

## RESEARCH ARTICLE

# Safety and Management of Toxicity Related to Afibercept in Combination with Fluorouracil, Leucovorin and Irinotecan in Malaysian Patients with Metastatic Colorectal Cancer

Mastura Md Yusof<sup>1\*</sup>, Nik MA Abdullah<sup>2</sup>, MSN Mohd Sharial<sup>3</sup>, Adel Zaatar<sup>4</sup>

## Abstract

**Background:** Between October 2012 and February 2015, 25 patients with metastatic colorectal cancer (mCRC) (mean age, 57.0 ± 12.1 years) were granted access to afibercept via the Afibercept Named Patient Program at four centers. **Materials and Methods:** Here we reported the initial experience of afibercept / FOLFIRI in combination. We evaluated treatment-related adverse events (AEs), progression-free survival (PFS) and overall survival (OS). **Results:** The majority of the patients experienced gastrointestinal toxicity (grade 1-2), with diarrhea (52%), mucositis (52%), and nausea/vomiting (20%) being largely observed. Neutropenia (16%) and febrile neutropenia (8%) were common grade 3-4 hematological events. Afibercept-related toxicity was managed as per practice guidelines. No grade 5 event was reported. Median PFS was 6.12 months (95% CI, 4.80-7.20) and OS was 12 months (95% CI, 9.80-14.18). The partial response (PR), stable disease (SD), and progressive disease (PD) rates were 25% (95% CI: 23.4-27.0), 37.5% (95% CI: 31.6-43.3), and 37.5% (95% CI: 22.5-52.5), respectively. **Conclusions:** Afibercept/FOLFIRI can be administered safely in a second line setting to Malaysian patients with mCRC, as the AEs experienced were generally reversible and manageable. The safety and efficacy outcomes were consistent with those observed in Western populations.

**Keywords:** Afibercept - metastatic colorectal cancer - FOLFIRI - gastrointestinal toxicity - safety - Malaysia

*Asian Pac J Cancer Prev*, 17 (3), 973-978

## Introduction

Colorectal cancer (CRC) has shown a rising trend in many Asia-Pacific countries, and is the second most common cancer among the Malaysian population (12.3%) with slightly higher rates reported in men (age standardized rate [ASR] 13.4 per 100,000) than women (ASR 10.2 per 100,000 population) (Malaysia Cancer Statistics., 2007; Pourhoseingholi., 2012; Norwati et al., 2014). Compared with Western countries, a lower rate is observed in Asian, African, and South American countries; however, incidence rate is rapidly increasing which might be attributable to increasing age, known hereditary conditions, environmental and lifestyle factors (Pourhoseingholi., 2012; Lim., 2014). Moreover, lack of awareness which might be the potential reason for most of the cases being diagnosed at later stage (Lim., 2014). According to the National Cancer Registry Report of Malaysia (2007), nearly 32% of the patients were diagnosed with advanced stage CRC, and up to 50% eventually developed metastases following their curative treatment (Malaysia Cancer Statistics., 2007; Pourhoseingholi., 2012; Norwati et al., 2014; Lim., 2014).

Advances in the management of CRC in the last two

decades have predominantly involved the development of therapies targeting known mutations [Kirsten rat sarcoma (KRAS) or BRAF, Neuroblastoma RAS (NRAS)] with the aim to deliver maximum benefit to patients. (Muhammad et al., 2013; Wong et al., 2014; Do et al., 2015). Antiangiogenic therapies, bevacizumab, regorafenib, and afibercept (known as ziv-afibercept in the United States), have been approved which are known to inhibit pathway for angiogenic signaling, a vital process in cancer growth, survival, and metastases (Van Cutsem et al., 2012; Jitawatanarat and Wee, 2013; Patel and Sun., 2014; Lee and Chu., 2014; Chiron et al., 2015; Garcia-Alfonso et al., 2015).

Afibercept has a higher vascular endothelial growth factor (VEGF)-A binding affinity (approximately 100 fold-higher) than bevacizumab. Moreover, placental growth factor (PlGF) levels increases with bevacizumab exposure and the ability of afibercept to additionally target PlGF-1,-2 may be of potential significant interest in the treatment of angiogenesis (Papadopoulos et al., 2012; Tang and Moore, 2013; Chiron et al., 2014). Nonetheless, afibercept/irinotecan with fluorouracil combination (FOLFIRI) resulted in a consistent trend of increased overall survival (OS) and progression free

<sup>1</sup>Pantai Cancer Institute, Pantai Hospital Kuala Lumpur, <sup>2</sup>Department of Oncology, Pusat Perubatan Universiti Kebangsaan Malaysia, Kuala Lumpur, <sup>3</sup>Department of Oncology, Pantai Hospital Ipoh, Ipoh, Perak, <sup>4</sup>Department of Oncology, Gleneagles Medical Center, Oncology Clinic, Penang, Malaysia \*For correspondence: drmasturamy@gmail.com

survival (PFS), regardless of prior bevacizumab use (Van Cutsem et al., 2012; Tang and Moore, 2013). On the contrary, not many studies are reported for bevacizumab/FOLFIRI combination. Regorafenib is another promising anti-angiogenic agent that has demonstrated significant survival benefit as a single-agent as third line therapy in patients with metastatic CRC (mCRC) refractory to standard therapies. (Jitawatanarat and Wee, 2012; Grothey et al., 2013). Given the expanding armamentarium of agents for mCRC, deciding the best treatment strategy remains challenging. In 2012, the investigators of phase III VELOUR evaluated the efficacy of the FOLFIRI/aflibercept combination in western patients with mCRC who had progressed on or after previous treatment with an oxaliplatin-based chemotherapy regimen, and reported statistically significant prolongation of both PFS and OS (Van Cutsem et al., 2012).

Currently there is a paucity of data in the Malaysian population in terms of safety and efficacy of aflibercept. Based on the established efficacy of the aflibercept/FOLFIRI combination in mCRC observed in VELOUR trial, aflibercept was approved by United States Food and Drug Administration (US FDA) in 2012 and European Medicines Agency (EMA) in 2013. Pending local registration of aflibercept with health authority, aflibercept Named Patient Programme (NPP) was initiated to provide access to patients to aflibercept in the context of an unmet medical need. Aflibercept NPP was terminated in Malaysia as soon as aflibercept was registered with local authority. Here, we report the first retrospective analysis of the safety and efficacy of aflibercept/FOLFIRI combination in Malaysian patients with mCRC who failed oxaliplatin-based chemotherapy. This analysis during the Malaysian NPP provided an indication of the experience with aflibercept in the local population.

## Materials and Methods

### *Study design and patient population*

We conducted this retrospective, multi-center analysis to report the results of the effect of aflibercept in combination with FOLFIRI in patients with mCRC who failed oxaliplatin-based chemotherapy in Malaysia. Between October 2012 and February 2015, 25 patients from 4 centers in Malaysia were granted access to aflibercept via the aflibercept NPP provided by the Sanofi. The primary end point of the analysis was treatment-related adverse events (AEs). The secondary end point included the assessment of PFS, OS and treatment response.

The eligibility criteria for the NPP were at least 18 years of age; an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1, unlike VELOUR trial which allowed patients with ECOG PS of 0 to 2; histologically proven metastatic colorectal adenocarcinoma previously treated with an oxaliplatin-containing regimen (only one prior metastatic regimen allowed); documented disease progression during or after oxaliplatin-containing regimen for mCRC; or a recurrent or metastatic relapse during or within 6 months of adjuvant oxaliplatin based chemotherapy. Patients were

excluded if they were previously treated with irinotecan; had inadequate hematologic, hepatic, and renal function; were contraindicated to any of the active substances used (irinotecan, 5-fluorouracil, and folinic acid) or their excipients; had concurrent or planned treatment with anticonvulsant agents that are CYP3A4 inducers; had an occurrence of deep vein thrombosis within 4 weeks before enrollment; were pregnant or breastfeeding; or had known dihydropyrimidine dehydrogenase deficiency or Gilbert's syndrome. The eligible patients received 4 mg/kg of aflibercept IV, over 1 hour on day 1 every 2 weeks, followed immediately by the FOLFIRI regimen (irinotecan 180 mg/m<sup>2</sup> IV over 90 minutes, with leucovorin 400 mg/m<sup>2</sup> intravenously over 2 hours, followed by 5-FU 400 mg/m<sup>2</sup> bolus and 5-FU 2400 mg/m<sup>2</sup> continuous infusion over 46 hours). New cycles of therapy did not begin until drug-related toxicity was adequately resolved as per the physician's clinical judgment. Patients screened for eligibility were informed of the unlicensed access to the drug, describing its toxicities. The protocol was approved by the local institutional review boards and ethics committees in accordance with the national and international guidelines. Informed consent was signed and obtained from all the patients.

### *Safety and efficacy assessments*

Pretreatment evaluation of eligible patients included either ultrasound, contrast-enhanced computed tomography and/or magnetic resonance imaging, physical examination, positron emission tomography and other laboratory tests. The patients were evaluated for clinical response every 8 weeks. As per the protocol, a baseline clinical measurement was performed 1 week before the commencement of treatment in order to determine disease extent. Serial clinical measurements were performed every 8 weeks until 4 weeks after the last dose of chemotherapy or until clinical disease progression. The treatment efficacy was determined using serum carcinoembryonic antigen marker (CEA) and imaging after 4 to 6 cycles. Enrolled patients had dipstick, blood pressure (BP), full blood count, and liver and kidney function tests measured and repeated every cycle along with monitoring of any AEs. AEs were analyzed using the NCI-CTCAE v4.0 in all patients who received at least one dose of aflibercept (CTCAE, 2009).

The toxicity data was based on the highest grade ever reported for each AE in each patient and categorized as mild to moderate (grade 1), moderate (grade 2), severe (grade 3) and life-threatening (grade 4). Efficacy analyses were conducted in the treated population according to the reported assessment by the attending specialists using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) (Nishino et al., 2010). PFS was defined as the time taken from the approval of aflibercept to the date of the first documented clinical and/or imaged progression or death. Any death without any signs of progression was censored in the analysis. OS was defined as the time interval from when the drug was approved for the patient to death from any cause. We examined tumor responses which include complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD)

rates, as the secondary outcome for the patients treated with this combination therapy. Response rate was defined as the proportion of patients with CR and PR in the analyzed population. Patients alive or lost to follow-up were censored at their last follow-up date.

#### Statistical analysis

The sample size was not defined on the basis of an end point hypothesis, but rather to provide information about the safety and efficacy of the analysis. Continuous data were expressed as mean  $\pm$  SD or as median, as appropriate, whereas categorical data were summarized as frequencies and percentages. No comparative analyses were performed. Statistical analyses were performed using the SPSS version 22.0. Time-to-event parameters were estimated using the Kaplan-Meier analysis. Safety was analyzed using descriptive methods, in the treated population, according to the treatment received by patients who received at least one dose of aflibercept. The hazard ratio and 95% CI estimates were provided using a Cox proportional hazards model. The stratified log-rank (Mantel-Cox) tests were used for the assessment of OS according to the ECOG status, time to progression, and also to test the equality of survival distributions for the different levels of treatment setting.

## Results

#### Patient demographics and clinical characteristics

Between October 2012 and February 2015, 12 female and 15 male patients were screened and gained approval to receive aflibercept via the NPP- (aflibercept provided by Sanofi Aventis) in selected centers in Malaysia. Of which, 2 male patients died before commencing the therapy (due to massive tumor perforation leading to bleeding and neutropenic sepsis following FOLFIRI while waiting for approval of aflibercept import permit from local regulatory), leaving a total of 25 patients. The overall mean age of the patients was  $56.96 \pm 12.13$  years, with the majority being Chinese (60%) followed by the Malay (36%) ethnic group. At enrollment into NPP, all patients screened were in ECOG status 0-1. However, at study drug initiation, about 84% of patients had ECOG status of 0 to 1, while the remainder had status 2. Duration from enrollment to approval of import permit from local authority and arrival of vials at study sites was around 4-6 weeks, few patients had deteriorated in their ECOG status but treatment was continued. The patients with declined ECOG were started at lower dose of chemotherapy physicians' discretion. The patient cohort consisted of 3 patients receiving aflibercept upon progressing, during, or within 6 months from their adjuvant oxaliplatin based chemotherapy, and 22 patients receiving second-line therapy after failure of first-line oxaliplatin-based therapy with or without bevacizumab. Only two patients had prior treatment with bevacizumab and cetuximab (Table 1). The mean treatment cycles for assessable patients were 9.80 (1-44) cycles. The majority of the patients (48%) received 5 to 8 cycles of chemotherapy followed by patients receiving 9 to 12 cycles (24%), 1 to 4 cycles (20%), and more than 12 cycles of chemotherapy (8%).

#### Aflibercept-related toxicities

Grade 1-2 events were experienced by up to 52% of patient cohort followed by grade 3 (4%) and grade 4 events (20%). The majority of the gastrointestinal

**Table 1. Demographics and Clinical Characteristics of Patients with mCRC**

Clinical Characteristics	N=25
Age, mean $\pm$ (SD)	56.96 $\pm$ 12.13
Gender, n (%)	
Male	13(52)
Female	12(48)
Ethnic group/race, n (%)	
Malay	9(36)
Chinese	15(60)
Indian	1(4)
ECOG performance status, n (%)	
0	12 (48)
1	9 (36)
2	4 (16)
Molecular Status of K-RAS, n (%)	
Unknown	12(48)
Wild type	8(32)
Mutated	5(20)
Comorbidities, n (%)	
Hypertension	5(20)
Diabetes Mellitus and hypertension	3(12)
Diabetes mellitus	2(8)
Renal impairment	1(4)
None	14(56)
Tumor Characteristics	
Primary tumor site, n (%)	
Cecum	11(44)
Sigmoid colon	5(20)
Rectum	9(36)
Site of Metastases, n (%)	
Limited liver disease	3(12)
Multiple distant metastases	14(56)
Loco-regional and distant metastases	8(32)
Stage at first diagnosis of CRC, n (%)	
Stages 1-3	9(36)
Stage 4	16(64)
Treatment Indication, n (%)	
First-line metastatic treatment*	3(12)
Second-line therapy**	22(88)
Previous chemotherapy received, n (%)	
FOLFOX/XELOX	18(72)
FOLFOX/XELOX plus bevacizumab	2(8)
FOLFOX/XELOX plus cetuximab	2(8)
None	3(12)
Number of chemotherapy therapy cycles, mean (range)	9.8 (1-44)
Aflibercept start dose, n (%)	
2 mg	3(12)
4 mg	22(88)

\*after progressing during or within 6 months of adjuvant oxaliplatin chemotherapy; \*\*after failure of first-line oxaliplatin-based therapy with or without bevacizumab

(GI) toxicities were of grade 1-2, with diarrhea (52%), mucositis (52%), and nausea/vomiting (20%) being largely observed. Grade 3-4 diarrhea commonly associated with FOLFIRI chemotherapy was observed in one patient. Among the patients with antiangiogenic class effects, 24% had grade 1-2 proteinuria. Two patients developed grade 3-hypertension secondary to aflibercept use. Grade 2 posterior reversible encephalopathy syndrome (PRES) was reported in one patient with preexisting hypertension. Amongst Grade 3-4 hematological toxicity; neutropenia (16%) and febrile neutropenia (8%) were reported. A life-threatening event such as neutropenic sepsis was seen in only one patient at cycle 3. Grade 3-4 infection affected 12% of patients. One patient reported Grade 1 scrotal ulcer, started at cycle 2 (Table 2).

**Management of toxicities**

Patients receiving aflibercept underwent baseline documentation of their BP, liver and renal function tests, urine protein and full blood count within one week

**Table 2. Toxicity of the Patients with mCRc Following Aflibercept/FOLFIRI Treatment**

Toxicity	Grade 1-2	Grade 3-4
	N (%)	N (%)
Gastrointestinal toxicities		
Nausea and vomiting	5(20)	0
Diarrhea	13(52)	1(4)
Mucositis	13(52)	0
Antiangiogenic class effects/toxicity		
Hypertension	3(12)	2(8)
Proteinuria	6(24)	1(4)
Renal impairment	2(8)	0
PRES	1(4)	0
Hematological toxicity		
Neutropenia	8(32)	4(16)
Thrombocytopenia	5(20)	0
Febrile neutropenia	2(8)	2(8)
Neutropenic sepsis	0	1(4)
Anemia	8(32)	1(4)
Others		
Hand-foot syndrome	9(36)	0
Infection	2(8)	3(12)
Weight loss/anorexia	5(20)	5(20)
Scrotal ulcer	0	1(4)
Peritoneal metastases	1(4)	0

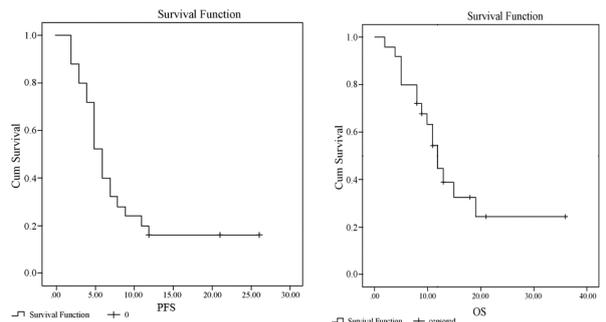
Add PRES - grade 2 as stated in the text - 1 patient

**Table 3. Means and Medians for Survival Time**

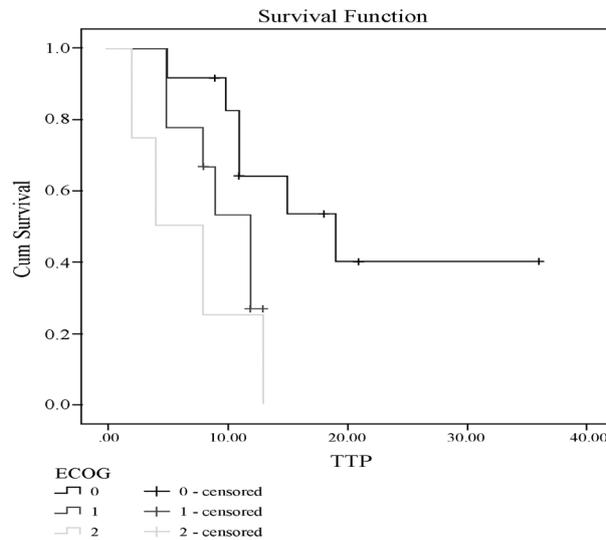
Treatment Setting	Meana			Median		
	Estimate	95% CI		Estimate	95% CI	
		Lower Bound	Upper Bound		Lower Bound	Upper Bound
First-line metastatic treatment after progressing during or within 6 months of adjuvant oxaliplatin chemotherapy	8.33	5.49	11.18	8	4.8	11.2
Second-line therapy after failure of first-line oxaliplatin-based therapy with or without bevacizumab	8.91	5.41	12.4	5	3.69	6.31
Overall	8.84	5.75	11.93	6	4.8	7.2

<sup>a</sup>Estimation is limited to the largest survival time if it is censored

before starting treatment. Upon commencement, repeat monitoring of these parameters were done at least once every 2 weeks while on treatment. For patients with grade 2 hypertension, antihypertensive medications such as calcium channel blockers, beta blockers, and/or angiotensin-converting enzyme inhibitors were considered. We considered temporary discontinuation of chemotherapy if the BP was not controlled with antihypertensive medications; however, treatment resumed once the hypertension was <140/90 mmHg. For patients with grade 3 hypertension, once the BP was satisfactorily controlled, subsequent cycles were resumed at a reduced aflibercept dose of 2 mg/kg. In patients with proteinuria where > 2 + recorded on the dipstick, aflibercept treatment was withheld until proteinuria improved to < 2g/24 hours



**Figure 1. K-M curve for PFS and OS in patients with mCRc**



**Figure 2. OS according to the ECOG status in patients with mCRc**

of protein. If recurrent, subsequent dose was reduced to 2 mg/kg.

In patients with scrotal ulceration, treatment was continued without any modification, however, the condition worsened to grade 2 at cycle 3. Treatment was delayed and aflibercept dose was reduced to 2 mg/kg. Oral antibiotics and topical steroids were prescribed. Following cycle 4, scrotal ulceration deteriorated to grade 3, treatment was stopped at cycle 5 due to disease progression.

For grade 1-2 hematological toxicities, patient's chemotherapy cycle was delayed for about 3 -7 days. There was a 25% dose reduction of only 5-FU bolus or the entire FOLFIRI regimen at initiation of chemotherapy for patients with ECOG 2 to prevent neutropenia. Dose delay was executed together when deemed necessary. The use of granulocyte colony-stimulating factor (G-CSF) prophylaxis was not practiced in this palliative setting, but was used therapeutically in cases with febrile neutropenia or neutropenic sepsis. Chemotherapy + aflibercept treatment was delayed until the neutrophil counts recovered ( $\geq 1.5 \times 10^9/L$ ). A patient with neutropenic sepsis was admitted to the ward for aggressive management that includes septic work out, to rule out any source of infection. Complete blood count and cultures were monitored daily in the ward. Broad spectrum IV antibiotics with or without antifungals, therapeutic G-CSF administration, fluid replacement as well as blood product transfusion were amongst the supportive therapy provided. Similar management strategies were applied to other patients with suspected infection, and referral to other relevant specialties such as nephrology, surgery or urology was done as appropriate. For patients with frequent diarrhea (grade 1-2, outpatient), oral loperamide and rehydration salts were prescribed. A patient admitted to the ward for grade 3 diarrhea was given aggressive supportive treatment with IV hydration, electrolyte replacement and antibiotics. When patients developed GI toxicities (diarrhea, nausea, and vomiting), aflibercept was temporarily discontinued. All-grade elevated liver enzymes were observed in the early course of treatment, but rapidly improved with FOLFIRI dose adjustment or by delay in chemotherapy. One patient with multiple peritoneal metastases required hospitalization and acute care owing to the development of an acute intestinal obstruction during chemotherapy, and later, was discontinued from the therapy as performance status (PS) deteriorated. The patient with grade 3 scrotal ulcer had his treatment delayed and later discontinued after cycle 4 due to disease progression. None of the patients experienced any grade 5 toxicity from this combination treatment.

### *Efficacy*

At the date of censor, the median follow-up time for all patients was 11 months. The median PFS was 6.12 months [95% confidence interval (CI): 4.80-7.20] and median OS was 12 months (95% CI: 9.80-14.18) (Figure 1). Patient with ECOG status of 0 followed by 1 seemed to have a better efficacy from treatment compared with an ECOG status of 2 (Figure 2). The results showed that by treatment setting, the number of patients who are considered fast

progressers, defined as patients receiving aflibercept upon progressing during or within 6 months from their adjuvant chemotherapy; were too small to make valid conclusions on the magnitude of benefit in comparison to patients receiving the drug after failure to first-line chemotherapy (Table 3). Only 24 patients were assessable for response. The PR, SD, and PD rates were 25%, 37.5% and 37.5% respectively. No patient achieved complete response (CR).

### **Discussion**

To our knowledge, this is the first retrospective analysis conducted in Malaysia to report the initial clinical experience of aflibercept/FOLFIRI combination treatment in patients with mCRC and highlighting the treatment-related toxicities and management of AEs. The analysis demonstrated an acceptable side effect profile in the Malaysian population. Patients reported mild-to-moderate toxicity, which was found to be consistent with the characterized tolerability and safety profile for aflibercept (Van Cutsem et al., 2012). Reasonable results were obtained with this retrospective analysis in terms of all efficacy end points (OS, PFS, and response rate) with the aflibercept/FOLFIRI combination.

In VELOUR trial, diarrhea (99.2%) and anemia (82.3%) were the most commonly reported AEs associated with aflibercept treatment (Van Cutsem et al., 2012). In our analysis, 52% of the patients reported grade 1-2 diarrhea and mucositis. Grade 3-4 neutropenia (16%) and infections (12%) were seen in fewer patients. The risk of developing proteinuria was also observed with bevacizumab-related therapies in other studies (Bai et al., 2015; Passardi et al., 2015; Yoshida et al., 2015; Majid et al., 2015). The control of BP is complicated and may be related to the factors affecting cardiac output or total peripheral vascular resistance (Syed and McKeage., 2015). During the NPP, 3 patients developed hypertension of grade 1-2, whereas, 2 patients had grade 3-hypertension. Hypertension in these patients was controlled by antihypertensive medications such as calcium channel blockers, beta blockers, and/or angiotensin-converting enzyme inhibitors. One patient with grade 3 hypertension also developed grade 2 PRES. The patient responded very well to medical treatment and at the same time reassessment of tumor showed good response hence the treating clinician decided to continue aflibercept at reduced dose of 2 mg/kg. This patient was able to continue treatment at a reduced dose for the next 3 months with careful monitoring without further episodes until 12 cycles. Aflibercept acts as a receptor that binds to the angiogenic VEGF, VEGF-A, and PlGF, thereby inhibiting VEGF-A activation that produces neovascularization and vascular permeability. VEGF has a fundamental role in maintaining the integrity of tissues and is a vital step in wound healing (ZALTRAP PI., 2012). A total of 2 (0.3%) patients showed wound healing after treatment with aflibercept/FOLFIRI in our study. Severe scrotal ulceration that increases in intensity despite dose reduction was observed in one patient in our study. It disappeared upon discontinuation of the therapy; suggesting the role of this drug in this non dose-dependent toxicity. We suggest that the severe

scrotal ulceration might be relative to the inhibitory effect of vascularization, through inhibition of VEGF-A by aflibercept. Although less common, hand-foot syndrome, also called palmar-plantar erythrodysesthesia, of mild to moderate nature, was observed in 9 (36%) patients, and this may be attributed as a side effect of infusional 5-FU chemotherapy. Patients were provided with topical anti-inflammatory medications such as corticosteroid creams until the symptoms improved.

As compared with VELOUR, our analysis showed comparable OS (12 vs 13.50 months) and PFS (6.12 vs 6.9 months). The response rates were comparable; although more patients in the Malaysian data set progressed. Our analysis has several limitations. First, an unintentional selection bias for a specified group of patients was possible because of the confounding nature of this analysis. Second, this analysis was done on a small sample size, conducted in four selected centers in Malaysia, making it difficult to extrapolate the results.

In conclusion, Our analysis results suggest that aflibercept in combination with FOLFIRI can be administered safely in Malaysian patients with mCRC. On the basis of current clinical practice and risk management guidelines, the AEs experienced by the patients receiving this therapy were generally reversible and manageable. Malaysian patients had reasonable benefit to aflibercept therapy in terms of safety and efficacy, the outcomes of which were consistent with the Western population. This combination therapy may become an integral part of the standard care of second line treatment in patients with mCRC. The NPP had allowed us to evaluate this novel therapy in our local setting. We await results from the global aflibercept safety and quality-of-life program (ASQoP [NCT01571284]; AFEQT [NCT01670721]) in patients with mCRC previously treated with an oxaliplatin-based regimen which involved bigger population as well as Asian patients to further provide data on the impact of aflibercept on quality of life.

## Acknowledgements

Editorial support was provided by Sanofi-aventis. The funding organization Sanofi-aventis had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors acknowledge Dr. Amit Bhat and Mrs. Nishi Gupta (Indegene Lifesystems Pvt. Ltd., Bangalore, India) for providing manuscript writing and editing support in the preparation of this manuscript.

## References

- Bai L, Zhang DS, Wu WJ, et al (2015). Clinical outcomes of Chinese patients with metastatic colorectal cancer receiving first-line bevacizumab-containing treatment. *Med Oncol*, **32**, 469.
- Chiron M, Bagley RG, Pollard J (2014). Differential antitumor activity of aflibercept and bevacizumab in patient-derived xenograft models of colorectal cancer. *Mol Cancer Ther*, **13**, 1636-44.
- Chiron M, Bagley RG, Pollard J, et al (2014). Differential antitumor activity of aflibercept and bevacizumab in patient-derived xenograft models of colorectal cancer. *Mol Cancer Ther*, **13**, 1636-44.
- Common Terminology Criteria for Adverse Events v4.0 (CTCAE 2009). U.S department of health and human services.
- Do K, Cao L, Kang Z, et al (2015). A phase II study of sorafenib combined with cetuximab in EGFR-expressing, KRAS-mutated metastatic colorectal cancer. *Clin Colorectal Cancer*, **14**, 154-61.
- García-Alfonso P, Ferrer A, Gil S, et al (2015). Neoadjuvant and conversion treatment of patients with colorectal liver metastasis: the potential role of bevacizumab and other antiangiogenic agents. *Target Oncol*, **10**, 453-65.
- Grothey A, Van Cutsem E, Sobrero A, et al (2013). Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*, **38**, 303-12.
- Jitawatanarat P, Wee W (2013). Update on antiangiogenic therapy in colorectal cancer: aflibercept and regorafenib. *J Gastrointest Oncol*, **4**, 231-8.
- Lee JJ, Chu E (2014). Sequencing of antiangiogenic agents in the treatment of metastatic colorectal cancer. *Clin Colorectal Cancer*, **13**, 135-44.
- Lim KG (2014). A review of colorectal cancer research in malaysia. *Med J Malaysia*, **69**, 23-32.
- Majid N, Ghissassi I, Mrabti H, et al (2015). Bevacizumab in clinical practice. *Gulf J Oncol*, **1**, 33-7.
- Malaysia cancer statistics- Data and figure (2007). National Cancer Registry Report.
- Muhammad S, Jiang Z, Liu Z, Kaur K, Wang X (2013). The role of EGFR monoclonal antibodies (MoABs) cetuximab/panitumab, and BRAF inhibitors in BRAF mutated colorectal cancer. *J Gastrointest Oncol*, **4**, 72-81.
- Nishino M, Jagannathan JP, Ramaiya NH, et al (2010). Revised RECIST guideline version 1.1: What oncologists want to know and what radiologists need to know. *AJR Am J Roentgeno*. **195**, 281-9.
- Norwati D, Harny MY, Norhayati MN, Amry AR (2014). Colorectal cancer screening practices of primary care providers: results of a national survey in Malaysia. *Asian Pac J Cancer Prev*, **15**, 2901-4.
- Papadopoulos N, Martin J, Ruan Q (2012). Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis*, **15**, 171-85.
- Passardi A, Nanni O, Tassinari D, et al (2015). Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: final results for first-line treatment from the ITACa randomized clinical trial. *Ann Oncol*, **26**, 1201-7.
- Patel A, Sun W (2014). Ziv-aflibercept in metastatic colorectal cancer. *Biologics*, **8**, 13-25.
- Pourhoseingholi MA (2012). Increased burden of colorectal cancer in Asia. *World J Gastrointest Oncol*, **4**, 68-70.
- Product Information (2012). ZALTRAP(R) intravenous injection, ziv-aflibercept intravenous injection. sanofi-aventis U.S.LLC (per FDA), Bridgewater, NJ.
- Syed YY, McKeage K (2015). Aflibercept: a review in metastatic colorectal cancer. *Drugs*, **75**, 1435-45.
- Tang PA, Moore MJ (2013). Aflibercept in the treatment of patients with metastatic colorectal cancer: latest findings and+ interpretations. *Therap Adv Gastroenterol*, **6**, 459-73.
- Van Cutsem E, Tabernero J, Lakomy R, et al (2012) Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol*, **30**, 3499-506.
- Wong NA, Gonzalez D, Salto-Tellez M (2014). RAS testing of colorectal carcinoma-a guidance document from the association of clinical pathologists molecular pathology and diagnostics group. *J Clin Pathol*, **67**, 751-7.
- Yoshida M, Muro K, Tsuji A (2015). Combination chemotherapy with bevacizumab and S-1 for elderly patients with metastatic colorectal cancer (BASIC trial). *Eur J Cancer*, **51**, 935-41.