Aflibercept in Combination With FOLFIRI as First-line Chemotherapy in Patients With Metastatic Colorectal Cancer (mCRC): A Phase II Study (FFCD 1302)

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Abstract

Chemotherapy with FOLFIRI (irinotecan, 5-fluorouracil, and leucovorin) + aflibercept improves survival in patients with previously treated metastatic colorectal cancer (mCRC). Our phase II study evaluated efficacy and tolerability of this treatment in non-pretreated patients with mCRC. Though the primary endpoint was not met, results showed that first line FOLFIRI + aflibercept for mCRC leads to survival close to those reported with standard first-line treatments, but with significant toxicities.

Background: FOLFIRI (irinotecan, 5-fluorouracil, and leucovorin) + aflibercept improves median overall survival (OS) and progression-free survival (PFS) in patients with previously treated metastatic colorectal cancer (mCRC). Our aim was to investigate efficacy and tolerability of this combination in the first line. **Patients and Methods:** Patients with untreated documented mCRC received aflibercept plus FOLFIRI every 14 days until progression or unacceptable toxicity in an open, phase II single-arm, multicenter trial. The primary endpoint was the 6-month PFS rate. Secondary endpoints were OS and tolerability. A 2-step Simon design was used with H_0: 55% and H_1= 75%. Data were analyzed in intention to treat. **Results:** Forty-one patients were included, and 40 were analyzed (1 consent withdrawal) in 9 French centers between October 2014 and February 2017. The median age was 65 years (range, 46-81 years), 55% had $\geq$ 2 metastatic sites, and 50% and 15% had *RAS* and *BRAF* mutations, respectively. Twenty-two (54.5%; 95% confidence interval, 38.9%-68.5%) patients were alive and non-progressive at 6 months. FOLFIRI + aflibercept was considered ineffective, resulting in the cessation of inclusions. The median follow-up was 34 months. The overall response rate was 55%, and the disease control rate was 80%. The median duration of treatment was 5.3 months; the median PFS and OS were 8.2 and 18.6 months, respectively. Grade 3 to 4 adverse events were mainly gastrointestinal (47.5%) and vascular (32.5%). Of the patients, 87.5% had at least 1 dose modification. **Conclusion:** Although the primary objective was not met, first-line FOLFIRI + aflibercept for mCRC leads to median PFS and OS close to those reported with classical doublet and targeted agents, but with significant toxicities needing dose reduction.

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Introduction

With approximately 1.4 millions of new cases per year, colorectal cancer (CRC) is the third most common malignancy worldwide in men, the second in women, and the fourth highest cause of cancer-related death.[1] Progresses in the last 20 years in the management of metastatic colorectal cancer (mCRC) has significantly improved survival of patients, with the use of chemotherapy combinations and targeted therapies.

First-line treatment of patients with mCRC typically involves the use of a fluoropyrimidine-based chemotherapy with either oxaliplatin or irinotecan, in association with a targeted therapy as an epidermal growth factor receptor monoclonal antibody or bevacizumab, according to the *RAS* molecular status of the tumor.[2-4] Bevacizumab is a fully humanized monoclonal antibody directed against vascular endothelial growth factor A (VEGF-A), and is actually the only anti-angiogenic therapy validated in the first-line setting in patients with mCRC, in both RAS wild type and mutated patients. In patients with mCRC, bevacizumab improves both progression-free survival (PFS) and overall survival (OS) in combination with chemotherapy, in the first-line setting[5,6] and in association with FOLFOX (folinic acid, 5-fluorouracil [5-FU], and oxaliplatin) in the second line.[7]

Aflibercept is a fusion protein composed of extracellular domains of VEGFR-1 and VEGFR-2, which inhibits tumor angiogenesis by targeting VEGF-A, VEGF-B, and placental growth factor (PlGF). Aflibercept in association with FOLFIRI (irinotecan, 5-FU, and leucovorin) significantly improves both the OS and the PFS, as well as the response rate of patients with mCRC compared with placebo plus FOLFIRI, after failure of an oxaliplatin-based regimen.[8] In this trial, patients received FOLFOX ± bevacizumab as first-line treatment for their mCRC and, interestingly, even patients initially treated with bevacizumab (28%) tend to benefit from the addition of aflibercept to chemotherapy. This suggests that the broader antiangiogenic spectrum of this molecule may potentially overcome the mechanisms of resistance of bevacizumab.

We hypothesize that the association of aflibercept plus FOLFIRI from the first line may be an active regimen in patients with mCRC.

The primary objective of this multicentric phase II study was to investigate efficacy and safety of the combination of aflibercept plus FOLFIRI in patients with CRC not previously treated for their metastatic disease.

Patients and Methods

Eligibility Criteria

Inclusion criteria were: age $\geq$ 18 years, Eastern Cooperative Oncology Group performance score (ECOG PS) of 2 or less, histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum with unresectable metastatic disease, and at least 1 measurable target by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.1. Patients also had to have adequate hematopoietic, hepatic (especially serum bilirubine $<$ 1.5 times the upper limit of normal) and renal function (with proteinuria $<$ 1 g/24 hours), and no uncontrolled hypercalcemia. Patients should not have received any prior chemotherapy for their metastatic disease (previous adjuvant chemotherapy completed 6 months or more prior to the diagnosis of metastasis was permitted).

Key exclusion criteria were brain metastasis, significant surgery during 28 days before treatment start, history of malignancy other than mCRC, and symptomatic disease (occlusion, hemorrhage). Patients with uncontrolled hypertension, clinically significant cardiovascular events (ie, cerebrovascular accidents or myocardial infarction) within 6 months before study inclusion, or thromboembolic or hemorrhagic events within 3 months before study inclusion were also excluded, as well as patients currently treated with new oral anticoagulants.

The promotor of the study was the French Federation of Digestive Oncology (FFCD). The study was registered under the number EudraCT 2013-004081-33. Study protocol was approved by the ethics committee (CPP ILE DE France VIII of Boulogne Billancourt on 06/01/2014) and by the National Agency for the Safety of Medicines and Health Products (ANSM) on January 30, 2014.

All patients were informed of the investigational nature of the study and provided written informed consent before inclusion.

Drug Administration and Study Design

This was a single-arm, multicentric phase II study. Every 14 days, eligible patients received 4 mg/kg of aflibercept intravenously [IV], over 1 hour, followed immediately by the FOLFIRI regimen (irinotecan 180mg/m^2 IV over 90 minutes, with leucovorin 400 mg/m^2 IV over 2 hours, followed by 5-FU 400 mg/m^2 bolus and 5-FU 2400 mg/m^2 continuous infusion over 46 hours). Patients were treated until occurrence of disease progression or unacceptable toxicity according to physician judgment.

Assessments

Within 21 days of starting treatment, a pretreatment evaluation included a clinical examination (body weight, temperature, blood pressure, ECOG PS status, and medical history), laboratory analyses (complete blood count and coagulation tests, blood chemistry, evaluation of proteinuria, carcinoembryonic antigen, and pregnancy test for women), and a computed tomography (CT) scan with and without contrast injection for tumor assessment. Before each chemotherapy cycle, patients underwent clinical examination and laboratory assessments (including urine analysis). Adverse events (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 4.0) were recorded. Every 8 weeks, a disease evaluation was performed (clinical examination and laboratory assessment including carcinoembryonic antigen and CT scan), until documented progression. Response was assessed according to RECIST (version 1.1) by the investigator. Patients who discontinued treatment underwent a medical visit within 30 days of treatment stop. Patients were followed every 2 months until progression; then every 3 months for 2 years; then every 6 months thereafter until death.

Statistical Analysis

The primary endpoint of this study was the rate of patients alive and progression-free 6 months after inclusion. Progression was evaluated by CT, according to RECIST criteria (version 1.1) by the investigator.

We hoped to reach an efficacy of 75% of patients alive and without progression at 6 months (H0: p0 = 55% and H1:

p1 = 75%). With a 5% "1-sided" alpha error risk and a 90% power, using the 2-step Simon method (Minimax) and with a rate of 10% of patients lost to follow-up, 54 patients have to be included. Step I was carried out after the inclusion of 33 patients and a minimum follow-up of 6 months (ie, in April 2017). The stop of inclusions was recommended. Eighteen (54.5%; 90% confidence interval [CI], 38.9%-69.5%) of 33 patients were alive and progression-free 6 months after inclusion, whereas 21 patients were expected. Final analyses presented on this paper are on the 40 patients included in the study, except for the primary endpoint (where analysis was done on the first 33 patients).

PFS, OS, and safety were secondary endpoints. The relative dose intensity is defined as the ratio of the cumulative treatment dose received to the theoretical dose to be received. All the analyses have been carried out on intention-to-treat population (ie, all patients included in the study regardless of the eligibility criteria and the treatment received). The safety population was all the patients receiving at least 1 dose of treatment.

Clinical variables are described using percentages, mean (standard deviation) and median (Q1, Q3, minimum, and maximum). Survival and time estimation is done by the Kaplan-Meier method. The median follow-up time is calculated using the so-called "reverse Kaplan-Meier" method.

Results

At the end of step 1 of our statistical design, 41 patients were included by 9 centers between October 2014 and February 2017, including 33 patients from step 1, and 9 patients included in the trial during the 6-month follow-up period. One patient withdrew his consent and was not analyzed; therefore, final analysis was done on 40 patients.

Patient Characteristics

The median age of patients was 65 years (range, 46-81 years); 42% were men, and 55% had 2 or more metastatic sites. *RAS* and *BRAF* mutation were observed respectively in 50% (n = 20) and 15% (n = 6). Ninety-five percent of patients had an ECOG PS of 0 or 1. Patient characteristics are summarized in Table 1.

Table 1 Patient Baseline Characteristics (ITT Population)

	N (%)
ECOG PS	
0	16 (40.0)
1	22 (55.0)
2	2 (5.0)
Age, y	
Median	64.85
Range	45.72-80.39
Gender	
Male	17 (42.5)
Female	23 (57.5)
Body weight, kg	
Median	65.00
Range	40.00-96.00
Median BMI, kg/m^2 (range)	22.85 (15.99-38.95)
Primary site	
Colon	33 (82.5)
Rectum	7 (17.5)
No. metastatic organs involved at baseline (excluding primary site)	
1	18 (45.0)
2	14 (35.0)
>2	8 (20.0)
Type of metastatic organs involved at baseline (excluding primary site)	
Liver	33 (82.5)
Lung	15 (37.5)
Peritoneal carcinomatosis	12 (30.0)
Surgery of metastasis	
Liver	2 (6.1)
Lung	1 (6.7)
Molecular status	
RAS	
wt	14 (35)
mt	20 (50)
nd	6 (15.0)
BRAF	
wt	25 (62.5)
mt	6 (15)
nd	9 (22.5)
Prior adjuvant chemotherapy	8 (20)

Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intention-to-treat; mt = mutated; nd = not determined; wt = wild type.

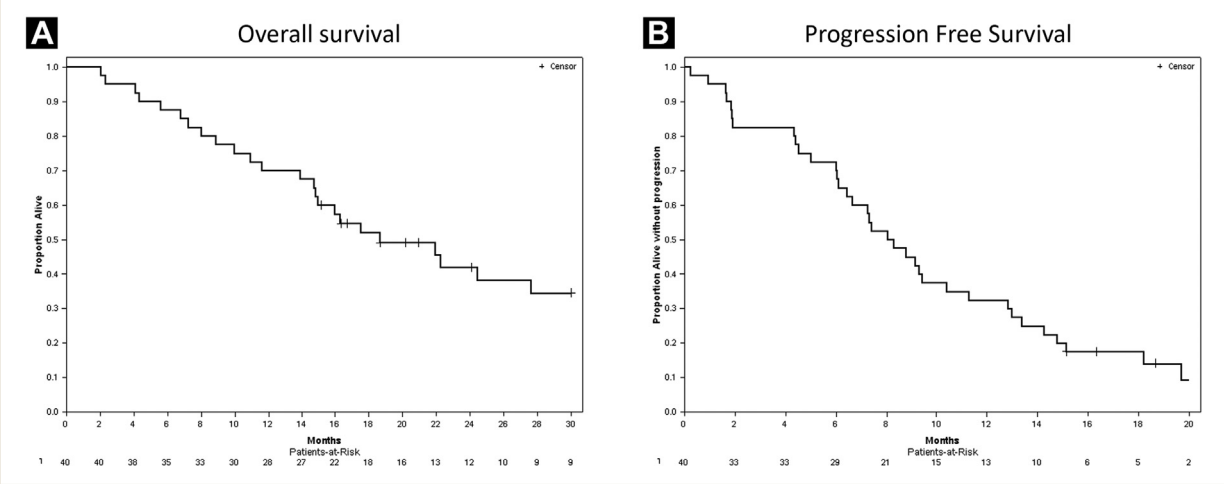
Efficacy Analyses

The median follow-up was 34.2 months (95% CI, 20.9-35.7 months). Twenty-two (55%) of 40 patients were alive and progression-free 6 months after inclusion. Twenty-five patients died (96% for disease progression), and the median OS was 18.6 months (95% CI, 14.7-30.7 months). Thirty-six patients had progression or death, and the median time to progression was 8.2 months (95% CI, 6.1-10.4 months). Based on CT scan evaluation, 22 (55%) patients achieved an objective response. The median time to response was 2.45 months (range, 1.64-37.13 months). The disease control rate (complete response + partial response + stable disease) was 80% (range, 64.3%-90.9%). Efficacy data are summarized in Figure 1 and Table 2.

Safety

Adverse events were reported in all patients treated with FOLFIRI plus aflibercept, with at least 1 grade 3 or 4 event reported in 90% of patients. However, no treatment-related death was reported, and corrective treatments and dose modifications allowed complete recovery in all patients. Nineteen (47.5%) patients had grade 3 or 4 digestive adverse events, including 15% with mucositis, 12.5% with diarrhea, and 12.5% with abdominal pain. Vascular toxicities occurred in 13 (32.5%) patients, including hypertension (17.5%) and venous thromboembolism (17.5%). One patient presented

Figure 1 Kaplan-Meier Estimates of Overall Survival (A) and Progression-free Survival (B)



Abbreviations: OS = overall survival; PFS = progression-free survival.

Table 2 Efficacy Summary

	N (%)
Time to progression, mos	
Median (range)	7.39 (0.23-29.54)
Best overall response	
Complete response	4 (10.0)
Partial response	18 (45.0)
Stable disease	10 (25.0)
Progressive disease	8 (20.0)
Disease control rate	32 (80)
Duration of disease control, mos	
Median (range)	9.45 (1.64-38.64)
Treatment discontinuation	
Owing to radiologic and/or clinical progression	
FOLFIRI	24 (60.0)
Aflibercept	17 (42.5)
Owing to toxicity	
FOLFIRI	3 (7.5)
Aflibercept	7 (17.5)
Owing to other reason	
FOLFIRI	11 (27.5)
Aflibercept	14 (35.0)
Post study treatments	
Second-line treatment	31 (77.5)
Third-line treatment	17 (42.5)
>Third-line treatment	5 (12.5)

Abbreviation: FOLFIRI = fluorouracil, leucovorin, and irinotecan.

with febrile neutropenia. Grade 3 or 4 neutropenia occurred in 27.5% of the patients. Table 3 summarizes the incidence of the most commonly reported adverse events. At least 1 dose modification during treatment was required in 18.5% of patients. One patient received granulocyte colony-stimulating factor (G-CSF) as primary prophylaxis, whereas 11 patients received G-CSF as secondary prophylaxis. Aflibercept was stopped for toxicity in 7 (18%) patients, whereas discontinuation of FOLFIRI owing to adverse events occurred in 3 (7.7%) patients.

Treatment Administration

Patients received a median of 11 cycles of chemotherapy (range, 1.0-58.0 cycles). The median duration of treatment was 5.3 months. Thirty-five (87.5%) patients had at least 1 dose modification. The median relative dose intensity (RDI) of 5-FU, irinotecan, and aflibercept are summarized in Table 4. RDI was 64% for 5-FU bolus and 94% for infusional 5-FU, owing to hematologic toxicity in, respectively, 54% and 48.1% of cases. RDI for irinotecan was 96% (40.1% of dose reduction for hematotoxicity) and 86% for aflibercept. Aflibercept was stopped for disease progression (clinic and/or radiologic) in 42.5% of patients and for toxicity in 17.5% of patients. FOLFIRI was stopped for disease progression (clinical and/or radiologic) in 60% of patients and for toxicity in 7.7% of patients. One patient was still under treatment with aflibercept at the time of the analysis.

Discussion

In combination with chemotherapy, anti-angiogenic treatments have been shown to slightly but significantly prolong survival in pretreated patients with mCRC.[7-11] In the phase III VELOUR trial, adding aflibercept to FOLFIRI significantly improved the OS of

Table 3 Adverse Events

Toxicity	All Patients (n = 40), n (%)	
	Grade 1-2	Grade ≥ 3
All	40 (100)	36 (90.5)
Gastro-intestinal	39 (97.5)	19 (47.5)
Nausea	27 (67.5)	2 (5.0)
Vomiting	14 (35.0)	3 (7.5)
Diarrhea	26 (65.0)	5 (12.5)
Abdominal pain	16 (40.0)	5 (12.5)
Mucositis	18 (45.0)	6 (15.0)
Colonic perforation	–	2 (5.0)
Vascular	16 (40)	13 (32.5)
Arterial TE event	–	1 (2.5)
Venous TE event	2 (5.0)	7 (17.5)
Hemorrhage	1 (2.5)	1 (2.5)
Hypertension	14 (35.0)	7 (17.5)
Renal and biliary	11 (27.5)	2 (5.0)
Proteinuria	11 (27.5)	2 (5.0)
Infection	12 (30)	7 (17.5)
Hematologic	28 (70.0)	3 (7.5)
Febrile neutropenia	NA	1 (2.5)
Investigations		
Anemia	28 (70)	2 (5)
Thrombocytopenia	5 (12.5)	1 (2.5)
Lymphopenia	1 (2.5)	0
Leucopenia	18 (45)	2 (5)
Neutropenia	15 (37.5)	11 (27.5)

Grades were determined according to National Cancer Institute Common Terminology Criteria of Adverse Events, version 4.0.
Abbreviation: TE = thromboembolism.

patients with mCRC, after failure of an oxaliplatin-based regimen, compared with chemotherapy alone (median OS, 13.5 vs. 12.1 months; hazard ratio, 0.82; 95% CI, 0.71-0.94; PFS, 6.9 vs. 4.7 months).[8] In the randomized phase II AFFIRM study, adding aflibercept to an oxaliplatin-based regimen (mFOLFOX6) in chemotherapy-naive patients with mCRC did not appear to increase efficacy over chemotherapy alone.[12] These results suggest a more synergistic action of aflibercept in association with irinotecan.

To our knowledge, our study is the first prospective multicentric phase II study that evaluated efficacy and toxicity of aflibercept in combination with FOLFIRI in the first-line setting in patients with mCRC. Our study was interrupted at the time of the interim analysis because the previously defined efficiency objectives were not achieved. At 6 months, 10% and 45% of patients had complete and partial response, respectively, 25% had stable disease, and 20% had progressive disease. The H_1 hypothesis targeting a 6-month PFS rate of 75% for this phase II study may have been too ambitious.

Table 4 Treatment Administration

RDI	5-FU Bolus	5-FU Continuous Infusion	Irinotecan	Aflibercept
Median	63.93	94.15	95.98	86.25
Q1; Q3	20.51; 94.34	83.99; 99.49	83.32; 99.40	66.31; 99.69
Min; Max	0.00; 101.62	70.34; 103.49	64.39; 102.84	24.16; 107.14

Abbreviations: 5-FU = 5-Fluorouracil; Q1; Q3 = quartiles; RDI = relative dose intensity.

The proportion of patients with *RAS* or *BRAF* mutated tumors (65% of our patients) was greater in our study than the prevalence usually reported in the literature (45%-50% for *RAS* and 5%-8% for *BRAF* mutations), which can partly explain our results.[13] Indeed, our survival results, with a median PFS of 8.2 months and a median OS of 18.6 months, seem to be worse than those observed in other studies associating FOLFIRI with an anti-angiogenic agent in the first line. In the PRODIGE 9 phase III trial evaluating FOLFIRI + bevacizumab induction chemotherapy followed by bevacizumab maintenance or observation, also conducted in France just before this study, the median OS was 22 months with a frequency of *RAS* and *BRAF* mutation rate of 46% and 8.6%, respectively.[14] In the FIRE 3 study, with a *RAS* and *BRAF* mutation rate, respectively, of 30% and 8.5% in patients in the FOLFIRI plus bevacizumab arm, the median PFS and OS were 10.3 and 25 months, respectively.[15] Similar survival rates have been reported for patients receiving FOLFIRI plus bevacizumab in the TRIBE study (median PFS and OS of 9.7 and 25.8 months, respectively) with a frequency of *RAS* and *BRAF* mutations of 46.5% and 4.7%, respectively.[16]

We can also point out that the RAS status was not taken into account at the time of inclusion for the selection of patients receiving the antiangiogenic agent in the first line.

However, more recent data from literature have reported that wild-type *RAS* patients seem to benefit more from anti-EGFR than anti-angiogenic treatment in the first-line setting and especially if the primary tumor location is left-sided.[13,17] Clinical patient characteristics at baseline could also have a negative influence on their prognosis. Indeed, 55% of patients had 2 or more metastatic sites at diagnosis, and most importantly, 30% of patients had peritoneal carcinomatosis at the time of inclusion, as compared with 12.3% in the VELOUR pivotal trial, knowing that this metastatic site has been reported to be associated with a particularly poor prognosis.[18]

Adverse effects were significant with grade 3 or 4 events reported in 90% of patients, attributable both to chemotherapy and to the anti-VEGF therapy. We observed mainly digestive and vascular adverse events, which led to dose adjustments in 87.5% of cases, mainly on bolus 5-FU that was reduced by 50% or omitted for subsequent cycles. Despite these adaptations, treatment dose intensity remained acceptable and in the range of what has been previously reported in patients with mCRC. The incidence of grade 3 or 4 diarrhea was similar in our study (12.5%) and in patients treated with FOLFIRI plus bevacizumab (13%),[15] whereas this rate was higher in patients receiving FOLFIRI plus aflibercept in the second line (19.3%).[8] The incidence of mucositis and neutropenia was similar for patients treated with FOLFIRI plus aflibercept in the first or second line, and a bit higher than those reported in patients treated with FOLFIRI plus bevacizumab in the first line. There were more grade 3 or 4 venous thromboembolic events in our study (17.5%), than in the 2 previously mentioned trials with aflibercept and bevacizumab (7%-8%), which could reflect patients with a more aggressive disease profile in our cohort. Approximately 25% of

patients required secondary prophylaxis with G-CSF that successfully prevented severe neutropenia. Finally, although toxicities observed with FOLFIRI plus aflibercept were significant, they were globally very similar to those reported in previous studies evaluating FOLFIRI plus aflibercept in the second line[8] or FOLFIRI plus bevacizumab in the first-line setting.[15,16] The rate of severe complications such as digestive perforation was similar in the 3 studies (< 1%), and no toxic deaths were reported in the present trial.

In conclusion, first-line FOLFIRI + aflibercept for patients with mCRC is feasible but with frequent toxicities requiring dose reductions and adequate management. Although the primary endpoint of the study was not met owing to an overly ambitious hypotheses and a possible poor patient population selection, this combination therapy led to median PFS and OS close to those reported with classical doublet and targeted agents in this setting.

Clinical Practice Points

- Antiangiogenic therapies have shown significant efficacy in patients with mCRC, preventing tumor progression by limiting tumor-induced angiogenesis.
- Administration of bevacizumab (anti VEGF-A targeted therapy) increases survival of patients with mCRC in the first-line setting in association with irinotecan-based chemotherapy or in the second-line setting with the FOLFOX regimen.
- Aflibercept has a broader anti-angiogenic spectrum than bevacizumab, by targeting VEGF-A, VEGF-B, and PlGF.
- It had been previously demonstrated that aflibercept in combination with FOLFIRI in the second line for patients with mCRC improves PFS and OS as compared with FOLFIRI with an acceptable toxicity profile.
- This phase II trial failed to reach its primary endpoint, but shows that FOLFIRI + aflibercept in the first line leads to PFS and OS close to those reported with classical doublet and targeted agents.
- Toxicities were similar to those reported for patients treated with FOLFIRI plus aflibercept in previous studies.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136:E359-86.
2. Phelip J, Benhaim L, Bouché O, et al. "Cancer colorectal métastatique". Thésaurus National de Cancérologie Digestive. Thésaurus Natl Cancérologie Dig [Internet]. 2019 Jan. Available at: https://www.snfge.org/content/4-cancer-colorectal-metastatique. Accessed: September 4, 2020.
3. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; 27: 1386-422.
4. Benson AB, Venook AP, Al-Hawary MM, et al. NCCN guidelines insights: colon cancer, version 2.2018. *J Natl Compr Cancer Netw* 2018; 16:359-69.
5. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350:2335-42.
6. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008; 26:2013-9.
7. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Eastern Cooperative Oncology Group Study E3200. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007; 25:1539-44.
8. Van Cutsem E, Tabernero J, Lakomy R, et al. 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* 2012; 30:3499-506.
9. Bennouna J, Sastre J, Arnold D, et al. ML18147 Study Investigators. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013; 14:29-37.
10. Grothey A, Van Cutsem E, Sobrero A, et al. CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; 381:303-12.
11. Tabernero J, Yoshino T, Cohn AL, et al. RAISE Study Investigators. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol* 2015; 16: 499-508.
12. Folprecht G, Pericay C, Saunders MP, et al. Oxaliplatin and 5-FU/folinic acid (modified FOLFOX6) with or without aflibercept in first-line treatment of patients with metastatic colorectal cancer: the AFFIRM study. *Ann Oncol* 2016; 27:1273-9.
13. Taieb J, Jung A, Sartore-Bianchi A, et al. The evolving biomarker landscape for treatment selection in metastatic colorectal cancer. *Drugs* 2019; 79:1375-94.
14. Aparicio T, Ghiringhelli F, Boige V, et al. PRODIGE 9 Investigators. Bevacizumab maintenance versus no maintenance during chemotherapy-free intervals in metastatic colorectal cancer: a randomized phase III trial (PRODIGE 9). *J Clin Oncol* 2018; 36:674-81.
15. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; 15:1065-75.
16. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol* 2015; 16:1306-15.
17. Gallois C, Pernot S, Zaanan A, Taieb J. Colorectal cancer: why does side matter? *Drugs* 2018; 78:789-98.
18. Franko J, Shi Q, Meyers JP, et al. Analysis and Research in Cancers of the Digestive System (ARCAD) Group. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *Lancet Oncol* 2016; 17: 1709-19.