



pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Aflibercept (Zaltrap) for Metastatic Colorectal Cancer

September 5, 2014

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

TABLE OF CONTENTS

DISCLAIMER AND FUNDING	ii
INQUIRIES	iii
TABLE OF CONTENTS.....	iv
1 GUIDANCE IN BRIEF	1
1.1. Background.....	1
1.2. Key Results and Interpretation.....	1
1.3. Conclusions.....	3
2 CLINICAL GUIDANCE.....	4
2.1 Context for the Clinical Guidance.....	4
2.2 Interpretation and Guidance	9
2.3 Conclusions	10
3 BACKGROUND CLINICAL INFORMATION.....	12
4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT	16
5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT.....	22
6 SYSTEMATIC REVIEW	24
6.1 Objectives.....	24
6.2 Methods.....	24
6.3 Results	27
6.4 Ongoing Trials.....	38
7 SUPPLEMENTAL QUESTIONS.....	39
7.1 Contextual Information and Critical Appraisal of submitted Network Meta- Analysis comparing Aflibercept with Bevacizumab	38
8 ABOUT THIS DOCUMENT.....	51
APPENDIX A: LITERATURE SEARCH STRATEGY.....	52
REFERENCES.....	53

1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of aflibercept (Zaltrap), in combination with FOLFIRI, on patient outcomes compared with appropriate comparators in treatment of patients and associated subgroups with non-resectable, metastatic colorectal cancer who have previously been treated with an oxaliplatin containing chemotherapy regimen. Previous treatment included oxaliplatin containing chemotherapy regimen with, or without, Bevacizumab. The recommended dose of aflibercept is 4 mg/kg administered every two weeks.

Aflibercept is a recombinant protein which has the capacity to bind to VEGF-A, VEGF-B, and PlGF, pro-angiogenic factors which promote tumor cell migration and survival. Aflibercept is thought to prevent the interaction of VEGFs with their receptors (VEGFRs) and, thereby, prevent the resultant intracellular signaling cascades that facilitate angiogenesis. Aflibercept has Health Canada approval for use in combination with irinotecan-fluoropyrimidine-based chemotherapy in patients with metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen⁵⁴.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One placebo-controlled, double-blind randomised controlled trial (*VELOUR*¹) was set aside in the systematic review. This trial randomised patients to receive either aflibercept (4mg/kg)/FOLFIRI (n=612) or placebo/FOLFIRI (n=614). Both arms received FOLFIRI at the same dose (irinotecan 180mg/m² IV over 90 minutes, leucovorin 400 mg/m² IV over 2 hours, FU 400 mg/m² bolus and FU 2400 mg/m² continuous infusion over 46 hours). Treatment assignment was stratified according to prior therapy with bevacizumab and ECOG PS.

Baseline patient characteristics were well balanced between arms with the majority of patients having an ECOG PS of 0 (57.0% vs. 57.0) or 1 (40.8% vs. 40.7%) in the aflibercept vs placebo arms, respectively. The number of patients' who received prior bevacizumab therapy was also the same in both arms (30.4% vs 30.5% in the aflibercept and placebo arms, respectively).

Efficacy

The primary outcome in the *VELOUR*¹ study was overall survival (OS) with progression free survival (PFS), response rate, and safety as secondary outcomes.

After a 22.28 month follow up period, patients receiving aflibercept/FOLFIRI had a statistically longer median overall survival compared to those receiving FOLFIRI alone (13.05 vs. 12.06 months, respectively, HR 0.817 95.34% CI 0.713-0.937, p=0.0032). For the secondary outcome, statistically longer PFS was also reported for patients receiving aflibercept in combination with FOLFIRI compared with those receiving FOLFIRI alone (6.90 vs. 4.67, respectively, HR 0.758 95% CI 0.661-0.869). Subgroup analyses based on prior bevacizumab status exhibited a consistent trend in OS and PFS advantage for the aflibercept arm over the control arm.

Quality of life was not measured in the study.

Harms

Incidence of adverse events was higher in the aflibercept vs placebo arm including higher frequency of grade 3/4 events (83.5% vs 62.5%, respectively).

Grade 3/4 AE's that were increased in the aflibercept vs placebo arm included neutropenia (36.7% vs. 29.5%), diarrhea (19.3% vs. 7.8%), hypertension (19.1% vs. 1.5%), asthenia (16.9% vs. 10.6%), stomatitis (13.7% vs. 5.0%), infection (12.3% vs. 6.9%), proteinuria (7.9% vs. 1.2%), venous thromboembolic events (7.9% vs. 6.3%), hemorrhage (2.9% vs. 1.7%), and arterial thromboembolic events (1.8% vs. 0.5%) are all increased when compared to placebo plus FOLFIRI. Discontinuation of treatment due to adverse events occurred in 26.8% vs. 12.1% of patients in the aflibercept arm vs. placebo arm, respectively. No information on treatment related deaths was reported.

1.2.2 Additional Evidence

pCODR received input on aflibercept (Zaltrap) for metastatic colorectal cancer from one patient advocacy group, Colorectal Cancer Association of Canada ("CCAC"). Provincial Advisory group input was obtained from eight of the nine provinces participating in pCODR.

In addition, one supplemental question was identified during development of the review protocol as relevant to the pCODR review of aflibercept (Zaltrap) and is discussed as supporting information:

- Contextual information and critical appraisal of a network meta-analysis comparing aflibercept/FOLFIRI with bevacizumab/FOLFIRI, for the treatment of patients with metastatic colorectal cancer previously treated with oxaliplatin containing chemotherapy regimen.

1.2.3 Interpretation and Guidance

Burden of Illness and Need:

Colorectal cancer represents the second and third most common causes of cancer death in Canadian males and females, respectively.² Other than in very specific situations where resection of a liver or lung metastasis is possible, metastatic colorectal cancer is considered an incurable situation.

Efforts to enhance the benefits of established cytotoxic therapies such as FOLFIRI, have led to the use of monoclonal antibodies, multi-targeted tyrosine kinase inhibitors, and other novel agents that try to exploit cancer's dependence on angiogenesis to grow and metastasize. Such targeted therapies include bevacizumab and aflibercept which both target vascular endothelial growth factor (VEGF-A for bevacizumab and both VEGF-A and VEGF-B for aflibercept) and placental growth factor (aflibercept only). With chemotherapy^{3, 4} (e.g.: FOLFIRI) and targeted agents, median survivals are now reliably measured in the 20-24-four month range. Despite these improvements, however, prolongation of survival beyond 24 months remains rare and cures are still not anticipated.

Effectiveness:

The *VELOUR*¹ trial has demonstrated that the addition of aflibercept to FOLFIRI prolongs overall survival and progression-free survival when compared with placebo plus FOLFIRI. The strength of the evidence comes from *VELOUR*¹'s statistical superiority in the primary (18.3% improvement in overall survival) and secondary (24.2% improvement in progression-free survival) end-points in both the intention-to-treat and predefined subgroups along with the

lack of confounding that often results from significant post-progression cross-over. Thus far however, no study has directly compared the efficacy and toxicity of aflibercept with bevacizumab.

Safety:

Incidence of adverse events was higher in the aflibercept vs placebo arm including higher frequency of grade 3/4 events (83.5% vs 62.5%, respectively). Although patient advocacy groups argue that patients want access to therapies that maintain quality of life and prolong both progression-free and overall survival, it is recognized that patients already experience disease-related toxicities such as asthenia and diarrhea. As a result, it is relevant when the frequency of grade 3/4 treatment-related toxicities is increased by treatment.

1.3 Conclusions

The evidence for Aflibercept supports the notion that anti-angiogenic therapy adds to the value of chemotherapy through a mechanism of action distinct from that of the cytotoxic backbone and compliments the evidence for the modest benefit achieved from continuation of an anti-angiogenic agent beyond progression. Only a single high-quality randomized controlled trial demonstrates that Aflibercept offers a superior progression-free and overall survival when compared to chemotherapy alone (as mimicked by placebo). However, knowledge about its true impact upon quality of life remains unresolved. It is only in jurisdictions where an Oxaliplatin-based regimen is required in first line that Aflibercept would potentially fulfill an unmet need. In addition and based upon clinical opinion, the CGP also considered that until further evidence is available to support the efficacy of one drug over another (aflibercept vs. bevacizumab), clinicians are likely to use aflibercept as a treatment option in provinces where bevacizumab is not available to patients in the second line setting. Because of this regional variability in practice patterns across Canada and because any approval for Aflibercept will be in the second-line setting with FOLFIRI (after progression on FOLFOX with or without Bevacizumab), Canadian patients' access to Aflibercept will remain limited.

Based upon the results of the well-conducted and valid *VELOUR* clinical trial, the Clinical Guidance Panel believes that there is a modest overall clinical benefit for the addition of Aflibercept to FOLFIRI after progression on FOLFOX with or without Bevacizumab in patients with metastatic colorectal cancer. This impression is congruent with that of the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding aflibercept (Zaltrap) for metastatic colorectal cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding Aflibercept conducted by the Gastro-intestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on Aflibercept and a summary of submitted Provincial Advisory Group Input on Aflibercept are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

The 2013 Canadian estimates for the number of new cases of mCRC reported 23,900 new cases of colorectal cancer and an incidence rate of 49.1 per 100,000 people². Patient deaths related to colorectal cancer have been decreasing in both men and women, most likely as a result of improved chemotherapy treatments⁵. Colorectal cancer deaths are second highest in men and third highest in women as a percentage of total deaths attributed to cancer. As a percentage this is 12.7% of cancer deaths in men and 11.6% of cancer deaths in women⁵.

In patients with mCRC primary treatment is resection of metastases where this is possible. However the great majority of patients present with non-resectable disease. In patients with unresectable metastatic disease the primary goal is prolongation of survival. Anti-angiogenic therapies have been combined with chemotherapy treatment in both first line and second line settings and have been associated with favorable outcomes^{6, 7}. Given the favorable effects, as well as a growing number of new angiogenic agents available, assessment of treatment schedules including angiogenic agents is crucial in order to determine treatments with maximal efficacy.

Aflibercept is a recombinant protein in which the extracellular VEGF-binding domains of VEGFR-1 and VEGFR-2 are fused to the Fc portion of human immunoglobulin IgG1; it has the capacity to bind to VEGF-A, VEGF-B, and PlGF, pro-angiogenic factors which promote tumor cell migration and survival, with greater affinity than Bevacizumab, which only binds to VEGF-A. Both agents are thought to prevent the interaction of their specific VEGFs with the respective receptors (VEGFRs) and, thereby, the resultant intracellular signaling cascades that encourage angiogenesis. This permits "normalization" of the tumor vasculature, facilitates the delivery of chemotherapy into the tumor, and prevents the development of other blood vessels.

Aflibercept is indicated for use in combination with irinotecan-fluoropyrimidine-based chemotherapy for patients with metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness of aflibercept (Zaltrap) in combination with irinotecan-fluoropyrimidine (FOLFIRI) based chemotherapy, on patient outcomes compared with appropriate comparators in treatment of patients and associated subgroups with non-resectable, metastatic colorectal cancer who have been previously treated with an oxaliplatin containing chemotherapy regimen.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

One randomized trial met the eligibility criteria for this review (*VELOUR*¹). The *VELOUR* trial is a multicentre, randomised, placebo-controlled, double-blind, comparative study comparing the use of aflibercept + FOLFIRI to FOLFIRI alone in patients with mCRC (N=1,226) who were previously treated with an Oxaliplatin containing regimen. Patients were enrolled between November 2007 and March 2010 and were eligible for *VELOUR*¹ if they were at least 18 years old; with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 to 2. Eligible patients had histologically or cytologically proven colorectal adenocarcinoma with metastatic disease not amenable to potentially curative treatment; measurable disease was not a requirement for participation. Although patients were to have documented progression while on or after completion of a single prior Oxaliplatin containing regimen they were not selected for the timing of their progression. Patients who relapsed within 6 months of completion of Oxaliplatin-based adjuvant therapy were eligible. Prior Bevacizumab was permitted, but not prior irinotecan. Patients with a broad range of characteristics were enrolled, suggesting generalizability of trial results in the real world context of patients previously treated with a single Oxaliplatin-containing regimen. Patients were randomised to receive either Aflibercept 4 mg/kg IV on day 1 + FOLFIRI every 2 weeks or placebo IV on day 1 + FOLFIRI every 2 weeks. Full dose of FOLFIRI at cycle 1 was mandatory. FOLFIRI was given at a dose of (180 mg/m² (Irinotecan), 400 mg/m² (Leucovorin) and 400 mg/m² (Fluorouracil).

Treatment assignment was stratified according to prior therapy with Bevacizumab (yes or no), and Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs. 1 vs. 2). The primary objective of the trial was to determine superiority in overall survival (OS) with Aflibercept + FOLFIRI compared with placebo + FOLFIRI.

Demographics and disease characteristics were well balanced between the treatment arms. Of the 1226 patients randomized in the study, the median age was 61 years, 58.6% were male, and 97.8% had a baseline ECOG performance status (PS) of 0 or 1.

Subgroup analysis and the effect on OS and PFS was determined pre-hoc and included ECOG PS, prior Bevacizumab, and baseline characteristics including age, gender, geographic region, prior hypertension, number of metastatic sites, disease confined to liver and location of primary tumour.

Aflibercept in combination with FOLFIRI was found to have statistically significant improvements in median OS in a broad based mCRC patient population previously treated with an Oxaliplatin based regimen, when compared to chemotherapy alone. The study satisfied its primary endpoint in that median OS for Aflibercept + FOLFIRI vs. placebo + FOLFIRI was statistically longer in the Aflibercept arm than the placebo arm (13.50 ms vs 12.06 ms, stratified hazard ratio [HR]: 0.817, 95.34% CI: 0.713 to 0.937; P=0.0032). This hazard ratio indicates an 18.3% (95.34 CI: 6.3% to 28.7%) reduction in the risk of death

associated with treatment containing Aflibercept + FOLFIRI compared with placebo + FOLFIRI.

Statistically significant and clinically meaningful improvements were also demonstrated for PFS, with improvements observed as early as 3 months. The median PFS based on RECIST tumour assessment by the Independent Review Committee was significantly longer with 6.90 months for Aflibercept + FOLFIRI versus 4.67 months for placebo + FOLFIRI (HR=0.758, 95% CI: 0.661 to 0.869; P<0.0001). Pre-planned subgroup analysis showed that the benefits of Aflibercept + FOLFIRI treatment were consistent across all pre-specified subgroups for both OS and PFS and regardless of prior treatment with Bevacizumab. There was no significant interaction between 'treatment arm' and 'prior Bevacizumab' at the 2-sided 10% level for either OS (P=0.5668) or PFS (P=0.1958).

All grades adverse events were reported in 99.2% and 97.9% of the aflibercept and control arms, respectively. Grade 3 or 4 events were reported in 83.5% and 62.5% of patients respectively. Grade 3/4 adverse events more commonly associated with anti-VEGF therapy and which occurred in the aflibercept vs. placebo arms respectively included hypertension (19.1% vs. 1.5%), hemorrhage (3% vs. 1.7%), arterial thromboembolic events (1.8% vs. 0.5%), and venous thromboembolic events (7.8% vs. 6.2%).

Grade 3/4 adverse events commonly associated with chemotherapy and which occurred at a higher frequency in the aflibercept versus the placebo arm respectively included diarrhea (19.3% vs. 7.8%), asthenic conditions (16.8% vs. 10.6%), stomatitis and ulceration (13.8% vs. 5.0%), infections (12.3% vs. 6.9%), and palmar-plantar erythrodysesthesia (2.8% vs. 0.5%), neutropenia (36.7% vs. 29.5%), complicated neutropenia (5.7% vs. 2.9%), and thrombocytopenia (3.4% vs. 1.6%).

The most frequent hematological grade 3/4 AE was neutropenia which occurred in 36.7% vs. 29.5% of patients in the aflibercept/FOLFIRI vs. placebo/FOLFIRI arms, respectively. The most frequent non-hematological grade 3/4 AE was proteinuria which occurred in 7.8% vs. 1.2% of patients in each arm, respectively.

Deaths due to causes other than disease progression occurring within 30 days of last administration of study treatment were reported in 2.6% of patients treated with the aflibercept/FOLFIRI regimen and 1.0% of patients treated with the placebo/FOLFIRI regimen⁸.

This study is a well-designed randomized control trial. Randomization procedures are well defined, and concealment, is not defined in the paper. Patient population appears broad and results are generalizable as a result. Overall, methods used in design and analysis allow users to draw conclusions that are applicable and generalizable. Limitations include the fact that primary analysis was conducted by sponsor company personnel as well as the inability to assess and account for practice variation between centres.

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

Following the posting of the pERC initial recommendation, the submitter commented on pERC's Initial Recommendation regarding studies they identified that should have been included in this systematic review but were excluded. Although these studies were

identified in the literature search, they were subsequently excluded during title and abstract screening phase because the analyses were based upon single arm, open label, cohort studies.

The pCODR review team created a pre-specified review protocol that did not include single arm, open label, cohort studies because they do not address the objective which is to compare treatment using Aflibercept with other standard treatments. Choosing to include studies that do not meet the pre-specified eligibility criteria of the systematic review has the potential to bias the results in the direction that is of interest to the author while also negating the reason for having eligibility criteria.

Two studies were identified by the submitter assessing quality of life based upon interim results from the global safety and quality of life program (ASQoP & AFEQt). These are single arm studies that measured quality of life through the self-reported EQ-5D questionnaire. Sobrero, 2013^{9, 10} reported on safety and utility levels - QOL, while Bordonaro, 2013¹¹ reported on safety in the "Italian subgroup", and quality of life from the ASQoP study. Internal bias and influence is a major concern with these studies due to the use of self-reporting. Patients are often unable to remain unbiased in their reporting while they are undergoing treatment as they are not blinded to their treatment. As such, the results should be interpreted with a degree of uncertainty and caution.

Although the abovementioned studies did not include comparative analysis, conclusions are made by the submitter regarding comparative efficacy with the VELOUR study. These conclusions are however not considered to be valid because a detailed analysis of between study differences and results was not conducted (study populations, care pathways, dosing etc).

Additionally, two publications were identified by the Patient Advocacy Group feedback document on the initial Recommendation suggesting the availability of additional safety information on aflibercept in the patient population under review. These consisted of a review article of phase two trials which were not eligible in our review (Cartwright, 2013) and an abstract that reports on a North American subgroup from the VELOUR trial (Mitchell, 2013). The Mitchell 2013 study clearly indicates that the analysis performed, although pre-specified, was not powered to compare between subgroups.

Both of these articles take information from the VELOUR trial. As the systematic review has reported on pre-specified sub-groups taken from the final results of the VELOUR study, no additional information can be gathered from the abovementioned publications which only provide further perspective on results from the VELOUR trial.

2.1.5 Summary of Supplemental Questions

Contextual Information and Critical Appraisal of submitted Network Meta-Analysis comparing Aflibercept with Bevacizumab

Results from the primary analysis found no statistical difference between treatment arms using fixed effects, random effects, and pairwise comparisons, modeling. In the primary analysis, no statistically significant differences were found between Aflibercept/FOLFIRI and Bevacizumab/FOLFOX groups for overall survival (HR=0.851, 95% CI: 0.505 to 1.4301) or progression-free survival (HR=1.385, 95%CI: 0.805 to 2.380). Similarly, in the secondary analysis, which assumed that FOLFOX and FOLFIRI are clinically equivalent, no statistically significant differences were found between Aflibercept/ FOLFOL (FOLFIRI and/or FOLFOX) and Bevacizumab/FOLFOL groups for overall survival (HR=1.044, 95%CI: 0.873 to 1.25) or progression-free survival (HR=1.151, 95%CI: 0.961 to 1.36)

The primary safety analysis showed non-significant differences in AEs with relative risks of 2.78, 0.12, 0.04, 0.77, and 10.31 for diarrhea, nausea, vomiting, fatigue, and stomatitis respectively. The secondary safety analysis also showed non-significant differences in different AEs, however the magnitude and type of AEs differed. Relative risks of 1.86, 0.23, 0.39, 1.14, 1.17, 1.28, 1.03, and 5.33 for diarrhea, nausea, vomiting, fatigue, stomatitis, abdominal pain, Neutropenia, and hypertension were observed, respectively.

Population and treatment heterogeneity, assumptions about treatment efficacy equivalence, small study populations, and heterogeneity in measurement of progression are major factors that limit validity of conclusions drawn and ability to use efficacy results in comparative analysis of anti-angiogenesis agents in the second-line treatment of mCRC. Unique limitations associated with the safety analysis include inconsistent AE reporting thereby limiting the number of studies that could be used. Limitations described for the efficacy analysis also apply in that there was significant difference in patient heterogeneity, disease staging and treatment heterogeneity. Overall, the limitations associated with this network meta-analysis restricts the ability to make recommendations or draw conclusions regarding comparative efficacy of Aflibercept versus Bevacizumab. Any modeling or analysis using the information found in this NMA could produce misleading results and this information should be used with caution.

See section 7.1 for more information.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival is extremely important, and CCAC submits that patients should be afforded the opportunity to have a choice in the selection of the best therapeutic option in the treatment of their mCRC. According to the patient survey and informal patient conversations, the most frequently reported disease-related symptoms are fatigue, abdominal pain, bloody stools, painful diarrhea/constipation; all of which impact a patient's QoL significantly. While patients are aware of the fact that all drug therapies have associated risks, 63% of patients surveyed would not refuse taking a cancer therapy based on a severe toxicity profile of the therapy. Over 65% of patients surveyed reported that it would be very important to access additional treatments whose benefits might only be short term despite treatment adverse effects. Patients with mCRC view that long term health is relative and that any extension in life is considered to be an extension in long term health

PAG Input

Input on aflibercept (Zaltrap) for mCRC was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, the key enabler for implementation of aflibercept is that FOLFIRI is the current funded second-line treatment in most provinces and aflibercept would be add-on therapy. PAG identified that the main barrier to implementation is in provinces where FOLFOX is not the current funded first-line treatment or standard of care. Other barriers include the

additional infusion time required to administer aflibercept, drug wastage and the management of toxicities (e.g. neutropenia) associated with this therapy.

Please see below for more details.

Other⁵⁴

Serious warnings associated with aflibercept include:

Hemorrhage: Severe and sometimes fatal hemorrhage, including gastrointestinal (GI) hemorrhage, has been reported in the patients who have received ZALTRAP in combination with FOLFIRI.

Gastrointestinal Perforations: Gastrointestinal (GI) perforation, including fatalities, has been observed in patients treated with ZALTRAP.

Compromised Wound Healing: Treatment with ZALTRAP is associated with compromised wound healing. ZALTRAP should be suspended for at least 4 weeks prior to major surgery and not resumed for at least 4 weeks after surgery and until the surgical wound is fully healed.

Immunogenicity: Similar to other therapeutic proteins, there is a potential for immunogenicity with aflibercept. Positive responses in the ADA assay in the ¹trial were observed at higher levels in patients treated with placebo/FOLFIRI regimen [18/526 (3.4%)] than with ZALTRAP/FOLFIRI regimen [8/521 (1.5%)]. Positive results in the neutralizing antibody assay in the MCRC pivotal study were also higher in patients treated with placebo/FOLFIRI regimen [2/526 (0.38%)] than with ZALTRAP/FOLFIRI regimen [1/521 (0.19%)].

2.2 Interpretation and Guidance

Colorectal cancer represents the second and third most common causes of cancer death in Canadian males and females, respectively.² Considerable progress is being made to develop and deliver effective treatments that control advanced disease, maintain or improve quality of life, and delay death. In an effort to enhance the benefits of established cytotoxic therapies such as fluoropyrimidine (5-Fluorouracil and Capecitabine), Irinotecan, and Oxaliplatin, monoclonal antibodies, multi-targeted tyrosine kinase inhibitors, and other novel agents have been (and are being) developed to try to exploit cancer's dependence on angiogenesis to grow and metastasize.

Bevacizumab, a monoclonal antibody with affinity for vascular endothelial growth factors (VEGFs), has been evaluated in metastatic colorectal cancer in combination with multiple chemotherapy backbones and over different lines of therapy; its risks and benefits have been established in multiple published clinical trials, systematic reviews, and meta-analyses (summarized in section 3) dating back to 2003.

Aflibercept, a recombinant protein with the capacity to bind to vascular endothelial and placental growth factors (VEGF and PlGF), has now been evaluated in *VELOUR*¹, a large ($n = 1,226$), prospective, multi-national, double-blind, parallel-arm, phase III clinical trial. After patients with a good performance status (ECOG 0, 1, or 2) progress on or after a single line of Oxaliplatin-based chemotherapy (with or without Bevacizumab), the addition of Aflibercept to FOLFIRI prolongs overall survival (13.50 months *versus* 12.06 months, HR 0.817, CI_{95%} 0.713-0.937, $p = 0.0032$) and progression-free survival (6.90 months *versus* 4.67 months, HR 0.758, CI_{95%} 0.661-0.859, $p < 0.0001$) when compared with placebo plus FOLFIRI.

Thus far, no health technology assessments, systematic reviews, or other phase III randomized controlled trials have been published to corroborate this trial's efficacy and safety findings in metastatic colorectal cancer. Although the CGP agree that clinical evidence on the second line use of bevacizumab has not yet been reviewed, level 1 evidence suggests that bevacizumab when continued into second line after treatment in first line is likely to be a relevant comparator for aflibercept use in the second line setting. To date, no study has directly compared the efficacy and toxicity of Aflibercept with Bevacizumab.

Although patient advocacy groups argue that patients want access to therapies that maintain quality of life and prolong both progression-free and overall survival, it is recognized that patients already experience disease-related toxicities such as asthenia and diarrhea. As a result, it is relevant when the frequency of grade 3/4 treatment-related toxicities is increased by treatment. When Aflibercept is added to FOLFIRI, neutropenia (36.7% versus 29.5%), diarrhea (19.3% versus 7.8%), hypertension (19.1% versus 1.5%), asthenia (16.9% versus 10.6%), stomatitis (13.7% versus 5.0%), infection (12.3% versus 6.9%), proteinuria (7.9% versus 1.2%), venous thromboembolic events (7.9% versus 6.3%), hemorrhage (2.9% versus 1.7%), and arterial thromboembolic events (1.8% versus 0.5%) are all increased when compared to placebo plus FOLFIRI. Although quality of life data was not collected in the VELOUR study, two single arm studies providing interim results from the global safety and quality of life program (ASQoP & AFEQt) were identified. These studies were not included in the pCODR systematic review as they did not meet the review inclusion criteria. Due to the potential for bias and limitations associated with the study design, the results of these studies should be interpreted with caution.

Aflibercept's availability in Canada has mainly been through clinical trials or Special Access Programs. As a result, only a handful of medical oncologists have any direct clinical experience with Aflibercept. With more familiarity, better management of the treatment-related adverse effects (83.5% experienced grade 3/4 toxicities on the VELOUR trial) might decrease the high number of discontinuations (26.8% on the VELOUR trial) but result in expanded drug use, incremental costs, and different pharmacoeconomics. Further, the administration of Aflibercept adds one hour to a patient's time in the Medical Daycare Unit (for comparison, Bevacizumab is routinely administered over ten minutes in clinical practice).

There are no validated biomarkers identified to limit the population of Canadians with metastatic colorectal cancer eligible for Aflibercept. There is no evidence from clinical testing to suggest that Aflibercept's higher affinity for VEGF confers an advantage over Bevacizumab. Aflibercept has not offered a benefit in non-small cell lung cancer (VITAL trial⁹), pancreas cancer (VANILLA trial¹⁰), or prostate cancer (VENICE trial).

The strength of the evidence comes from VELOUR¹'s statistical superiority in the primary (18.3% improvement in overall survival) and secondary (24.2% improvement in progression-free survival) end-points in both the intention-to-treat and predefined subgroups along with the lack of confounding that often results from significant post-progression cross-over. However, criticisms of this trial include the primary analysis being conducted by Sanofi personnel, the modest clinical benefit, the absence of quality of life data, the perception of increased toxicity when compared to trials using Bevacizumab, and the lack of confirmatory studies in face of the volume of robust and established clinical data for Bevacizumab.

2.3 Conclusions

The evidence for Aflibercept supports the notion that anti-angiogenic therapy adds to the value of chemotherapy through a mechanism of action distinct from that of the cytotoxic

backbone and compliments the evidence for the modest benefit achieved from continuation of an anti-angiogenic agent beyond progression. Only a single high-quality randomized controlled trial demonstrates that Aflibercept offers a superior progression-free and overall survival when compared to chemotherapy alone (as mimicked by placebo). However, knowledge about its true impact upon quality of life remains unresolved. It is only in jurisdictions where an Oxaliplatin-based regimen is required in first line that Aflibercept would potentially fulfill an unmet need. In addition and based upon clinical opinion, the CGP also considered that until further evidence is available to support the efficacy of one drug over another (aflibercept vs. bevacizumab), clinicians are likely to use aflibercept as a treatment option in provinces where bevacizumab is not available to patients in the second line setting. Because of this regional variability in practice patterns across Canada and because any approval for Aflibercept will be in the second-line setting with FOLFIRI (after progression on FOLFOX with or without Bevacizumab), Canadian patients' access to Aflibercept will remain limited.

Based upon the results of the well-conducted and valid *VELOUR* clinical trial, the Clinical Guidance Panel believes that there is a modest overall clinical benefit for the addition of Aflibercept to FOLFIRI after progression on FOLFOX with or without Bevacizumab in patients with metastatic colorectal cancer. This impression is congruent with that of the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

3 BACKGROUND CLINICAL INFORMATION

3.1 Description of the Condition

This section was prepared by the pCODR Gastrointestinal Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

The Canadian Cancer Society estimates that, in 2013, 23,900 Canadians were diagnosed with colorectal cancer and that 9,200 Canadians died as a consequence of this disease. Colorectal cancer represents the second most common cause of cancer death in males and third most common cause of cancer death in females². It is second only to lung cancer when potential years of life lost are considered.

Angiogenesis is a recognized hallmark of cancer:¹¹ For a cluster of cancer cells to grow beyond a volume of 1 to 2 mm¹² (the equivalent of a sphere with a diameter of 1.24 mm), tumors encourage the production of pro-angiogenic factors such as hypoxia inducible factor 1 (HIF1), fibroblast growth factor, and a family of vascular endothelial growth factors (VEGFs). The persistent imbalance between these pro-angiogenic and anti-angiogenic factors creates an environment through which activated endothelial cells can assemble to create new blood vessels. However, the resultant vasculature is abnormal: the disorganized placement of endothelial cells without the stability offered by pericytes renders the network of vessels tortuous, permeable, and collapsible.¹²

VEGF-A, VEGF-B, and Placental Growth Factor (PlGF) interact with Vascular Endothelial Growth Factor Receptor 1 (VEGFR1 or *flt1*) to promote recruitment of endothelial progenitor cells and to activate matrix metalloproteinases and pericytes. VEGF-A, -C, -D, and -E interact with VEGFR2 (*KDR* or *flk-1*) to promote proliferation of the vascular endothelial cells, vascular permeability, and tumor cell migration and survival. VEGF-C and -D interact with VEGFR-3 (*flt-4*) to encourage proliferation of lymphatic endothelial cells as well as tumor cell migration and survival.

Bevacizumab is a humanized monoclonal IgG₁ antibody with some affinity for all VEGF isoforms, but most affinity for VEGF-A. Aflibercept is a recombinant protein in which the extracellular VEGF-binding domains of VEGFR-1 and VEGFR-2 are fused to the Fc portion of human immunoglobulin IgG₁; it has the capacity to bind to VEGF-A, VEGF-B, and PlGF with greater affinity than Bevacizumab. Both agents are thought to prevent the interaction of their specific VEGFs with the respective VEGFRs and, thereby, the resultant intracellular signaling cascades that encourage angiogenesis. This permits “normalization” of the tumor vasculature, facilitates the delivery of chemotherapy into the tumor, and prevents the development of other blood vessels.

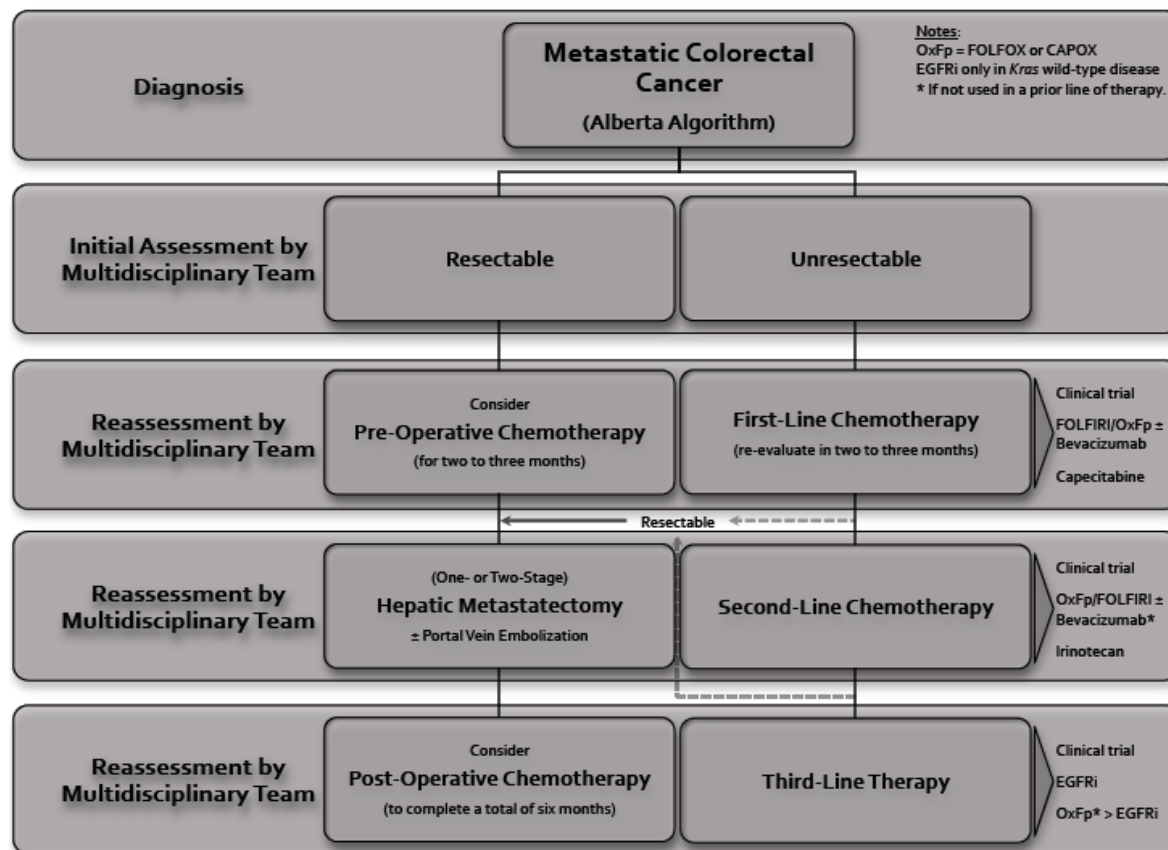
For more detailed data from trials evaluating bevacizumab that was summarized by the Clinical Guidance Panel and critiqued by the Methods Team, please see section 7.1

3.2 Accepted Clinical Practice

Other than in very specific situations where resection of a liver or lung metastasis is possible, metastatic colorectal cancer is considered an incurable situation. Untreated, historical series describe survivals in the range of six to ten months.^{13, 14} With chemotherapy^{3, 4} (e.g.: fluoropyrimidines, Oxaliplatin, Irinotecan) and targeted agents (e.g.: Bevacizumab, Cetuximab, Panitumumab), median survivals are now reliably measured in the twenty to twenty-four month range. Contemporary systemic therapies are cost effective¹⁵⁻¹⁹, delay the onset of tumor-related symptoms, and improve quality of life.^{20, 21} Despite these improvements, however, prolongation of survival beyond twenty-four months remains rare and cures are still not anticipated.

An algorithm summarizing the usual trajectory of care is presented here:

Figure 1. Alberta algorithm of care



Modified from Alberta Health Services clinical practice guideline²²

Anti-Angiogenic Therapy for Patients with Previously Untreated Metastatic Colorectal Cancer

Multiple randomized phase II^{23, 24} and III^{6, 25-27} studies suggest that the addition of Bevacizumab to fluoropyrimidine-based chemotherapy delays progression by between 1.4 and 4.4 months and offers an incremental overall survival benefit that ranges from 0.0 months to a statistically significant 4.7 months (when used with a no longer relevant Irinotecan backbone).

A meta-analysis supports that the greatest reduction in the risk of progression (HR 0.41, CI_{95%} 0.28-0.60) and death (HR 0.60, CI_{95%} 0.44-0.84) is attributed to the addition of Irinotecan *plus* Bevacizumab to 5-Fluorouracil and Leucovorin³. The Cochrane Collaboration²⁸ (and three other systematic reviews²⁹⁻³¹) also independently concludes that Bevacizumab improves progression-free survival (HR 0.61, CI_{95%} 0.45-0.83) and overall survival (HR 0.81, CI_{95%} 0.73-0.90) for patients with previously untreated metastatic colorectal cancer.

The “Bevacizumab Regimens: Investigation of Treatment Effects” (*BRiTE*)³², the “Bevacizumab Expanded Access Trial” (*First BEAT*)³³, and the *AVIRI*³⁴ studies prospectively collected safety and efficacy outcomes for patients with previously untreated metastatic colorectal cancer treated with chemotherapy and Bevacizumab. *BRiTE*³² describes a median progression-free survival of 9.9 months (CI_{95%} 9.5-10.3) and a median overall survival of 22.9 months (CI_{95%} 21.9-24.4). *First BEAT* describes median progression-free survivals between 8.6 and 11.6 months and overall survivals between 18.0 and 25.9 months, depending upon the chemotherapy backbone to which Bevacizumab was added. *AVIRI* describes a median progression-free survival of 11.1 months (CI_{95%} 10.3-12.1 months) and an overall survival of 22.2 months (CI_{95%} 20.5-25.9 months).

In patients who received prior treatment with Irinotecan and a fluoropyrimidine, the addition of Bevacizumab to FOLFOX4 improves both the primary outcome measure of overall survival (12.9 months *versus* 10.8 months, HR 0.75, $p = 0.011$) and the secondary outcome measure of progression-free survival (7.3 months *versus* 4.7 months, HR 0.61, $p < 0.0001$). The Cochrane Collaboration's analysis supports these results too.²⁸

Note that trials of anti-angiogenic agents routinely exclude patients with diagnoses such as clinically significant cardiovascular, cerebrovascular, and/or peripheral vascular disease; uncontrolled hypertension; non-healing wounds or major surgery within the preceding twenty-eight days; bleeding diatheses; known brain metastases; regular use of acetylsalicylic acid over 325 mg/day (or equivalent non-steroidal anti-inflammatory agent); or therapeutic anti-coagulation.

Anti-Angiogenic Therapy Beyond First Progression:

Resistance to Bevacizumab (attributed to the development of alternative angiogenesis pathways) is unlikely to occur at the same time as resistance to chemotherapy (often agent-specific and attributed to changes in cell biology). Indeed, in non-randomized observational studies (e.g.: *BRiTE*³⁵, *ARIES*³⁶), the continuation of Bevacizumab beyond progression correlates with prolonged survival when compared with no continuation of Bevacizumab. In fact, in a multivariate analysis of a subset of patients who experienced disease progression on the *BRiTE* study, treatment with Bevacizumab beyond progression was independently associated with improved survival (HR 0.48, $p < 0.001$).³⁵ Whereas patients who receive post-progression treatment without Bevacizumab have a median overall survival of 19.9 months, patients who receive Bevacizumab with their post-progression therapy have a median overall survival of 31.8 months.

The efficacy and safety of Bevacizumab beyond progression have now been prospectively evaluated in a randomized phase III study (*ML18147*).³⁷ Between February 2006 and June 2010, 820 patients with metastatic colorectal cancer not amenable to potentially curative treatment were randomized to receive chemotherapy (fluoropyrimidine *plus* Irinotecan if an Oxaliplatin-based regimen was given previously or fluoropyrimidine *plus* Oxaliplatin if an Irinotecan-based regimen was given previously) *plus* Bevacizumab or chemotherapy alone. The addition of Bevacizumab improves both the primary end-point of overall survival (from 9.8 months to 11.2 months, HR 0.81, CI_{95%} 0.69-0.94, $p = 0.0062$) and the secondary end-point of progression-free survival (from 4.1 months to 5.7 months, HR 0.68, CI_{95%} 0.59-0.78, $p < 0.0001$).

3.3 Evidence-Based Considerations for a Funding Population

Aflibercept has been evaluated in the *VELOUR*⁷ study, a prospective, multi-national, randomized, double-blind, parallel-arm, phase III clinical trial. Between November 2007 and March 2010, 176 centres in twenty-eight countries randomly assigned patients with histologically- or cytologically-proven metastatic colorectal cancer not amenable to potentially curative treatment, documented progression on or after a single line of Oxaliplatin-based chemotherapy (not Irinotecan), and a good performance status (ECOG 0, 1, or 2) to receive FOLFIRI *plus* Aflibercept 4 mg/kg IV over one hour every two weeks ($n = 612$) or FOLFIRI *plus* Placebo ($n = 614$). No cross-over from placebo to Aflibercept was permitted after progression. It revealed statistical superiority in the primary outcome measure of overall survival (13.50 months *versus* 12.06 months, HR 0.817, CI_{95%} 0.713-0.937, $p = 0.0032$) and in the secondary outcome measure of progression-free survival (6.90 months *versus* 4.67 months, HR 0.758, CI_{95%} 0.661-0.859, $p < 0.0001$).

The addition of Aflibercept to FOLFIRI is associated with higher rates of grade 3/4 neutropenia (36.7% *versus* 29.5%), diarrhea (19.3% *versus* 7.8%), hypertension (19.1% *versus* 1.5%), asthenia (16.9% *versus* 10.6%), stomatitis (13.7% *versus* 5.0%), infection (12.3% *versus* 6.9%), proteinuria (7.9% *versus* 1.2%), venous thromboembolic events (7.9% *versus* 6.3%), hemorrhage (2.9% *versus* 1.7%), and

arterial thromboembolic events (1.8% versus 0.5%). Discontinuation due to adverse events is more frequent in the FOLFIRI *plus* Aflibercept arm (26.8% versus 12.1%), but discontinuation due to progression is less frequent in the FOLFIRI *plus* Aflibercept arm (48.9% versus 71.2%).

In Canada, there is regional variability in practice patterns. However, patients with metastatic colorectal cancer are often first treated with FOLFIRI with or without Bevacizumab. If patients are inappropriate for bevacizumab therapy in the first line setting they may receive it in the second line setting. Patients may become inappropriate for bevacizumab in the first line setting due to clinically significant coronary artery disease, cerebrovascular disease, and/or peripheral vascular disease; uncontrolled hypertension; non-healing wounds; bleeding diatheses; and known brain metastases. If Bevacizumab was deemed contraindicated (or patient declined its use) in the first-line setting, for subsequent second line therapy, Aflibercept would be considered contraindicated in these populations too.

Until evidence surfaces to support the efficacy and safety of Aflibercept with regimens other than FOLFIRI and/or in previously untreated patients, any funding criteria in Canada would follow the eligibility criteria of the *VELOUR* study. Therefore, it is anticipated that patients' access to Aflibercept will remain limited (assuming that 70% of the 9,200 Canadians with metastatic colorectal cancer are eligible to pursue systemic therapy, that 40% receive a non-Irinotecan-based first-line regimen, and that a 30% drop-off occurs moving from first- to second-line therapy, this would amount to 775 patients).

Currently, there are no biomarkers that are able to predict a response to anti-angiogenic therapy. There is no evidence from clinical testing to suggest that Aflibercept's higher affinity for VEGF confers an advantage over Bevacizumab.

While Bevacizumab can be administered over ten to fifteen minutes (5.0 mg/kg Q2week dose and 7.5 mg/kg Q3week dose, respectively), Aflibercept is administered over sixty minutes (4 mg/kg Q2week dose).

3.4 Other Patient Populations in Whom the Drug May Be Used

While this pCODR evaluation focuses on the use of Aflibercept in metastatic colorectal cancer, Aflibercept has not offered a benefit in non-small cell lung cancer (*VITAL*⁹ trial), pancreas cancer (*VANILLA* trial¹⁰), or prostate cancer (*VENICE* trial)

No other potential uses of the drug that may impact on its utilization were identified.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

A patient advocacy group, the Colorectal Cancer Association of Canada (“CCAC”), provided input on Aflibercept (Aflibercept) in combination with irinotecan-fluoropyrimidine (FOLFIRI) based therapy for patients with metastatic colorectal cancer (“mCRC”) previously treated with an Oxaliplatin-containing regimen, which is summarized below.

The CCAC conducted online surveys from November 22 to December 3, 2013 for metastatic colorectal cancer patients and caregivers in Canada who were contacted through the CCAC Medical Advisory Board of medical oncologists who treat mCRC, as well as through CCAC’s database of registered colorectal cancer patients and their respective caregivers residing in Canada. The survey received a total of 54 responses. The CCAC noted that due to access limitations, there is a lack of robust patient/caregiver input as it relates specifically to the Aflibercept+FOLFIRI experience following an Oxaliplatin-containing regimen. One (1) U.S. based patient did, however, complete the survey to relay their experience with Aflibercept therapy.

Recognizing the importance of providing a robust patient perspective, the input included past conversations with patients and caregivers, as well as publications focusing on the treatment in question. An additional Quality of Life (QoL) survey conducted by the CCAC in March 2011 was also included.

From a patient perspective, accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival is extremely important, and CCAC submits that patients should be afforded the opportunity to have a choice in the selection of the best therapeutic option in the treatment of their mCRC. According to the patient survey and informal patient conversations, the most frequently reported disease-related symptoms are fatigue, abdominal pain, bloody stools, painful diarrhea/constipation; all of which impact a patient’s QoL significantly. While patients are aware of the fact that all drug therapies have associated risks, 63% of patients surveyed would not refuse taking a cancer therapy based on a severe toxicity profile of the therapy. Over 65% of patients surveyed reported that it would be very important to access additional treatments whose benefits might only be short term despite treatment adverse effects. Patients with mCRC view that long term health is relative and that any extension in life is considered to be an extension in long term health.

Please see below for a summary of specific input received from the patient advocacy group.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with mCRC

Depending upon the metastatic site, CCAC reported that symptoms of metastatic colorectal cancer (“mCRC”) include but are not limited to severe abdominal pain, shortness of breath, coughing, fatigue, bloating and loss of appetite.

According to the patient survey and informal patient conversations, the most frequently reported disease-related symptoms were: fatigue, abdominal pain, bloody stools, painful diarrhea/constipation; all of which reported to impact a patient’s QoL significantly. One respondent reported: *“Before my diagnosis, I experienced fatigue, nausea, blood in my stools, frequency and urgency of bowel movements and weight loss.”*

Approximately 90% of the respondents identified the following aspects of colorectal cancer as being the most important and difficult to control:

- Fatigue
- Nausea
- Pain
- Weakness
- Diarrhea

The limitations resulting from those symptoms included but are not limited to the following:

- Work Cessation
- Cessation of Physical Activity/Lack of Mobility
- Inability to meet family and social obligations
- Stress Induction/Psychological Impact

Below are excerpts from two of the respondents:

"All aspects of life are limited to less activity, including: work, exercise, recreation, social activity."

"I was working on a contract at one of the local universities when I was diagnosed. It took everything to finish the contract but I had to do it or I would not receive EI. When my EI ran out in the 6 or 8 weeks, I had to go on CP disability which meant we could barely afford to eat after the monthly expenses and mortgage were paid. I then had to apply for welfare. They wouldn't accept me until I had cashed in all my RRSPs and emptied my bank account. As I was so fatigued and weighed down by responsibility I had no appetite and couldn't sleep. My daughter was traumatized and stopped coming home after school. Everything I did was coloured by the fact that this might be my last year on earth and I am too sick to function. I had to prepare to sell the house and get all my financial papers in order. Make decisions about my funeral but I just didn't have the energy."

The CCAC stated that first and second line therapy (FOLFIRI/FOLFOX) in combination with a biologic therapy (Bevacizumab) has proven to successfully shrink tumours and stop the progression of the disease for a period of time for a subset of the population. According to the survey, 56% of respondents reported an improvement in the symptoms resulting from their colorectal cancer after accessing these systemic therapies. However, there were some patients who were unable to tolerate, or have a contraindication to Oxaliplatin in first line therapy. 65% of respondents reported having experienced Oxaliplatin-induced neuropathy and 25% reported cessation of the therapy following the onset of that neuropathy.

The CCAC believes that this subset of the patient population would be required to access another biological therapy in combination with FOLFIRI to ensure significant and clinically meaningful survival gains.

4.1.2 Patients' Experiences with Current Therapy for mCRC

The CCAC noted that standard treatment for mCRC, which is used by approximately 50% of the colorectal cancer population, involves chemotherapy based on fluoropyrimidines, Oxaliplatin and irinotecan - used in combination i.e. FOLFIRI and FOLFOX, and sequentially; and monoclonal antibodies (MAB) targeting vascular endothelial growth factor (VEGF; Bevacizumab). In patients with KRAS wild type tumours, monoclonal antibodies targeting epidermal growth factor receptor (EGFR; cetuximab) and panitumumab) may also be used.

Differences exist across Canada as they relate to access to treatments both to the therapy itself and in some cases, the line of treatment in which it is available. According to the survey, over 50% of

the Canadians respondents believe that geographical location impacts their quality of treatment when diagnosed with cancer.

The CCAC noted that access to Bevacizumab is not readily available in both first and second line therapy. According to CCAC, respondents reported that funding restrictions necessitate cessation of Bevacizumab in second line. One respondent noted *“Avastin should be funded in second line therapy.”* Respondents have also reported forfeiting the addition of Bevacizumab in the first line treatment of their mCRC so that it may be introduced in second line.

56% of surveyed respondents reported an improvement in the symptoms resulting from their colorectal cancer after accessing therapies such as FOLFIRI/FOLFOX in combination with Bevacizumab. However, there were some respondents who were unable to tolerate, or have a contraindication to Bevacizumab as well as Oxaliplatin.

The CCAC believes that for these patients, the addition of an anti-angiogenic agent such as Afibercept to FOLFIRI in second line may prove helpful, especially in those provinces where funding restrictions prevent access to the anti-VEGF therapy Bevacizumab in second line therapy.

From the patient survey results, it was noted that neurotoxicity is the most frequent dose-limiting toxicity of Oxaliplatin. A cumulative sensory peripheral neuropathy may also develop with prolonged treatment with Oxaliplatin. Respondents reported tingling or a feeling of pins and needles in hands and feet with severe numbness and found it difficult to do small tasks with their hands like buttoning a shirt. In some cases, neuropathy can cause pain and difficulty with daily life, including walking or balancing. If Oxaliplatin-induced neuropathy is severe, cessation of the therapy is recommended. In these cases, patients generally proceed to second line therapy and to access the most effective therapy clinically proven to shrink their metastatic disease.

In addition to the above, 44% of respondents surveyed reported financial implications associated with the management of their disease. They cited travel-related and parking costs as the most highly incurred expenditures when accessing their drug therapies. When asked if patients would be willing to pay out of pocket to access new drug therapies for the treatment of their mCRC, 83% replied “Yes”. Below were some of the open-ended replies from the respondents:

“I would do anything to fight cancer”

“I would do anything within my financial means to eradicate the cancer”

According to the survey, 43.8% of respondents also noted that their current therapy was not meeting their needs and identified the following key concerns:

- The funding of Bevacizumab or other anti-VEGF therapy in second line therapy
- More treatment options to help manage their mCRC
- Unsuccessful treatment of their mCRC

From a patient perspective, access to new treatments for mCRC remains paramount to managing the progression of this disease. Over 65% of patients surveyed reported that it would be very important to access additional treatments whose benefits might only be short term despite treatment adverse effects.

A QoL survey conducted by the CCAC in March 2011 indicated that patients were interested in treatment even in end of life situations when the benefit was just a few weeks provided there was good QoL. The results of the CCAC QoL Survey determined that part of maintaining QoL is linked to providing greater access to therapies that treat mCRC.

According to the CCAC, 80% of patients surveyed believe it is very important to access new treatments for mCRC. Over 65% of patients surveyed reported that it would be very important to access additional treatments whose benefits might only be short term despite treatment adverse effects.

4.1.3 Impact of mCRC and Current Therapy on Caregivers

According to the survey, patients and caregivers have both reported a significant impact on the caregiver in caring for patients with mCRC. Caregivers provide supportive care to the patient in managing adverse side effects, providing emotional support and assuming additional unpaid work duties in the home.

Additionally, caregivers of mCRC patients may be burdened with financial challenges relating to disability and cost of accessing treatments in those provinces that have reimbursement restrictions. Travel and parking costs are also often assumed by the caregiver when accessing drug therapies. Respondents reported the following difficulties in caring for mCRC patients:

"Taking time off work to take spouse to treatments and appointments, dealing with patient side effects."

"Difficulty understanding treatment and side effects."

"Fear for the loved one; tiredness, uncertainty about outcome; feelings of inadequacy; lack of support and information"

Caregivers reported that accessing drug therapies significantly impacted their daily routine as follows:

"take over household chores, care for ill person, support the rest of family and friends, being the advocate."

"Need to be ready and available for frequent appointments and prepared to assist in coping with side effects"

"Loss of work time, loss of sleep, loss of personal time, social time, recreational time"

"Lack of sleep; time taken from work to drive to oncology treatments; holidays suspended"

The majority of caregivers surveyed also reported the following challenges in dealing with adverse effects from the current therapies:

"Helping patients figure out what they are able to eat due to lack of appetite, watching them deal with all the pains they are experiencing and not being able to do much to help"

"Dealing with loss of appetite, decreased energy levels"

"Knowing what is a normal side effect and what would be considered adverse or dangerous reaction"

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with mCRC

Respondents have expressed their desire to continue accessing therapies to help control their mCRC with respect to quality of life (QoL), progression free survival (PFS) and overall survival (OS) as reported by anecdotal and survey input. The CCAC referenced the Phase III VELOUR trial, which was noted to be of particular interest to patients with mCRC since it appears to show that patients with mCRC receiving Aflibercept in combination with FOLFIRI experienced statistically significant

improvements in OS, PFS and overall response rate (ORR) when compared with those receiving placebo + FOLFIRI after failure with an Oxaliplatin-containing regimen.

In the metastatic setting, the CCAC reported that long term health is relative and is viewed by patients in small increments. Any extension in life is considered an extension in long term health by mCRC patients and caregivers.

While patients are aware of the fact that all drug therapies have associated risks, 63% of patients surveyed would not refuse taking a cancer therapy based on a severe toxicity profile of the therapy. Together with their treating oncologist, 88% of patients would very much appreciate choosing the best therapeutic option for the management of their disease.

The CCAC noted that the majority of the metastatic colorectal cancer population is fraught with colorectal liver metastases. Fewer than 20% of these patients are considered candidates for surgical resection. Reducing tumour burden in this patient population may increase resection rates, a benefit which may be obtained by administering Aflibercept + FOLFIRI in the second line treatment of mCRC patients.

As such, accessing therapies which may ultimately lead to a liver resection is highly sought after by mCRC patients. They are eager to access any therapy that will confer an additional benefit which may ultimately lead to a liver resection. Based on reports from those surveyed and those patients with whom CCAC have had discussions maintained they were in favor of accessing any new treatment that can potentially improve patient outcomes. Below are comments from the respondents:

"Immunity and routine chemo drugs warrant newer and better advanced drugs"

"Another option when all other drugs have been exhausted"

One patient surveyed had received Aflibercept + FOLFIRI therapy and reported that disease improvement was a positive effect. In terms of managing Aflibercept-induced side effects, CCAC noted that it may require intervention of health care professionals and caregivers similar to other approved drug therapies used in the treatment of mCRC.

4.3 Additional Information

The CCAC also surveyed 11 medical oncologists from the CCAC Medical Advisory Board and other affiliated experts from within Canada who treat mCRC. The survey included input on prescribing decisions for first and second line therapy, key factors contributing to treatment choice and challenges in preventing best outcomes for their patient populations. This survey and the summary of results were provided to pCODR along with this patient advocacy group's input.

The CCAC believes that patients who are not permitted to access Bevacizumab in second line therapy due to provincial funding restrictions are underserved, as are the patients who progress after first line containing Bevacizumab. As such, these patients might benefit from Aflibercept + FOLFIRI in second line as it would allow them to continue with another anti-VEGF therapy that has the potential to target a broader set of pro-angiogenic growth factors when compared to Bevacizumab. Moreover, CCAC believes that Aflibercept also has the theoretical advantage of more effective angiogenic suppression and overcoming Bevacizumab-induced resistance.

The CCAC also noted that in the case where third line options are either not available to or not appropriate for mCRC patients, maximizing the therapeutic benefits in second line therapy is of

paramount importance since a smaller proportion of the mCRC patient population may be able to proceed to third line therapy.

The CCAC surmised that in the event that the pricing of Aflibercept is brought in line with its comparator, then it may well be a viable option for patients with mCRC for the reasons set out above.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group at the beginning of the review as factors that potentially affect the feasibility of implementing a funding recommendation for aflibercept (Zaltrap) for metastatic colorectal cancer. The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on aflibercept (Zaltrap) for mCRC was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, the key enabler for implementation of aflibercept is that FOLFIRI is the current funded second-line treatment in most provinces and aflibercept would be add-on therapy. PAG identified that the main barrier to implementation is in provinces where FOLFOX is not the current funded first-line treatment or standard of care. Other barriers include the additional infusion time required to administer aflibercept, drug wastage and the management of toxicities (e.g. neutropenia) associated with this therapy.

Please see below for more details.

5.1 Factors Related to Comparators

With respect to comparators in the second-line setting, FOLFIRI is currently funded second-line treatment in most provinces. This is an enabler as aflibercept is to be used in combination with FOLFIRI.

PAG noted that aflibercept is indicated for use as second-line treatment after first-line treatment with Oxaliplatin containing regimens. This is a barrier in provinces where FOLFOX is not funded for the first-line treatment.

In the trial, 30% of patients received bevacizumab in the first-line setting. PAG is asking pERC to clarify if the benefit of treatment with aflibercept is representative of the patients who had prior therapy with bevacizumab.

5.2 Factors Related to Patient Population

PAG noted that aflibercept is an add-on drug for this group of patients already on FOLFIRI. This would be an enabler as this is an existing patient population and not a new patient group.

However, it was noted that the indication for aflibercept is second-line treatment following first-line treatment with Oxaliplatin-containing regimen. In provinces where FOLFOX is not funded as first-line treatment, patients would not be eligible to receive aflibercept as second-line treatment with FOLFIRI. This would be a barrier.

In those jurisdictions where FOLFOX is funded for both first-line and second-line treatment there may be indication creep for use of aflibercept in the first-line setting or for use in the second-line setting with FOLFOX instead.

5.3 Factors Related to Accessibility

In many provinces, FOLFIRI is already provided for second-line treatment. Aflibercept is an add-on intravenous therapy with the same frequency as FOLFIRI. Since patients are already in the infusion clinics for FOLFIRI, this would be an enabler.

5.4 Factors Related to Dosing

Drug wastage is a concern and a barrier, when vial sharing is not possible, especially in smaller centers or when multiple patients are not in clinics at the same time. The single-use vials are available in 100mg/4mL and 200mg/8mL sizes, with a short stability. There will be many instances where a small portion of another vial would be needed to make the 4mg/kg dose.

5.5 Factors Related to Implementation Costs

Barriers to implementation identified are the additional one hour of infusion time required and the increase in workload to manage the Grade 3 to 4 toxicities associated with aflibercept. PAG noted that neutropenia was greater in the aflibercept group in the clinical trial and the impact of this on cost-effectiveness should be addressed.

5.6 Other Factors

PAG noted that there is no direct comparison with bevacizumab in the second-line setting. PAG is also seeking clarity on the use of aflibercept in patients who received bevacizumab in the first-line setting. PAG is seeking clarity for these settings.

PAG also noted that the net clinical benefit is small (approximately 6 weeks incremental benefit in overall survival) and the impact of this on cost-effectiveness should be addressed

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness of aflibercept (Zaltrap) in combination with irinotecan-fluoropyrimidine (FOLFIRI) based chemotherapy, on patient outcomes compared with appropriate comparators in the treatment of patients and associated subgroups with, non-resectable metastatic colorectal cancer who have previously been treated with an Oxaliplatin containing chemotherapy regimen.

The following supplemental questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Contextual information and critical appraisal of a network meta-analysis (NMA) comparing aflibercept/FOLFIRI with bevacizumab/FOLFIRI for the treatment of patients with metastatic colorectal cancer previously treated with oxaliplatin containing chemotherapy regimen.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Double-blind, randomized controlled trials	Confirmed metastatic colorectal cancer not amenable to potentially curative treatment, previously treated with Oxaliplatin based chemotherapy Subgroups: Previously treated with Bevacizumab	Aflibercept AND Irinotecan-fluoropyrimidine (FOLFIRI)	Irinotecan-fluoropyrimidine (FOLFIRI) based chemotherapy ± Bevacizumab	OS, PFS, Hematologic SAE's Non- Hematologic SAE's Chemo Related AEs Anti-VEGF related AEs Quality of Life (QOL)
[Abbreviations] OS=Overall Survival; PFS=Progression Free Survival; AE: adverse events; SAE: serious adverse events, FOLFIRI: fluorouracil, leucovorin, and irinotecan				

* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946- December 18, 2013) with in-process records & daily updates via Ovid; EMBASE (1980-December 18, 2013) via Ovid; The Cochrane Central Register of Controlled Trials (2010, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Aflibercept (Zaltrap) and metastatic colorectal cancer.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Retrieval was limited to the human population, and to the English language. Retrieval was not limited by publication year. The search is considered up to date as of June 5th, 2014.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health - clinictrials.gov and Ontario Institute for Cancer Research - Ontario Cancer Trials) and relevant conference abstracts ASCO and ESMO. Search of conference abstracts of the American Society of Clinical Oncology (ASCO) was limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

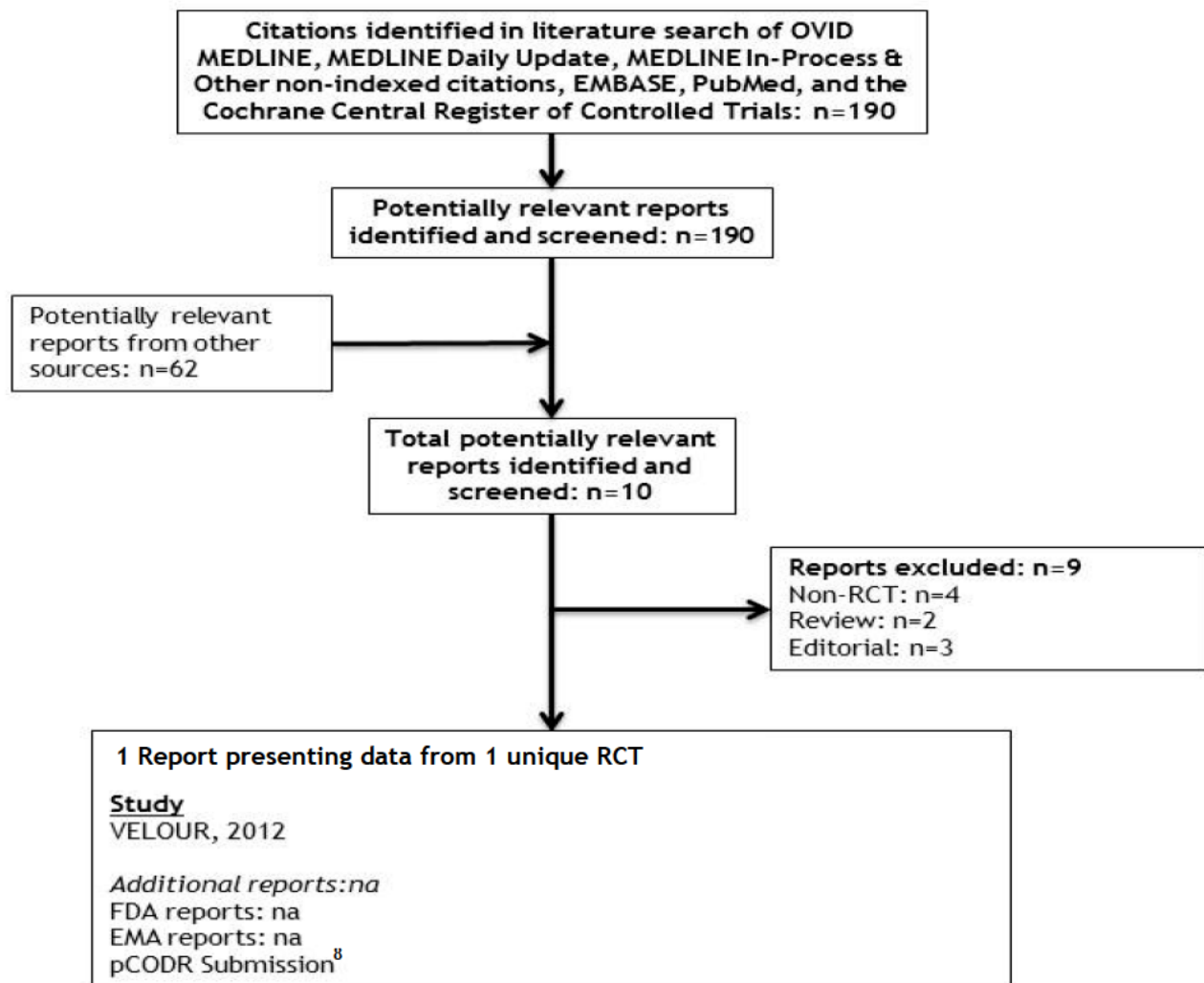
6.3 Results

6.3.1 Literature Search Results

A total of 190 unique citations were identified through searches of MEDLINE (OVID), MEDLINE Daily Update (OVID), MEDLINE In-Process & Other Non-Indexed Citations (OVID), EMBASE (OVID), Cochrane Central Register of Controlled Trials, and PubMed (Figure 1). Twelve additional abstracts were identified through searches of the annual conferences of ASCO, and another 50 abstracts were reviewed from ESMO. Of those 252 citations, 10 potentially relevant reports were retrieved for full text review.^{1, 38-45} One report was included in the pCODR systematic review and nine reports were excluded. Studies were excluded because they were not randomized trials, were review articles, or were editorial commentary regarding trials that had been conducted.³⁸⁻⁴⁵

Following the posting of the pERC initial recommendation, the submitter commented on pERC's Initial Recommendation regarding a study they identified that should have been included in this systematic review but were excluded. Although these studies were identified in the literature search, they were subsequently excluded during title and abstract screening phase because the analyses were based upon a single arm, open label, cohort studies.

Figure 1. Aflibercept (Zaltrap) - Flow diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

One randomized control trial was included in the review. Supplemental question review included two other reports comparing treatment regimens with and without Bevacizumab.

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of Trial characteristics

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Pre-Specified Outcomes
<p>Phase III, Multicenter</p> <p>Funding: Sanofi, in collaboration with Regeneron Pharmaceuticals.</p> <p>Location: Multi-national</p> <p>Beginning date: Nov. 2007</p> <p>Finish date: Mar. 2010</p> <p>Trial Type: Randomized control trial</p> <p>Analysis pop: Confirmed metastatic colorectal cancer previously treated with Oxaliplatin containing chemotherapy</p> <p>Sample Size: 1226</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • 18 years old; with an (ECOG) performance status (PS) of 0 to 2, histologically or cytological proven colorectal adenocarcinoma with metastatic disease not amenable to potentially curative treatment. • Patients who experienced relapse within 6 months of completion of Oxaliplatin-based adjuvant therapy were eligible. • Prior Bevacizumab was permitted, but not prior irinotecan. • Although patients were to have documented progression while on or after completion of a single prior Oxaliplatin-containing regimen, they were not selected for the timing of their progression. 	<p>4 mg/kg of Aflibercept or placebo (intravenously [IV]), over 1 hour on day 1 every 2 weeks, followed immediately by the FOLFIRI (irinotecan 180mg/m² IV over 90 minutes, with leucovorin 400 mg/m² IV over 2 hours, followed by FU 400 mg/m² bolus and FU 2400 mg/m² continuous infusion over 46 hours) regimen</p>	<p>OS PFS ORR (CR, PR)</p> <p>Hematologic AE's Anemia, hemorrhage, neutropenia, neutropenic complications, thrombocytopenia</p> <p>Non- Hematologic AE's Proteinuria, ALT increased</p> <p>Chemo Related AE's Diarrhea, stomatitis, nausea, diarrhea, asthenic conditions, infections and infestations, hypertension, GI/abdominal pain, vomiting, decreased appetite, alopecia, dysphonia, constipation, headache, palmar-plantar erythrodysesthesia syndrome</p> <p>Anti-VEGF related AE's (Arterial/Venous thromboembolic events, fistula from GI origin/other origin, GI perforation)</p>
<p>OS=Overall Survival; PFS=Progression Free Survival, ORR=Overall Response Rate; CR= complete response; PR=Partial Response; AE=Adverse Events; DB= double-blind; PC= placebo controlled; PR= partial response; RECIST= Response Evaluation Criteria in Solid Tumours; RCT= randomized controlled trial</p>			

a) Trials

One randomized trial, *VELOUR*¹, was included in this systematic review. This trial evaluated the use of Aflibercept in combination with FOLFIRI, compared with FOLFIRI alone (placebo). The main endpoint was overall survival, and tests for superiority were carried out using Kaplan Meier estimates, and log rank testing. Secondary endpoints included progression free survival and safety. Trial design is a randomized, double blind, parallel assignment. Blinding of subject and investigators was used. No cross over was permitted. Analysis methods were all described thoroughly in the published reference. Demographics were well balanced between the treatment arms (age, race, ECOG performance status, and prior bevacizumab status). Of the 1226 patients randomized in the study, the median age was 61 years, 58.6% were male, and 97.8% had a baseline ECOG performance status (PS) of 0 or 1. Disease characteristics were well balanced between arms with the most frequently involved organs were the liver (72.6%) followed by the lungs (44.7%), lymph nodes (28.9%), and peritoneum (12.7%). Subgroup analysis and the effect on OS and PFS was determined pre-hoc and included ECOG PS, prior Bevacizumab, and baseline characteristics including age, gender, geographic region, prior hypertension, number of metastatic sites, disease confined to liver and location of primary tumour.

b) Populations

Figure 2. Baseline Patient Characteristics

Characteristic	Placebo/ FOLFIRI (n = 614)		Aflibercept/ FOLFIRI (n = 612)	
	No.	%	No.	%
ECOG PS				
0	350	57.0	349	57.0
1	250	40.7	250	40.8
2	14	2.3	13	2.1
Prior bevacizumab*				
Yes	187	30.5	186	30.4
No	427	69.5	426	69.6
Sex				
Male	353	57.5	365	59.6
Female	261	42.5	247	40.4
Age, years				
Median		61.0		61.0
Range		19-86		21-82
Primary site				
Colon	302	49.2	289	47.2
Rectosigmoid	136	22.1	123	20.1
Rectum	174	28.3	197	32.2
Other	2	0.3	3	0.5
No. of metastatic organs involved at baseline (excluding primary site)				
0	6	1.0	2	0.3
1	271	44.1	256	41.8
> 1	337	54.9	354	57.8
Metastatic organs involved at baseline (excluding primary site)				
Any site	608	99.0	610	99.7
Liver	431	70.2	459	75.0
Lung	277	45.1	271	44.3
Lymph nodes	181	29.5	173	28.3
Peritoneum	88	14.3	68	11.1
Liver metastasis				
None, or liver and other metastases	468	76.2	459	75.0
Liver metastasis only	146	23.8	153	25.0
Prior hypertension	268	43.6	266	43.5
Prior chemotherapy				
Adjuvant only†	64	10.4	60	9.8
Adjuvant and metastatic disease	108	17.6	102	16.7
Metastatic disease	442	72.0	450	73.5

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, infusional fluorouracil, leucovorin, and irinotecan.
*Prior bevacizumab status as provided at randomization (stratification variable).
†Relapse within 6 months of completion of oxaliplatin-based adjuvant therapy.

Source: Van Cutsem, 2012¹

A total of 1226 patients were randomized to receive either Aflibercept (612 patients) or placebo (614 patients). Proportion of patients by gender was 59.6%/57.5% male and 40.4%/42.5% female in the Aflibercept/Placebo arms respectively. Median age was 61 in both arms with age ranges of 21-82 in the Aflibercept arm and 19-86 in the placebo arm. ECOG performance status was similar between groups (Aflibercept/Control): 57.0%/57.0%, 40.8%/40.7%, and 2.1%/2.3% for status levels 0, 1, and 2 respectively. The number of patients who received prior Bevacizumab therapy was the same in both arms with 186 and 187 having received Bevacizumab therapy in the Aflibercept and Placebo arms, respectively. Small differences were noted in the number of metastatic organs involved at baseline, and the organs involved, with 41.8% having one organ involved in the Aflibercept arm and 44.1% of patients in the placebo arm. Three hundred fifty four patients (57.8%) in the Aflibercept arm and 337 patients (54.9%) in the placebo arm had greater than one organ involved at baseline. Four hundred and fifty nine (75%) and 431 patients (70.2%) had liver involvement in the Aflibercept and placebo arms respectively. One hundred seventy three 173 (28.3%) patients had lymph node involvement in the Aflibercept arm while 181 (29.5%) had lymph node involvement in the Placebo arm.

c) Interventions

Van Cutsem, 2012¹ examined the use of the FOLFIRI regimen with or without Aflibercept. FOLFIRI is a fluoropyrimidine-based chemotherapy regimen that combines infusional fluorouracil (FU) and leucovorin with irinotecan. Patients received 4 mg/kg of Aflibercept or placebo (intravenously [IV]), according to treatment assignment, over 1 hour on day 1 every 2 weeks, followed immediately by the FOLFIRI regimen (irinotecan 180mg/m² IV over 90 minutes, with leucovorin 400 mg/m² IV over 2 hours, followed by FU 400 mg/m² bolus and FU 2400 mg/m² continuous infusion over 46 hours). Premedication with atropine and antiemetic's was permitted. Granulocyte colony stimulating factor was used according to American Society of Clinical Oncology guidelines. Dose modifications were implemented in more patients in the aflibercept arm than in the control arm (aflibercept/placebo, 16.7% v 4.8%; irinotecan, 37.2% v 22.6%; FU, 39.1% v 21.7%, respectively).

d) Patient Disposition

One thousand, four hundred and one patients (1,401) were assessed for eligibility of which 175 were excluded because they did not meet the inclusion criteria, declined to participate or for "other reasons". Of the 1,226 patients randomized only those patients that received study treatment were analysed in the primary analysis. One hundred sixty five patients were excluded from the response rate analysis due to non-measurable disease. Due to large numbers of deaths and low survival during follow up there are limited details for the evaluation of treatment follow-up. Patients who discontinued prior to disease progression were followed every 6 weeks for progression free survival. Those with disease progression and that survived, were followed every 8 weeks until death or study cut-off. Two patients were lost to follow up from the placebo arm and none from the aflibercept arm, indicating results are considered complete.

e) Limitations/Sources of Bias

A review of factors associated with study quality was undertaken and results indicate limited concern regarding methods. There were two limitations found within the study:

- 1) Final analyses were conducted by Sanofi personnel. This raises the concern that methods and assumptions used may not be detailed and may create bias within results.

- 2) Any variation in practice between centres participating in the trial cannot be determined leading to the possibility that practice differences may have had an impact on aggregate outcomes.

Otherwise trial methods were very well described.

- Randomization methods were carried out using a centralized interactive voice response system based on a permuted-block randomization, stratified according to prior therapy with Bevacizumab (yes or no), and ECOG PS (0, 1, or 2). Intention to treat analysis was conducted along with pre-specified subgroup analysis.
- Treatment and control groups were found to be similar in terms of patient characteristics indicating the only difference between groups was treatment.
- Measurement and statistical methods were all verified and deemed acceptable with known limitations.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Table 3. Efficacy outcomes reported in VELOUR (Van Cutsem, 2012¹) in patients with non-resectable, metastatic colorectal cancer who have previously treated with an oxaliplatin containing chemotherapy regimen.

Treatment arms	OS*, median (mos)	PFS*, median (mos)
Aflibercept + FOLFIRI, n=612	13.05	6.9
FOLFIRI, n=614	12.06	4.7
	HR 0.817 95%CI 0.713-0.937 p=0.0032	HR 0.758 95%CI 0.661-0.859 p<0.0001
Subgroup analysis of patients with (A) or without (B) prior bevacizumab treatment		
(A)		
Aflibercept + FOLFIRI, n=186	HR 0.862 95%CI 0.673-1.104	HR 0.661 95%CI 0.512-0.852
FOLFIRI, n=187	p=0.5668**	p=0.1958**
(B)		
Aflibercept + FOLFIRI, n=426	HR 0.788 95%CI 0.669-0.927	HR 0.797 95%CI 0.679-0.936
FOLFIRI, n=427		
Notes: 95%CI=95% confidence interval; HR=hazard ratio; mos=months; n=number of patients; OS=overall survival; PFS=progression-free survival.		
*Data is based on a 22 month follow up period.		
**P-value at 10% level of significance for interaction between treatment and stratification factors		

Overall Survival (OS)

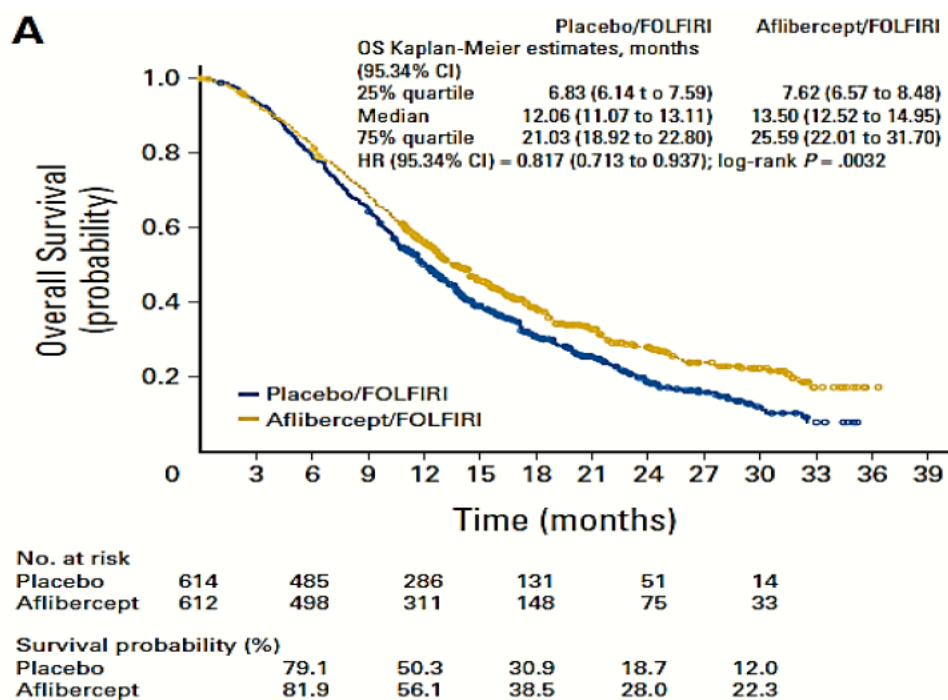
Results from Van Cutsem, 2012¹ reported a statistically longer median overall survival for patients receiving Aflibercept in combination with FOLFIRI compared with those receiving FOLFIRI alone (13.05 vs. 12.06 months, respectively, HR=0.817 with 95.34% CI 0.713 to 0.937, p-value of p=0.0032. Kaplan Meier curves are shown in figure 3. Survival results are based upon a total of 863 events during a 22.28 month follow up period. Pre-specified subgroup analyses based on prior Bevacizumab status indicated a treatment effect in this

subgroup that exhibited a consistent trend, with Aflibercept improving OS without significant interaction effects. Forest plots for group and sub-group analysis can be found in figure 4.

Progression Free Survival (PFS)

Statistically longer progression free survival was also reported for patients receiving aflibercept in combination with FOLFIRI compared with those receiving FOLFIRI alone (table 3) Van Cutsem 2012¹ reported 2 yr median PFS of 6.90 (95% CI 6.51-7.2) months and 4.67 (95% CI 4.21-5.36) months in the Aflibercept + FOLFIRI and placebo + FOLFIRI arms respectively (HR=0.758, 95% CI 0.661-0.869, *p*-value of *p*<0.0001). Kaplan Meier curves are shown in figure 3. PFS results are based upon a total of 847 events during a 22.28 month follow up period. Subgroup analyses based on prior Bevacizumab status exhibited a consistent trend in PFS advantage for the Aflibercept arm over the control arm. Forest plots for group and sub-group analysis can be found in figure 4.

Figure 3. Kaplan-Meier curves for overall survival (A) and progression free survival (PFS) (B) in the primary analysis population



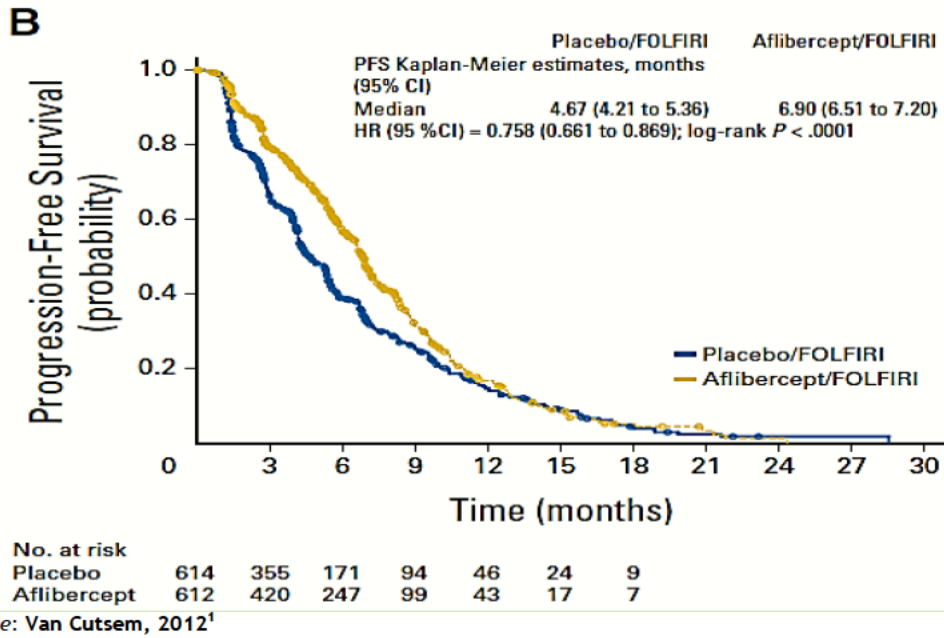
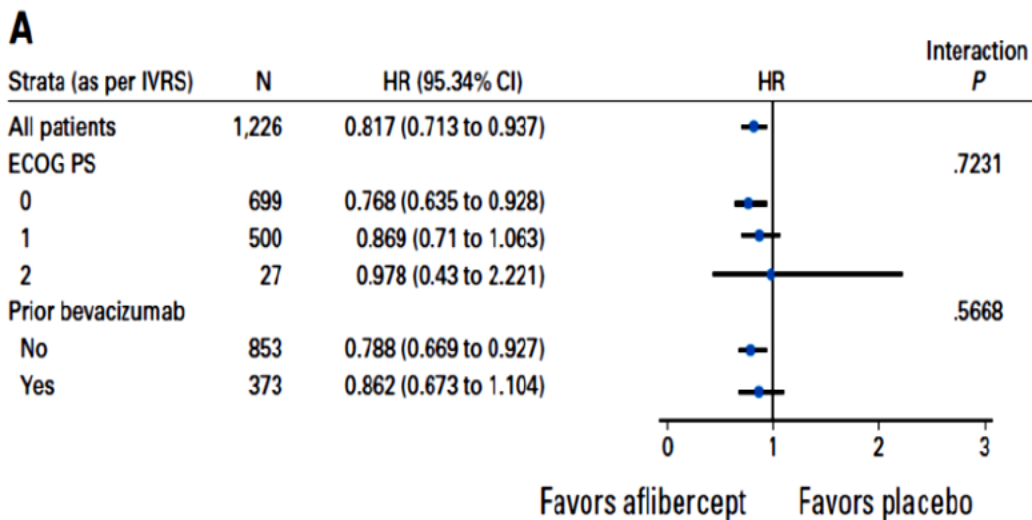
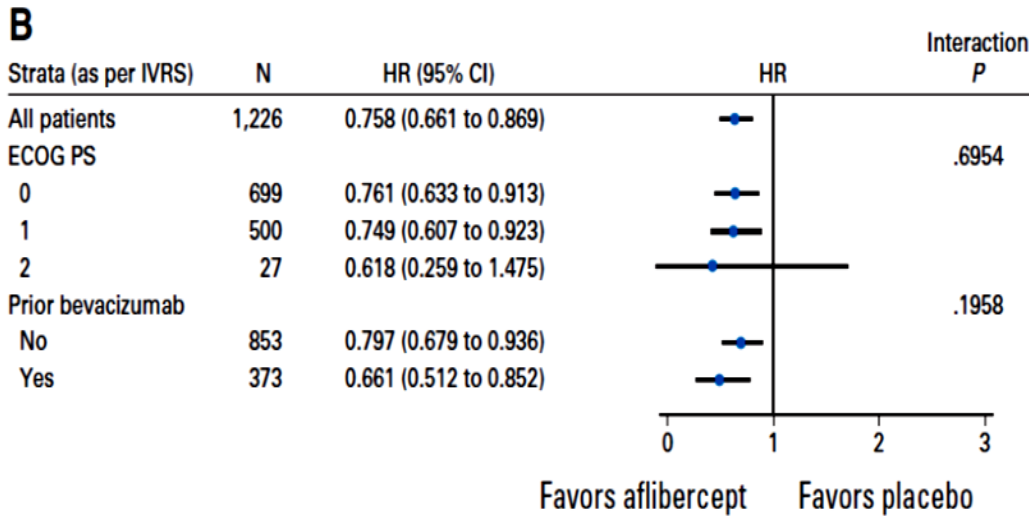


Figure 4. Forest plots for (A) overall survival and (B) progression-free survival in planned subgroup analyses by stratification factors in the primary analysis population





Source: Van Cutsem, 2012¹

Response Rate

Disease assessment was performed every 6 weeks until documented progression. ORR was assessed according to RECIST by an Independent Review Committee blinded to patient treatment. In addition to improvements in median OS and PFS, there were statistically and clinically significant improvements in ORR with Aflibercept + FOLFIRI compared with placebo + FOLFIRI. The ORR (complete response or partial response) was significantly greater for the Aflibercept + FOLFIRI arm compared with the placebo + FOLFIRI arm (19.8% [95% CI: 16.4 to 23.2] vs. 11.1% [95% CI: 8.5 to 13.8]; P=0.001).

Quality of Life

The submitter was asked and confirmed that quality of life data was not measured in the study.

Harms Outcomes

Anti-VEGF therapy related AE's

Adverse events more commonly associated with anti-VEGF therapy include hypertension, hemorrhage, arterial thromboembolic events, and venous thromboembolic events.

Grade 3 hypertension occurred in 19.1% vs. 1.5% of patients in the aflibercept vs. placebo/FOLFIRI arms, respectively while only one patient in the Aflibercept arm (0.2%) experienced grade 4 hypertension. Grade 3/4 hemorrhage occurred in 3.0% vs. 1.7% of patients, respectively and any hemorrhage events occurred in 37.8% vs. 19.0%, in the aflibercept versus control arms respectively. Grade 3/4 arterial thromboembolic events occurred in 1.8% vs. 0.5% of patients in the aflibercept and control arms respectively while any arterial thromboembolic event occurred in 2.6% and 1.5% of patients. Grade 3/4 venous thromboembolic event occurred in 7.8% vs. 6.2% of patients, in the Aflibercept and control arms respectively while any venous thromboembolic event occurred in 9.3% and 7.3% of patients, respectively.

Chemotherapy related AE's

Grade 3/4 adverse events commonly associated with Chemotherapy and which occurred at a higher frequency in the Aflibercept arm versus the placebo arm included diarrhea

(19.3%/7.8%), asthenic conditions (16.8%/10.6%), stomatitis and ulceration (13.8%/5.0%), infections (12.3%/6.9%), and palmar-plantar erythrodysesthesia (2.8%/0.5%), neutropenia (36.7%/29.5%), complicated neutropenia (5.7%/2.9%), and thrombocytopenia (3.4%/1.6%). All grades proteinuria was reported in 62.2% vs. 40.7% of cases in the Aflibercept + FOLFIRI vs. Aflibercept + placebo arms respectively.

Hematologic and non-hematological AE's

The most frequent hematological grade 3/4 AE was neutropenia which occurred in 36.7% vs. 29.5% of patients in the aflibercept/FOLFIRI vs. placebo/FOLFIRI arms, respectively. The most frequent non-hematological grade 3/4 AE was proteinuria which occurred in 7.8% vs. 1.2% of patients in each arm, respectively.

Frequent AEs

All grades adverse event were reported in 99.2% vs 97.9% of patients in the aflibercept/FOLFIRI vs placebo/FOLFIRI arms respectively. The most frequently occurring grades 3/4 AE's (defined as incidence $\geq 20\%$ or $\geq 5\%$ higher in aflibercept arm; safety population) were diarrhea, asthenic conditions, stomatitis, infection and infestations, hypertension, neutropenia and proteinuria.

Table 5. Harms outcomes in patients receiving aflibercept/FOLFIRI vs. placebo/FOLFIRI in the VELOUR study.				
Adverse Events	FOLFIRI <i>plus</i> Aflibercept (n = 611)		FOLFIRI <i>plus</i> Placebo (n = 605)	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Any	99.2%	83.4%	97.9%	62.5%
Diarrhea	69.2%	19.3%	56.5%	7.8%
Asthenia	60.4%	16.8%	50.2%	10.6%
Stomatitis	54.8%	13.8%	34.9%	5.0%
Nausea	53.4%	1.8%	54.0%	3.0%
Infection	46.2%	12.3%	32.7%	6.9%
Hypertension	41.4%	19.3%	10.7%	1.5%
Hemorrhage (all)	37.8%	3.0%	19.0%	1.7%
Hemorrhage (epistaxis)	27.7%	0.2%	7.4%	0.0%
Abdominal pain	34.0%	5.4%	29.1%	3.3%
Emesis	32.9%	2.8%	33.4%	3.5%
Decreased Appetite	31.9%	3.4%	23.8%	1.9%
Other anti-VEGF associated events				
Arterial thromboembolic	2.6%	1.8%	1.5%	0.5%

Table 5. Harms outcomes in patients receiving aflibercept/FOLFIRI vs. placebo/FOLFIRI in the VELOUR study.				
Adverse Events	FOLFIRI <i>plus</i> Aflibercept (n = 611)		FOLFIRI <i>plus</i> Placebo (n = 605)	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Venous thromboembolic	9.3%	7.8%	7.3%	6.2%
Fistula (GI)	1.1%	0.3%	0.3%	0.2%
Perforation (GI)	0.5%	0.5%	0.5%	0.4%
Hematologic AE				
Neutropenia	67.8%	36.7%	56.3%	29.5%
Non-hematologic AE				
Proteinuria	62.2%	7.8%	40.7%	1.2%
Discontinuation				
Adverse Events	26.6%		12.1%	
Disease Progression	49.8%		71.2%	
Patient Request	13.6%		7.3%	
Investigator Decision	3.3%		3.4%	
Surgery for Metastasis	2.0%		1.6%	
Subsequent Therapies	59.5%		59.6%	

Dose Adjustment/Discontinuation

Median relative dose intensity was 83% for patients in the aflibercept arm versus 92% for patients in the control arm. Cycle delays were reported in 77.7% of patients in the aflibercept arm and 69.4% of patients in the control arm; dose modifications were implemented in more patients in the aflibercept arm than in the control arm (aflibercept/placebo, 16.7% v 4.8%; irinotecan, 37.2% v 22.6%; FU, 39.1% v 21.7%, respectively). Discontinuation of treatment due to adverse events occurred in 26.8% of patients in the Aflibercept arm and 12.1% of patients in the placebo arm.

Patient Deaths

Deaths due to causes other than disease progression occurring within 30 days of last administration of study treatment were reported in 16/611 patients (2.6%) treated with the ZALTRAP/FOLFIRI regimen and 6/605 patients (1.0%) treated with the placebo/FOLFIRI regimen. The causes for these deaths in patients receiving the ZALTRAP/FOLFIRI regimen were infection (including neutropenic sepsis) in 4 patients, dehydration in 2 patients, hypovolemia in 1 patient, metabolic encephalopathy in 1 patient, respiratory events (acute respiratory failure, aspiration pneumonia, and pulmonary embolism) in 3 patients, GI disorders (duodenal ulcer hemorrhage, GI inflammation, and large intestinal obstruction) in 3 patients, and death of unknown cause in 2 patients.

6.4 Ongoing Trials

Table 6. Ongoing Trials

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
<p>Multinational 3 Randomized Control Trial</p> <p>Start Date: July 2012</p> <p>Trial Name: A Multinational, Randomized, Double-Blind Study of Aflibercept Versus Placebo With irinotecan/5-FU Combination (FOLFIRI) in Patients With Metastatic Colorectal Cancer (MCRC) After Failure of an Oxaliplatin Based Regimen</p> <p>ClinicalTrials.gov Identifier: NCT01661270</p>	<ul style="list-style-type: none"> • Histological or cytological proven adenocarcinoma of the colon or rectum. • Metastatic disease not amenable to potentially curative treatment. • One and only one prior chemotherapeutic regimen for metastatic disease. Chemotherapy must be an Oxaliplatin containing regimen. Relapse within 6 months of completion of Oxaliplatin based adjuvant chemotherapy 	<p>Experimental arm: One (1) hour intravenous (IV) on day 1 of each cycle, every 2 weeks in combination with FOLFIRI (irinotecan, 5-Fluorouracil and leucovorin) regime</p> <p>Vs.</p> <p>Placebo arm: Placebo One (1) hour intravenous(IV) on Day 1 of each cycle, every 2 weeks in combination with FOLFIRI (irinotecan, 5-Fluorouracil and leucovorin) regimen</p>	<p>Primary: PFS</p> <p>Secondary: OS, ORR, Immunogenicity</p>

7 SUPPLEMENTAL QUESTIONS

7.1 Contextual Information and Critical Appraisal of submitted Network Meta-Analysis comparing Aflibercept with Bevacizumab

7.1.1 Objective

To summarize and critically appraise the methods and findings of the key studies evaluating bevacizumab as well as the manufacturer-submitted network meta-analysis (NMA)⁸. The main objective of the manufacturer-submitted NMA was to estimate the comparative efficacy of Aflibercept versus Bevacizumab, when used alone or in combination with chemotherapy for the treatment of metastatic colorectal cancer that has progressed following initial therapy with Oxaliplatin containing chemotherapy regimen.

A systematic review was conducted by the submitter to gather evidence for development of a treatment network. Following the systematic review a Network meta-analysis (NMA) was conducted and included as part of the submission for Aflibercept. Due to a lack of head to head comparisons, multiple assumptions needed to be made regarding treatments. In an attempt to limit the number of assumptions made in the network two different networks were created and analysed. The primary analysis included a network that compared Aflibercept and FOLFIRI with Bevacizumab and FOLFOX. The secondary analysis included a network that compared Chemotherapy (FOLFIRI/FOLFOX) and Aflibercept with Chemotherapy (FOLFIRI/FOLFOX) and Bevacizumab.

7.1.2 Findings

Contextual Information on Bevacizumab

Bevacizumab and Aflibercept are two angiogenesis inhibiting agents that are being studied, and are considered comparator interventions, for second line treatment of mCRC. Bevacizumab has been evaluated in the following randomized studies, which are included in the subsequent network meta-analysis^{7, 37}.

- Giantonio, 2007⁷ is a three arm RCT - Oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) with Bevacizumab; FOLFOX4 without Bevacizumab; or Bevacizumab alone. Inclusion criteria required that patients had been treated with prior chemotherapy including irinotecan and a fluoropyrimidine for advanced disease, and that the previous use of Oxaliplatin or Bevacizumab was not permitted. Median survival was 12.9 months for those treated with FOLFOX and Bevacizumab compared with 10.8 months for those treated with FOLFOX4 alone (hazard ratio $h=0.75$; $P=.0011$). The median survival for those treated with Bevacizumab alone was 10.2 months though Bevacizumab monotherapy arm was discontinued due to inferior survival.
- Bennouna, 2013³⁷ was an open label, multi center phase 3 study. Patients with unresectable, histologically confirmed metastatic colorectal cancer progressing up to 3 months after discontinuing first-line Bevacizumab plus chemotherapy including a fluoropyrimidine plus either Oxaliplatin or irinotecan, and they were not candidates for primary metastasectomy. Patients were randomly assigned to infusional or bolus fluorouracil or oral capecitabine at the investigator's discretion plus irinotecan or Oxaliplatin with or without Bevacizumab. In this trial the choice of second line therapy was determined by the first line regimen. Those who were given first line Oxaliplatin were switched with second line irinotecan. Median overall survival in the Bevacizumab plus chemotherapy group was 11.2 months (95% CI 10.4-12.2) versus 9.8 months (8.9-10.7) for chemotherapy (HR 0.81, 95% CI 0.69-0.94; un-stratified log-rank $p=0.0062$). Median progression-free survival was 5.7 months (95% CI 5.2-6.2) in the Bevacizumab plus

chemotherapy group and 4.1 months (3.7-4.4) in the chemotherapy group (HR 0.68, 95% CI 0.59-0.78; un-stratified log-rank $p < 0.0001$).

Quantitative assessments via pooled analysis require assumptions of similarity for multiple study characteristics, such as patient populations, prior therapies, treatment choice and comparator arms. Because of differences between studies, comparative modeling and interpretation of outcomes from comparative analysis between Aflibercept and Bevacizumab based upon information presented in the trials noted above should be treated with caution. In Bennouna, 2007³⁷, patients were treated in the fistline setting with either Irinotecan or Oxaliplatin containing chemotherapy regimens combined with Bevacizumab. Patients were not previously treated with an Oxaliplatin containing chemotherapy regimen in Giantonio, 2007⁷. The heterogeneity of firstline treatment regimens makes any generalization of results less valid because the population of interest for Aflibercept is only those who have been previously treated with Oxaliplatin containing regimens.

Summary of Network Meta-Analysis⁸

For the systematic review Medline, EMBASE, and Cochrane Library databases were searched for relevant randomized trials containing interventions including Irinotecan, FOLFIRI, Bevacizumab + FOLFIRI, Bevacizumab + FOLFOX, FOLFOX4, FOLFOX6, CapeOX, XELOX and Aflibercept. Two reviewers completed the initial title and abstract review. In cases of disagreement references were discussed with a third party. Grey literature was also searched for abstract papers. These sources included ESMO and ASCO. Databases were searched between dates January 1, 1992, and December 19, 2012. Abstracts were searched between the years 2010 and 2012. From the evidence identified for that systematic review, the authors identified twenty seven randomized controlled trials that were conducted in patients with mCRC. All studies included patients who had been previously treated, though initial treatment was not common between studies. Progression of disease was not a requirement in all studies. Subgroup analysis was conducted in many studies and included previous treatment with Bevacizumab. Only one randomized study examined the use of Aflibercept in secondline therapy. All other studies investigated many dose and treatment related permutations for firstline and secondline therapies.

Of twenty seven studies, two studies included best supportive care, six studies included FOLFOX4 as monotherapy comparators, 13 used irinotecan based therapy, 5 used FOLFIRI based chemotherapy, one used WR-2721 + mitomycin, and three used Bevacizumab in combination with chemotherapy. A summary of the trial and patient characteristics was provided in a table format in the NMA report, which has been reproduced here as figure 3 & 4. Of note, the authors did provide an assessment of the quality of the individual trials but also did indicate uncertainty, or unclear risk of bias, resulting from methods not being adequately reported. Seventeen studies scored between 0-3, 2 ranked between -1-0, and eight studies between 4-7, using assessment criteria based on recommendations by the Cochrane Collaboration, Centre for Reviews and Dissemination (CRD), and National Institute for Health and Clinical Excellence (NICE). Higher score indicates lower overall risk of bias.

Network developed for the primary analysis is seen in figure 1. Network for the secondary analysis in figure 2. Fixed Effects & Random Effects Meta-analysis, and pairwise comparison modelling was conducted on endpoints in both networks.

Figure 1. Network diagram for primary analysis.

The primary analysis includes six studies at a maximum, based on available data reported within each study. Red: 5-FU prior therapy; Yellow: Irinotecan or Oxaliplatin based prior therapy; Green: Irinotecan plus 5-FU based prior therapy; Blue: Oxaliplatin based prior therapy; *Trial included various standard chemotherapy based on fluoropyrimidines plus Oxaliplatin or irinotecan.

Abbreviations: 5-FU = 5-fluorouracil; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil plus folinic acid plus irinotecan; FOLFOX = 5-fluorouracil plus folinic acid plus Oxaliplatin; FOLFOX4 = 5-fluorouracil plus folinic acid plus Oxaliplatin; NCCN = National Comprehensive Cancer Network

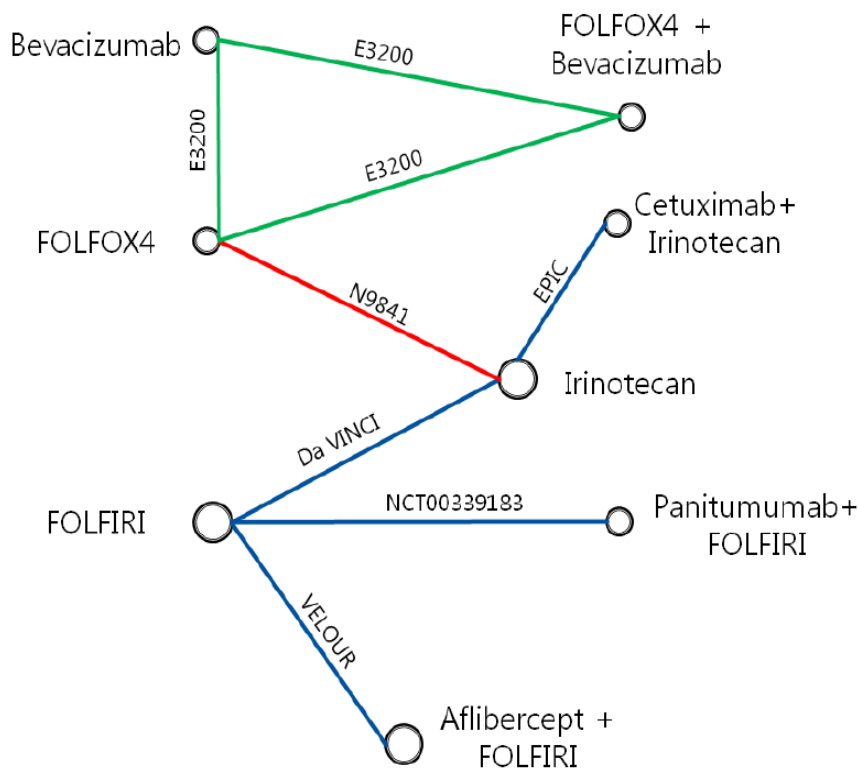
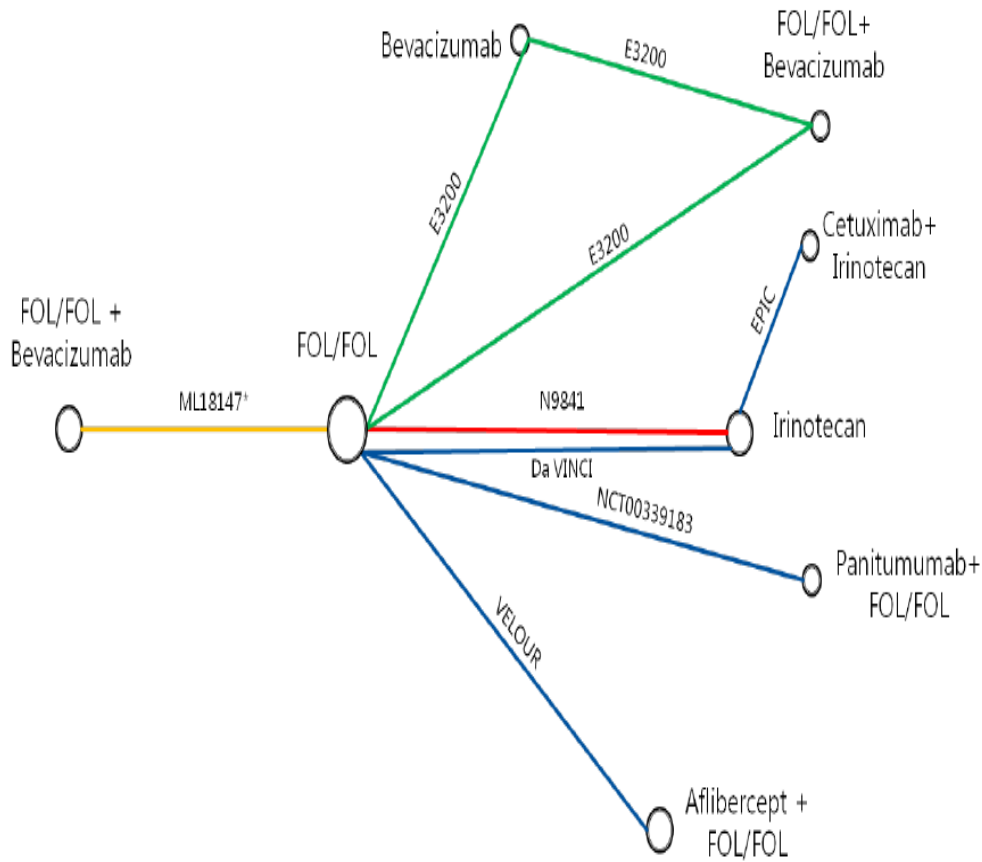


Figure 2. Network diagram for Secondary analysis.

The secondary analysis includes seven studies at a maximum, based on available data reported within each study. The secondary analysis is based on the assumption that FOLFOX and FOLFIRI are clinically equivalent. In this case, the ML18147 study can be included and the FOLFOX and FOLFIRI nodes are combined. Red: 5-FU prior therapy; Yellow: Irinotecan or Oxaliplatin based prior therapy; Green: Irinotecan plus 5-FU based prior therapy; Blue: Oxaliplatin based prior therapy; *Trial included various standard chemotherapy based on fluoropyrimidines plus Oxaliplatin or irinotecan. Abbreviations: 5-FU = 5-fluorouracil; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil plus folinic acid plus irinotecan; FOLFOX = 5-fluorouracil plus folinic acid plus Oxaliplatin; FOLFOX4 = 5-fluorouracil plus folinic acid plus Oxaliplatin; NCCN = National Comprehensive Cancer Network.



Primary and secondary analyses were conducted on efficacy and safety endpoints. The primary analysis was based on all possible connections in the network of included studies (Figure 1). The secondary analysis was based on the assumption that FOLFIRI and FOLFOX are clinically equivalent and therefore all studies with such treatment arms could be collapsed into one node that represented a combination chemotherapy regimen including FOLFIRI and FOLFOX (i.e., FOL/FOL) (Figure 2.) Due to differences in the outcomes measured and measurement techniques, nine outcomes were included in the safety analysis: Abdominal pain, diarrhea, nausea, vomiting, neutropenia, hypertension, fatigue, any grade 3 or AE/toxicity, and Stomatitis. Overall survival and progression free survival results were collected from the included studies. These results can be found in figure 5 and Figure 6. In the 24 studies that evaluated OS, median OS ranged from four to 18 months across all treatments. Full results are presented in figure 5. In the primary analysis, conducted using pairwise comparison methods, Aflibercept + FOLFIRI had relatively longer OS durations compared with cetuximab + irinotecan (HR: 0.603, 95% CI: 0.372-0.979) and compared to irinotecan (HR: 0.588, 95%CI: 0.369; 0.937). The comparison of the remaining treatments resulted in point estimates of effect that were not significant; however, aflibercept + FOLFIRI tended to consistently perform better than panitumumab + FOLFIRI and bevacizumab + FOLFIRI. Results from the fixed effects model were much more variable. Fifteen of the 27 included clinical efficacy and safety trials assessed PFS as an endpoint and median PFS ranged from 2.4 to 8.5 months across all treatments. In the primary analysis using pairwise comparisons Bevacizumab + FOLFOX4 generated a lower risk of progression or death when compared with FOLFIRI (HR: 0.546, 95% CI: 0.323-0.923). Aflibercept + FOLFIRI generated a lower risk of progression or death when compared with irinotecan (HR: 0.614, 95% CI: 0.388-0.972). The comparison of the remaining treatments resulted in point estimates of effect that were not significant. FOLFOX4 tends to perform better than FOLFIRI, although this result was also not

statistically significant. It was noted in the review that the definition of progression free survival was only provided in seven studies and that there was variance across these definitions. Hazard Ratio's and 95% confidence intervals (95% CI) for overall survival and progression free survival can be found in figure 6.

Figure 3. Primary Analysis Network: Trial Characteristics

Trial Name, Author Year	Alternate Indicator	Interventions	Patients Randomized	Study Population	Location & Centers
DaVINCI, Clarke 2011 ⁴⁶	Phase II trial	FOLFIRI	44	Patients with advanced CRC who progressed after one prior chemotherapy regimen for advanced disease and/or after prior adjuvant therapy	Australia/New Zealand (17 centers)
		Irinotecan	45		
E3200, Giantonio 2007 ⁴⁷	Phase III trial	Bevacizumab ^a + FOLFOX4	286*	mCRC patients previously treated with fluoropyrimidine and irinotecan	US/South Africa (221 centers)
		FOLFOX4	291*		
		Bevacizumab ^a	243*		
EPIC, Sobrero 2008 ⁴⁸	Phase III trial	Cetuximab + irinotecan	648	Patients with epidermal growth factor receptor-expressing mCRC who had experienced first-line fluoropyrimidine and Oxaliplatin treatment failure to cetuximab plus irinotecan or irinotecan alone	Multinational (221 centers)
		Irinotecan	650		
N9841, Kim 2009 ⁴⁹	Phase III trial	FOLFOX4	246	Patients with histologically or cytologically proven unresectable colorectal adenocarcinoma who experienced treatment failure with front-line FU therapy	US (multicenter)
		Irinotecan	245		
Peeters 2010 ⁵⁰	Phase III trial, NCT00339183	Panitumumab + FOLFIRI (<i>KRAS</i> WT)	303	Patients with previously treated mCRC who had received one prior therapy regimen consisting of fluoropyrimidine-based chemotherapy	Multinational
		FOLFIRI (<i>KRAS</i> WT)	294		
		Panitumumab + FOLFIRI (<i>KRAS</i> MT)	238		
		FOLFIRI (<i>KRAS</i> MT)	248		
VELOUR, Van Cutsem 2012 ⁵¹	Phase III trial, NCT00561470	Aflibercept + FOLFIRI	612	Patients with mCRC after failure of an Oxaliplatin-based regimen	Multinational (176 centers in 28 countries)
		FOLFIRI	614		

Figure 4. Secondary Analysis Network: Trial Characteristics

Trial Name, Author Year	Alternate Indicator	Interventions	Patients Randomized	Study Population	Location & Centers
DaVINCI, Clarke 2011 ⁴⁶	Phase II trial	FOLFIRI	44	Patients with advanced CRC who progressed after one prior chemotherapy regimen for advanced disease and/or after prior adjuvant therapy	Australia/New Zealand (17 centers)
		Irinotecan	45		
E3200, Giantonio 2007 ⁴⁷	Phase III trial	Bevacizumab ^a + FOLFOX4	286*	mCRC patients previously treated with fluoropyrimidine and irinotecan	US/South Africa (221 centers)
		FOLFOX4	291*		
		Bevacizumab ^a	243*		
EPIC, Sobrero 2008 ⁴⁸	Phase III trial	Cetuximab + irinotecan	648	Patients with epidermal growth factor receptor-expressing mCRC who had experienced first-line fluoropyrimidine and Oxaliplatin treatment failure to cetuximab plus irinotecan or irinotecan alone	Multinational (221 centers)
		Irinotecan	650		
N9841, Kim 2009 ⁴⁹	Phase III trial	FOLFOX4	246	Patients with histologically or cytologically proven unresectable colorectal adenocarcinoma who experienced treatment failure with front-line FU therapy	US (multicenter)
		Irinotecan	245		
Peeters 2010 ⁵⁰	Phase III trial, NCT00339183	Panitumumab + FOLFIRI (<i>KRAS</i> WT)	303	Patients with previously treated mCRC who had received one prior therapy regimen consisting of fluoropyrimidine-based chemotherapy	Multinational
		FOLFIRI (<i>KRAS</i> WT)	294		
		Panitumumab + FOLFIRI (<i>KRAS</i> MT)	238		
		FOLFIRI (<i>KRAS</i> MT)	248		
ML18147, Bennouna 2013 ⁵² (available online as of Nov. 2012)	Phase III trial, NCT00700102; AIO KRK 0504	Bevacizumab ^c + CT*	409	mCRC patients who have progressed on a first-line bevacizumab plus standard chemotherapy regimen	Multinational (220 centers)
		CT*	411		
VELOUR, Van Cutsem 2012 ⁵¹	Phase III trial, NCT00561470	Aflibercept + FOLFIRI	612	Patients with mCRC after failure of an Oxaliplatin-based regimen	Multinational (176 centers in 28 countries)
		FOLFIRI	614		

Figure 5. OVERALL SURVIVAL

Trial Name, Author	Interventions	Patients Randomized	Patients Evaluated	HR (CI Lower-CI Upper)	Median OS Duration (months)	Median OS Difference Between Arms (months)	Trial Phase
Combination Chemotherapy + Targeted Agent vs. Combination Chemotherapy (FOLFIRI or FOLFOX)							
E3200, Giantonio 2007 ⁴⁷	Bevacizumab ^a + FOLFOX4	286	286	0.75, <i>p</i> =0.0011	12.9	2.1 0.6	3
	FOLFOX4	291	291		10.8		
	Bevacizumab ^a	243	243		10.2		
Peeters 2010 ⁵⁰	Panitumumab + FOLFIRI (<i>KRAS</i> WT)	303	303	0.85 (0.7-1.04) <i>p</i> =0.115	14.5 (13.0-16.0)	2	3
	FOLFIRI (<i>KRAS</i> WT)	294	294		12.5 (11.2-14.2)		
	Panitumumab + FOLFIRI (<i>KRAS</i> MT)	238	238	0.94 (0.76-1.15) <i>p</i> =NR	11.8 (10.4-13.3)	0.7	
	FOLFIRI (<i>KRAS</i> MT)	248	248		11.1 (10.3-12.4)		
ML18147, Bennouna 2013 ⁵²	Bevacizumab ^c + CT	409	409	0.81* (0.69-0.94) <i>p</i> =0.0062	11.2 (10.4-12.2)	1.4	3
	CT	411	411		9.8 (8.9-10.7)		
VELOUR, Van Cutsem 2012 ⁵¹	Aflibercept + FOLFIRI	612	612	0.817** (0.71-0.94) <i>p</i> =0.0032	13.5 (12.52-14.95)	1.44	3
	FOLFIRI	614	614		12.06 (11.07-13.11)		
Single/other Agents vs. Standard of Care Combination Chemotherapy (FOLFIRI or FOLFOX4)							
DaVINCI, Clarke 2011 ⁴⁶	FOLFIRI	44	44	0.72 (0.46-1.12) <i>p</i> =0.14	15.4 (8.1-19.3)	4.2	2
	Irinotecan	45	44		11.2 (8.3-13.3)		
N9841, Kim 2009 ⁴⁹	FOLFOX4	246	246	0.92 (0.8-1.1) <i>p</i> =0.956	14.3 (12.0-15.9)	0.5	3
	Irinotecan	245	245		13.8 (12.2-15.0)		
Irinotecan-Containing Regimens vs. Single-Agent Irinotecan							
EPIC, Sobrero 2008 ⁴⁸	Cetuximab + irinotecan (EGFR-positive patients only, <i>KRAS</i> status not defined)	648	648	0.975 (0.85-1.11), <i>p</i> =0.71	10.7 (9.6-11.3)	0.7	3

Trial Name, Author	Interventions	Patients Randomized	Patients Evaluated	HR (CI Lower-CI Upper)	Median OS Duration (months)	Median OS Difference Between Arms (months)	Trial Phase
	Irinotecan (EGFR-positive patients only, <i>KRAS</i> status not defined)	650	650		10 (9.1-11.3)		

Abbreviations: 5-FU = 5-fluorouracil; BSC = best supportive care; CI = confidence interval; CT = chemotherapy; EGFR = epidermal growth factor receptor; FC/FO = 5-FU/FA combined with alternating irinotecan (also called CPT-11) and Oxaliplatin; FOLFIRI = 5-fluorouracil plus folinic acid plus irinotecan; FOLFOX = 5-fluorouracil plus folinic acid plus Oxaliplatin; FOLFOX4 = 5-fluorouracil plus folinic acid plus Oxaliplatin (same medications as FOLFOX but with different administration schedule); FOLFOX6 = 5-fluorouracil plus folinic acid plus Oxaliplatin (same medications as FOLFOX but with different administration schedule); HR = hazard ratio; IFL = irinotecan, leucovorin, fluorouracil; IRIS = irinotecan and S-1 (tegafur, 4-chloro-2, 4-dihydropyridine, and potassium oxonate); IROX = irinotecan + Oxaliplatin; MT = mutant type; NR = not reported; OS = overall survival; PTK/ZK = PTK 787/ZK 222584 (vatalanib); WT = wild type; CT = FOLFOX, FOLFIRI, capecitabine + irinotecan, other irinotecan-based regimens or other Oxaliplatin-based regimens
Notes: The HR in this table is presented such that the treatment occurring first is compared with the subsequent treatments. A HR >1 represents a reduction in the risk of death for the first treatment

‡Most recent data for the FIRIS trial were obtained from a meeting abstract in which the number of patients evaluated was unclear. This study is a non-inferiority study.

¥This study has additional data by total population (WT + MT).

¥¥This study has additional HR data on WT and MT subgroups.

*HR (log-rank) is unstratified.

**HR (log-rank) is stratified by ECOG performance status and prior bevacizumab therapy.

aBevacizumab dose used was 10 mg/kg.

cBevacizumab dose used was 2.5 mg/kg/wk equivalent (5 mg/kg every two weeks or 7.5 mg/kg every three weeks).

Figure 6. PROGRESSION FREE SURVIVAL RESULTS

Trial Name, Author	Interventions	Patients Randomized	Patients Evaluated	HR (CI Lower-CI Upper)	Median PFS Duration (months)
Combination Chemotherapy + Targeted Agent vs. Combination Chemotherapy (FOLFIRI or FOLFOX4)					
E3200, Giantonio 2007 ⁴⁷	Bevacizumab ^a + FOLFOX4	286	286	0.61 (NR) $p=0.0001$	7.3
	FOLFOX4	291	291		4.7
	Bevacizumab ^a	243	243		2.7
Peeters 2010 ⁵⁰	Panitumumab + FOLFIRI (KRAS WT)†	303	303	0.73 (0.59-0.9) $p=0.004$	5.9 (5.5-6.7)
	FOLFIRI (KRAS WT)†	294	294		3.9 (3.7-5.3)
	Panitumumab + FOLFIRI (KRAS MT)	238	238	0.85 (0.68-1.06) $p=NR$	5.0 (3.8-5.6)
	FOLFIRI (KRAS MT)	248	248		4.9 (3.6-5.6)
ML18147, Bennouna 2013 ⁵²	Bevacizumab ^b + CT	409	409	0.68** (0.59-0.78) $p<0.0001$	5.7 (5.2-6.2)
	CT	411	411		4.1 (3.7-4.4)
VELOUR, Van Cutsem 2012 ⁵¹	Aflibercept + FOLFIRI	612	612	0.758*** (0.661-0.869) $p=0.00007$	6.90 (6.51-7.2)
	FOLFIRI	614	614		4.67 (4.21-5.36)
Single/Other Agents vs. Standard of Care Combination Chemotherapy (FOLFIRI or FOLFOX4)					
DaVINCI, Clarke, 2011 ⁴⁶	FOLFIRI	44	44	0.81 (0.52-1.25) $p=0.34$	6.2 (5.4-6.7)
	Irinotecan	45	44		4 (2.7-5.7)
Irinotecan-Containing Regimens vs. Single-Agent Irinotecan					
EPIC, Sobrero 2008 ⁴⁸	Cetuximab + irinotecan (EGFR-positive patients only, KRAS status not defined)	648	648	0.692 (0.617-0.776) $p=0.0001$	4 (3.2-4.1)
	Irinotecan (EGFR-positive patients only, KRAS status not defined)	650	650		2.6 (2.1-2.7)

Safety outcomes, including selected adverse events (AEs) and toxicities were analyzed in the NMA. Adverse Events were required to meet the following criteria in order to be included:

- The AE was of grade 3 or higher
- The AE was considered common or clinically important
- Reported data were available in either published or grey literature
- There were enough studies reporting the AE to complete either the primary or secondary analysis as defined by the networks

In addition to the studies used in the primary and secondary networks additional supplemental reports from the E3200 study and the N9841 study were reviewed because they contained extra information on adverse events that was not fully reported in the published reference.

Assumptions were made in order to facilitate development of network and analysis. These assumptions included: i. that a small number of sources were lower quality, or had a higher risk of bias were considered in the analysis; ii. Patient heterogeneity was taken as a given, and iii. Treatment using FOLFOX assumed equivalent to treatment using FOLFIRI

Results of Safety Analysis

Adverse events collected in the network studies were divided into one of five categories: Gastrointestinal (diarrhea, nausea, and vomiting), hematologic (neutropenia, anemia, and thrombocytopenia), Cardiorespiratory (Hypertension, thromboembolism, Dyspnea), Systemic (fever, infection, dehydration, asthenia, fatigue) , and Other (any, hypersensitivity, mucositis, stomatitis, neuropathy) Adverse events related to GI and Hematologic events had highest incidence, or percentage of affected patients. Neutropenia was the most commonly reported adverse event in studies, being reported in all but two. Combination therapies, either with or without a targeted therapy, were typically associated with a higher incidence of grade 3/4 AEs compared with chemotherapy alone.

Primary analysis using fixed effects model produced relative risk ratios for aflibercept versus bevacizumab. Results from the primary safety analysis found non-significant differences in likelihood of adverse events occurring in patients receiving aflibercept versus those receiving Bevacizumab. Relative risks of Diarrhea, nausea, vomiting, fatigue, and stomatitis were 2.78, 0.12, 0.04, 0.77, and 10.31 respectively. All 95% credible intervals included 1, indicating non-significant difference in the probability of adverse events occurring in either group.

Results from the secondary safety analysis using random effects model found non-significant differences in likelihood of adverse events occurring in patients receiving aflibercept versus those receiving Bevacizumab. Relative risks of Diarrhea, nausea, vomiting, fatigue, stomatitis, abdominal pain, Neutropenia, and hypertension were 1.86, 0.23, 0.39, 1.14, 1.17, 1.28, 1.03, and 5.33 respectively. All 95% credible intervals included 1, indicating non-significant difference in the probability of adverse events occurring in either group.

Limitations of Network Meta-Analysis

The quality of methods used in the manufacturer-submitted NMA were assessed by reviewing studies included in the network as well as using NMA-specific methodology recommendations developed by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.⁵³

1. Reference to recommended practice in Canada may not be generalizable to recommendations found in U.S. and European practice guidelines.
2. The quality of data sources were variable and certain sources, such as grey literature, increase the likelihood of bias existing in the network meta-analysis. Trial types include non-superiority trials whose study questions and framing of the null hypothesis is opposite of those found in superiority trials and their null hypotheses. In a non-inferiority trial the null hypothesis states that the two interventions are different. Including non-inferiority trials with

- their respective HR's, *p*-values, creates a pool of outcomes that are heterogeneous because they are not testing the same hypothesis. This contradicts the intention for the NMA and adds to methodological heterogeneity, and coherence, which makes conclusions more questionable.
3. Protocols for analysis were not predefined and were not discussed in detail. Meta-analysis models (FE, RE), reasons why these models were used, and limitations imposed by modeling, were not specified in detail which does not provide user with information regarding limitations imposed upon results due to model type used. It was indicated in this analysis that fixed effects model results were preferred because random effects model relied heavily on a-priori probabilities. However, this assumption does not account for the fact that significant heterogeneity does exist between trials, and that authors should place less emphasis on the probabilities of a network meta-analysis output and greater emphasis on the treatment effects and their uncertainty.
 4. Patient and treatment heterogeneity, both first and second line, were present in both the efficacy and safety analyses of NMA. Heterogeneity increases the uncertainty of final results and limits the ability of the results to address the population of interest, and the detailed indication for this product.
 5. Measurement of disease progression is commonly viewed as problematic due to differences in how progression is defined or measured. The approach to measuring PFS was specified in seven studies but varied in definition.
 6. This lack of standard introduces uncertainty in the HR's and credible intervals for the indirect comparisons for investigator-assessed progression-free survival. It is not possible to estimate the magnitude or direction of potential bias but it is interesting to note the difference in magnitude for estimates for overall survival and progression free survival.
 7. There was no calculation of effect size.

7.1.3 Summary

Results from the primary analysis found no statistical difference between treatment arms using fixed effects, random effects, and pairwise comparisons, modeling. In the primary analysis, no statistically significant differences were found between Aflibercept/FOLFOLI and Bevacizumab/FOLFOX groups for overall survival (HR=0.851, 95% CI: 0.505 to 1.4301) or progression-free survival (HR=1.385, 95%CI: 0.805 to 2.380). Similarly, in the secondary analysis, which assumed that FOLFOX and FOLFIRI are clinically equivalent, no statistically significant differences were found between Aflibercept/ FOLFOL (FOLFIRI and/or FOLFOX) and Bevacizumab/FOLFOL groups for overall survival (HR=1.044, 95%CI: 0.873 to 1.25) or progression-free survival (HR=1.151, 95%CI: 0.961 to 1.36)

The primary safety analysis showed non-significant differences in AEs with relative risks of 2.78, 0.12, 0.04, 0.77, and 10.31 for diarrhea, nausea, vomiting, fatigue, and stomatitis respectively. The secondary safety analysis also showed non-significant differences in different AEs, however the magnitude and type of AEs differed. Relative risks of 1.86, 0.23, 0.39, 1.14, 1.17, 1.28, 1.03, and 5.33 for diarrhea, nausea, vomiting, fatigue, stomatitis, abdominal pain, Neutropenia, and hypertension were observed, respectively.

Population and treatment heterogeneity, assumptions about treatment efficacy equivalence, small study populations, and likely heterogeneity in measurement of progression were major limitations in this NMA. Overall, the limitations associated with this network meta-analysis restricts the ability to draw conclusions regarding the comparative efficacy of Aflibercept versus Bevacizumab. Any modeling or analysis using the information found in this NMA could produce misleading results and this information should be used with caution.

8 ABOUT THIS DOCUMENT

This Final Clinical Guidance Report was prepared by the pCODR the Gastro-intestinal Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on aflibercept (Zaltrap) and metastatic colorectal cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Gastrointestinal Clinical Guidance Panel is comprised of 3 medical oncologists selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update.

1. colorectal cancer/ or cancer, colon/
2. (metastatic colorectal cancer: or mCRC:).ti,ab,rn,nm,sh,hw,ot.
3. (afibercept or zaltrap).ti,ab,rn,nm,sh,hw,ot.
4. *afibercept/
5. 1 or 2
6. or/3-5
7. 6 and 7

Human Filter

9. exp animals/
10. exp animal experimentation/
11. exp models animal/
12. exp animal experiment/
13. nonhuman/
14. exp vertebrate/
15. or/9-14
16. exp humans/
17. exp human experiment/
18. or/16-17
19. 15 not 18
20. 8 not 19

PubMed

1. Afibercept* OR Zaltrap*
2. publisher[sb]
3. 1 AND 2

Cochrane Library

Search terms: **Afibercept*** OR **Zaltrap*** in Cochrane Central Register of Controlled Trials.

4. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: Afibercept, Zaltrap,

Select International Agencies:

Food and Drug Administration (FDA): www.fda.gov

European Medicines Agency (EMA): www.ema.europa.eu

Conference Abstracts:

American Society of Clinical Oncology (ASCO)

via the *Journal of Clinical Oncology* search portal: <http://jco.ascopubs.org/search>

Search terms: "Aflibercept" OR "Aflibercept OR Zaltrap" AND "colorectal",
"Aflibercept" OR "Zaltrap" AND "colon", "Aflibercept" OR "Zaltrap" AND "mCRC"

European Society for Medical Oncology (ESMO)

The abstracts for each of the ESMO annual conference are available here:

2013: 38th ESMO (European Cancer Congress 2013): *European Journal of Cancer* 2013;49(Suppl 2)

2012: 37th ESMO: *Annals of Oncology* 2012;23(Suppl 9)

2011: 36th ESMO (European Cancer Congress 2011): *European Journal of Cancer* 2011;47(Suppl 1)

2010: 35th ESMO: *Annals of Oncology* 2010;21(Suppl 8)

2009: 34th ESMO (European Cancer Congress 2009): *European Journal of Cancer* 2009;45(Suppl 1)

Search terms: "Aflibercept" OR "Aflibercept OR Zaltrap" AND "colorectal",
"Aflibercept" OR "Zaltrap" AND "colon", "Aflibercept" OR "Zaltrap" AND "mCRC"

Note: Every two years, ESMO annual conference is held jointly with other European professional medical organizations. This joint conference is named the European Cancer Congress.

REFERENCES

1. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausova J, Macarulla T, 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 01 Oct;30(28):3499-506.
2. Casagrande M, Cremolini C, Loupakis F, Aprile G. A perspective on the current management of advanced colorectal cancer. *Future Oncology*. 2013 November;9(11):1687-91.
3. Golfopoulos V, Salanti G, Pavlidis N, Ioannidis JP. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. *Lancet Oncol*. 2007 October;8(10):898-911.
4. Grothey A, Sargent D, Goldberg RM, Schmolli HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol*. 2004 1 Apr;22(7):1209-14.
5. Canadian Cancer Society CCS, <http://www.cancer.ca/~media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/canadian-cancer-statistics-2013-EN.pdf>; Accessed: January 20th, 2013 MHmpiCdoc.
6. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004 3 Jun;350(23):2335-42.
7. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al. 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 20 Apr;25(12):1539-44.
8. pan-Canadian Oncology Drug Review Manufacturer Submission: ZALTRAP™ in combination with irinotecan-fluoropyrimidine-based chemotherapy is indicated for patients with metastatic colorectal cancer (MCRC) previously treated with an oxaliplatin containing regimen; Company: Sanofi-aventis Canada Inc. 2905, Place Louis-R.-Renaud, Laval, Québec; 2013 Nov 25. .
9. Ramlau R, Gorbunova V, Ciuleanu TE, Novello S, Ozguroglu M, Goksel T, et al. Aflibercept and docetaxel versus docetaxel alone after platinum failure in patients with advanced or metastatic non-small-cell lung cancer: A randomized, controlled phase III trial. *J Clin Oncol*. 2012 10 Oct;30(29):3640-7.
10. Rougier P, Riess H, Manges R, Karasek P, Humblet Y, Barone C, et al. Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. *Eur J Cancer*. 2013 August;49(12):2633-42.
11. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell*. 2011 04 Mar;144(5):646-74.
12. Thornton AD, Ravn P, Winslet M, Chester K. Angiogenesis inhibition with bevacizumab and the surgical management of colorectal cancer. *Br J Surg*. 2006 December;93(12):1456-63.
13. Bengmark S, Hafstrom L. The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. *Cancer*. 1969;23(1):198-202.

14. Pestana C, Reitemeier RJ, Moertel CG, Judd ES, Dockerty MB. The Natural History of Carcinoma of the Colon and Rectum. *Am J Surg.* 1964;108:826-9.
15. Hillner BE, Schrag D, Sargent DJ, Fuchs CS, Goldberg RM. Cost-effectiveness projections of oxaliplatin and infusional fluorouracil versus irinotecan and bolus fluorouracil in first-line therapy for metastatic colorectal carcinoma. *Cancer.* 2005 26 Oct;104(9):1871-84.
16. Iveson TJ, Hickish T, Schmitt C, Van Cutsem E. Irinotecan in second-line treatment of metastatic colorectal cancer: Improved survival and cost-effect compared with infusional 5-FU. *Eur J Cancer.* 1999 December;35(13):1796-804.
17. Shiroiwa T, Fukuda T, Tsutani K. Cost-effectiveness analysis of XELOX for metastatic colorectal cancer based on the NO16966 and NO16967 trials. *Br J Cancer.* 2009 7 Jul;101(1):12-8.
18. Tumej JW, Shenoy PJ, Moore SG, Kauh J, Flowers C. A Markov model assessing the effectiveness and cost-effectiveness of FOLFOX compared with FOLFIRI for the initial treatment of metastatic colorectal cancer. *Am J Clin Oncol.* 2009 Feb;32(1):49-55.
19. Ward S, Kaltenthaler E, Cowan J, Brewer N. Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: Systematic review and economic evaluation. *Health Technol Assess.* 2003;7(32).
20. Cunningham D, Pyrhönen S, James R, Cornelis J, Punt D, Hickish T, et al. Randomized trial of Irinotecan plus supportive care versus supportive care alone after Fluorouracil failure for patients with metastatic colorectal cancer. *The Lancet.* Volume 352, 31 October 1998(Issue 9138):1413 - 8.
21. Simmonds P. Palliative chemotherapy for advanced colorectal cancer: Systematic review and meta-analysis. *Br Med J.* 2000 02 Sep;321(7260):531-5.
22. Alberta Health Services Clinical Practice Guideline (GI-003 V, Algorithm for the Treatment of Liver Metastasis from Colorectal Cancer. March, 2014.
23. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol.* 2003 1 Jan;21(1):60-5.
24. Kabbinavar FF, Schulz J, McCleod M, Patel T, Hamm JT, Hecht JR, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: Results of a randomized phase II trial. *J Clin Oncol.* 2005;23(16):3697-705.
25. Cunningham D, Lang I, Marcuello E, Lorusso V, Ocvirk J, Shin DB, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): An open-label, randomised phase 3 trial. *The Lancet Oncology.* 2013 October;14(11):1077-85.
26. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, 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 20 Apr;26(12):2013-9.
27. Tebbutt NC, Wilson K, Gebiski VJ, Cummins MM, Zannino D, van Hazel GA, et al. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. *J Clin Oncol.* 2010 1 Jul;28(19):3191-8.

28. Wagner AD, Arnold D, Grothey AA, Haerting J, Unverzagt S. Anti-angiogenic therapies for metastatic colorectal cancer. *Cochrane database of systematic reviews (Online)*. 2009 (3):CD005392.
29. Welch S, Spithoff K, Rumble RB, Maroun J. Bevacizumab combined with chemotherapy for patients with advanced colorectal cancer: A systematic review. *Ann Oncol*. 2010;21(6):1152-62.
30. Loupakis F, Bria E, Vaccaro V, Cuppone F, Milella M, Carlini P, et al. Magnitude of benefit of the addition of bevacizumab to first-line chemotherapy for metastatic colorectal cancer: meta-analysis of randomized clinical trials. *Journal of experimental & clinical cancer research : CR*. 2010;29:58.
31. Cao Y, Tan A, Gao F, Liu L, Liao C, Mo Z. A meta-analysis of randomized controlled trials comparing chemotherapy plus bevacizumab with chemotherapy alone in metastatic colorectal cancer. *Int J Colorectal Dis*. 2009;24(6):677-85.
32. Kozloff M, Yood MU, Berlin J, Flynn PJ, Kabbinavar FF, Purdie DM, et al. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: The BRiTE observational cohort study. *Oncologist*. 2009 September;14(9):862-70.
33. Van Cutsem E, Rivera F, Berry S, Kretzschmar A, Michael M, Dibartolomeo M, et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: The BEAT study. *Ann Oncol*. 2009;20(11):1842-7.
34. Chiara S. Phase IV study of bevacizumab in combination with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) in first-line metastatic colorectal cancer (*Oncology (2009) 77 (113-119)*). *Oncology*. 2009 September;77(3-4):256.
35. Grothey A, Sugrue MM, Purdie DM, Dong W, Sargent D, Hedrick E, 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 20 Nov;26(33):5326-34.
36. Bendell JC, Bekaii-Saab TS, Cohn AL, Hurwitz HI, Kozloff M, Tezcan H, et al. Treatment patterns and clinical outcomes in patients with metastatic colorectal cancer initially treated with FOLFOX-Bevacizumab or FOLFIRI-bevacizumab: Results from ARIES, a bevacizumab observational cohort study. *Oncologist*. 2012;17(12):1486-95.
37. Bannouna J, Sastre J, Arnold D, Osterlund P, Greil R, Van Cutsem E, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): A randomised phase 3 trial. *The Lancet Oncology*. 2013 January;14(1):29-37.
38. Ferry D, Kim TW, Guren TK, Desai J, Villanueva LM, Andria ML, et al. On-treatment progression-free survival analysis of ziv-aflibercept/FOLFIRI treatment within 28 days of end of treatment in metastatic colorectal cancer: Updated efficacy results from the VELOUR study. *J Clin Oncol*. 2013 20 May;1).
39. Ferry DR, Won Kim T, Guren TK, Desai J, Villanueva LM, Andria ML, et al. On-treatment progression-free survival analysis of aflibercept-FOLFIRI treatment within 28 days of progression in metastatic colorectal cancer: Updated efficacy results from the VELOUR study. *Journal of Clinical Oncology*. 2013 01 Feb;1).
40. Joulain F, Van Cutsem E, Iqbal SU, Hoyle M, Allegra CJ. Aflibercept versus placebo in combination with FOLFIRI in previously treated metastatic colorectal cancer (mCRC): Mean overall survival (OS) estimation from a phase III trial (VELOUR). *Journal of Clinical Oncology*. 2012 20 May;1).
41. Mitchell EP, Guarino MJ, Allegra CJ, Boelle E, Andria ML, Bhargava P, et al. North American (NA) subgroup results from VELOUR: Ziv-aflibercept versus placebo (pbo) plus FOLFIRI in mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen. *J Clin Oncol*. 2013 01 Feb;1).

42. Mitchell EP, Guarino MJ, Andria ML, Bhargava P, Kirshner JJ. North American (NA) subgroup results from VELOUR: Ziv-aflibercept versus placebo plus FOLFIRI in mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen. *Journal of Clinical Oncology*. 2013 20 May;1).
43. Punt CJA. New developments in gastrointestinal cancer-ASCO 2012. *Memo - Magazine of European Medical Oncology*. 2012 December;5(4):266-8.
44. Saltz L. Systemic therapy for metastatic colorectal cancer. *JNCCN Journal of the National Comprehensive Cancer Network*. 2013 01 May;11(5 SUPPL.):649-52.
45. Tabernero J, Van Cutsem E, Lakomy R, Prausova J, Ruff P, Van Hazel G, et al. Results from VELOUR, a phase 3 study of aflibercept (A) versus placebo (pbo) in combination with FOLFIRI for the treatment of patients (pt) with previously treated metastatic colorectal cancer (MCRC). *European Journal of Cancer*. 2011 September;47:5.
46. Clarke SJ, Yip S, Brown C, van Hazel GA, Ransom DT, Goldstein D, et al. Single-agent irinotecan or FOLFIRI as second-line chemotherapy for advanced colorectal cancer; results of a randomised phase II study (DaVINCI) and meta-analysis [corrected]. *European journal of cancer*. 2011 Aug;47(12):1826-36.
47. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007 Apr 20;25(12):1539-44.
48. Sobrero AF, Maurel J, Fehrenbacher L, Scheithauer W, Abubakr YA, Lutz MP, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008 May 10;26(14):2311-9.
49. Kim GP, Sargent DJ, Mahoney MR, Rowland KM, Jr., Philip PA, Mitchell E, et al. Phase III noninferiority trial comparing irinotecan with oxaliplatin, fluorouracil, and leucovorin in patients with advanced colorectal carcinoma previously treated with fluorouracil: N9841. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009 Jun 10;27(17):2848-54.
50. Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010 Nov 1;28(31):4706-13.
51. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausova J, Macarulla T, 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012 Oct 1;30(28):3499-506.
52. Bannouna J, Sastre J, Arnold D, Osterlund P, Greil R, Van Cutsem E, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *The lancet oncology*. 2013 Jan;14(1):29-37.
53. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2011;14(4):417-28.

54. Zaltrap. Aflibercept vials. 100 and 200mg aflibercept. Recombinant Fusion Protein [product monograph]. Laval (QC): Sanofi-Aventis Canada Inc.; 2014 Feb 12.