	18.1	0.6	7.4	0	19.3	0.2
Infections and infestations (SOC)	6.4	1.2	12.9	0.6	6.0	0.7	10.2	1.6
Stomatitis (PT)	3.5	0	10.5	0	5.1	0	13.4	0.2
Hypertension (PT)	0.6	0	16.4	0	1.8	0	20.0	0.2
Fatigue (PT)	8.7	0	14.6	0	7.2	0.2	10.9	0.9
Other anti-VEGF-associated events								
Proteinuria	0.6	0	9.4	0	1.4	0	7.3	0
Haemorrhage	1.2	0	3.5	0	1.8	0	2.5	0.2
GI disorders (SOC)	0.6	0	3.5	0	1.2	0	1.1	0.2
Headache (PT)	0	0	0.6	0	0.5	0	2.0	0
Venous thromboembolic event	2.9	2.9	4.7	2.3	2.5	3.9	2.5	5.7
Pulmonary embolism (PT)	0	2.9	0	2.3	0	3.7	0	5.5
Arterial thromboembolic event	0.6	0	0.6	1.2	0.5	0	0.9	0.9
GI perforation	0	0	0	0	0.2	0.2	0.2	0.5
AEs leading to permanent treatment discontinuation								
Any	9.3		25.7		13.2		27.3	
Grade 3/4 in >1% of patients	Grade 3/4		Grade 3/4		Grade 3/4		Grade 3/4	
Fatigue	0.6		1.8		0.7		1.8	
Diarrhoea	0.6		1.8		0.2		1.8	
Hypertension	0		0		0		2.3	
Pulmonary embolism	0		0.6		1.6		1.4	
Asthenia	0		0.6		0.2		1.4	
Dehydration	0		1.2		0.2		0.7	
Rectal haemorrhage	0		1.2		0		0	
Neutropenic infection	1.2		0		0		0.5	

Abbreviations: AE, adverse event; e-CRF, electronic case report form; FOLFIRI, fluorouracil, leucovorin and irinotecan; PD, progressive disease; PT, preferred term; SOC, system organ class.
[a] Grades were determined according to NCI-CTCAE, version 3.0.
[b] Deaths within 30 days of last treatment dose.

bevacizumab plus chemotherapy (crossed over from first-line treatment) therapy was continued beyond progression [8].

As previously reported for this study and consistent with other clinical studies of aflibercept [4,9], aflibercept in combination with FOLFIRI was associated with a safety profile expected for the addition of an anti-VEGF agent to chemotherapy and no new toxicity signals were observed [4]. The present analysis suggests that this profile was not markedly impacted upon by prior treatment with bevacizumab.

In conclusion, the significant improvement in OS and PFS when aflibercept is added to FOLFIRI in the treatment of mCRC patients previously treated with an oxaliplatin-based regimen is robust, with consistency across demographic and baseline characteristics and stratification factors at randomisation. Efficacy was maintained, with a similar safety profile, irrespective of prior treatment with bevacizumab. Aflibercept has the potential to provide a new therapeutic option in the treatment of mCRC previously treated with an oxaliplatin regimen.

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Conflict of interest statement

J.T. and D.F. report consultant/advisory roles and honoraria from Sanofi. E.V.C. and R.L. report research funding from Sanofi. J.M. and C.A. report consultant/advisory roles for Sanofi. P.R. reports receiving honoraria, research funding and other remuneration from Sanofi. K.S.-L. and S.C. are employees of Sanofi. All other authors report no conflicts of interest.

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