PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Aflibercept (Zaltrap) for Metastatic Colorectal Cancer

September 5, 2014

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Zaltrap (aflibercept)
Role in Review (Submitter and/or Manufacturer):	In combination with irinotecan-fluoropyrimidine (FOLFIRI) based therapy for patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen
Organization Providing Feedback *:	Sanofi-Aventis Canada Inc.

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part __X__ disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) *agrees, agrees in part or disagrees with the initial recommendation.*

Sanofi does not agree with the pERC initial recommendation. The VELOUR trial clearly showed clinically meaningful efficacy results based on consistency of endpoints (incl. doubling of ORR), and continued divergence of the curve/survival at 2 years.

b) Please indicate if the Submitter would support this initial recommendation proceeding to final pERC recommendation, which would occur within 2 business days of the end of the consultation period.

____ Support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.

__X__ Do not support conversion to final recommendation.
Recommendation should be reconsidered by pERC.

c) Feedback on the initial recommendation

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
2	Summary of pERC deliberations	2, 3	Magnitude of clinical benefit: Need to get clarity on what threshold pCODR is looking at in terms of OS and PFS, as this is reported as a topic of debate among the pERC members and that discussions of equity versus pervious pERC recommendations have occurred. See attached summary of pCODR solid tumours decisions - July 2014.
2	Summary of pERC deliberation	Line 15	The actual standard of care in 2nd-line setting post-oxaliplatin would be FOLFIRI ± bevacizumab (not bevacizumab alone) and therefore the most relevant comparator should be FOLFIRI ± bevacizumab. This is better stated in the Initial Economic Guidance Report – Section 1.2. Considering that bevacizumab is used in the majority of 1st-line patients, its use in 2nd-line would be primarily beyond progression. This indication is not funded and not officially approved by Health Canada. Finally, bevacizumab in 2nd-line (if not used already in 1st-line) is only

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			supported by E3200 study in combination with FOLFOX and at a 10 mg dosage (twice the standard dose)
2	Summary of pERC deliberation	Line 29	The ASQoP trial 3rd interim analysis based on 450 patients presented at ASCO 2014 has revealed lower levels of Grade 3-4 diarrhea (14.0%) similar to historical rates reported with FOLFIRI alone.
2	Summary of pERC deliberation	Lines 33-34	It should at least be acknowledged that Extensive quality of life data using the EORTC-QLQ and EQ-5D has been collected in the ASQoP trial, a large real world study, and explain why this evidence was not considered by the pERC group.
4	Evidence in brief – QoL	2nd paragraph	
3	Summary of pERC deliberation	Line 15	It must be made explicit that bevacizumab is only available for use once. It is available in 1st-line only or in 2nd-line when it has not been used in 1st-line. It must be made clear that patients do not have access to bevacizumab beyond progression. This is a population where there is an unmet need for new biologic treatment options.
5	Patient-based values	Top of page 1st paragraph 1st line	
6	Adoption feasibility	Last paragraph	
4	Evidence in brief – Safety	3rd paragraph	It should at least be acknowledged that additional safety data was collected in the large ASQoP trial which showed a lower rate of adverse events
4	Evidence in brief – Overall clinical benefit	4th paragraph, last line before next section	The comparator should be based on the actual standard of care in the 2nd line setting post-oxaliplatin. Therefore the most relevant comparator should be FOLFIRI ± bevacizumab. Also considering the large proportion of patients receiving bevacizumab in 1st-line, the proportion of patients in 2nd-line that should be eligible to bevacizumab as per current funding criteria should be minimal. So it is not clear why it is perceived as the most relevant comparator. Please be more explicit in that respect.

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
2	Initial Clinical Guidance Report Section 1.2.3		The VELOUR trial demonstrates that 28% of patients in the Aflibercept + FOLFIRI group were still alive at 2 years, 10% more than in the FOLFIRI alone group (18%) and the confidence interval for the two arms do not overlap – demonstrating a clear benefit at 2 years. Many other pCODR approved therapies have not shown overall survival and only PFS. The committee needs to acknowledge and discuss that all 3 efficacy endpoints (OS, PFS and ORR) were statistically significant and that the survival curves continue to diverge at 2 years.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
22	Initial Clinical Guidance Report – Section 5.6.	Second to Last paragraph on the page	The second part of this statement is untrue, unless not clearly understood. In the VELOUR trial, 30% of the patients who received aflibercept had received bevacizumab in the first-line setting, and the treatment effect was consistent in this sub-group.
4	Initial Economic Guidance Report	1st large section on lines 5-12	It should be more clearly stated that the cost-savings are in favor of aflibercept, particularly in the first bullet point of that section.
18	Initial Economic Guidance Report	Section 2.2.2 Second bullet point – infusion time	The infusion time was addressed in the CEA model and was costed as per the product monograph recommendations. This was done for both the comparison against FOLFIRI alone and the comparison against bevacizumab + Chemo.
22	Initial Economic Guidance Report	Paragraph just above section 2.4	It seems that the statement: "Of further note, trial ML18147 was included in the manufacturer's secondary NMA where the comparison was bevacizumab + chemotherapy and not in the primary NMA". This statement does not seem to belong here and should be stated earlier in the document.
23	Initial Economic Guidance Report	Section 2.4 Evaluation of Submitted Budget Impact Analysis – 5th paragraph – lines 13-16	The BIA model did increase the market share of FOLFOX in 1st line to account for a possible greater usage. However, the additional cost for FOLFOX usage in 1st line was not included in the BIA as only incremental costs related to the second-line setting were considered. The cost for bevacizumab's use in 1st line should not change due to a change of 1st line chemotherapy back-bone. In fact the use of bevacizumab in combination with FOLFOX may be lower than with FOLFIRI for patients potentially resectable. To be noted that the data protection for oxaliplatin will end in December 2015.

3.3 Additional Comments About the Initial Recommendation Document

Page Number	Section Title	Paragraph, Line Number	Additional Comments
			It appears that because the use of aflibercept would be limited to a small population (only those that would have received prior oxaliplatin), its value was considered more limited. Under this premise, drugs with proven efficacy but targeted for more limited patient population should not be developed. This negates the premise of a more personalized medicine.
			It is surprising to note that PERC seems satisfied with the access of bevacizumab for patients at a supposedly similar efficacy to aflibercept, and it is not willing to offer aflibercept as another option with similar efficacy and at a lower price.