pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Aflibercept (Zaltrap) **Submitted Funding Request:** In combination with irinotecan-fluoropyrimidine (FOLFIRI) based therapy for patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen	
Submitted By: Sanofi-Aventis Canada Inc.	**Manufactured By:** Sanofi-Aventis Canada Inc.
NOC Date: February 12, 2014	**Submission Date:** November 26, 2013
Initial Recommendation Issued: July 4, 2014	**Final Recommendation:** September 5 ,2014

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) does not recommend funding aflibercept in combination with an irinotecan-fluoropyrimidine (FOLFIRI) based therapy for patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen. The Committee made this recommendation because compared with placebo plus FOLFIRI, aflibercept plus FOLFIRI had only a very modest overall survival and progression-free survival benefit, significant toxicities and an unknown impact on quality of life. Additionally, the combination of aflibercept plus FOLFIRI was not cost-effective when compared to FOLFIRI alone.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified

SUMMARY OF pERC DELIBERATIONS

pERC noted that metastatic colorectal cancer (mCRC) results in a substantial burden of illness and is the second leading cause of cancer deaths in Canada. pERC discussed that mCRC is generally considered incurable and survival beyond two years is uncommon. Therefore, pERC agreed that there is a need for effective therapies that provide a clinically meaningful extension in overall survival. Bevacizumab, an anti-angiogenic therapy, combined with oxaliplatin-based and irinotecan- fluoropyrimidine-based chemotherapies, are standard first-line therapies in the management of mCRC. For patients that do not receive it as part of first line treatment, bevacizumab may be available in the second-line setting, in combination with chemotherapy. pERC noted that the combination chemotherapy regimens used and their sequencing vary across provinces. However, pERC discussed that FOLFIRI ± bevacizumab would be a relevant comparator in the second-line setting and that both bevacizumab and aflibercept are anti-VEGF therapies.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

One double-blind randomized controlled trial (VELOUR, Van Cutsem 2012) compared aflibercept plus fluorouracil, leucovorin and irinotecan (FOLFIRI) with placebo plus FOLFIRI in patients previously treated with an oxaliplatin-based regimen. pERC noted that the magnitude of benefit in median overall survival for aflibercept plus FOLFIRI compared with placebo plus FOLFIRI (13.5 vs. 12.1 months, respectively; HR=0.82) and in median progression free survival (6.9 vs. 4.7 months, respectively; HR=0.76) was very modest. pERC members debated the magnitude of benefit that was clinically meaningful and various opinions were expressed. pERC also discussed equity issues associated with the progression-free survival estimates it has considered across different tumour types and how the committee has valued that information in relation to the other components of their deliberative framework in past pERC recommendations. pERC also deliberated upon the toxicity profile of aflibercept. It was noted that substantially more patients receiving aflibercept plus FOLFIRI reported grade three and four toxicities compared with patients receiving placebo plus FOLFIRI (83.5% versus 62.5%, respectively), including grade three/four diarrhea (19.3% vs. 7.8%, respectively). pERC noted that a Network Meta-Analysis (NMA) was conducted that provided an indirect comparison of aflibercept to bevacizumab. No statistically significant differences in adverse events were detected. However, pERC discussed that the analysis lacked face validity, when considering the toxicity profile of aflibercept that was suggested by the VELOUR study. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Patient Advocacy Group, Provincial Advisory Group and the manufacturer regarding the relevance of bevacizumab as a comparator in the second line setting. pERC clarified its understanding that bevacizumab in combination with chemotherapy is available as a first line treatment option in most provinces while second line use is limited to patients who are bevacizumab naive. pERC acknowledged that most patients are, therefore, likely to receive bevacizumab/chemo combination therapy in the first line setting and that the number of patients eligible in the second line setting is small. pERC agreed that bevacizumab + FOLFIRI is a relevant comparator in the second line setting, along with FOLFIRI monotherapy. pERC noted that both comparisons were considered in its deliberations. pERC also discussed the manufacturer's feedback regarding the magnitude of benefit of bevacizumab in the second line setting as it relates to pERC's decision to not recommend funding aflibercept. pERC noted that the review and adoption of bevacizumab combination therapy in the second line setting occurred before pCODR came into existence. In this context, pERC is unable to comment on the net clinical benefit of bevacizumab combination therapy versus previous regimens and compare it to the net clinical benefit to aflibercept in combination with FOLFIRI.

Finally, pERC discussed that the impact of aflibercept on quality of life is unknown as it was not measured in the VELOUR study. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding two additional studies providing data on quality of life for patients receiving aflibercept. pERC noted that these studies had been identified but excluded from the pCODR systematic review because they were single arm, open label cohort studies. pERC was satisfied with the Clinical Guidance Panel's position that the results of these studies did not provide the comparative

information needed to address the impact of treatment on quality of life between aflibercept/FOLFIRI and FOLFIRI. Considering these factors, pERC deliberated upon the extent of clinical benefit that would be required to support a funding recommendation in this context. It was suggested that aflibercept had a very modest overall survival and progression-free survival benefit, significant toxicity and an unknown impact on quality of life. Various opinions were expressed on these factors; however, the majority of pERC members considered that in this specific context, the net clinical benefit associated with aflibercept was insufficient to recommend funding. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Patient Advocacy Group and the manufacturer regarding the magnitude of clinical benefit in the VELOUR study. pERC discussed that determination of net clinical benefit is based on its deliberative framework, which takes into consideration the four distinct components of burden of illness, need, safety and efficacy. While agreeing that there was a modest statistically significant improvement in overall survival and progression free survival, pERC further reiterated that the higher rates of grade three and four toxicities and an unknown impact on quality of life, compared to existing treatments, when taken together with the very modest survival benefit, represent insufficient net clinical benefit to recommend funding.

pERC deliberated upon patient advocacy group input, which indicated that patients valued extending life as well as maintaining quality of life. Patients also indicated that they valued access to new treatments and that they were willing to tolerate the toxicities of new therapies as well as accept only small or short-term clinical benefits. pERC acknowledged that based on this input and the results of the VELOUR study, access to aflibercept aligned with patient values. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Patient Advocacy Group reiterating patients' value of having access to treatment that provides overall survival benefit. pERC acknowledged that, while quality of life was not available for assessment, aflibercept aligns with patients' value in providing a modest overall survival benefit.

pERC deliberated upon the cost-effectiveness of aflibercept plus FOLFIRI compared with FOLFIRI alone. pERC reviewed the incremental cost-effectiveness estimates provided by both the manufacturer and the pCODR Economic Guidance Panel (EGP). It was noted that the EGP's best estimates were higher than the manufacturer's because of two factors that the EGP subsequently modified: removing a calibration factor and shortening the time horizon. The calibration factor was applied by the submitter only to the number of treatment cycles, so that it could align the treatment cycles (and therefore the cost of treatment) to what was observed in the VELOUR study. However, the calibration factor was not applied to other variables in the model that might also be affected by an overestimation of cycles (e.g. other costs, utility values, adverse events).The EGP removed the calibration factor because it may have biased results in favour of aflibercept. In addition, the manufacturer's economic analysis was based on a 16 year time horizon and the EGP shortened the time horizon to five years based on input from the pCODR Clinical Guidance Panel. pERC agreed with the EGP's best estimates and concluded that aflibercept plus FOLFIRI is not cost-effective at the submitted price compared with FOLFIRI alone. pERC also noted that the cost-effectiveness of aflibercept compared with bevacizumab was unknown based on the uncertainty in the analyses submitted by the manufacturer and the extensive methodological limitations in the network meta-analysis. Upon reconsideration of the Initial Recommendation, pERC discussed the impact of cost effectiveness on the funding recommendation for aflibercept. While pERC acknowledged that aflibercept was not cost effective according to the Economic Guidance Panel's reanalysis, the lack of cost effectiveness did not factor into pERC's initial or final recommendation.

pERC discussed factors that could impact the feasibility of implementing a funding recommendation for aflibercept. It was noted that aflibercept only has regulatory approval in Canada for use in combination with FOLFIRI, after use of an oxaliplatin-based regimen (e.g. FOLFOX) in the first-line setting. pERC discussed the possibility that access to aflibercept could be impacted by regional variability in the availability of FOLFOX and FOLFIRI. In considering currently funded therapies, it was noted that although the sequence and combinations of therapies available varies across provinces, all patients can access FOLFOX, FOLFIRI and bevacizumab, which is an anti-VEGF therapy.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy groups (Colorectal Association of Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- one patient advocacy group (Colorectal Association of Canada)
- the Submitter (sanofi-aventis Canada Inc.)

The pERC Initial Recommendation was to not fund aflibercept in combination with an irinotecan-fluoropyrimidine (FOLFIRI) based therapy for patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen. Feedback on the pERC Initial Recommendation indicated that the manufacturer and patient advocacy group disagreed with the Initial Recommendation and pCODR's Provincial Advisory Group agreed in part with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The objective of the systematic review was to evaluate the efficacy and safety of aflibercept (Zaltrap) in combination with irinotecan-fluoropyrimidine (FOLFIRI) based chemotherapy compared with appropriate comparators in the treatment of patients with non-resectable, metastatic colorectal cancer who have been previously treated with an oxaliplatin containing chemotherapy regimen.

Studies included: one randomized controlled trial

The pCODR systematic review included one randomized, placebo-controlled, double-blind trial, VELOUR (Van Cutsem 2012), which compared the use of aflibercept plus FOLFIRI to FOLFIRI alone in patients with mCRC who were previously treated with an oxaliplatin-based regimen.

The pCODR review also provided contextual information on a network meta-analysis comparing aflibercept with bevacizumab for the second line treatment of patients with metastatic colorectal cancer. The pCODR critique of the network meta-analyses concluded that heterogeneity was a major limitation of the analysis that restricted the ability to draw conclusions regarding the comparative effectiveness and safety of aflibercept versus bevacizumab. pERC noted that no statistically significant differences in efficacy or adverse events were detected between aflibercept and bevacizumab. However, pERC considered that the analysis lacked face validity when considering the toxicity profile of aflibercept that was identified in the VELOUR study.

Patient populations: ECOG performance status 0-2, prior bevacizumab use in some patients

Patients in the two arms of VELOUR study were closely matched and had an ECOG performance status of 0 (57% in both arms) or 1 (40.8% vs. 40.7%) or 2 (2.1% vs. 2.8%) in each treatment arm. In addition, approximately 30% of patients in each treatment arm had received prior bevacizumab therapy. Patients who relapsed within 6 months of completion of oxaliplatin-based adjuvant therapy were eligible for the study but prior irinotecan use was not permitted.

Key efficacy results: modest improvements in overall survival and progression-free survival

Key efficacy outcomes on which pERC deliberated included overall survival and progression-free survival. A statistically significant improvement in median overall survival was demonstrated in patients receiving aflibercept plus FOLFIRI compared to placebo plus FOLFIRI (13.5 vs 12.1 months, respectively HR=0.82, 95% CI: 0.71 to 0.94; p=0.0032). Median progression-free survival was significantly longer in the aflibercept plus FOLFIRI arm versus placebo plus FOLFIRI arm (6.9 vs 4.7 months, respectively HR=0.76, 95% CI: 0.66 to 0.87; p<0.0001). pERC discussed the magnitude of benefit observed in both median overall

survival and in median progression free survival. It was noted that the CGP concluded that the addition of aflibercept to FOLFIRI conferred a modest overall clinical benefit and pERC members debated whether that magnitude of benefit was clinically meaningful. Various opinions were expressed on this issue. pERC also discussed the equity of accepting different progression-free survival estimates across different tumour types and how it had been viewed in previous pERC recommendations. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Patient Advocacy Group and the manufacturer regarding pERC's assessment of the magnitude of clinical benefit observed in the VELOUR study. As previously discussed, while agreeing that there was a modest statistically significant improvement in overall survival and progression free survival, pERC further reiterated that the higher rates of grade three and four toxicities and an unknown impact on quality of life, compared to existing treatments, when taken together with the very modest survival benefit, represented an insufficient net clinical benefit to recommend funding. pERC also considered feedback from the Patient Advocacy Group describing a potential for aflibercept to increase resectability rates in patients with liver only metastasis as suggested by a small increase in response rate (eg., tumour shrinkage). pERC discussed the Clinical Guidance Panel's position outlining the clinical context under which resectability is a relevant option and noted that the ability to resect the cancer is rarely possible beyond the first line setting. pERC concluded that in a population of heavily pre-treated patients, the likelihood of converting patients to resectability is exceedingly low and is an outcome that is difficult to achieve beyond the first line setting.

Quality of life: not measured therefore impact unknown

Quality of life was not measured in the VELOUR study. Therefore, pERC concluded that the impact of aflibercept on quality of life is unknown. pERC noted that quality of life is valued by patients and that it would be important to understand aflibercept's impact, particularly in light of the toxicities observed in the VELOUR study. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Patient Advocacy Group reiterating patient's value of having access to treatment that provides overall survival benefit. pERC acknowledged that, while quality of life was not available for assessment, aflibercept aligns with patients value in providing a modest overall survival benefit. pERC also considered feedback from the manufacturer regarding two additional studies providing data on quality of life for patients receiving aflibercept. pERC noted that these studies were identified but excluded from the pCODR systematic review because they were single arm, open label cohort studies. pERC was satisfied with the Clinical Guidance Panel's position outlining the potential for bias and limitations associated with the design of these studies and concluded that they did not provide comparative information relevant to assess the impact of treatment on quality of life between aflibercept/FOLFIRI and FOLFIRI.

Safety: increased grade 3 and 4 adverse events, including diarrhea

pERC also deliberated upon the toxicity profile of aflibercept. In the VELOUR study, grade 3 or 4 adverse events were reported in 83.5% and 62.5% of patients on aflibercept plus FOLFIRI and placebo plus FOLFIRI arms, respectively. Grade 3 or 4 adverse events that 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%), venous thromboembolic events (7.8% vs. 6.2%), 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%), 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%). pERC discussed the toxicity profile in the context of known toxicities associated with other mCRC therapies and was concerned with the high proportion of patients reporting grade 3 or 4 diarrhea (19.3% vs. 7.8%).

Need: therapies that meaningfully prolong survival

pERC noted that mCRC results in a substantial burden of illness and is the second leading cause of cancer deaths in Canada. The 2013 Canadian number of new cases of mCRC was 23,900 new cases of colorectal cancer with an incidence rate of 49.1 per 100,000 people. Colorectal cancer deaths are second highest in men (12.7%) and third highest in women (11.6%) as a percentage of total deaths attributed to cancer.

In patients with unresectable metastatic disease the primary goal is prolongation of survival. pERC discussed that mCRC is generally considered incurable and survival beyond two years is uncommon. Anti-angiogenic therapies are combined with chemotherapy in both the first line and second line settings. In Canada, there is regional variability in practice patterns. However, patients with mCRC are often first treated with FOLFIRI with or without bevacizumab. During reconsideration of the Initial Recommendation, pERC considered feedback from the Patient Advocacy Group regarding practice patterns in the first line setting especially when metastatic disease is confined to the liver. pERC noted that although various options may be available, actual use will likely be dependent on the accepted standard of care and the available evidence to support the options in this setting. With combination

chemotherapy (e.g., fluoropyrimidines, oxaliplatin, irinotecan) and targeted agents (e.g., bevacizumab, cetuximab, panitumumab), median survivals are now reliably measured in the 20 to 24 month range. Despite these improvements, however, long term survival months is uncommon and cures are still not anticipated. Therefore, pERC agreed that there is a need for effective therapies that provide a clinically meaningful extension in overall survival. pERC noted that bevacizumab would be the most relevant comparator in the second-line setting and that both bevacizumab and aflibercept are anti-VEGF therapies.

PATIENT-BASED VALUES

Values of patients with metastatic colorectal cancer: quality of life, access to treatments

pERC deliberated upon patient advocacy group input and discussed the values of patients with mCRC. The most frequently reported disease-related symptoms are fatigue, abdominal pain, bloody stools, painful diarrhea and constipation. All of these symptoms significantly impact a patient's quality of life. However, pERC considered that the impact of aflibercept on quality of life was unknown as it was not measured in the VELOUR study. Although the majority of patients experience improvements in their symptoms with currently available treatments, some patients are unable to tolerate, or have a contraindication to currently available therapies. pERC noted that patients consider having access to new treatments for their disease as essential to managing the progression of mCRC. pERC discussed that although some patients may be unable to tolerate bevacizumab, the Network Meta-Analysis (NMA) comparing aflibercept with bevacizumab had limitations and despite the results, pERC was not confident that the two therapies have similar toxicities. pERC also discussed the variability in funding of mCRC treatments across provinces and considered access from a patient perspective. pERC noted that although the combinations of therapies available and their sequencing varies across provinces, all patients can access FOLFOX, FOLFIRI and bevacizumab, which is an anti-VEGF therapy.Regardless, a recommendation to fund aflibercept would provide patients with access to another treatment, which would align with their values.

Patient values on treatment: extending life even for a short period and accepting toxicity trade-offs

pERC deliberated upon patient advocacy group input and discussed patient values related to treatment. From a patient perspective, accessing therapies to improve their quality of life, and increase their progression free survival and overall survival is extremely important. Patients also value having the opportunity to have a choice in the selection of the best therapeutic option in the treatment of their mCRC. Despite associated adverse effects, patients reported that it would be very important to access additional treatments whose benefits might only be short term. Patients indicated that they value treatment even in end of life situations, when the benefit is just a few weeks, provided that there is good quality of life. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Patient Advocacy Group reiterating patients value having access to treatment that provides overall survival benefit. pERC acknowledged that, while quality of life was not available for assessment, aflibercept aligns with patients value in providing a modest overall survival benefit. Patients report that greater accessibility to therapy was linked to the maintenance of quality of life. pERC acknowledged that based on this input and the results of the VELOUR study, aflibercept aligned with patient values, although the impact of aflibercept on quality of life is unknown.

However, pERC also noted that input suggested that although patients with mCRC experienced unmet patient needs, respondents to the patient advocacy group's survey and many oncologists were unclear what specific patient needs aflibercept would address. In addition, pERC was interested to better understand how palliative care options were viewed by patients but noted that patient input did not provide any insights on this issue. pERC also discussed that input from the patient advocacy group included only one patient with direct experience with aflibercept. pERC noted that other approaches which may be needed to identify patients with such experience, such as contacting global collaborations, when there are only a small number of patients in Canada who have experience with a drug at the time of evaluation by pERC.

ECONOMIC EVALUATION

Economic model submitted: cost utility and cost effectiveness

The pCODR Economic Guidance Panel assessed a cost-effectiveness analysis comparing aflibercept plus FOLFIRI to placebo plus FOLFIRI in patients with mCRC who had been previously treated with oxaliplatin. A comparison with bevacizumab plus FOLFIRI was also conducted based on a network meta-analysis.

Basis of the economic model: clinical and economic inputs

Costs considered in the analysis included drug and drug administration, disease management costs, subsequent treatment options, and adverse events.

The clinical effects considered in the analysis were based on progression free and overall survival results obtained from the VELOUR study and utility values reported in the literature. The clinical effects for the comparison to bevacizumab plus FOLFIRI were based on a network meta-analysis that did not identify any statistically significant differences in safety or effectiveness between aflibercept and bevacizumab. However, pERC noted that there was a high level of uncertainty associated with the Network Meta-Analysis (NMA) based on methodological concerns raised in the pCODR Clinical Guidance Report. In addition, pERC considered that the NMA lacked face validity when considering the toxicity profile of aflibercept as observed in the VELOUR study.

Drug costs: drug wastage considered in both manufacturer's and EGP's estimates

At the list price, aflibercept costs $500.00 per 100mg vial and $1000.00 per 200mg vial. At the recommended dose of 4mg/kg every two weeks, for a 70 kg patient, aflibercept costs on average $100.00 per day or $2800.00 per 28 day course. Aflibercept is only available in two single use vial sizes: 100mg and 200mg/vial. If any remaining aflibercept is not used by another patient, drug wastage is likely as the drug has a short stability. However, the manufacturer considered wastage in its sensitivity analyses and the EGP incorporated wastage into their best estimates. Upon reconsideration of the Initial Recommendation, pERC considered feedback received from the Provincial Advisory Group regarding the average weight of patients with metastatic colorectal cancer and its impact on weight based dosing. pERC noted that in the context of metastatic colorectal cancer, patients are likely to weigh above the pCODR reporting standard of 70kg. In general, pERC acknowledged that a reporting standard is valuable when providing dosing and costing information. However, in this instance, pERC agreed that the dose and associated costs may be underestimated as patients with mCRC on average weigh more than 70kg and will require additional drug during treatment.

Bevacizumab cost $125.00 per 25mg vial at the list price. At the recommended dose of 5 mg/kg every two weeks, for a 70 kg patient, the average cost per day of bevacizumab is $125.00 or $3500.00 per 28 day course.

FOLFIRI (Irinotecan, Leucovorin, Fluorouracil) costs $10.00, $0.50 and $1.50 per 20mg/ml, 10mg/ml and 50mg/ml vials, respectively. At the recommended dose of 180 mg/m^2 (Irinotecan), 400 mg/m^2 (Leucovorin) and 400 mg/m^2 (Fluorouracil) every two weeks, for a 70 kg patient, FOLFIRI costs on average $14.38 per day or $402.56 per 28-day course.

Cost-effectiveness estimates: not cost-effective at submitted price compared with FOLFIRI

pERC deliberated upon the cost-effectiveness of aflibercept plus FOLFIRI compared with FOLFIRI alone. pERC reviewed the incremental cost-effectiveness estimates provided by both the manufacturer and the pCODR Economic Guidance Panel (EGP). It was noted that the EGP's best estimates were higher than the manufacturer's because of two factors that the EGP changed: removing a calibration factor and shortening the time horizon. The calibration factor on the number of treatment cycles was used in the submitted model to align the treatment cycles (and therefore the cost of treatment) to what was observed in the VELOUR study. However, the calibration factor was not applied to other variables in the model that might also be affected by an overestimation of cycles (e.g. other costs, utility values, adverse events). Therefore, the EGP removed the calibration factor because it may have biased the results in favour of aflibercept. In addition, the manufacturer's economic analysis was based upon a 16 year time horizon. The EGP shortened the time horizon to five years based on input from the pCODR Clinical Guidance Panel. pERC noted that a lifetime horizon is appropriate in models when sufficient data is available to accurately extrapolate over the long-term. However, pERC noted the limited data available on aflibercept, likely led to an overestimate of the survival benefit associated with aflibercept and pERC agreed with the EGP's approach to address by of shortening the time horizon. Therefore, pERC agreed

with the EGP's best estimates and concluded that aflibercept plus FOLFIRI is not cost-effective at the submitted price compared with FOLFIRI alone.

pERC also noted that the cost-effectiveness of aflibercept compared with bevacizumab was unknown based on the uncertainty in the analyses submitted by the manufacturer and the extensive methodological limitations in the NMA. Although the NMA suggested the possibility of non-significant differences in safety between bevacizumab and aflibercept, these results were not statistically significant and there were serious limitations to this NMA. Therefore, the EGP indicated that these should only be considered rough estimates to be used with extreme caution. pERC noted this and considered that the NMA lacked face validity when considering the toxicity profile of aflibercept that was observed in the VELOUR study. Therefore, pERC's concerns regarding the potential for significant adverse events associated with aflibercept and their potential impact on cost-effectiveness remain.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: drug wastage, accessibility of drug if funded, additional resources needed to manage toxicities

pERC discussed factors that could impact the feasibility of implementing a funding recommendation for aflibercept. It was noted that aflibercept only has regulatory approval in Canada for use in combination with FOLFIRI, in patients who have received an oxaliplatin-based regimen (e.g. FOLFOX) in the first-line setting. pERC discussed that access to aflibercept could be impacted by regional variability in the availability of FOLFOX in the first-line setting and FOLFIRI in the second-line setting. pERC also took into consideration the fact that bevacizumab is available in all provinces. In considering currently funded therapies, it was noted that although the combinations of therapies and their sequencing varies across provinces, all patients can access FOLFOX, FOLFIRI and bevacizumab, which is an anti-VEGF therapy. pERC also discussed the health system impact of the recommendation to not fund aflibercept and noted that this could provide opportunities to fund alternative, more effective therapies that could improve outcomes for some patients.

DRUG AND CONDITION INFORMATION

Drug Information	• Anti-angiogenic, anti-VEGF therapy • 4 mL and 8 mL single-use vials of concentrated solution (25 mg/mL) • 4 mg/kg as IV infusion over 1 hour, every 2 weeks
Cancer Treated	• Metastatic colorectal cancer (mCRC) • Second-line after treatment with FOLFOX • Only in combination with FOLFIRI
Burden of Illness	• In 2013, 23,900 Canadians were diagnosed with colorectal cancer and 9,200 died from mCRC • CRC is the second and third most common cause of cancer death in Canadian males and females, respectively
Current Standard Treatment	• FOLFOX or FOLFIRI, alone or in combination with bevacizumab in the first line setting. Bevacizumab (with either FOLFOX or FOLFIRI) may be accessible in many jurisdictions in the second line setting if a patient did not receive it in the first line setting.
Limitations of Current Therapy	• Prolongation of survival beyond twenty-four months remains uncommon and cures are still not anticipated

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

Dr. Maureen Trudeau chaired the meeting in her capacity as Vice-Chair of pERC. All members participated in deliberations and voting on the initial recommendation except:

- Anthony Fields who was excluded from chairing and voting due to a conflict of interest
- Sunil Desai, Bill Evans, Chaim Bell and Danica Wasney who were not present for the meeting
- Scott Berry who was excluded from voting due to a conflict of interest
- Carole McMahon who did not vote due to her role as a patient member alternate

Dr. Maureen Trudeau chaired the meeting in her capacity as Vice-Chair of pERC. All members participated in deliberations and voting on the final recommendation except:

- Anthony Fields who was excluded from Chairing and voting due to a conflict of interest
- Chaim Bell, Scott Berry, Mario De Lemos and Peter Venner who were not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of Aflibercept (Zaltrap) for metastatic colorectal cancer, through their declarations, seven members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this recommendation

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