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European Medicines Agency approval summary: Zaltrap for the treatment of patients with oxaliplatin-resistant metastatic colorectal cancer

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ABSTRACT

On 1 February 2013, a marketing authorisation valid throughout the European Union was issued for aflibercept (Zaltrap) in combination with irinotecan/5-fluorouracil/folinic acid chemotherapy for the treatment of adults with metastatic colorectal cancer resistant to or progressive after an oxaliplatin-containing regimen. Aflibercept is a recombinant fusion protein which blocks the activation of vascular endothelial growth factor (VEGF) receptors and the proliferation of endothelial cells, acting as a soluble decoy receptor that binds to VEGF-A with higher affinity than its native receptors, as well as placental growth factor and VEGF-B. The use of aflibercept was studied in a randomised, double-blind, placebo-controlled phase III study, in patients with metastatic colorectal cancer (mCRC) who had previously been treated with an oxaliplatin-based treatment with or without prior bevacizumab. Aflibercept (n=612) was compared with placebo (n=614), both in combination with FOLFIRI (infusional fluorouracil, leucovorin and irinotecan). The primary endpoint of the study was overall survival (OS). The median OS in the intent-to-treat population was 13.5 months in subjects treated with aflibercept compared with 12.1 months for subjects in the control arm (stratified HR=0.817, 95% CI 0.714 to 0.935, stratified pvalue=0.0032). The frequency of adverse events was higher in the aflibercept arm compared with the placebo arm, reflecting the toxicity profile of anti-VEGF agents in combination with chemotherapy. This paper is based on the scientific review of the application leading to approval of aflibercept in the EU. The detailed scientific assessment report and product information for this product are available on the European Medicines Agency website (<http://www.ema.europa.eu>). **Trial registration number** NCT00561470, Results.

INTRODUCTION

Colorectal cancer (CRC) is the second-most frequently diagnosed cancer, representing 13.2% and 12.7% of all cancer cases in men and women, respectively. CRC was responsible for 215 000 deaths in Europe in 2012. At diagnosis, 25% of the patients present with metastases and 50% of the patients will develop metastases during the course of the

disease. The 5-year survival rate is approximately 60%.¹

Significant advances in the treatment of metastatic colorectal cancer (mCRC) have been made due to the introduction of agents such as 5-fluorouracil (5FU), leucovorin (LV), irinotecan, oxaliplatin and their use at different doses and schedule (ie, bolus and continuous infusion). Different combinations of these agents have been studied for the treatment of mCRC, establishing FOLFOX (5-Fluorouracil, Leucovorin and Oxaliplatin) and FOLFIRI (infusional fluorouracil, leucovorin and irinotecan) as standard of care for first-line and second-line treatment of mCRC. Patients with mCRC who have received first-line oxaliplatin-based chemotherapy typically receive second-line irinotecan-based chemotherapy.^{2,3}

Currently, there are several approved targeted therapies used in the treatment of mCRC. A benefit was demonstrated in the first-line setting with vascular endothelial growth factor (VEGF) targeted treatment (bevacizumab) combined with irinotecan, 5FU and LV chemotherapy.⁴ Bevacizumab was also found to be effective in second-line treatment when added to FOLFOX4.⁵ Cetuximab and panitumumab are anti-epidermal growth factor receptor (EGFR) monoclonal antibodies which showed benefit in patients with mCRC with wild-type KRAS tumours in combination with irinotecan-based chemotherapy.^{6–8} The multiple kinase inhibitor regorafenib may also be used in patients who cannot be treated with fluoropyrimidine-based chemotherapy, anti-VEGF or anti-EGFR therapies.⁹

This review focuses on the approval of aflibercept (ziv-aflibercept in USA), a recombinant human fusion protein acting as a high-affinity soluble decoy receptor that

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can block VEGF activation by preferentially binding to VEGF-A, VEGF-B and placental growth factor (PlGF) and preventing these factors from activating their endogenous receptors.¹⁰ Aflibercept was approved for the treatment of adults with mCRC that is resistant to or has progressed after an oxaliplatin-based regimen. At the time of evaluation, no VEGF-targeted agents had shown clinical benefit for this indication in randomised clinical trials.

Non-clinical aspects and clinical pharmacology

Aflibercept is a fusion protein composed of domain 2 of vascular endothelial growth factor receptor 1 (VEGFR-1) and domain 3 of VEGFR-2 fused to the hinge region of the Fc domain of human immunoglobulin G1. The antiangiogenic effects of aflibercept were studied *in vitro* where the drug inhibited microvessel outgrowth from rat aorta. *In vivo* pharmacology studies indicated that treatment with aflibercept inhibited tumour growth of a wide variety of mice-implanted tumour cell lines. Aflibercept treatment of several established tumours also resulted in a decrease in tumour vessel density. The combination of aflibercept with 5FU was synergistic in inhibiting the growth of early mammary MA13/C tumours. Combining aflibercept with irinotecan was also synergistic over several dose levels in advanced colon HCT 116 tumours.

In mice, subcutaneous aflibercept administration showed activity in gastric and colon adenocarcinoma xenografts, generally at doses above 2.5 mg/kg. Aflibercept formed complexes with endogenous and tumour-derived VEGF at active doses. Reductions in microvessel density in the liver, pancreatic islets and thyroid follicles were noted at all doses.

Pathology findings suggested that the target organs for aflibercept toxicity were: bone (interference with growth plate maturation, vertebral exostoses), kidney (reversible glomerular changes), testis (reversible changes in sperm motility and morphology) and ovary (decreased number of maturing follicles). Aflibercept was shown to be embryotoxic and teratogenic when administered to pregnant rabbits during embryogenesis. Female *Cynomolgus* monkeys stopped exhibiting signs of regular menstrual bleeding during treatment and this effect did not fully resolve during recovery. Decreases in sperm motility and increases in the incidence of morphologically abnormal spermatozoa were seen in males. The effects seen in males were fully reversible within 8–18 weeks of the last dose.

A population pharmacokinetic analysis was conducted with aflibercept using data from 1507 patients with various malignancies. At the recommended dose regimen of 4 mg/kg every 2 weeks, the concentrations of free drug were near steady state levels by the second cycle of treatment with a volume of distribution of 7.77 L. Being a protein, no metabolism studies were conducted with aflibercept. Since the drug forms a high molecular weight complex by binding to VEGF, it was expected that the clearance would be minimal via the renal route. Non-clinical findings suggest that clearance of aflibercept occurs via multiple mechanisms, including saturable binding

to endogenous VEGF as well as proteolytic degradation. Weight had an effect on free aflibercept clearance, with a 29% increase in exposure in patients weighing ≥ 100 kg. There was limited data available regarding pharmacokinetic changes in patients with severe renal (creatinine clearance < 30 mL/min) or hepatic impairment (total bilirubin > 3 times of the upper limit of normal and any aspartate aminotransferase).

Clinical efficacy

The marketing authorisation application was based on the pivotal VELOUR study, which was a randomised, double-blind study, comparing the efficacy of aflibercept versus placebo in patients treated with FOLFIRI for mCRC after failure of an oxaliplatin-based regimen.¹¹ Eligible patients had inoperable, histologically or cytologically proven adenocarcinoma of the colon or rectum and had progressed on or following a first-line oxaliplatin-based chemotherapy regimen, or had relapsed within 6 months of oxaliplatin-based adjuvant chemotherapy completion. Patients were excluded if they had received prior therapy with irinotecan, within 28 days of prior radiotherapy, surgery or chemotherapy or had a history of central nervous system metastases. Patients had to have adequate bone marrow and serum biochemistry laboratory results and no contraindications for anti-VEGF or FOLFIRI treatment.

Aflibercept was administered at a dose of 4 mg/kg by a 1-hour intravenous infusion, every 2 weeks. Placebo was administered to the control group using a similar dose and schedule. FOLFIRI was administered immediately after the aflibercept or placebo infusion using standard doses.

A total of 1226 subjects were enrolled in 176 centres in 28 countries across Europe, North and South America, Australia, South Africa and South Korea. Recruited patients were stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1 vs 2) and prior bevacizumab treatment (yes or no).

The primary endpoint of the study was overall survival (OS). The final survival analysis was performed after a median follow-up of 22.3 months and showed a difference in median OS of 1.44 months in favour of the aflibercept-FOLFIRI arm (13.50 months vs 12.06 months with placebo-FOLFIRI), with a stratified HR of 0.817 (95% CI 0.714 to 0.935), $p=0.0032$ (figure 1, table 1).

In subgroup analyses, a survival benefit, although less pronounced, was also noted in patients who had received prior bevacizumab treatment, with a median OS of 12.5 months in the aflibercept arm versus 11.7 months with placebo, HR=0.862 (95% CI 0.676 to 1.100) (table 2).

Secondary endpoints included progression-free survival (PFS) and overall response rate (ORR) (by RECIST version 1.0). Difference in median PFS was 2.23 months in favour of the aflibercept-FOLFIRI arm (median PFS: 6.9 months vs 4.67 months with placebo-FOLFIRI), with a HR of 0.758 (95% CI 0.661 to 0.869), $p=0.00007$ (table 1). In patients evaluable for response rate (1061 subjects),

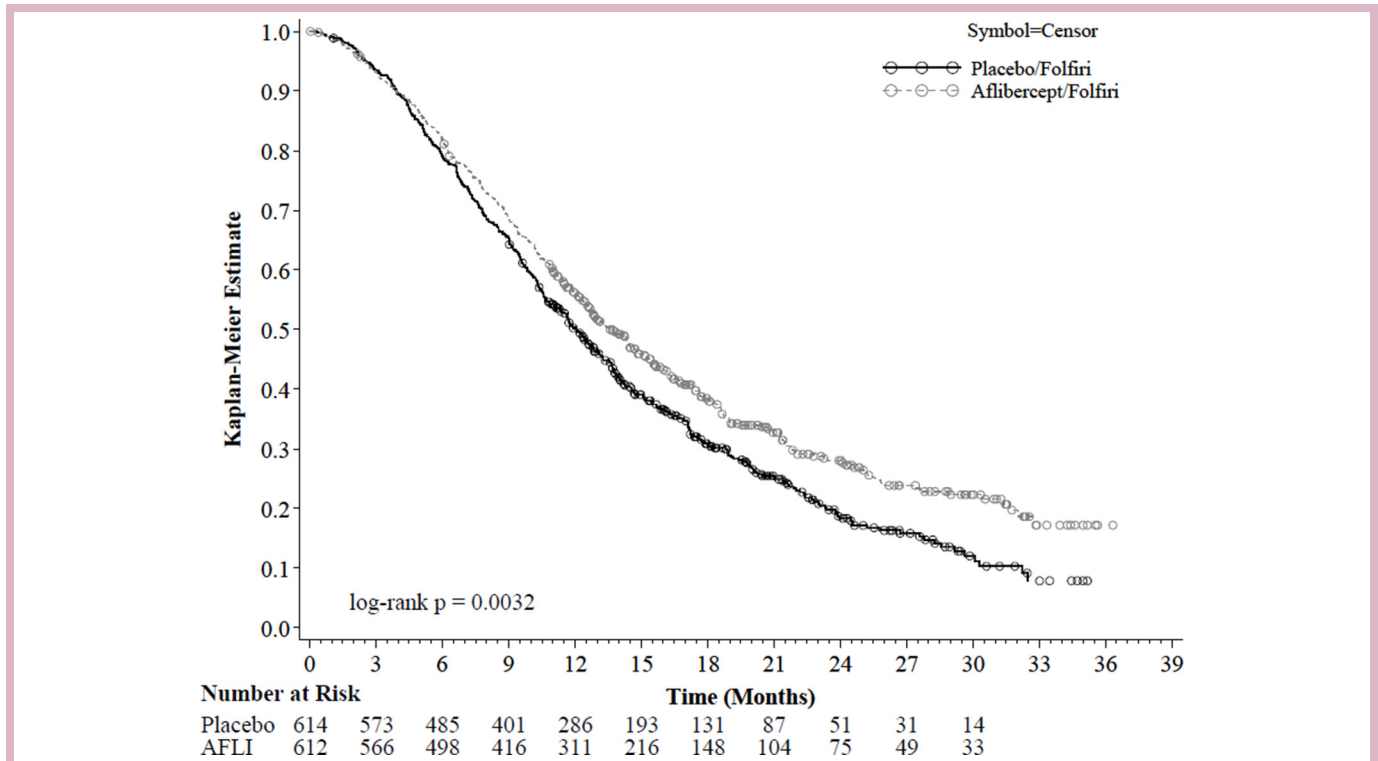


Figure 1 Kaplan -Meier plot for Overall Survival, VELOUR study.

the ORR was also in favour of the aflibercept arm (19.8% vs 11.1% in the placebo arm), $p=0.0001$ (table 1).

Clinical safety

The core safety data originated from the pivotal VELOUR study of aflibercept in combination with FOLFIRI for oxaliplatin-resistant mCRC. The safety population in the aflibercept-FOLFIRI arm included 611 patients (vs 605 patients in the placebo-FOLFIRI arm).

Patients in the aflibercept arm experienced more treatment-emergent adverse events (AEs) compared with the placebo arm (table 3).

Overall, AEs with a notably higher incidence in the aflibercept arm included hypertension, dysphonia, epistaxis and stomatitis and ulceration (table 4).

Grade 3 or 4 AEs were reported in 62.5% of the patients in the placebo arm and 83.5% of the patients

Table 1 Main efficacy endpoints, VELOUR study

Efficacy endpoint	Placebo-FOLFIRI (n=614)	Aflibercept-FOLFIRI (n=612)
OS		
No of death events, n (%)	460 (74.9)	403 (65.8)
Median OS (months) (95% CI)	12.06 (11.07 to 13.08)	13.50 (12.52 to 14.95)
Stratified HR (95% CI)	0.817 (0.714 to 0.935)	
Stratified log-rank test p value	0.0032	
PFS		
No of events, n (%)	454 (73.9)	393 (64.2)
Median PFS (months) (95% CI)	4.67 (4.21 to 5.36)	6.90 (6.51 to 7.20)
Stratified HR (95% CI)	0.758 (0.661 to 0.869)	
Stratified log-rank test p value	0.00007	
ORR, CR+PR (%) (95% CI)	11.1 (8.5 to 13.8)	19.8 (16.4 to 23.2)
Stratified Cochran-Mantel-Haenszel test p value	0.0001	

Stratification factors: ECOG performance status (0 vs 1 vs 2), prior bevacizumab (yes vs no).

PFS based on tumour assessment by IRC.

ORR based on tumour assessment by IRC.

CR, complete response; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

**Table 2** OS and PFS by prior bevacizumab exposure, VELOUR study

Efficacy endpoint	Placebo-FOLFIRI (n=614)	Aflibercept-FOLFIRI (n=612)
OS		
Patients with prior bevacizumab, n (%)	187 (30.5)	186 (30.4)
Median OS (months) (95% CI)	11.7 (9.96 to 13.77)	12.5 (10.78 to 15.47)
HR (95% CI)	0.862 (0.676 to 1.100)	
Patients with no prior bevacizumab, n (%)	427 (69.5)	426 (69.6)
Median OS (months) (95% CI)	12.4 (11.17 to 13.54)	13.9 (12.72 to 15.64)
HR (95% CI)	0.788 (0.671 to 0.925)	
PFS		
Patients with prior bevacizumab, n (%)	187 (30.5)	186 (30.4)
Median PFS (months) (95% CI)	3.9 (3.02 to 4.30)	6.7 (5.75 to 8.21)
HR (95% CI)	0.661 (0.512 to 0.852)	
Patients with no prior bevacizumab, n (%)	427 (69.5)	426 (69.6)
Median PFS (months) (95% CI)	5.4 (4.53 to 5.68)	6.9 (6.37 to 7.20)
HR (95% CI)	0.797 (0.679 to 0.936)	

OS, overall survival; PFS, progression-free survival.

in the aflibercept arm (table 4). As expected, patients on the study drug experienced more anti-VEGF associated effects, reflecting the pharmacology of aflibercept (table 4). There was a trend for more AEs in patients over 65 years of age. Certain biological abnormalities (decreased blood cell counts, increased alanine aminotransferase, proteinuria) were reported with a higher incidence in the aflibercept arm (table 4).

More deaths due to AEs were recorded in patients treated with aflibercept (2.3% vs 0.7% for placebo). The most common AEs leading to death not related to disease progression were: infection (four deaths), gastrointestinal disorders (three deaths) and respiratory disorders (three deaths). Dehydration and hypovolaemia were contributing factors for four deaths.

Other important identified risks included posterior reversible encephalopathy syndrome, thrombotic microangiopathy, hypersensitivity reactions, wound healing complications and increased chemotherapy associated toxicity. The risk management plan will address these

issues as well as potential risks (intravitreal off-label use, reproductive and developmental toxicity, cardiac dysfunction, osteonecrosis, delayed fracture healing, bone exostosis). Missing information concerns the use in patients with renal or hepatic impairment, children and adolescents, elderly, non-Caucasians, pregnant women, fertile men, low performance status (ECOG ≥ 2), immune response to aflibercept and long-term administration.

Benefit–risk assessment

Based on the results of the pivotal study, aflibercept improved OS in patients with oxaliplatin-resistant mCRC. However, the difference in median OS in favour of the aflibercept arm was modest, of only approximately 1.4 months. Improvements in PFS and ORR were also noted.

During the evaluation procedure, a major issue for discussion was how the modest survival benefit provided by aflibercept could be clinically relevant in the current treatment landscape, especially in patients pretreated

Table 3 Summary of TEAEs, VELOUR study

	Placebo/FOLFIRI (n=605) N (%)	Aflibercept/FOLFIRI (n=611) N (%)
Patients with any TEAE	592 (97.9)	606 (99.2)
Patients with any grades 3–4 TEAE	378 (62.5)	510 (83.5)
Patients with any grades 3–4 related TEAE	284 (46.9)	451 (73.8)
Patients with any serious TEAE	198 (32.7)	294 (48.1)
Patients with any serious related TEAE	93 (15.4)	194 (31.8)
Patients with any TEAE with a fatal outcome*	29 (4.8)	37 (6.1)
Any patient who permanently discontinued due to TEAE	73 (12.1)	164 (26.8)

*The number (%) of events based on the start date of the adverse events includes all TEAEs leading to death whatever the date and cause of death.

TEAEs, treatment-emergent adverse events.

**Table 4** AEs, VELOUR study

AE	Placebo-FOLFIRI (n=605)		Aflibercept-FOLFIRI (n=611)	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Any	97.9	62.5	99.2	83.5
Diarrhoea (PT)	56.5	7.8	69.2	19.3
Asthenic conditions (HLT)	50.2	10.6	60.4	16.9
Stomatitis and ulceration (HLT)	34.9	5	54.8	13.7
Infections and infestations (SOC)	32.7	6.9	46.2	12.3
Hypertension	10.7	1.5	41.4	19.3
Epistaxis	7.4	0	27.7	0.2
Weight decreased	14.4	0.8	31.9	2.6
Dysphonia (PT)	3.3	0	25.4	0.5
Headache (PT)	8.8	0.3	22.3	1.6
Dehydration	3	1.3	9	4.3
Palmar-plantar erythrodysesthesia syndrome	4.3	0.5	11	2.8
Other anti-VEGF-associated AEs				
Arterial thromboembolic event	1.5	0.5	2.6	1.8
Venous thromboembolic event	7.3	6.3	9.3	7.9
Fistula formation (GI and non-GI)	0.5	0.2	1.4	0.3
GI perforation	0.5	0.3	0.5	0.5
Haemorrhage	19.0	1.7	37.8	2.9
Biological abnormalities				
Neutropaenia	56.3	29.5	67.8	36.7
Thrombocytopaenia	33.8	1.6	47.4	3.4
Proteinuria	40.7	1.2	62.2	7.8
ALT increased	37.1	2.2	47.3	2.7

AEs, adverse events; ALT, alanine aminotransferase; FOLFIRI, infusional fluorouracil, leucovorin and irinotecan; GI, gastrointestinal; HLT, high-level term; PT, preferred term; SOC, system organ class; VEGF, vascular endothelial growth factor.

with bevacizumab, since the two drugs have a similar mechanism of action.

Pharmacologically, aflibercept was shown to induce a broader angiogenesis blockade (VEGF-A, VEGF-B and PlGF) compared with bevacizumab (VEGF-A). The binding affinity of aflibercept to its receptors was also found to be much higher than that of bevacizumab.¹⁰ At the time of approval, aflibercept was the first antiangiogenesis agent to show an OS benefit when combined with FOLFIRI in a randomised controlled trial (VELOUR). ML18147 study was a large open-label trial that investigated the use of continuing bevacizumab treatment in case of progression up to 3 months after discontinuing first-line bevacizumab plus chemotherapy. Although results also showed modest improvements in PFS and OS, no direct comparisons with the VELOUR study were possible due to differences in trial design as well as the small number of patients treated with second-line bevacizumab-FOLFIRI in the ML18147 study (64 patients).¹²

Previous research has shown that angiogenesis blockade may be continued beyond initial progression, with improvements in OS.^{12,13} In the aflibercept VELOUR study, the improvement in OS noted in patients pretreated

with bevacizumab was numerically lower compared with patients without prior bevacizumab treatment. However, the pivotal study was not powered for a formal survival comparison between bevacizumab-naïve and bevacizumab-treated patients.

The potential to identify angiogenic biomarkers to better predict clinical outcomes in mCRC has been reviewed in the medical literature.^{14,15} Taking into account the modest survival benefit seen in the study population, the EMA requested, as a post-authorisation measure, that the applicant conduct a biomarker study on plasma and tissue samples available from clinical trials, to better define the target population in which the benefit–risk balance would be optimal. Hypothesis generating data was produced initially in the phase II AFFIRM study (FOLFOX6 with or without aflibercept in first-line treatment of mCRC).¹⁶ The programme was expanded to include samples from the pivotal VELOUR study and another phase III study of aflibercept in Asian patients (with a similar design to the VELOUR study). The full results of the biomarker programme are expected to be submitted in December 2016.

The toxic potential of adding aflibercept to FOLFIRI was reflected in the safety data. Compared with the placebo arm, there were more treatment discontinuations in the aflibercept arm. Grade 3 and 4 AEs were more frequent, notably gastrointestinal disorders and infections.

There were more deaths from progressive disease in the placebo arm (72.1% vs 60.4% with aflibercept); however, more patients in the aflibercept arm died due to AEs (2.3% vs 0.7% with placebo). Aflibercept was also associated with a range of anti-VEGF class AEs, such as hypertension, haemorrhage and non-gastrointestinal fistulas.

Patients with severe renal impairment (creatinine clearance below 30 mL/min) were not included in the pivotal study. Patients with severe liver impairment were also not included in the pivotal trial. Given the fact that aflibercept would have to be administered in clinical practice together with FOLFIRI, the risk of dosing in patients with renal and hepatic impairment was judged to be low.

The incidence of grade 3 and 4 AEs was higher in patients over 65, which was of concern considering the epidemiology of CRC. At the time of approval, it was decided to include information in the summary of product characteristics about potentially increased risks of AEs in the elderly. In order to better characterise the safety profile of aflibercept in patients with renal or hepatic impairment, as well as the elderly population, the applicant proposed to conduct a post-approval observational study to further address the issue of missing information in the real-life clinical setting. To address the concern related to off-label use of aflibercept, notably regarding the contraindication of intravitreal use due to the hyperosmotic properties of the formulation, the applicant also committed to performing a drug utilisation study.

Based on the totality of evidence provided during the assessment procedure, the benefit–risk of aflibercept in combination with FOLFIRI for oxaliplatin-resistant mCRC was considered positive.

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Disclaimer This publication is based on the European Public Assessment Report (EPAR) available in the public domain, on the summary of product characteristics (SmPC) and other product information on the EMA website (www.ema.europa.eu). The authors remain solely responsible for the opinions expressed therein.

Competing interests None declared.

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REFERENCES

1. Van Cutsem E, Cervantes A, Nordlinger B, *et al*. ESMO Guidelines Working Group. Metastatic colorectal Cancer: esmo clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25(Suppl 3):iii1–9.
2. Tournigand C, André T, Achille E, *et al*. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal Cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22:229–37.
3. Goldberg RM, Sargent DJ, Morton RF, *et al*. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004;22:23–30.
4. 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.
5. 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.
6. Wilke H, Glynne-Jones R, Thaler J, *et al*. Cetuximab plus irinotecan in heavily pretreated metastatic colorectal Cancer progressing on irinotecan: mabel study. *J Clin Oncol* 2008;26:5335–43.
7. Cunningham D, Humblet Y, Siena S, *et al*. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal Cancer. *N Engl J Med* 2004;351:337–45.
8. Peeters M, Price TJ, Cervantes A, *et al*. Randomized phase III study of Panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal Cancer. *J Clin Oncol* 2010;28:4706–13.
9. 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.
10. Rudge JS, Holash J, Hylton D, *et al*. VEGF trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade. *Proc Natl Acad Sci U S A* 2007;104:18363–70.
11. 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.
12. 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.
13. Grothey A, Sugrue MM, Purdie DM, *et al*. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). *J Clin Oncol* 2008;26:5326–34.
14. Kopetz S, Hoff PM, Morris JS, *et al*. Phase II trial of infusional fluorouracil, irinotecan, and Bevacizumab for metastatic colorectal Cancer: efficacy and circulating angiogenic biomarkers associated with therapeutic resistance. *J Clin Oncol* 2010;28:453–9.
15. Asghar U, Hawkes E, Cunningham D. Predictive and prognostic biomarkers for targeted therapy in metastatic colorectal cancer. *Clin Colorectal Cancer* 2010;9:274–81.
16. 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.



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