Composition comprising aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinocetan (FOLFIRI)

The present invention relates to combinations of aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinocetan which are therapeutically useful in the treatment of Colorectal Cancer (CRC) and in particular metastatic Colorectal Cancer (CRC).

Colorectal cancers are among the most frequent tumor types in the western countries, second to breast in women and third to lung and prostate in males. The end prognosis is dependent upon the extent of the disease. The five year survival rate in early localized stage of about 90%, decreased to approximately 60-65% after spread to adjacent organ(s) or lymph nodes and is of less than 10% after spread to distant sites.

When diagnosed before nodal involvement treatment is usually limited to surgical resection (and radiotherapy for patients with rectal cancer) and potential participation to clinical trials for adjuvant therapy. Patients with nodal involvement are candidates for adjuvant chemotherapy following initial surgery in the attempt to prevent metastatic recurrence of the disease. Once spread to distant sites treatment essentially consists of palliative chemotherapy.

About 75 to 80% of all the patients with colorectal carcinoma will present at a stage when all gross carcinoma can be surgically removed. However, almost half of these patients will ultimately die from metastatic disease. Furthermore 20 to 25 % of the patients present with metastatic disease at diagnosis. Once metastases are present median overall survival with available combination therapy is around 20 months.

Over the past decades 5-Fluorouracil (5-FU) has remained the mainstay of the chemotherapy in colorectal cancer. During years the major determinant in the treatment of colorectal cancer patients has been the improvement in the schedules of 5-FU administration.

Among these, the bimonthly regimen (LV5FU2) of 5-FU given as bolus/infusion over 2 days has been shown to be superior to the monthly 5 day bolus regimen (Mayo regimen) in terms of response rate (RR) (32.6% *vs* 14.4%), in terms of progression free survival (PFS) (27.6 *vs* 22.0 weeks), and safety (de Gramont et al, Journal of Clinical Oncology 1997;15(2):808-815).

However, no statistically significant improvement in the overall survival (OS) was seen until development, starting in the beginning of nineties, of two novel cytotoxic agents, oxaliplatin, a DACH platinum, and the topoisomerase I inhibitor, irinotecan. With each of these two new agents median overall survival in the first line metastatic setting reached 15 to 19 months in multiple Phase III trials.

In a study, published in 2004 by Tournigand et al. (Journal of Clinical Oncology 2004;22(2):229-237), where these two drugs were administered in sequence in the same protocol, as first then second line treatment in metastatic colorectal cancer patients, the threshold of 20 months median overall survival was crossed whatever was the order of the treatment sequence.

Aflibercept is synthesized as a fusion protein comprising the signal sequence of VEGFR1 fused to the D2 Ig domain of the VEGFR1 receptor, itself fused to the D3 Ig domain of the VEGFR2 receptor, in turn fused to the Fc domain of IgG1Aflibercept is also referred to as as VEGFR1R2-Fc.DELTA.C1 or Flt1D2.Flk1D3.Fc.DELTA.C1.

The amino acid sequence (SEQ ID N°1) of Aflibercept is illustrated in Figure 1 and is also shown inter alia in FIG. 24) of patent application WO 00/75319.

5-fluorouracil (5-FU or f5U) is a drug that is a pyrimidine analog which is used in the treatment of cancer. It is a suicide inhibitor and works through irreversible inhibition of thymidylate synthase. It belongs to the family of drugs called antimetabolites.

Folinic acid or leucovorin is an adjuvant to cancer chemotherapy used in combination with 5-fluorouracil.

Irinotecan is a drug used for the treatment of cancer. Irinotecan is a topoisomerase 1 inhibitor, which prevents DNA from unwinding.

FOLFIRI is the combination of folinic acid, 5-fluorouracil (5-FU) and irinocetan and will be used throughout the document.

In a phase I study (TCD6118) aflibercept was administered IV in combination with irinotecan (180 mg/m² on day 1), leucovorin (200 mg/m² on day 1 and day 2), and 5-FU (bolus/infusional 400/600 mg/m² on day 1 and day 2), every 2 weeks in patients

with advanced solid malignancies. The aflibercept 4 mg/kg dose every 2 weeks was considered to be the optimum dose.

In a phase II trial (NCI7498) aflibercept was administered in previously treated patients with metastatic colorectal cancer. This trial showed that aflibercept is well tolerated in pre-treated patients with MCRC. The conclusions are that based on the study results, studies of aflibercept as single agent or in combination should be explored (Tang et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 4027).

But the results provided in these two studies provided no insight as to efficacy.

Furthermore a phase III trial of aflibercept in metastatic pancreatic cancer was discontinued in 2009 and in 2011 the data of a phase III trial evaluating aflibercept for the second-line treatment of non-small cell lung cancer (NSCLC) showed that adding aflibercept to the chemotherapy drug docetaxel did not meet the pre-specified criteria for the primary endpoint of improvement in overall survival compared with a regimen of docetaxel plus placebo.

It has now been found, and this is an object of the present invention, that the effectiveness of aflibercept on Overal Survival (OS) in patients with Colorectal Cancer (CRC) can be significantly improved when it is administered in combination with FOLFIRI.

It has also been found, and this is another object of the present invention, that the effectiveness of aflibercept on Progression Free Survival (PFS) in patients with Colorectal Cancer (CRC) can be significantly improved when it is administered in combination with FOLFIRI.

It has also been found, and this is yet another object of the present invention, that the effectiveness of aflibercept on Overal Response Rate (ORR) in patients with Colorectal Cancer (CRC) can be significantly improved when it is administered in combination with FOLFIRI.

The invention relates to methods, compositions and articles as disclosed herein.

In one aspect the invention provides for a method of treating Colorectal Cancer (CRC) or Colorectal Cancer (CRC) symptom in a patient in need thereof, said method

comprising administering to said patient therapeutically effective amounts of aflibercept and FOLFIRI. This method is safe and effective.

In a second aspect the invention provides for a method of increasing Overall Survival (OS) in a patient afflicted with CRC, said method comprising administering to said patient therapeutically effective amounts of aflibercept and FOLFIRI.

In a third aspect the invention provides a method of increasing Overall Response Rate (ORR) in a patient afflicted with CRC, said method comprising administering to said patient therapeutically effective amounts of aflibercept and FOLFIRI.

In a fourth aspect the invention provides a method of increasing Progression Free Survival (PFS) in a patient afflicted with CRC, said method comprising administering to said patient therapeutically effective amounts of aflibercept and FOLFIRI.

In a first feature the invention provides a method according to any one of the first to fourth aspects wherein said patient has already been treated for the CRC or CRC symptom (second-line treatment).

In a specific embodiment CRC is a Metastatic Colorectal Cancer.

In a second feature the invention provides for a method according to any one of the first to fourth aspects or the first feature wherein said patient has previously been treated with chemotherapy, radiotherapy or surgery. In an embodiment said patient has failed chemotherapy, radiotherapy or surgery.

In a third feature the invention provides a method according to any one of the first to fourth aspects or the first feature wherein said patient has previously been treated with therapy based on oxaliplatin or on bevacizumab.

In an embodiment said patient has failed therapy based on oxaliplatin or on bevacizumab.

In a fourth feature the invention provides a method wherein folinic acid at a dosage comprised between about 200 mg/m^2 and about 600 mg/m^2, 5-fluorouracil (5-FU) at a dosage comprised between about 2000 mg/m^2 and about 4000 mg/m^2, irinocetan at a dosage comprised between about 100 mg/m^2 and about 300 mg/m^2 and aflibercept at

a dosage comprised between about 1 mg/kg and about 10 mg/kg are administered to patient.

In the present application the dosage of folinic acid indicated should be understood as the dosage of the racemate of folinic acid, i.e. comprising the D and L forms. Should only the L form be used the dosage should be half of the dosage indicated for the racemate.

In other words a dosage of folinic acid of about 200 mg/m^2 as indicated in the present application corresponds to about 200 mg/m^2 of racemate and about 100 mg/m^2 of L form.

In a fifth feature the invention provides a method wherein folinic acid at a dosage of about 400 mg/m^2, 5-fluorouracil (5-FU) at a dosage of about 2800 mg/m^2, irinocetan at a dosage of about 180 mg/m^2 and aflibercept at a dosage of about 4 mg/kg are administered to patient.

In a sixth feature the invention provides a method wherein said patient receives intravenous folinic acid at a dosage comprised of about 400 mg/m^2, intravenous 5-fluorouracil (5-FU) at a dosage of about 2800 mg/m^2, intravenous irinocetan at a dosage comprised of about 180 mg/m^2 and intravenous aflibercept at a dosage of about 4 mg/kg every two weeks.

In a seventh feature the invention provides a method wherein said patient receives intravenous folinic acid, intravenous 5-fluorouracil (5-FU), intravenous irinocetan and intravenous aflibercept every two weeks for a period comprised between about 9 and about 18 weeks.

In another feature the invention provides a method wherein said patient receives intravenous folinic acid immediately after aflibercept administration.

In another feature the invention provides a method wherein said patient receives intravenous irinocetan immediately after aflibercept administration.

In another feature the invention provides a method wherein said patient receives intravenous irinocetan immediately after aflibercept administration over almost 90 minutes.

In another feature the invention provides a method wherein said patient receives intravenous 5-fluorouracil (5-FU) immediately after aflibercept administration.

In another feature the invention provides a method wherein said patient receives a first quantity of intravenous 5-fluorouracil (5-FU) immediately after aflibercept administration and a second quantity in continous infusion.

In another feature the invention provides a method wherein said patient receives about 400 mg/m^2 of intravenous 5-fluorouracil (5-FU) over about 2 to 4 minutes after aflibercept administration and 2400 mg/m^2 over about 46 hours after aflibercept administration in continuous infusion.

In a fifth aspect the invention features a composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinocetan for treating patients with CRC for simultaneous administration.

In a sixth aspect the invention features a composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinocetan for treating patients with CRC for sequential administration.

In a seventh aspect the invention features a composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinocetan for treating patients with CRC for administration that is spaced out over a period of time so as to obtain the maximum efficacy of the combination.

In a eighth aspect the invention features a composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinocetan and comprising a pharmaceutically acceptable carrier for treating patients with CRC.

In on feature of any of these aspects the patient has liver metastases.

In an ninth aspect the invention features an article of manufacture comprising:

a) a packaging material

b) aflibercept, and

c) a label or package insert contained within said packaging material indicating that aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinocetan is effective for the treatment of CRC

In one feature of the ninth aspect the label or package insert contained within said packaging material indicates that aflibercept in combination with FOLFIRI improves Overall Survival (OS).

In one feature of the ninth aspect the label or package insert contained within said packaging material indicates that aflibercept in combination with FOLFIRI improves Progression Free Survival (PFS).

In one feature of the ninth aspect the label or package insert contained within said packaging material indicates that aflibercept in combination with FOLFIRI improves Overall Response Rate (ORR).

In a tenth aspect the invention features a kit for treating patients with CRC comprising:

a) at least one compound chosen from the list consisting of aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinocetan; and

b) a label or package insert contained within said kit indicating that aflibercept is to be used in combination with folinic acid, 5-fluorouracil (5-FU) and irinocetan (FOLFIRI) or folinic acid, 5-fluorouracil (5-FU) and irinocetan (FOLFIRI) is to be used in combination with Aflibercept

In an eleventh aspect the invention features a kit comprising in separate containers pharmaceutical compositions for combined use in treating CRC in a patient which comprises (1) a pharmaceutical composition comprising aflibercept, (2) a pharmaceutical composition comprising folinic acid, (3) a pharmaceutical composition comprising 5-fluorouracil (5-FU) and (4) a pharmaceutical composition comprising irinocetan.

The aflibercept can be formulated as described in WO2006/104852. The man skilled in the art may refer in particular to WO2006/104852 or to WO 00/75319 to carry out the present invention.

Figures

Figure 1 : Aflibercept amino acid sequence (SEQ ID NO:1)

Figure 2 : Overall survival (months) – Kaplan-Meier curves by treatment group– ITT population

Figure 3 : Overall survival (months) – Subgroup analyses (forest plot) – By stratification factors as per IVRS – ITT population

Figure 4 : Overall survival (months) – Subgroup analyses (forest plot) – By patient demographics - ITT population

Figure 5 : Overall survival (months) – Subgroup analyses (forest plot) – By baseline characteristics – ITT population

Figure 6 : PFS based on tumor assessment by the IRC (months) – Subgroup analysis (forest plot) – By stratification factors as per IVRS – ITT population

The following example illustrates a combination according to the invention.

EFC10262 (VELOUR)/ A Multinational, Randomized, Double-blind Study, Comparing the Efficacy of Aflibercept Once Every 2 Weeks versus Placebo in Patients with Metastatic Colorectal Cancer (MCRC) Treated with Irinotecan / 5-FU Combination (FOLFIRI) after failure of an oxaliplatin based regimen

EFC10262 was designed as a randomized, double-blind, multi-centre study comparing aflibercept at 4 mg/kg to placebo, in combination with Irinotecan and 5 Fluorouracil combination (FOLFIRI) given intravenously every 2 weeks as second line treatment for patients with metastatic colorectal cancer (MCRC) after failure of an oxaliplatin based regimen. Each randomized patient was to be treated until disease progression, death, or unacceptable toxicity.

The primary objective of EFC10262 was to demonstrate improvement in overall survival (OS) for aflibercept + FOLFIRI compared to placebo + FOLFIRI. The predefined statistical significance level for this final analysis was 0.0466 after adjusting the type I error spent for the two interim analyses using the O'Brien-Fleming spending function.

The study included one formal interim analysis, planned for the purpose of efficacy, when 561 death events (65% information time) had occurred. Upon request of the independent Data Monitoring Committee (DMC), an additional interim analysis of OS was performed to provide an early evaluation of the benefit-risk ratio, when 315 death events (36.5% information fraction) had occurred.

A total of approximately 863 deaths were required to detect 20% hazard rate reduction in OS with 90% power using the two-sided log rank test at an overall 0.0499 alpha level. The median survival times was expected to be 11 months for the control group. The overall alpha level was split between overall survival (0.0499) and progression-free survival as a secondary efficacy endpoint (0.0001).
Approximately 1200 patients (i.e. 600 patients per treatment group) were planned to be randomized. Treatment assignment was stratified according to prior therapy with bevacizumab (yes or no), and ECOG performance status (PS) (0 vs 1 vs 2).
The enrolment started in November 2007 and was completed in March 2010. A total of 1226 patients were randomized. The efficacy analysis was based on all randomized patients (Intent-to-Treat (ITT) population: 614 in the placebo arm and 612 patients in the aflibercept arm). The safety analysis was based on all treated patients (safety population: 605 and 611 patients in the placebo and aflibercept arms, respectively). Treatment arms were evenly balanced for demographics, disease characteristics and prior anti-cancer treatments, including prior exposition to bevacizumab.

Dosage and schedule of administration

Patients were administered either aflibercept or placebo, depending on arm assigned. Immediately after, patients received irinotecan, 5-FU and leucovorin (FOLFIRI regimen).
This treatment was repeated every 2 weeks.

Aflibercept/placebo

Arm A, aflibercept: 4 mg/kg was administered IV over 1 hour on Day 1, every 2 weeks,
OR
Arm B, placebo: 4 mg/kg was administered IV over 1 hour on Day 1, every 2 weeks.

FOLFIRI regimen

Immediately after aflibercept/placebo administration, all the patients received:

- Irinotecan 180 mg/m^2 IV infusion in 500 mL in 5% dextrose solution in water (D5W) over 90 minutes and dextro-levogyre (dl) leucovorin 400 mg/m² IV infusion over 2 hours, at the same time, in bags using a Y-line, followed by:
- 5-FU 400 mg/m² IV bolus given over 2-4 minutes, followed by:

- 5-FU 2400 mg/m² continuous IV infusion in 500 mL D5W (recommended) over 46-hours.

Results of EFC10262

Demographics and baseline characteristics

Patient demographics and characteristics at baseline were similar the 2 treatment arms (Table 1).

Table 1 – Summary of patient demographics and patient characteristics at baseline – ITT population

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)	All (N=1226)
Gender [n(%)]			
Number	614	612	1226
Male	353 (57.5%)	365 (59.6%)	718 (58.6%)
Female	261 (42.5%)	247 (40.4%)	508 (41.4%)
Age (Years)			
Number	614	612	1226
Median	61.0	61.0	61.0
Mean (SD)	60.2 (10.8)	59.5 (10.5)	59.8 (10.7)
Min : Max	19 : 86	21 : 82	19 : 86
Age class [n(%)]			
Number	614	612	1226
<65	376 (61.2%)	407 (66.5%)	783 (63.9%)
≥65 but <75	199 (32.4%)	172 (28.1%)	371 (30.3%)
≥75	39 (6.4%)	33 (5.4%)	72 (5.9%)
Race [n(%)]			
Number	614	612	1226
Caucasian/White	523 (85.2%)	548 (89.5%)	1071 (87.4%)
Black	27 (4.4%)	16 (2.6%)	43 (3.5%)
Asian/Oriental	51 (8.3%)	35 (5.7%)	86 (7.0%)
Other	13 (2.1%)	13 (2.1%)	26 (2.1%)

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)	All (N=1226)
Region			
Number	614	612	1226
Western Europe	217 (35.3%)	208 (34.0%)	425 (34.7%)
Eastern Europe	136 (22.1%)	161 (26.3%)	297 (24.2%)
North America	75 (12.2%)	63 (10.3%)	138 (11.3%)
South America	56 (9.1%)	62 (10.1%)	118 (9.6%)
Other countries	130 (21.2%)	118 (19.3%)	248 (20.2%)
Note: Other countries = Australia, New Zeland, South Africa and Korea			

Disease characteristics at initial diagnosis and time from diagnosis to randomization were similar in the 2 treatment arms (Table 2).

Table 2 - Disease characteristics at initial diagnosis – ITT population

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)	All (N=1226)
Primary site [n(%)]			
Number	614	612	1226
Colon	302 (49.2%)	289 (47.2%)	591 (48.2%)
Recto sigmoid	136 (22.1%)	123 (20.1%)	259 (21.1%)
Rectum	174 (28.3%)	197 (32.2%)	371 (30.3%)
Other	2 (0.3%)	3 (0.5%)	5 (0.4%)
- cea & ck20 postive - presumed colorectal primary	1 (0.2%)	0	1 (<0.1%)
- Appendix	0	1 (0.2%)	1 (<0.1%)
- Colon plus appendix	0	1 (0.2%)	1 (<0.1%)
- Presumed colorectal,cea positive and history of colon cancer>20 years ago	0	1 (0.2%)	1 (<0.1%)
- Synchronous primary, cecum and rectum	1 (0.2%)	0	1 (<0.1%)

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)	All (N=1226)
Histology type [n(%)]			
Number	614	612	1226
Adenocarcinoma	614 (100%)	612 (100%)	1226 (100%)
Time from 1st diagnosis to randomization (months) [n(%)]*			
Number	614	611	1225
Mean (SD)	20.88 (21.10)	20.98 (24.08)	20.93 (22.62)
Median	13.67	14.62	14.26
Min : Max	2.4 : 214.7	2.1 : 325.1	2.1 : 325.1
*If the day of initial date of diagnosis is missing, it is considered as the first day of the month			

Patient accountability

Overall, 30.4% of the randomized patients were allocated in the prior bevacizumab stratum (Table 3).

Table 3 - Summary of randomized patients by stratification factor (as per IVRS) – ITT population

Stratification factors	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)	All (N=1226)
ECOG PS [n(%)]			
0	350 (57.0%)	349 (57.0%)	699 (57.0%)
1	250 (40.7%)	250 (40.8%)	500 (40.8%)
2	14 (2.3%)	13 (2.1%)	27 (2.2%)
Prior Bevacizumab [n(%)]			
Yes	187 (30.5%)	186 (30.4%)	373 (30.4%)
No	427 (69.5%)	426 (69.6%)	853 (69.6%)
Note: ECOG: Eastern Cooperative Oncology Group, PS: Performance Status, IVRS: Interactive Voice response System			

Dosage and duration

The median overall study treatment exposure (i.e. either both study drugs aflibercept/placebo and FOLFIRI, or one of them alone) was 8.0 and 9.0 cycles in the placebo and aflibercept treatment arms, respectively (Table 4).

Table 4 - Summary of overall study treatment exposure – Safety population

	Placebo/Folfiri (N=605)	**Aflibercept/Folfiri (N=611)**
Number of cycles received by patient		
Sum	6127	6358
Mean (SD)	10.1 (8.1)	10.4 (7.6)
Median	8.0	9.0
Min : Max	1 : 67	1 : 50
SD: standard deviation		

The median number of aflibercept/placebo infusions was 8.0 and 7.0 in the placebo and aflibercept treatment arms, respectively (Table 5). The median relative dose intensity was 83% with aflibercept as compared to 92% with placebo.

Table 5 – Exposure to Aflibercept/Placebo – Safety population

	Placebo/Folfiri (N=605)	**Aflibercept/Folfiri (N=611)**
Number of cycles received by patient		
Sum	6035	5632
Mean (SD)	10.0 (8.0)	9.2 (7.2)
Median	8.0	7.0
Min : Max	1 : 67	1 : 35
1	24 (4.0%)	43 (7.0%)
2	32 (5.3%)	52 (8.5%)
3	85 (14.0%)	70 (11.5%)
4	31 (5.1%)	45 (7.4%)
5	32 (5.3%)	43 (7.0%)
6	45 (7.4%)	29 (4.7%)
7	29 (4.8%)	28 (4.6%)
8	34 (5.6%)	29 (4.7%)
9	45 (7.4%)	29 (4.7%)
10	21 (3.5%)	28 (4.6%)
11-15	112 (18.5%)	94 (15.4%)
16-20	57 (9.4%)	68 (11.1%)
21-25	28 (4.6%)	34 (5.6%)
>25	30 (5.0%)	19 (3.1%)

	Placebo/Folfiri (N=605)	**Aflibercept/Folfiri (N=611)**
Duration of exposure to aflibercept/placebo (weeks)		
Number	605	611
Mean (SD)	22.3 (17.5)	21.7 (16.7)
Median	18.0	17.9
Min : Max	2 : 135	2 : 85
Total cumulative dose received (mg/kg)		
Number	605	611
Mean (SD)	39.63 (31.65)	35.69 (27.96)
Median	32.00	28.00
Min : Max	0.6 : 266.4	3.8 : 140.0
Actual dose intensity (mg/kg/week)		
Number	605	611
Mean (SD)	1.78 (0.25)	1.55 (0.44)
Median	1.84	1.66
Min : Max	0.3 : 2.1	0.1 : 2.1
Relative dose intensity		
Number	605	611
Mean (SD)	0.89 (0.12)	0.78 (0.22)
Median	0.92	0.83
Min : Max	0.2 : 1.1	0.1 : 1.1
Number of cycles received: Number of cycles with at least one dose infusion of aflibercept/placebo.		

The median number of irinotecan infusions was 8.0 and 9.0 in the placebo and aflibercept treatment arms, respectively (table 6). The median relative dose intensity was 84% in the aflibercept arm as compared to 91% in the placebo arm. Of note, two patients did not receive irinotecan; the dose was considered equal to 0 for the calculation of the cumulative dose, actual and relative dose intensity.

Table 6 – Exposure to irinotecan– Safety population

	Placebo/Folfiri (N=605)	**Aflibercept/Folfiri (N=611)**
Number of cycles received by patient		
Sum	5992	6157
Mean (SD)	9.9 (7.8)	10.1 (7.4)
Median	8.0	9.0
Min : Max	1 : 67	1 : 50
1	23 (3.8%)	34 (5.6%)
2	29 (4.8%)	39 (6.4%)
3	87 (14.4%)	64 (10.5%)
4	33 (5.5%)	36 (5.9%)
5	29 (4.8%)	37 (6.1%)
6	48 (7.9%)	31 (5.1%)
7	27 (4.5%)	27 (4.4%)
8	32 (5.3%)	29 (4.8%)
9	47 (7.8%)	29 (4.8%)
10	21 (3.5%)	38 (6.2%)
11-15	114 (18.9%)	111 (18.2%)
16-20	58 (9.6%)	78 (12.8%)
21-25	31 (5.1%)	35 (5.7%)
>25	25 (4.1%)	22 (3.6%)
Duration of exposure to irinotecan (weeks)		
Number	604	610
Mean (SD)	22.2 (17.2)	23.5 (16.9)
Median	18.1	21.0
Min : Max	2 : 135	2 : 105
Total cumulative dose received (mg/m^2)		
Number	605	611
Mean (SD)	1736.30 (1355.52)	1730.37 (1273.76)
Median	1440.00	1472.50
Min : Max	0.0 : 11948.1	0.0 : 9046.1

	Placebo/Folfiri (N=605)	Aflibercept/Folfiri (N=611)
Actual dose intensity (mg/m²/week)		
Number	605	611
Mean (SD)	78.82 (11.74)	73.59 (13.68)
Median	82.08	75.60
Min : Max	0.0 : 95.0	0.0 : 95.0
Relative dose intensity		
Number	605	611
Mean (SD)	0.88 (0.13)	0.82 (0.15)
Median	0.91	0.84
Min : Max	0.0 : 1.1	0.0 : 1.1
Number of cycles received: Number of cycles with at least one dose infusion of irinotecan.		

The median number of 5-FU infusions was 8.0 and 9.0 in the placebo and aflibercept treatment arms, respectively (Table 7). The median relative dose intensity was 83% in the aflibercept arm as compared to 91% in the placebo arm. Of note, two patients did not receive 5-FU; the dose was considered equal to 0 for the calculation of the cumulative dose, actual and relative dose intensity.

Table 7 - Exposure to 5-FU – Safety population

	Placebo/Folfiri (N=605)	Aflibercept/Folfiri (N=611)
Number of cycles received by patient		
Sum	6030	6155
Mean (SD)	10.0 (7.9)	10.1 (7.4)
Median	8.0	9.0
Min : Max	1 : 67	1 : 50

	Placebo/Folfiri (N=605)	Aflibercept/Folfiri (N=611)
1	22 (3.6%)	35 (5.7%)
2	28 (4.6%)	39 (6.4%)
3	88 (14.6%)	63 (10.3%)
4	33 (5.5%)	35 (5.7%)
5	28 (4.6%)	37 (6.1%)
6	48 (8.0%)	32 (5.2%)
7	27 (4.5%)	28 (4.6%)
8	33 (5.5%)	28 (4.6%)
9	47 (7.8%)	29 (4.7%)
10	20 (3.3%)	39 (6.4%)
11-15	114 (18.9%)	113 (18.5%)
16-20	59 (9.8%)	77 (12.6%)
21-25	28 (4.6%)	35 (5.7%)
>25	28 (4.6%)	21 (3.4%)
Duration of exposure to 5-FU (weeks)		
Number	603	611
Mean (SD)	22.4 (17.5)	23.5 (16.9)
Median	18.1	21.0
Min : Max	2 : 135	2 : 105
Total cumulative dose received (mg/m^2)		
Number	605	611
Mean (SD)	27142.02 (21341.89)	26644.81 (19245.24)
Median	22400.00	22702.44
Min : Max	0.0 : 185874.8	409.0 : 126701.4
Actual dose intensity (mg/m^2/week)		
Number	605	611
Mean (SD)	1227.42 (190.51)	1140.36 (214.35)
Median	1276.38	1165.56
Min : Max	0.0 : 1477.3	177.0 : 1491.3

	Placebo/Folfiri (N=605)	Aflibercept/Folfiri (N=611)
Relative dose intensity		
Number	605	611
Mean (SD)	0.88 (0.14)	0.81 (0.15)
Median	0.91	0.83
Min : Max	0.0 : 1.1	0.1 : 1.1
Number of cycles received: Number of cycles with at least one dose infusion of 5-FU.		

Results of EFC10262

1. Overall survival

The median follow-up time at the cutoff date (07 February 2011) for the ITT population was 22.28 months (Figure 2 and Table 8). The study met its primary endpoint demonstrating a significant difference in overall survival in favor of aflibercept over placebo (stratified HR: 0.817, 95.34% CI: 0.713 to 0.937; p = 0.0032). The hazard ratio translates into a reduction of risk of death of 18.3% (95.34 CI: 6.3% to 28.7%) with aflibercept compared to placebo. After 12 and 18 months from randomization, the estimated probabilities of being alive were 50.3% in placebo arm and 56.1% aflibercept arm, and 30.9% in placebo arm and 38.5% in aflibercept arm. Median overall survival was 13.50 months *vs* 12.06 months in aflibercept and placebo treatment arms, respectively. Sensitivity analyses and subgroup analyses showed a very consistent treatment effect confirming robustness of results on the primary endpoint.

Table 8 - Overall survival (months) – Kaplan-Meier survival estimates by treatment group– Primary analysis- Stratified according to stratification factors at randomization (IVRS) - ITT population

Time to Event or Censoring	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)
Overall		
Number of death events, n/N(%)	460/614 (74.9%)	403/612 (65.8%)
Median overall survival (95.34% CI) (months)	12.06 (11.072 to 13.109)	13.50 (12.517 to 14.949)

Time to Event or Censoring	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)
Number of patients at risk		
3 months	573	566
6 months	485	498
9 months	401	416
12 months	286	311
18 months	131	148
24 months	51	75
Survival probability (95.34% CI)		
3 months	0.935 (0.915 to 0.955)	0.931 (0.911 to 0.951)
6 months	0.791 (0.759 to 0.824)	0.819 (0.788 to 0.850)
9 months	0.654 (0.616 to 0.692)	0.687 (0.650 to 0.725)
12 months	0.503 (0.462 to 0.543)	0.561 (0.521 to 0.602)
18 months	0.309 (0.269 to 0.348)	0.385 (0.343 to 0.427)
24 months	0.187 (0.149 to 0.225)	0.280 (0.237 to 0.324)
Stratified Log-Rank test p-value[a]		
vs Placebo/Folfiri	-	**0.0032**
Stratified Hazard ratio (95.34% CI)[a]		
vs Placebo/Folfiri	-	**0.817 (0.713 to 0.937)**

Cutoff date = 7 FEBRUARY 2011

Median follow-up time = 22.28 in months

[a] : Stratified on ECOG Performance Status (0 vs 1 vs 2) and Prior Bevacizumab (yes vs no) according to IVRS . Significance threshold is set to 0.0466 using the O'Brien-Fleming alpha spending function.

Subgroup analyses of Overall survival (OS)

Subgroup analyses did not show any significant interaction (at the 2-sided 10% level) between treatment arms and stratification factors, indicating that the treatment effect

was consistent across subgroups. This is illustrated in Table 9 and in Figures 3, 4 and 5.

Table 9 - Overall survival (months) – Summary of subgroup analyses – By stratification factors as per IVRS – ITT population

	Placebo/Folfiri Median (Months) (95.34% CI)	**Aflibercept/Folfiri Median (Months) (95.34% CI)**	**Hazard Ratio (95.34% CI) vs Placebo/Folfiri**	**P-value for interaction [a]**
All patients	12.1 (11.07 to 13.11)	13.5 (12.52 to 14.95)	0.817 (0.713 to 0.937)	
Prior bevacizumab				
No	12.4 (11.17 to 13.54)	13.9 (12.71 to 15.64)	0.788 (0.669 to 0.927)	0.7231
Yes	11.7 (9.82 to 13.77)	12.5 (10.78 to 15.51)	0.862 (0.673 to 1.104)	
ECOG PS				
0	14.1 (12.88 to 16.62)	16.9 (14.78 to 18.79)	0.768 (0.635 to 0.928)	0.5668
1	10.1 (9.20 to 11.53)	10.7 (9.36 to 12.35)	0.869 (0.71 to 1.063)	
2	4.4 (1.97 to 10.02)	2.8 (0.92 to 9.82)	0.978 (0.43 to 2.221)	
Cutoff date = 7 FEBRUARY 2011 Median follow-up time = 22.28 in months [a] : Interaction test from the Cox proportional hazard model including the factor, treatment effect and the treatment by factor interaction				

Treatment effect for OS was consistent across subgroups with regards to baseline characteristics at study entry. Of note, the interaction between treatment arms and the presence of liver metastasis factor was significant at 10% level, indicating a higher treatment effect in 'liver metastasis only' group (HR (95.34% CI): 0.649 (0.492 to 0.855)) than in 'no liver metastasis, or other metastases' group (HR (95.34% CI): 0.868 (0.742 to 1.015)) (quantitative interaction, p=0.0899) This is illustrated in Table 10.

Table 10 - Overall survival (months) – Summary of subgroup analyses – By baseline characteristics – ITT population

	Placebo/Folfiri Median (Months) (95.34% CI)	Aflibercept/Folfiri Median (Months) (95.34% CI)	Hazard Ratio (95.34% CI) vs Placebo/Folfiri	P-value for interaction[a]
All patients	12.1 (11.07 to 13.11)	13.5 (12.52 to 14.95)	0.817 (0.713 to 0.937)	
Prior hypertension				
No	11.7 (10.41 to 13.11)	12.7 (11.17 to 14.39)	0.883 (0.74 to 1.054)	0.1309
Yes	12.7 (10.78 to 14.00)	15.5 (12.91 to 18.56)	0.714 (0.577 to 0.884)	
Number of metastatic organs involved				
> 1	10.5 (9.72 to 12.06)	12.1 (10.71 to 13.11)	0.825 (0.692 to 0.982)	0.6992
<= 1	13.7 (12.29 to 16.30)	16.0 (14.42 to 20.86)	0.767 (0.618 to 0.953)	
Liver Metastasis only				
No	12.3 (11.07 to 13.73)	13.2 (12.06 to 15.28)	0.868 (0.742 to 1.015)	0.0899
Yes	11.4 (9.86 to 12.88)	14.4 (12.68 to 18.04)	0.649 (0.492 to 0.855)	
Location of primary tumor				
Colon	10.6 (9.66 to 12.06)	12.9 (11.50 to 16.16)	0.739 (0.607 to 0.899)	0.1421
Recto sigmoid/Other	14.1 (12.71 to 17.08)	14.3 (12.35 to 16.39)	1.039 (0.772 to 1.4)	
Rectum	12.6 (10.35 to 14.55)	13.5 (11.93 to 15.87)	0.806 (0.629 to 1.031)	
Median follow-up time = 22.28 in months [a]: Interaction test from the Cox proportional hazard model including the factor, treatment effect and the treatment by factor interaction				

2. Progression free survival based on tumor assessment by the IRC

The final analysis for PFS was performed at the time of the second interim analysis of OS (i.e. cut off date = 06 MAY 2010). Improvement in progression free survival (PFS) was demonstrated in patients of the aflibercept treatment arm compared to patients in the placebo treatment arm (stratified HR: 0.758, 99.99%CI: 0.578 to 0.995; p = 0.00007). Median PFS was 6.90 months in the aflibercept arm and 4.67 months in the placebo arm (Table 11).

Table 11 - PFS based on tumor assessment by the IRC (months) – Kaplan-Meier survival estimates by treatment group - Stratified according to stratification factors at randomization (IVRS) – ITT population

Time to Event or Censoring	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)
Overall		
Number of events, n/N(%)	454/614 (73.9%)	393/612 (64.2%)
Median PFS (99.99% CI) (months)	4.67 (4.074 to 5.552)	6.90 (5.881 to 7.852)
Number at risk		
3 months	355	420
6 months	171	247
9 months	94	99
12 months	46	43
18 months	9	7
Probability of surviving (99.99% CI)		
3 months	0.664 (0.587 to 0.741)	0.793 (0.727 to 0.859)
6 months	0.390 (0.306 to 0.475)	0.573 (0.488 to 0.659)
9 months	0.254 (0.174 to 0.334)	0.313 (0.222 to 0.404)
12 months	0.146 (0.076 to 0.216)	0.166 (0.085 to 0.246)
18 months	0.043 (0.000 to 0.091)	0.051 (0.000 to 0.108)
Stratified Log-Rank test p-value[a]		
vs Placebo/Folfiri	-	0.00007

Time to Event or Censoring	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)
Stratified Hazard ratio (99.99% CI)[a]		
vs Placebo/Folfiri	-	0.758 (0.578 to 0.995)
Cutoff date = 06 MAY 2010 [a] : Stratified on ECOG Performance Status (0 vs 1 vs 2) and Prior Bevacizumab (yes vs no) according to IVRS Significance threshold is set to 0.0001.		

Subgroup analyses of Progression free survival

Progression free survival (PFS) was analyzed in subgroups as illustrated in Table 12 and in Figure 6. No interaction between treatment arms and stratification factors was observed (Table 12).

Table 12 - PFS based on tumor assessment by the IRC (months) – Summary of subgroup analyses – By stratification factors as per IVRS – ITT population

	Placebo/Folfiri Median (Months) (99.99% CI)	Aflibercept/ Folfiri Median (Months) (99.99% CI)	Hazard Ratio (99.99% CI) vs Placebo/Folfiri	P-value for interaction[a]
All patients	4.7 (4.07 to 5.55)	6.9 (5.88 to 7.85)	0.758 (0.578 to 0.995)	
Prior bevacizumab				
No	5.4 (4.17 to 6.70)	6.9 (5.82 to 8.15)	0.797 (0.58 to 1.096)	0.6954
Yes	3.9 (2.86 to 5.42)	6.7 (4.76 to 8.74)	0.661 (0.399 to 1.095)	
ECOG PS				
0	5.4 (4.24 to 6.77)	7.2 (6.37 to 8.87)	0.761 (0.529 to 1.094)	0.1958
1	4.1 (2.83 to 5.55)	5.6 (4.60 to 7.46)	0.749 (0.494 to 1.135)	

	Placebo/Folfiri Median (Months) (99.99% CI)	Aflibercept/ Folfiri Median (Months) (99.99% CI)	Hazard Ratio (99.99% CI) vs Placebo/Folfiri	P-value for interaction[a]
2	2.0 (1.18 to 5.75)	2.7 (0.53 to 12.88)	0.618 (0.11 to 3.476)	
Cutoff date = 06 MAY 2010 [a] : Interaction test from the Cox proportional hazard model including the factor, treatment effect and the treatment by factor interaction				

For PFS, no significant interaction was shown between treatment arms and demographic variables or regions.

Treatment effect for PFS was consistent across subgroups with regards to baseline characteristics at study entry. Of note, the interaction between treatment arms and the presence of liver metastasis factor, that was noted on OS, was also significant at 10% level, indicating a higher treatment effect 'in liver metastasis only' group (HR (99.99%CI): 0.547 (0.313 to 0.956)) than in 'no liver metastasis, or other metastases' group (HR (99.99%CI): 0.839 (0.617 to 1.143)) (quantitative interaction, p=0.0076).

Results of the two sensitivity analyses for PFS were consistent with those of the primary PFS analysis. Moreover, adherence to the protocol-defined schedule for tumor assessment was assessed and showed no imbalance between treatment arms.

3. Overall Response rate

Overall response rate -IRC reviewed- was significantly higher in the aflibercept treatment arm when compared to the placebo treatment arm: 19.8% (95%CI: 16.4% to 23.2%) vs 11.1% (95%CI: 8.5% to 13.8%) respectively (p=0.0001) (Table 13).

Table 13 - Summary of overall objective response rate by IRC – Evaluable patient population for response rate

	Placebo/Folfiri (N=530)	Aflibercept/Folfiri (N=531)
Best Overall Response [n(%)]		
Complete response	2 (0.4%)	0
Partial response	57 (10.8%)	105 (19.8%)
Stable disease	344 (64.9%)	350 (65.9%)
Progressive disease	114 (21.5%)	55 (10.4%)
Not evaluable	13 (2.5%)	21 (4.0%)
Overall Response		
Responders (Complete response or Partial response)	59 (11.1%)	105 (19.8%)
95% CI[a]	8.5% to 13.8%	16.4% to 23.2%
Stratified Cochran-Mantel-Haenszel test p-value[b]		
Vs Placebo/Folfiri	-	0.0001
[a]estimated by Normal approximation [b]Stratified on ECOG Performance Status (0 vs 1 vs 2) and Prior Bevacizumab (yes vs no) according to IVRS.		

4. Further anti-cancer therapy

Overall 60% of patients in both treatment groups received further antitumor therapies (Table 14).

Table 14 - Summary of first further anti-cancer therapies – ITT population

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)
At least one further therapy [n(%)]		
Yes	366 (59.6%)	364 (59.5%)
No	248 (40.4%)	248 (40.5%)
Type of first further therapy [n(%)]		
Systemic anti-cancer treatment	303/366 (82.8%)	296/364 (81.3%)
Radiotherapy	43/366 (11.7%)	34/364 (9.3%)
Surgery	20/366 (5.5%)	34/364 (9.3%)

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)
Time from last IV to first further systemic anti-cancer therapy (months)[a]		
Number	297	293
Mean (SD)	1.87 (1.71)	2.37 (2.45)
Median	1.35	1.58
Min : Max	0.3 : 14.0	0.2 : 20.5
Time from last IV to first further radiotherapy (months)[a]		
Number	43	33
Mean (SD)	3.02 (3.86)	3.25 (3.38)
Median	1.31	2.07
Min : Max	0.4 : 16.5	0.6 : 14.6
Time from last IV to first further surgery (months)[a]		
Number	20	34
Mean (SD)	1.62 (1.41)	2.42 (2.08)
Median	1.15	1.48
Min : Max	0.4 : 7.2	0.2 : 8.5
Systemic anti-cancer therapies include chemotherapy and biologics. Only the earliest date of further therapy in each category (systemic anti-cancer treatment, radiotherapy or surgery) is kept [a]Time from last IV to first futher therapy is not calculated for patients randomized but not treated.		

About 32% of patients in each group receive further anticancer treatment that includes a “biologic (Table 15).

Table 15 - Summary of all further anti-cancer therapies – ITT population

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)
Any further therapy	366 (59.6%)	364 (59.5%)
Surgery	31 (5.0%)	47 (7.7%)
Radiotherapy	81 (13.2%)	79 (12.9%)

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)
Systemic anti-cancer treatment	329 (53.6%)	329 (53.8%)
Biologics / Small molecules	197 (32.1%)	195 (31.9%)
Cetuximab	91 (14.8%)	108 (17.6%)
Bevacizumab	75 (12.2%)	55 (9.0%)
Panitumumab	52 (8.5%)	52 (8.5%)
Other	14 (2.3%)	21 (3.4%)
Chemotherapy	297 (48.4%)	287 (46.9%)
Fluoropyrimidine	233 (37.9%)	223 (36.4%)
Irinotecan	160 (26.1%)	174 (28.4%)
Other	79 (12.9%)	71 (11.6%)
Oxaliplatin	66 (10.7%)	53 (8.7%)
Other[a]	6 (1.0%)	5 (0.8%)
[a] : include patients randomized in placebo control trials for whom exact nature of the treatment is unknown A patient can be counted both in chemotherapy and biologics (categories can not be added).		

5. Safety

Adverse events

Treatment emergent adverse events, all grades, were reported in nearly 100% of the patients in both treatment arms, whereas occurence of grade 3-4 events was greater in the aflibercept treatment arm (83.5% *vs* 62.5%).

The rate of permanent discontinuation of study treatment due to adverse events was higher in the aflibercept treatment arm (26.8% vs 12.1%). A similar pattern was observed for premature treatment discontinuation due to adverse events (19.5% *vs* 2.8%). Premature treatment discontinuation corresponds to an earlier discontinuation of either FOLFIRI, aflibercept/placebo being continued, or aflibercept/placebo, FOLFIRI being continued.

Within 30 days of last dosing, respectively 37 (6.1%) and 29 (4.8%) patients in the aflibercept and placebo arm, respectively, experienced, adverse events that eventually led to death within 30 days (28 *vs* 17 in the aflibercept and placebo arm, respectively) or after 30 days (9 *vs* 12 in the placebo and aflibercept arm, respectively) of last dosing. These included death due to disease progression.

A summary of safety data is illustrated in Table 16 and Table 17.

Table 16 - Summary of the most frequent TEAEs: incidence ≥ 20% in aflibercept arm or (incidence < 20% in aflibercept arm and Δ all grades ≥5 %) – Safety population

% of patients (in the safety population)	Placebo/Folfiri N = 605		Aflibercept/Folfiri N = 611		Δ≥10% all Gr	5≤Δ<10 % all Gr	Δ≥2% Gr 3/4
	All Gr	Gr 3/4	All Gr	Gr 3/4			
	Incidence ≥ 20% (aflibercept arm)						
Diarrhea (PT)	56.5	7.8	69.2	19.3	X		X
Asthenic condition (HLT)	50.2	10.6	60.4	16.9	X		X
Stomatitis & ulceration (HLT)	34.9	5.0	54.8	13.7	X		X
Nausea (PT)	54.0	3.0	53.4	1.8			
Infections (SOC)	32.7	6.9	46.2	12.3	X		X
Hypertension (grouping)	10.7	1.5	41.4	19.3	X		X
GI and abdominal pains (HLT)	29.1	3.3	34.0	5.4			
Vomiting (PT)	33.4	3.5	32.9	2.8			
Decrease appetite (PT)	23.8	1.8	31.9	3.4		X	
Weight decrease (PT)	14.4	0.8	31.9	2.6	X		
Epistaxis (PT)	7.4	0	27.7	0.2	X		
Alopecia (PT)	30.1	NA	26.8	NA			
Dysphonia (PT)	3.3	0	25.4	0.5	X		

% of patients (in the safety population)	Placebo/Folfiri N = 605		Aflibercept/Folfiri N = 611		Δ≥10% all Gr	5≤Δ<10 % all Gr	Δ≥2% Gr 3/4
	All Gr	Gr 3/4	All Gr	Gr 3/4			
	Incidence ≥ 20% (aflibercept arm)						
Musculoskeletal & connective pain & discomfort (HLT)	21.2	2.3	23.1	1.3			
Constipation (PT)	24.6	1.0	22.4	0.8			
Headache (PT)	8.8	0.3	22.3	1.6	X		
	Incidence < 20% (aflibercept arm) and Δ all grades ≥ 5 %						
Palmar plantar erythrodysaesthesia (PT)	4.3	0.5	11.0	2.8		X	
Dehydration (PT)	3.0	1.3	9.0	4.3		X	
Skin hyperpigmentation (PT)	2.8	0	8.2	0		X	
Medra classification: SOC (system organ class), HLT (high level term), PT (Preferred term). Grouping: grouping of selected PTs Δ: difference in incidence in aflibercept arm compared to placebo							

Table 17 - Overview of safety, number (%) of patients – Safety population

	Placebo/Folfiri (N=605)	Aflibercept/Folfiri (N=611)
Patients with any TEAE	592 (97.9%)	606 (99.2%)
Patients with any grade 3-4 TEAE	378 (62.5%)	510 (83.5%)
Patients with any serious TEAE	198 (32.7%)	294 (48.1%)
Patients with any TEAE leading to death	29 (4.8%)	37 (6.1%)
Patients with any related TEAE leading to death	3 (0.5%)	6 (1.0%)
Patients with any TEAE leading to permanent treatment discontinuation	73 (12.1%)	164 (26.8%)

	Placebo/Folfiri (N=605)	Aflibercept/Folfiri (N=611)
Patients with any TEAE leading to premature treatment discontinuation	17 (2.8%)	119 (19.5%)
Note : Adverse Events are reported using MedDRA version MEDDRA13.1 and graded using NCI CTC Version 3.0.		

5. Conclusions

The study met its primary endpoint, with a significant improvement in overall survival in the aflibercept arm when compared to placebo.

In addition, a significant improvement was demonstrated on secondary efficacy endpoints (PFS and RR).

The safety profile was qualitatively consistent with that of anti VEGF treatment with enhancement of known toxicities of the background chemotherapy (such as diarrhea, stomatitis, infections, neutropenia/neutropenic complications).

CLAIMS

1. A method of treating Colorectal Cancer (CRC) or Colorectal Cancer (CRC) symptom in a patient in need thereof, said method comprising administering to said patient therapeutically effective amounts of aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinocetan.

2. A method of increasing Overall Survival (OS) in a patient afflicted with CRC, said method comprising administering to said patient therapeutically effective amounts of aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinocetan.

3. A method of increasing Progression Free Survival (PFS) in a patient afflicted with CRC, said method comprising administering to said patient therapeutically effective amounts of aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinocetan.

4. A method of increasing Overall Response Rate (ORR) in a patient afflicted with CRC, said method comprising administering to said patient therapeutically effective amounts of aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinocetan.

5. A method according to any one of claims 1 to 4 which is safe and effective.

6. A method according to any one of claims 1 to 5 wherein said patient has already been treated for the CRC or CRC symptom.

7. A method according to any one of claims 1 to 6 wherein said patient has previously been treated with chemotherapy, radiotherapy or surgery.

8. A method according to any one of claims 1 to 7 wherein said patient has previously been treated with therapy based on oxaliplatin or on bevacizumab.

9. A method according to any one of claims 7 and 8 wherein said patient has failed with chemotherapy, radiotherapy or surgery.

10. A method according to any one of claims 1 to 9 wherein CRC is a Metastatic CRC.

11. A method according to any one of claims 1 to 10 wherein folinic acid at a dosage comprised between about 200 mg/m^2 and about 600 mg/m^2, 5-fluorouracil (5-FU)

at a dosage comprised between about 2000 mg/m^2 and about 4000 mg/m^2 , irinocetan at a dosage comprised between about 100 mg/m^2 and about 300 mg/m^2 and aflibercept at a dosage comprised between about 1 mg/kg and about 10 mg/kg are administered to patient.

12. A method according to any one of claims 1 to 11 wherein folinic acid at a dosage of about 400 mg/m^2, 5-fluorouracil (5-FU) at a dosage of about 2800 mg/m^2, irinocetan at a dosage of about 180 mg/m^2 and aflibercept at a dosage of about 4 mg/kg are administered to patient.

13. A method according to any one of claims 1 to 12 wherein folinic acid is administered intravenously at a dosage of about 400 mg/m^2, 5-fluorouracil (5-FU) is administered intravenously at a dosage of about 2800 mg/m^2, irinocetan is administered intravenously at a dosage of about 180 mg/m^2 and aflibercept is administered intravenously at a dosage of about 4 mg/kg and wherein the comination is administered every two weeks.

14. A method according to any one of claims 1 to 13 wherein the folinic acid, 5-fluorouracil (5-FU), irinocetan and aflibercept are administered intravenously every two weeks for a period comprised between 9 and 18 weeks.

15. A method according to any one of claims 1 to14 wherein the folinic acid is administered intravenously immediately after aflibercept administration.

16. A method according to any one of claims 1 to 15 wherein the folinic acid is administered intravenously immediately after aflibercept administration over a period of about 2 hours.

17. A method according to any one of claims 1 to 16 wherein the irinocetan is administered intravenouslyimmediately after aflibercept administration.

18. A method according to any one of claims 1 to 17 wherein the irinocetan is administered intravenously immediately after aflibercept administration over a period of about 90 minutes

19. A method according to any one of claims 1 to 18 wherein the 5-fluorouracil (5-FU) is administered immediately after aflibercept administration.

20. A method according to any one of claims 1 to 19 wherein a first quantity of 5-fluorouracil (5-FU) is administered intravenously immediately after aflibercept administration and a second quantity of 5-FU is administered intravenously after the first quantity in continous infusion.

21. A method according to any one of claims 1 to 20 wherein about 400 mg/m^2 of 5-fluorouracil (5-FU) is administered intravenously over a period of 2 to 4 minutes after aflibercept administration and wherein 2400 mg/m^2 of 5-FU is administered intravenously over almost 46 hours after the administration of the 400 mg/m^2 in continous infusion.

22. A method according to any one of claims 1 to 21 wherein the patient has liver metastases.

23. Composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinocetan for treating patients with CRC wherein the composition is for simultaneous administration.

24. Composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinocetan for treating patients with CRC wherein the composition is for sequential administration.

25. Composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinocetan for treating patients with CRC wherein wherein the composition is for administration spaced out over a period of time so as to obtain the maximum efficacy of the combination.

26. An article of manufacture comprising:

a) a packaging material

b) aflibercept, and

c) a label or package insert contained within said packaging material indicates that aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinocetan is effective for the treatment of CRC.

27. An article of manufacture according to claim 26, wherein said treatment of CRC comprises improvement in Overall Survival (OS).

28. An article of manufacture according to claim 26, wherein said treatment of CRC comprises improvement in Progression Free Survival (PFS).

29. An article of manufacture according to claim 26, wherein said treatment of CRC comprises improvement in Overall Response Rate (ORR).

30. Composition comprising therapeutically effective amounts of aflibercept in combination with folinic acid, 5-fluorouracil (5-FU) and irinocetan and comprising a pharmaceutically acceptable carrier for treating patients with CRC.

31. A kit for treating patients with CRC comprising:

a) at least one compound chosen from the list consisting of aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinocetan; and

b) a label or package insert contained within said kit indicating that aflibercept is to be used in combination with folinic acid, 5-fluorouracil (5-FU) and irinocetan (FOLFIRI) or that folinic acid, 5-fluorouracil (5-FU) and irinocetan (FOLFIRI) is to be used in combination with Aflibercept.

32. A kit comprising in separate containers pharmaceutical compositions for combined use in treating CRC in a patient which comprises (1) a pharmaceutical composition comprising aflibercept , (2) a pharmaceutical composition comprising folinic acid, (3) a pharmaceutical composition comprising 5-fluorouracil (5-FU) and (4) a pharmaceutical composition comprising irinocetan.

SEQUENCE LISTING

<110> SANOFI

<120> Composition comprising aflibercept, folinic acid, 5-fluorouracil (5-FU) and irinocetan (FOLFIRI)

<130> FR2011-027 PCT

<160> 1

<170> PatentIn version 3.3

<210> 1
<211> 431
<212> PRT
<213> Artificial

<220>
<223> Aflibercept

<400> 1

Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu
1 5 10 15

Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val
20 25 30

Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr
35 40 45

Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
50 55 60

Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
65 70 75 80

Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg
85 90 95

Gln Thr Asn Thr Ile Ile Asp Val Val Leu Ser Pro Ser His Gly Ile
100 105 110

Glu Leu Ser Val Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg Thr
115 120 125

Glu Leu Asn Val Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys
130 135 140

His Gln His Lys Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser Gly
145 150 155 160

Ser Glu Met Lys Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val Thr
165 170 175

Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met

```
            180                 185                 190

Thr Lys Lys Asn Ser Thr Phe Val Arg Val His Glu Lys Asp Lys Thr
        195                 200                 205

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
    210                 215                 220

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
225                 230                 235                 240

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
                245                 250                 255

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
            260                 265                 270

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
        275                 280                 285

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
    290                 295                 300

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
305                 310                 315                 320

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
                325                 330                 335

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
            340                 345                 350

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
        355                 360                 365

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
    370                 375                 380

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
385                 390                 395                 400

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
                405                 410                 415

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
            420                 425                 430
```