Aflibercept plus FOLFIRI in Asian patients with pretreated metastatic colorectal cancer: a randomized Phase III study

Jin Li^{‡,1}, Ruihua Xu^{‡,2}, Shukui Qin³, Tianshu Liu⁴, Hongming Pan⁵, Jianming Xu⁶, Feng Bi⁷, Robert Lim⁸, Suzhan Zhang⁹, Yi Ba¹⁰, Yuxian Bai¹¹, Nanfeng Fan¹², Akihito Tsuji¹³, Kun-Huei Yeh¹⁴, Brigitte Ma¹⁵, Vivian Wei¹⁶, Dongmei Shi¹⁶, Emmanuelle Magherini¹⁷ & Lin Shen^{*,18}

¹Shanghai East Hospital, Tongji University School of Medicine, Shanghai, PR China

²Department of Medical Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, PR China

³People's Liberation Army (PLA) Cancer Center, 81 Military Hospital of China, Nanjing, PR China

⁴Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, PR China

⁵Department of Medical Oncology, Sir Run Run Shaw Hospital of Zhejiang University, Hangzhou, PR China

⁶Department of Oncology, 307 Hospital of the Chinese People's Liberation Army, Beijing, PR China

⁷Department of Medical Oncology, West China Hospital of Sichuan University, Chengdu, PR China

⁸Department of Haematology-Oncology, National University Cancer Institute, Singapore

⁹Cancer Institute, Second Affiliated Hospital of Zhejiang University, Hangzhou, PR China

¹⁰Department of Gastrointestinal Oncology, Tianjin Medical University Cancer Institute & Hospital, Tianjin, PR China

¹¹Cancer Hospital, Harbin Medical University, Harbin, PR China

¹²Department of Medical Oncology, Fujian Province Cancer Hospital, Fuzhou, PR China

¹³Department of Medical Oncology, Kobe City Medical Center General Hospital, Hyogo, Japan

¹⁴Department of Oncology, National Taiwan University Cancer Center, National Taiwan University Hospital, Taipei, Taiwan

¹⁵Department of Clinical Oncology, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, SAR

¹⁶Research and Development, Sanofi, Beijing, PR China

¹⁷Research and Development, Sanofi, Vitry-sur-Seine, France

¹⁸Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, PR China

*Author for correspondence: Tel.: +86 10 88196175; Fax: +86 10 88196561; linshenpku@163.com

‡Authors contributed equally

Aim: To investigate whether the benefit of combining aflibercept with 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) chemotherapy could be confirmed in patients from the Asia-Pacific region (ClinicalTrials.gov: NCT01661270). **Patients & methods:** Asian patients with oxaliplatin-pretreated metastatic colorectal cancer were randomized to receive aflibercept or placebo, followed by FOLFIRI. The primary end point was progression-free survival. **Results:** The intention-to-treat population comprised 332 patients. A clinical supply misallocation resulted in 198/332 (60%) patients receiving at least one cycle of misallocated treatment. Nevertheless, the addition of aflibercept to FOLFIRI was shown to improve progression-free survival (hazard ratio: 0.629; 95% CI: 0.488–0.812). Adverse events were in line with expectations. **Conclusion:** The beneficial treatment effect associated with the addition of aflibercept to FOLFIRI was confirmed in Asian patients with pretreated metastatic colorectal cancer.

Lay Abstract: The Phase III VELOUR study showed that the addition of aflibercept to FOLFIRI chemotherapy significantly improved outcome in a predominantly western population of patients with metastatic colorectal cancer (mCRC), who had failed prior oxaliplatin-containing therapy. This Phase III study confirmed the aflibercept treatment effect and benefit in patients from the Asia-Pacific region with oxaliplatin-pretreated mCRC.

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Keywords: aflibercept • Asia-Pacific • FOLFIRI • mCRC • oxaliplatin-pretreated

In patients with metastatic colorectal cancer (mCRC), meta-analyses have shown that the addition of antiangiogenic agents to first- and second-line chemotherapy regimens improves overall survival, progression-free survival (PFS) and antitumor response compared with chemotherapy alone [1,2]. Aflibercept (also known as ziv-aflibercept in the USA; VEGF Trap, AVE0005) is an antiangiogenic, soluble decoy receptor construct, which binds VEGFA, VEGFB and PGF [3,4].

The multinational, randomized, double-blind Phase III VELOUR study (ClinicalTrials.gov: NCT00561470) showed that the addition of aflibercept 4 mg/kg to infusional 5-fluorouracil (5-FU), folinic acid and irinotecan (FOLFIRI) significantly improved overall survival, PFS and response rate compared with placebo plus FOLFIRI in patients with mCRC who had failed one prior oxaliplatin-containing regimen [5]. Furthermore, the aflibercept PFS and overall survival benefits were maintained across prespecified subgroups defined by demographic and baseline characteristics, including in patients assigned at randomization to prior-bevacizumab-treated and bevacizumab-naïve stratification subgroups [6].

The majority of patients enrolled in the VELOUR study (1071 [87%] of 1226) were of Caucasian ethnicity, with only 86 (7%) of 1226 reported as being of Asian/oriental ethnicity. Due to the ethnicity distribution in this registrational trial, the aflibercept benefit in patients from the Asia-Pacific region needed to be further documented. A Phase I study in Japanese patients found that the combination of aflibercept plus FOLFIRI was well tolerated, demonstrated favorable pharmacokinetic characteristics and showed preliminary efficacy [7]. The recommended aflibercept dose for this combination in Japanese patients was 4 mg/kg administered once every 2 weeks (q2w). The current bridging study (ClinicalTrials.gov identifier: NCT01661270) was designed with the aim of confirming the efficacy and safety of the approved regimen of aflibercept 4 mg/kg q2w plus FOLFIRI in patients from the Asia-Pacific region (especially Chinese patients) with mCRC who had received a prior oxaliplatin-containing regimen.

Patients & methods

Study design & patients

This was a prospective, multicenter, multinational, randomized, double-blind, parallel-group, Phase III study carried out at 37 active sites in mainland China, Hong Kong, Japan, Singapore and Taiwan. Patients aged 18 years or older with histologically or cytologically proven adenocarcinoma of the colon or rectum that was metastatic and not amenable to potentially curative treatment (i.e., inoperable) were eligible. Disease had to be measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 [8], and patients should have received one and only one prior chemotherapy regimen for metastatic disease. This prior chemotherapy had to have been an oxaliplatin-containing regimen and patients had to have progressed during or following the last administration of this regimen. Patients who relapsed rapidly, within 6 months of completion of oxaliplatin-based adjuvant chemotherapy, were also eligible.

Key exclusion criteria included: prior therapy with irinotecan; Eastern Cooperative Oncology Group (ECOG) performance status >1 ; a history of brain metastases, uncontrolled spinal cord compression or carcinomatous meningitis or new evidence of brain or leptomeningeal disease; at the time of randomization, less than 28 days elapsed from prior radiotherapy, prior surgery (<42 days for major surgery) or prior chemotherapy; any severe acute or chronic medical condition that might have impaired the ability of the patient to participate in the study; unresolved toxicity of grade more than 1 from prior anticancer therapy; history of prior malignancy (excluding adequately treated basal cell or squamous cell skin cancer, carcinoma *in situ* of the cervix or any other cancer from which the patient had been disease free for >5 years); participation in another clinical trial with an investigational drug and any concurrent treatment with any investigational drug within 30 days prior to randomization. Patients were also excluded if they had a urine protein–creatinine ratio greater than 1 on morning spot urinalysis or proteinuria more than 500 mg/24 h; serum creatinine more than $1.5 \times$ upper normal limit (ULN); a history of uncontrolled hypertension; if they were on anticoagulant therapy with an unstable dose of warfarin and/or having an out-of-therapeutic range (international normalized ratio >3) within 4 weeks prior to randomization; if they had evidence of clinically significant bleeding diathesis including hemoptysis, underlying coagulopathy or nonhealing wound; if they had a known dihydropyrimidine dehydrogenase deficiency; inadequate bone marrow function (hemoglobin <9.0 g/dl; absolute neutrophil count $<1.5 \times 10^9$ /l; platelet count $<100 \times 10^9$ /l); inadequate

Figure 1. Study profile.

liver function (total bilirubin $>1.5 \times \text{ULN}$; or transaminases and alkaline phosphatase $>3 \times \text{ULN}$, unless liver metastasis were present, $5 \times \text{ULN}$ in that case).

The study was conducted in accordance with the recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments. The protocol was approved by the ethics committees of all participating centers. All patients provided written informed consent prior to the initiation of any study-related procedure.

Randomization & masking

Patients were randomly assigned (2:1), to aflibercept plus FOLFIRI or placebo plus FOLFIRI, centrally via an interactive voice response system (IVRS) using a permuted-block randomization, stratified according to baseline

Table 1. Distribution of patients with misallocated treatment cycles.		
Percentage of cycles with impacted kits [†]	Aflibercept + FOLFIRI (n = 122)	Placebo + FOLFIRI (n = 76)
0–<20%	37 (30)	13 (17)
20–<40%	56 (46)	29 (38)
40–<60%	21 (17)	7 (9)
60–<80%	8 (7)	11 (14)
80–<100%	0	6 (8)
100%	0	10 (13)

Data are number (%).

[†]Calculated as number of cycles with impacted kits/total number of cycles with aflibercept/placebo for each patient.

FOLFIRI: 5-Fluorouracil, folinic acid and irinotecan.

ECOG performance status (0 vs 1) and prior bevacizumab (yes vs no). It was anticipated that patients who were treated in the experimental arm would receive more anticancer benefit when compared with those patients treated in the control arm and the 2:1 randomization ratio was chosen in order to reduce patient exposure to potentially inferior treatment, and to gain more safety data for the experimental arm. The sponsor, patients, investigators and anybody responsible for study conduct and data analyses were blinded to treatment assignment.

Procedures

Treatment cycles were 2 weeks. Patients received either aflibercept, 4 mg/kg, administered as an intravenous (iv.) infusion over 1 h on day 1 or placebo; both immediately followed by FOLFIRI chemotherapy comprising: irinotecan 180 mg/m² iv. infusion over 90 min and folinic acid 400 mg/m² (racemic) iv. infusion over 2 h, at the same time; followed by 5-FU as a 400 mg/m² iv. bolus given over 2–4 min, then a 2400 mg/m² continuous iv. infusion over 46 h. Treatment was continued until disease progression or death, the occurrence of unacceptable toxicity, patient refusal or investigator decision. Dose modifications of aflibercept/placebo and of FOLFIRI (irinotecan, 5-FU) were permitted according to protocol-defined criteria.

A data monitoring committee (DMC) independent from the sponsor and from the investigators was responsible for reviewing unblinded accumulated safety data and to subsequently give recommendations on study conduct. Unblinding of the study data was performed by an external statistician who provided the data to DMC members before each of their meetings. Imaging assessment was performed at baseline, and then every 6 weeks until disease progression, and whenever disease progression was clinically suspected. Adverse events were classified according to the Medical Dictionary for Regulatory Activities Version 17.1 and were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

During the study treatment period, while preparing for a DMC meeting, the external statistician, who was independent of the sponsor, the DMC and the investigators, identified a clinical supply misallocation (patients randomized to placebo receiving aflibercept or the reverse, for at least one treatment cycle). It was found that this was the consequence of miscoding of some kits of blinded study medication. In relation to actual treatment received, this clinical supply misallocation resulted in three different populations: patients who had received placebo plus FOLFIRI only, patients who had received aflibercept plus FOLFIRI only and patients who had received a mix of placebo plus FOLFIRI and aflibercept plus FOLFIRI. In order to optimize the management of the patients who were impacted by this issue, the misallocated kits at each site were quarantined, and then replaced by correctly coded kits. All patients who received at least one cycle of misallocated treatment had to provide new consent to continue on-study after new clinical supplies were provided to sites.

Outcomes

The primary end point was PFS, defined as the time interval from the date of randomization to the time of occurrence of radiological tumor progression, as assessed by CT scan and/or MRI, or death due to any cause. Patients without a progression event by the cut-off date were censored at the date of their last protocol-driven tumor assessment. Secondary end points included objective response rate, overall survival and safety. Antitumor response was assessed according to RECIST 1.0 [8]. All tumor assessments for response and disease progression were based upon independent radiological review committee assessments. Overall survival was defined as the time interval from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive.

Table 2. Baseline characteristics: intention-to-treat population.

Characteristic	Aflibercept + FOLFIRI (n = 223)	Placebo + FOLFIRI (n = 109)
Age, years:		
– Median (range)	56 (26–77)	55 (27–80)
Age group, years:		
– <65	177 (79)	92 (84)
– ≥65 to <75	42 (19)	15 (14)
– ≥75	4 (2)	2 (2)
Weight, kg:		
– Median (range)	62.0 (33.0–99.0)	62.0 (40.0–119.4)
Sex:		
– Male	128 (57)	63 (58)
– Female	95 (43)	46 (42)
ECOG performance status: [†]		
– 0	89 (40)	42 (39)
– 1	134 (60)	67 (61)
Primary tumor site:		
– Colon	120 (54)	59 (54)
– Rectosigmoid	5 (2)	2 (2)
– Rectum	96 (43)	48 (44)
– Other	2 (0.9)	0
– Cecum	1 (0.4)	0
– Synchronous primary, ascending colon and rectum	1 (0.4)	0
Number of organs with metastases:		
– 0	1 (0.4)	0
– 1	91 (41)	38 (35)
– ≥1	131 (59)	71 (65)
Organs with metastases: [‡]		
– Liver	150 (67)	74 (68)
– Lung	112 (50)	68 (62)
– Lymph nodes	80 (36)	33 (30)
Extent of metastatic disease:		
– Liver and other organs, or no liver metastases	168 (75)	93 (85)
– Liver metastases only	55 (25)	16 (15)
Prior chemotherapy:		
– Neoadjuvant/adjuvant only	36 (16)	19 (17)
– Advanced only	152 (68)	71 (65)
– Neoadjuvant/adjuvant + advanced	35 (16)	19 (17)
Prior bevacizumab: [†]		
– No	187 (84)	93 (85)
– Yes	36 (16)	16 (15)

Data are n (%) unless otherwise stated.

[†]According to interactive voice response system assignment at randomization.

[‡]Only organs reported in more than 10% of patients are presented.

ECOG: Eastern Cooperative Oncology Group; FOLFIRI: 5-Fluorouracil, folinic acid and irinotecan.

Sample size calculation

Assuming that the hazard ratio (HR) for disease progression or death between aflibercept and placebo groups was 0.8, it was calculated that a total of 249 events would provide an 80% probability of observing at least a 10% reduction in the risk of progression or death (HR of 0.90) when comparing aflibercept with placebo. A 24-month enrollment period and a minimum of 6 months of follow-up were envisaged. Assuming the median time to progression or death would be approximately 4 months in the placebo group, and 5 months in the aflibercept group (for an HR of 0.8), it was anticipated that enrollment of approximately 330 patients would be needed (2:1

Table 3. Exposure to study treatment.

Drug exposure	Aflibercept + FOLFIRI only (n = 111)	Mixed administration [†] (n = 188)	Placebo + FOLFIRI only (n = 33)
Aflibercept/placebo			
Cycles per patient, n:			
– Median	4	9	5
– Range	1–21	2–30	1–16
Duration of exposure, weeks:			
– Median	8.14	22.86	13.00
– Range	2.0–48.9	3.9–97.4	2.0–48.9
Actual dose intensity, mg/kg per week:			
– Median	1.67	0.93	1.79
– Range	0.1–2.0	0.1–1.8	0.9–2.0
Relative dose intensity, %:			
– Median	84	47	89
– Range	0–100	10–90	50–100
Irinotecan			
Cycles per patient, n:			
– Median	5	10	5
– Range	1–44	2–36	1–16
Duration of exposure, weeks:			
– Median	12.43	23.71	13.00
– Range	2.0–119.4	4.0–97.4	2.0–48.9
Actual dose intensity, mg/m ² per week:			
– Median	74.76	71.95	77.80
– Range	49.0–90.3	31.9–91.9	51.4–90.0
Relative dose intensity, %:			
– Median	83	80	86
– Range	50–100	40–100	60–100
5-Fluorouracil			
Cycles per patient, n:			
– Median	5	10	5
– Range	1–44	2–36	1–16
Duration of exposure, weeks:			
– Median	12.43	23.71	13.00
– Range	2.0–119.4	4.0–97.4	2.0–48.9
Actual dose intensity, mg/m ² per week:			
– Median	1183.36	1107.29	1221.74
– Range	98.1–1404.2	492.3–1430.5	796.2–1401.5
Relative dose intensity, %:			
– Median	85	79	87
– Range	10–100	40–100	60–100

[†]Mixed administration group contains patients with at least one dose of both aflibercept and placebo. For calculation purposes (aflibercept/placebo exposure), the dose of placebo for patients in this group was considered to be 0 mg/kg and the denominator for relative dose intensity was 2 mg/kg per week.
FOLFIRI: 5-Fluorouracil, folinic acid and irinotecan.

aflibercept:placebo) to reach the required number of events. The cut-off date for the PFS analysis was to be the date when at least the required 249 events had been observed and confirmed by the independent radiological review committee.

Statistical analysis

No formal statistical hypothesis testing was planned. The primary population for the evaluation of efficacy was to be the intention-to-treat (ITT) population, which included all randomized patients, based on the treatment assigned

Table 4. Efficacy: intention-to-treat population.

Parameter	Aflibercept + FOLFIRI (n = 223)	Placebo + FOLFIRI (n = 109)
Progression-free survival: [†]		
– Events, n (%)	178 (80)	97 (89)
– Median, months	6.93	5.59
– 95% CI	6.045–7.655	4.632–6.111
– Hazard ratio [‡]	0.629	
– 95% CI	0.488–0.812	
Overall survival: [§]		
– Deaths, n (%)	154 (69)	82 (75)
– Median, months	14.59	11.93
– 95% CI	13.175–16.460	10.086–14.292
– Hazard ratio [‡]	0.794	
– 95% CI	0.606–1.042	
Best overall response, n (%):		
– Complete response	0	0
– Partial response	41 (18)	4 (4)
– Stable disease	133 (60)	78 (72)
– Progressive disease	33 (15)	18 (17)
– Not evaluable	9 (4)	4 (4)
– Missing	7 (3)	5 (5)
Objective response rate (CR + PR), n (%):		
– 95% CI	41 (18) 13.3–23.5	4 (4) NC

[†]Analysis cut-off date, 20 October 2014.[‡]Stratified on Eastern Cooperative Oncology Group performance status (0 vs 1) and prior bevacizumab (yes vs no) according to interactive voice response system assignment at randomization.[§]Analysis cut-off date, 19 March 2015.

CR: Complete response; FOLFIRI: 5-Fluorouracil, folinic acid and irinotecan; NC: Not calculated; PR: Partial response.

Table 5. Sensitivity analyses.

Analysis	Parameter	Number of patients	Aflibercept + FOLFIRI median, months (95% CI)	Placebo + FOLFIRI median, months (95% CI)	Hazard ratio (95% CI)
Primary	PFS in intention-to-treat population	332	6.93 (6.045–7.655)	5.59 (4.632–6.111)	0.629 (0.488–0.812)
Sensitivity 1	PFS in nonmisallocated patients	134	6.05 (4.961–8.148)	5.36 (3.778–6.702)	0.665 (0.421–1.05)
Sensitivity 2	PFS censor at first misallocated administration	332	7.36 (5.585–8.279)	5.82 (4.205–6.965)	0.652 (0.419–1.016)
Sensitivity 3	PFS by actual treatment group in patients with only placebo or aflibercept	144	5.59 (4.665–7.655)	5.36 (3.778–6.702)	0.716 (0.457–1.123)
Sensitivity 4	PFS censor late progression and new anticancer therapy	332	7.00 (6.341–8.246)	5.59 (4.172–5.979)	0.61 (0.453–0.82)
	PFS censor late progression and new anticancer therapy in nonmisallocated patients	134	7.13 (5.290–8.279)	4.17 (3.023–6.899)	0.631 (0.349–1.141)
Sensitivity 5	PFS using investigator assessments	332	5.75 (5.552–6.965)	5.19 (4.205–5.782)	0.734 (0.577–0.934)
	PFS using investigator assessments in nonmisallocated patients	134	4.99 (4.172–5.749)	3.84 (2.727–5.520)	0.702 (0.462–1.067)

Cut-off date, 20 October 2014.

FOLFIRI: 5-Fluorouracil, folinic acid and irinotecan; PFS: Progression-free survival.

Figure 2. Kaplan–Meier plots of progression-free and overall survival. For progression-free survival (A & B) the analysis cut-off date was 20 October 2014; for overall survival (C & D), the analysis cut-off date was 19 March 2015. Panels A & C show the intention-to-treat population and panels B & D show the nonmisallocated patient groups.

[†]Stratified by Eastern Cooperative Oncology Group performance status (0 vs 1) and prior bevacizumab (yes vs no) according to interactive voice response system assignment.

by IVRS. Safety was assessed in the population of patients who received at least one dose of study medication and was analyzed according to actual treatment received; in other words, in three treatment groups: aflibercept plus FOLFIRI only, placebo plus FOLFIRI only and mixed administration.

HRs and corresponding 95% CIs for PFS and overall survival were estimated using Cox proportional hazard models adjusted by the stratification factors specified at the time of randomization; median survivals, probabilities of survival over time and associated 95% CIs were estimated using the Kaplan–Meier method. Response rates were summarized using descriptive statistics and 95% CIs, using normal approximation.

Following the discovery of the treatment misallocation, the primary population for the efficacy analysis remained the ITT population to maintain the randomization scheme. Considering that the misallocation occurred due to an operational miscoding that was independent from any study findings, and given that this was a placebo-controlled study, the analysis based on the ITT population was deemed to be conservative. Meanwhile, three additional sensitivity analyses for efficacy were also specified in a statistical analysis plan (SAP) amendment in relation to the treatment misallocation issue. In total, five sensitivity analyses of PFS, which were prespecified in the final SAP, were conducted. These analyses further examined the aflibercept treatment effect in different subgroups of

Figure 3. Progression-free survival sensitivity analyses in subgroups of the intention-to-treat population and the Chinese subpopulation. For definitions of the sensitivity analysis populations, see Table 5.

HR: Hazard ratio.

patients, including in the nonmisallocated patient population. It was prespecified that all sensitivity analyses would be repeated in the Chinese subpopulation.

Statistical analyses were carried out using SAS version 9.2.

Results

Patients

Between 27 July 2012 and 19 March 2014, 332 patients were enrolled and randomly assigned to treatment groups; 223 to aflibercept plus FOLFIRI and 109 to placebo plus FOLFIRI. All patients were classified as of Asian/oriental ethnicity, 191 (58%) were male and the median age was 56 years. Most patients (270 [81%] of 332) were enrolled from mainland China. As a result of the clinical supply misallocation, 198 (60%) of 332 patients had received at least one cycle of misallocated treatment (aflibercept or placebo, all still received FOLFIRI), 122 of 223 in the aflibercept plus FOLFIRI group and 76 of 109 in the placebo plus FOLFIRI group (Figure 1). After the discovery of this issue, in April 2014, the DMC subsequently reviewed unblinded safety data and recommended that the study could continue since no major safety concern was apparent for treated and ongoing patients. In addition, all patients were receiving FOLFIRI, a recognized treatment option in this setting, and study recruitment was complete. Investigator sites, ethics committees and relevant health authorities were informed about the clinical supply misallocation and the actions taken in relation to patient safety, reconsenting and protocol and SAP amendments.

Only two (0.6%) of 332 patients received open-label study treatment, as allowed for by protocol amendment, following the discovery of the misallocation issue. These two patients were included in the final analysis. In the

Figure 4. Forest plot of progression-free survival, based on tumor assessment by the independent radiological review committee, in subgroups defined by baseline characteristics (analysis cut-off date, 20 October 2014).
[†]According to interactive voice response system assignment at randomization.
ECOG PS: Eastern Cooperative Oncology Group performance status; HR: Hazard ratio.

primary PFS analysis, they were both censored at their last protocol-driven tumor assessment before the code was broken.

All randomized patients received at least one dose of study treatment and were therefore included in the safety population. As detailed in Figure 1, ten of the 198 patients who received misallocated treatment and who were originally randomized to placebo plus FOLFIRI received aflibercept plus FOLFIRI from cycle 1 until the end of treatment. These ten patients were classified into the aflibercept plus FOLFIRI only group of the safety population (n = 111), while the other 188 patients were included in a mixed administration group for the safety analysis. The distribution of patients with misallocated treatment cycles is detailed in Table 1. The third subgroup of the safety population comprised those patients who received only placebo plus FOLFIRI (n = 33).

The cut-off date for analysis of the primary efficacy end point of PFS was 20 October 2014. By this date, there were 275 PFS events. The cut-off date for the overall survival analysis was 19 March 2015, corresponding to the date 1 year after the last patient was enrolled. By this date, there were 236 deaths. The median follow-up time for the ITT population was 22.2 months and for the nonmisallocated treatment population, 23.9 months.

Baseline characteristics were generally balanced between ITT population randomization treatment groups (Table 2).

Exposure

Treatment exposure is summarized in Table 3. Patients in the aflibercept plus FOLFIRI only group received a median of five cycles of treatment (range: 1–44), as did those in the placebo plus FOLFIRI only group (range: 1–16), while those in the mixed administration group received a median of ten cycles of treatment (range: 2–36).

Table 6. Summary of most frequent treatment-emergent adverse events.[†]

Adverse event	Aflibercept + FOLFIRI only (n = 111)		Mixed administration (n = 188)		Placebo + FOLFIRI only (n = 33)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any	111 (100)	84 (76)	188 (100)	153 (81)	32 (97)	18 (55)
Neutropenia	69 (62)	32 (29)	136 (72)	95 (51)	22 (67)	9 (27)
Diarrhea	61 (55)	19 (17)	122 (65)	30 (16)	14 (42)	3 (9)
Nausea	61 (55)	4 (4)	110 (59)	6 (3)	22 (67)	2 (6)
Leukopenia	59 (53)	20 (18)	84 (45)	31 (16)	20 (61)	9 (27)
Vomiting	56 (50)	3 (3)	107 (57)	15 (8)	22 (67)	3 (9)
Hypertension	43 (39)	20 (18)	65 (35)	28 (15)	1 (3)	0
Decreased appetite	42 (38)	4 (4)	90 (48)	6 (3)	15 (45)	2 (6)
Fatigue	37 (33)	8 (7)	85 (45)	13 (7)	9 (27)	2 (6)
Epistaxis	30 (27)	1 (0.9)	38 (20)	0	0	0
Stomatitis	27 (24)	12 (11)	62 (33)	19 (10)	5 (15)	1 (3)
Thrombocytopenia	23 (21)	8 (7)	24 (13)	9 (5)	4 (12)	0
Proteinuria	20 (18)	10 (9)	37 (20)	8 (4)	0	0
Abdominal pain	19 (17)	2 (2)	43 (23)	0	4 (12)	0
Hypokalemia	15 (14)	3 (3)	11 (6)	3 (2)	0	0
Constipation	14 (13)	0	35 (19)	2 (1)	8 (24)	0
Weight decreased	9 (8)	0	27 (14)	1 (0.5)	1 (3)	0
Alopecia	5 (5)	0	43 (23)	0	2 (6)	0

Data are n (%).

[†]Adverse events with an incidence ≥20% in any treatment group or with a ≥10% difference in incidence between placebo and either the aflibercept or mixed administration group: safety population.

FOLFIRI: 5-Fluorouracil, folinic acid and irinotecan.

Efficacy

In the primary ITT analysis, the addition of aflibercept to FOLFIRI was associated with longer PFS compared with placebo plus FOLFIRI (median: 6.93 months; 95% CI: 6.045–7.655 vs 5.59 months; 95% CI: 4.632–6.111, respectively; stratified HR: 0.629; 95% CI: 0.488–0.812; [Table 4](#) & [Figure 2A](#)). In addition, all sensitivity analyses of PFS showed a consistent treatment effect supporting the results on the primary efficacy end point ([Table 5](#) & [Figure 3](#)). In particular, in patients who received treatment in line with allocation at randomization (nonmisallocated treatment groups), PFS was longer in the aflibercept plus FOLFIRI group compared with the placebo plus FOLFIRI group (median: 6.05 vs 5.36 months, respectively; stratified HR: 0.665; 95% CI: 0.421–1.05; [Figure 2B](#)). Similar outcomes were apparent in the Chinese subpopulations ([Figure 3](#)).

A PFS treatment effect in favor of aflibercept over placebo was also generally observed across subgroups of the ITT population defined by stratification factors or other prespecified baseline characteristics ([Figure 4](#)). In particular, patients in both the prior bevacizumab and no prior bevacizumab subgroups, defined as per IVRS randomization, appeared to benefit from the addition of aflibercept to FOLFIRI.

Overall survival was longer in the aflibercept plus FOLFIRI group of the ITT population compared with the placebo plus FOLFIRI group (adjusted HR: 0.794; 95% CI: 0.606–1.042; [Table 4](#) & [Figure 2C](#)). A sensitivity analysis of the 134 patients of the ITT population who received nonmisallocated treatment also showed a survival advantage for aflibercept over placebo (adjusted HR: 0.785; 95% CI: 0.494–1.248; [Figure 2D](#)). The objective response rate was markedly higher in the aflibercept plus FOLFIRI group of the ITT population compared with the placebo plus FOLFIRI group (41 [18%] of 223 vs four [4%] of 109 patients, respectively; [Table 4](#)).

Safety

Safety was analyzed in three patient groups, those who received aflibercept plus FOLFIRI only, those who received mixed administration of aflibercept plus FOLFIRI and placebo plus FOLFIRI, and those who received placebo plus FOLFIRI only. Grade 3 or higher treatment-emergent adverse events (TEAEs) were more frequently reported in the aflibercept plus FOLFIRI only group as well as the mixed administration group compared with the placebo plus FOLFIRI only group. The most common grade 3 or higher TEAE was neutropenia, reported for 32 (29%) of 111 patients in the aflibercept plus FOLFIRI only group, 95 (51%) of 188 in the mixed administration group

and nine (27%) of 33 patients in the placebo plus FOLFIRI only group; diarrhea was reported for 19 (17%) of 111, 30 (16%) of 188 and three (9%) of 33 patients, respectively. The most frequently reported TEAEs (all grades and grade 3 or higher) according to preferred terms and those with a 10% or greater difference in incidence between placebo and either the aflibercept or mixed administration group are summarized in Table 6. TEAEs with the most pronounced differences in incidence between treatment groups (any grade: excess of 20% or more in the aflibercept plus FOLFIRI only group or mixed administration group vs the placebo plus FOLFIRI only group) were hypertension, proteinuria and epistaxis. Grade 3 hypertension was reported for 20 (18%) of 111 patients in the aflibercept plus FOLFIRI only group, 28 (15%) of 188 in the mixed administration group and none of 33 in the placebo plus FOLFIRI only group; grade 3 or higher proteinuria was reported for ten (9%) of 111, eight (4%) of 188 and none of 33 patients, respectively. Only one patient had a grade 3 epistaxis (aflibercept plus FOLFIRI only group).

The incidence of serious treatment-related TEAEs (all grades) was higher in the aflibercept plus FOLFIRI only group (22 [20%] of 111 patients) compared with the mixed administration group (25 [13%] of 188 patients) and the placebo plus FOLFIRI only group (five [15%] of 33 patients).

A higher percentage of patients in the aflibercept plus FOLFIRI only group (30 [27%] of 111 patients) permanently discontinued treatment due to a TEAE compared with the mixed administration group (37 [20%] of 188) or the placebo plus FOLFIRI only group (six [18%] of 33). The incidence of death due to a TEAE occurring during the study treatment period (i.e., within 30 days of the last study drug administration) was similar across treatment groups, including: two (2%) of 111 patients in the aflibercept plus FOLFIRI only group; four (2%) of 188 patients in the mixed administration group and one (3%) of 33 patients in the placebo plus FOLFIRI only group. All but two (mixed administration group) of these seven deaths were judged by the investigator to be related to the study treatment.

Discussion

In line with the global Phase III VELOUR study [5], the current study met its primary objective in demonstrating a PFS benefit associated with the addition of aflibercept to FOLFIRI in patients from the Asia-Pacific region with mCRC who had received one prior oxaliplatin-containing regimen. This benefit was apparent despite a clinical supply misallocation, which resulted in 198 patients receiving mixed treatment administration, one possible effect of which might have been to diminish the apparent magnitude of the aflibercept treatment benefit between the ITT experimental versus control group. A series of sensitivity analyses were, therefore, carried out to explore PFS in different subgroups, including in patients with nonmisallocated treatment. These analyses showed a similar magnitude of benefit conferred by the addition of aflibercept to FOLFIRI across all patient subgroups.

With the exception of the different ethnicity profile, the baseline characteristics of patients from the Asia-Pacific region in the current study are broadly in line with those of the mainly Caucasian patients in the VELOUR study [5]. Both aflibercept Phase III studies (VELOUR and the current study) carried out in patients with mCRC who had received one prior oxaliplatin-containing regimen have therefore confirmed the efficacy of aflibercept over placebo, when combined with FOLFIRI. In addition, subgroup analyses in both studies suggested an aflibercept treatment benefit in patients who had received prior bevacizumab [5,6].

The longer a patient stayed in the study, and therefore the more cycles of treatment they received, the higher the chance that they would have received one or more misallocated kits, with the sequencing of misallocated kits, if more than one was administered, being variable. Therefore, the analysis based on patients who did not receive misallocated treatment should be interpreted with caution in view of possible selection bias. Although the chance of receiving misallocated treatment may have differed between patients with different exposure times, given a group of patients with similar exposure durations and similar enrollment times, the probabilities of receiving misallocated treatment would have been the same. In short, conditioning on exposure duration and enrollment time, misallocation would be completely random. Of particular importance, it would have been independent of initial treatment randomization.

The generally higher exposure to treatment as a result of the longer treatment times in the mixed administration group (median of ten cycles) compared with the aflibercept plus FOLFIRI and placebo plus FOLFIRI groups (medians of five cycles in both) complicates the interpretation of the safety data. In particular, this higher exposure could explain the higher incidence of grade 3 or higher neutropenia, a side effect associated with FOLFIRI [9,10], in the mixed administration group compared with the other two groups. As expected, certain adverse events commonly associated with anti-VEGF agents [11], including: hypertension, hemorrhage (epistaxis) and proteinuria

were more frequently reported in the aflibercept plus FOLFIRI only and mixed administration groups compared with the placebo plus FOLFIRI only group. In addition, the incidence of diarrhea, a further side effect associated with FOLFIRI [9,12], was increased in the aflibercept plus FOLFIRI only group and mixed administration group, compared with the placebo plus FOLFIRI only group. Overall, the safety profile of aflibercept plus FOLFIRI in this Asia-Pacific patient population was in line with the established safety profile of this regimen.

Conclusion & future perspective

Despite the treatment misallocation issue, the current study demonstrated that the addition of aflibercept to FOLFIRI chemotherapy improved PFS, overall survival and response rate in patients from the Asia-Pacific region with oxaliplatin-pretreated mCRC. No new safety concerns were identified in this patient population. Together, these data suggest a favorable benefit–risk ratio for the aflibercept plus FOLFIRI combination in this setting.

Summary points

- In patients with metastatic colorectal cancer (mCRC), the addition of antiangiogenic agents to first- and second-line chemotherapy regimens has been shown to improve clinical outcome.
- The pivotal Phase III VELOUR study showed in a population of predominantly Caucasian patients that the addition of aflibercept to 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) significantly improved overall survival, progression-free survival and response rate compared with placebo plus FOLFIRI in patients with mCRC who had failed one prior oxaliplatin-containing regimen.
- This randomized Phase III bridging study, carried out at 37 active sites in mainland China, Hong Kong, Japan, Singapore and Taiwan, aimed to confirm the efficacy and safety of aflibercept plus FOLFIRI in patients from the Asia-Pacific region with mCRC who had received one prior oxaliplatin-containing regimen.
- The intention-to-treat (ITT) population comprised 332 Asian patients, 223 assigned to aflibercept plus FOLFIRI and 109 to placebo plus FOLFIRI. Due to a clinical supply misallocation, 198 (60%) of 332 patients received at least one cycle of misallocated treatment (aflibercept or placebo; all still received FOLFIRI) during the course of the trial.
- Efficacy was analyzed both in ITT and nonmisallocated treatment groups; safety was analyzed according to treatment received: in other words, in three treatment groups: aflibercept plus FOLFIRI only, placebo plus FOLFIRI only and mixed administration.
- In the primary ITT analysis, the aflibercept plus FOLFIRI regimen was associated with longer progression-free survival compared with placebo plus FOLFIRI (hazard ratio: 0.629; 95% CI: 0.488–0.812). A similar aflibercept treatment effect was seen in the subset of 134 patients who received all treatment cycles as per allocation at randomization (hazard ratio: 0.665; 95% CI: 0.421–1.05).
- Overall survival and antitumor response analyses also showed an aflibercept treatment benefit.
- Overall, the safety profile of aflibercept plus FOLFIRI in this Asia-Pacific patient population was in line with the established safety profile of this regimen.
- The current study confirmed a beneficial treatment effect associated with the addition of aflibercept to FOLFIRI in Asian patients with oxaliplatin-pretreated mCRC, despite the treatment misallocation.

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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