pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Panitumumab (Vectibix) for Left Sided metastatic Colorectal Carcinoma

March 29, 2018

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Panitumumab in combination with chemotherapy, for the first line treatment of metastatic colorectal cancer (mCRC) patients with left sided (LS) primary tumours that express wild-type (WT) RAS
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback	Amgen Canada Inc.

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not 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.*

Amgen recognizes that this is a unique submission based on retrospective subgroup data, and appreciates the time and effort that pCODR has taken with this review. The consistency of the anti-EGFR primary tumour location (PTL) data across five first-line clinical studies and several meta-analyses as well as the incorporation of LS recommendations into guidelines makes this an important area for consideration. Given the acceptance of this LS classification system within the community, there exists a low probability that prospective data will be available in the future making a recommendation based on the currently available data important. For these reasons, Amgen respectfully disagrees with the pERC decision to not recommend the reimbursement of panitumumab in combination with chemotherapy for the first-line treatment of mCRC patients with LS primary tumours that express WT RAS and who would otherwise be candidates to received bevacizumab.

Consistent to the larger meta- and pooled analyses of all commercially available anti-EGFR monoclonal antibodies (Holch et al. 2017, Arnold et al. 2017), the analysis in Boeckx et al. demonstrated the benefit of panitumumab in patients with LS tumours. Panitumumab provided better outcomes than the comparator treatment, including median overall survival (PRIME: 30.3 versus 23.6 months; PEAK: 43.4 versus 32.0 months) (Boeckx et al., 2017). While the current analysis lacks the power of the class level analysis due in

part of the multiple sub-setting that occurred (ie KRAS, RAS, PTL), the consistency seen across both studies and with the combined group as a whole is remarkable and is very analogous to the analyses that led to the global regulatory approvals and guideline development for anti-EGFR monoclonal antibodies in KRAS and then RAS WT mCRC patients specifically. Similarly, the pERC committee has shown its willingness to accept clinical practice patterns and guidelines in the absence of large randomized clinical trials in their recommendation of either chemotherapy backbone (FOLFOX/FOLFIRI) in combination with first-line panitumumab (Vectibix pCODR, 2015).

In addition to evidence from panitumumab studies, Amgen requests pERC to reconsider the evidence based on the totality of anti-EGFR evidence as clinical trials have demonstrated the comparable efficacy and safety of cetuximab and panitumumab in the monotherapy (ASPECCT; Price et al. 2014) and 1st line settings (CRYSTAL and PRIME; Van Cutsem et al 2009, Douillard et al. 2013). Amgen also conducted a network meta-analysis (NMA) evaluating panitumumab + chemotherapy vs. cetuximab + chemotherapy in WT RAS mCRC patients with LS tumours in the first line setting and it concluded that panitumumab + chemotherapy was non-inferior to cetuximab + chemotherapy for both PFS and OS (Amgen, 2017).

Amgen's NMA also evaluated the comparative efficacy of chemotherapy + anti-EGFR (panitumumab or cetuximab) relative to chemotherapy alone (FOLFOX or FOLFIRI), and chemotherapy + anti-VEGF (bevacizumab) in the treatment of WT RAS mCRC with LS tumours in the first-line treatment setting. Based on the NMA, statistically significant differences in OS (HR= 0.69, 0.58-0.83 vs. chemotherapy only; HR= 0.71, 0.59-0.85 vs. chemotherapy plus anti-VEGF) were found in favour of chemotherapy plus anti-EGFR. A relative risk reduction of 31% with chemotherapy plus anti-EGFR compared with treatment with chemotherapy alone translates into approximately 8, 22, and 29 lives saved at 1, 3 and 5 years respectively for every 100 patients treated. In comparison, a 29% risk reduction with chemotherapy plus anti-EGFR treatment vs. chemotherapy plus anti-VEGF translates into approximately 7, 20, and 26 lives saved at 1, 3 and 5 years respectively for every 100 patients treated. These absolute risk reductions are large in comparison to other cancer types and Amgen strongly believes this absolute risk of mortality is extremely important to patients.

In addition to the multiple meta- and pooled analyses and the included NMA, recent clinical review of the data has led to recommendations in the United States, Australia and Europe to preferentially treat patients with LS disease with anti-EGFR containing regimens (Benson et al 2017, Nott et al. 2017, Arnold et al. 2017). Similarly, a national evidence-based Consensus Statement was recently developed and published by Canadian mCRC experts and provides the following recommendations for the treatment of patients with mCRC (Abrahao et al, 2017):

- Patients with LS WT RAS mCRC receive standard chemotherapy (FOLFOX or FOLFIRI) plus an anti-EGFR monoclonal antibody (panitumumab or cetuximab) in the first-line setting. In patients with right-sided wild-type RAS mCRC, first-line anti-EGFR monoclonal antibodies are not recommended. Treatment with bevacizumab plus standard chemotherapy remains standard-of-care in these patients.

Overall, in patients with left-sided wild-type RAS mCRC, anti-EGFR such as panitumumab offer the most effective first-line therapeutic option. Panitumumab, with its more convenient dosing, lower infusion reaction concerns and lower cost represents the best option in this class.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

____ 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) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
p.1	pERC recommendation	2nd paragraph, line 6: "as well as significant toxicities associated with panitumumab"	pERC reviewed the adverse events observed in the PEAK and PRIME studies and noted that the information aligned with the expected toxicity profile of panitumumab, which is well-known and manageable (p. 8 of panitumumab current 2018 initial recommendation). Also, based on patient input from the previous panitumumab 1st line submission, pERC Final Recommendation (dated December 2015; Vectibix pCODR, 2015) noted that panitumumab had overall acceptable side effects, which allowed patients to maintain their usual health related quality of life. Amgen submitted a summary of adverse events stratified by tumour location status using data from the PEAK trial which showed that the percentage of grade 3-5 adverse events were similar between patients in the panitumumab arms vs. the bevacizumab arm. Adverse events of interest such as rash and hypomagnesemia were higher in the panitumumab arm but these are known, manageable and non-life threatening adverse events associated with the anti-EGFR class and have been demonstrated in multiple studies. For example, in a large randomized, phase 3 intergroup study comparing anti-EGFR cetuximab against bevacizumab, global QOL, as well as physical, role, social and emotional functioning, were not significantly different across treatment arms. However, as expected, cetuximab recipients reported greater symptoms and quality of life concerns relating to their skin than those receiving bevacizumab alone (Naughton et al. 2013).
p.5	Summary of pERC deliberations	2nd paragraph, lines 11-13: "pERC also had concerns... would lose overall access to bev… for access to	In a large Canadian observational study, a progressive decline in mCRC patients receiving subsequent lines of therapy was observed; 70%, 30%, and 15% receiving 2nd, 3rd, and 4th-line therapies respectively (Kennecke et al. 2015). Despite OS benefit, most patients (70%) will not receive anti-EGFR therapy in 3rd line mCRC. As demonstrated in PRIME, an OS of approximately 6 months was demonstrated for WT RAS patients (Douillard et al 2013). Upon the refinement to LS mCRC patients, OS was further increased highlighting the importance anti-EGFR in 1st line mCRC setting

		panitumumab in first line instead of third line."	(Boeckx et al. 2017). Given the significant OS improvements in 1st line patients with LS mCRC treated with anti-EGFR therapy in combination with a modern chemotherapy backbone (FOLFOX/FOLFIRI), it is important that these therapies are available, and offered to patients at a time when many can benefit as most ultimately won't receive the life extending therapies in third line.

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

References:

Abrahao A, Karim S, Colwell B, Berry S, & Biagi J. The predictive impact of primary tumour location in the treatment of metastatic colorectal cancer: a Canadian consensus statement. *Curr Oncol*. 2017; Dec;24(6):390-400.

Amgen Data on File. Systematic Review and Network Meta-analysis of Panitumumab with Chemotherapy in the First-line Treatment of Patients with Wild-type RAS Metastatic

Colorectal Cancer (mCRC) with Left-Sided Tumours. Version 3.0. Prepared by Cornerstone Research Group. 2017.

Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomised trials *Ann Oncol*. 2017;28:1713-1729.

Benson AB, Venook AP, Cederquist L *et al*. Colon cancer, version 1.2017, NCCN clinical practice guidelines in oncology*. J. Natl. Compr. Cancer Netw.* 15(3), 370-398 (2017).

Boeckx N, Koukakis R, Op de Beeck K, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies *Ann Oncol*. 2017;28:1862-1868.

Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369:1023-1034.

Holch JW, Ricard I, Stintzing S, Modest DP, & Heinemann V. The relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials. *Eur J Cancer*. 2017;70:87-98.

Kennecke et al. Retrospective observational study to estimate the attrition of patients across lines of systemic treatment for metastatic colorectal cancer. EJC 2015 abstract 2132.

Naughton MJ, Schrag D, Venook AP, Niedzwiecki D, Anderson RT, Lenz HJ, and Grubbs SS. Quality of life (QOL) and toxicity among patients in CALGB 80405. Journal of Clinical Oncology 2013 31:15_suppl, 3611-3611

Nott L, Khattak M, Price T *et al*. Cancer Council Australia Colorectal Cancer Guidelines Working Party. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer (2017).

Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol*. 2014;15:569-579

Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;360:1408-1417.

Vectibix® pCODR. pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) Final Recommendation for Panitumumab (Vectibix®) for Metastatic Colon Cancer. Available at:

https://www.cadth.ca/sites/default/files/pcodr/pcodr_panitumumab_vectibix_mcrc_fn_rec.pdf 2015.

1 About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation two (2) Business Days after the end of the feedback deadline date. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

2 Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer

of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.