

pCODR EXPERT REVIEW COMMITTEE (pERC) INITIAL 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.

Providing Feedback on this Initial Recommendation

Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this 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

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.

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 most frequent cause of potential years of life lost to cancer. 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. As standard of care, anti-angiogenic therapies, including bevacizumab, are combined with oxaliplatin-based and irinotecan-fluoropyrimidine-based chemotherapies, in both the first-line and second-line settings. pERC noted that the combination chemotherapy regimens used and their sequencing may vary across provinces. However, pERC discussed that bevacizumab would be the most 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 Custem 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 (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 for aflibercept plus FOLFIRI compared with placebo plus FOLFIRI. pERC members debated the magnitude of benefit that was clinically meaningful and various opinions were expressed on this issue. pERC also discussed equity issues associated with varying progression-free survival estimates across different tumour types and considered how it was valued, along with other components, in previous 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 was conducted that provided indirect estimates of aflibercept compared with 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. Finally, pERC discussed that the impact of aflibercept on quality of life is unknown as it was not measured in the VELOUR study. 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.

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 and accept 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.

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 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. 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 network meta-analysis.

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 vary 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 group (Colorectal Cancer Association of Canada) and input from pCODR's Provincial Advisory Group.

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 randomised, 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 VELOUR study 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 pERC members debated whether that

magnitude of benefit was clinically meaningful and various opinions were expressed on this issue. pERC also discussed equity issues associated with varying progression-free survival estimates across different tumour types and how it had been viewed in previous pERC recommendations.

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.

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 in the 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 most frequent cause of potential years of life lost to cancer. 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 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 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. 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, prolongation of survival beyond twenty-four 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 since this 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 NMA comparing aflibercept with bevacizumab had limitations and pERC was not confident that the two therapies have similar toxicities, even though the analysis results suggested this. 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. Patients report that greater accessibility to therapy was linked to maintaining 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 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 are necessary to identify patients with such experience, such as contacting global collaborations, may be appropriate 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 survival and overall survival 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 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 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 sensitivity analyses and the EGP incorporated wastage into their best estimates.

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 is bevacizumab \$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/m² (Irinotecan), 400 mg/m² (Leucovorin) and 400 mg/m² (Fluorouracil) every two weeks, for a 70 kg patient, FOLFIRI costs an average of \$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 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 of shortening the time horizon to compensate for this. 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 network meta-analysis (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 were not reduced regarding the potential for significant adverse events associated with aflibercept and their potential impact on cost-effectiveness.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: drug wastage, accessibility of drug if funded, additional resources 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 available vary 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 provide improved outcomes for some patients.

DRUG AND CONDITION INFORMATION

Drug Information	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Metastatic colorectal cancer (mCRC) • Second-line after treatment with FOLFOX • Only in combination with FOLFIRI
Burden of Illness	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • FOLFOX ± bevacizumab • FOLFIRI ± bevacizumab
Limitations of Current Therapy	<ul style="list-style-type: none"> • 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

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, six 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

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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