PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Regorafenib (Stivarga) Resubmission Metastatic Colorectal Cancer

July 16, 2015

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Stivarga® (regorafenib) mCRC (resubmission)
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	Bayer 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

Bayer disagrees with the initial recommendation.

Bayer specifically disagrees with pERC's findings related to net clinical benefit, toxicities, alignment with patient values and quality of life. Bayer reiterates the following:

- Stivarga offers a clinically important net benefit to patients with mCRC.
- Stivarga's overall survival benefit was statistically and clinically meaningful in two randomized placebo controlled phase III trials
- Stivarga's adverse event profile is well-characterized and manageable
- Stivarga delays deterioration in quality of life
- No other therapies are available for mCRC patients at this advanced stage of disease.

pERC must reconsider its initial recommendation for the following reasons:

1. pERC's assessment of efficacy, safety and overall net clinical benefit is inconsistent with pCODR's Clinical Guidance Panel report, treatment guidelines, the opinions of treating physicians and patient experiences shared by the CCAC.
2. pERC's assessment conflicts with the findings of the Clinical Guidance Panel, specifically the following conclusions (Page 4, Section 1.3, Initial Clinical Guidance Report) which clearly support the net clinical benefit of Stivarga in mCRC:

*"**Effectiveness:** The efficacy of regorafenib has been demonstrated in two similarly-designed, multi-centre RCTs, CORRECT and CONCUR, with a modest but consistent and statistically significant improvement in OS. There was no associated significant improvement in QoL measures. These trials include patients from Western and Asian populations and are considered generalizable to Canadian patients with treatment-refractory mCRC with an ECOG PS of 0-1.*

***Safety:** Regorafenib introduces the risk of toxicities such as hand-foot skin reaction, fatigue, diarrhea, hypertension, rash, and anorexia. These toxicities can be managed with early intervention and there is an increasing awareness among the Canadian oncology practitioner community regarding the profile and management of such toxicities. Patient advocacy input suggests that patients would be willing to tolerate moderate to significant treatment-related side effects in the hopes of controlling their disease.*

***Need and Burden of disease:** As a leading cause of cancer-related morbidity and mortality, the burden of mCRC among Canadians is significant. Regorafenib fulfills an unmet need for the treatment of patients with mCRC who have exhausted all currently available systemic therapies yet are still well enough to consider further treatment."*

3. Stivarga remains the only available treatment for mCRC patients advancing to this stage of their disease. With a positive clinical benefit supported by two (2) phase III clinical studies

Stivarga should be available in the continuum of care for patients with mCRC.

4. Late stage mCRC treatments such as Stivarga should be considered from a relative perspective to other late stage treatments that have been recommended by pCODR. As seen in Table 1, Stivarga showed comparable or better OS / PFS hazard ratios, discontinuation rates due to adverse events and cost effectiveness when compared to nab-paclitaxel for pancreatic cancer and everolimus for breast cancer.

Table 1: Comparison of Stivarga to other pCODR Conditional Recommendations

Drug	Cancer Type	OS H.R. (95% CI)	PFS H.R. (95% CI)	Rate of TEAE's leading to discontinuation[1]	EGP Best Estimate ICER[2]	pERC Final Recommendation
Stivarga	mCRC CORRECT	0.79 (0.66-0.94)	0.49 (0.42-0.58)	19.0% vs 12.3%	$189K/QALY (range N/R)	Pending
Stivarga	mCRC CONCUR	0.55 (0.40-0.77)	0.35 (0.22-0.44)	14.0% vs 5.9%	$115K/QALY[3]	
Nab-paclitaxel	Metastatic pancreatic cancer	0.72 (0.58-0.82)	0.69 (0.58-0.82)	30% vs 18%	Lower: $183K/QALY Upper: $193K/QALY	Fund at improved cost-effectiveness
Everolimus	advanced breast cancer	0.89 (0.73-1.10)[5]	0.38 (0.31-0.48)[4]	19.1% vs 4.6%	Lower: $162K/QALY Upper: N/R[6]	Fund at improved cost-effectiveness

1. TEAEs:Treatment emergent adverse events leading to discontinuation: Rates as reported in clinical guidance panel reports for Stivarga mCRC (resubmission) (pcodr_regorafenib_stivarga_resub_mcrc_in_cgr; Apr-15), Nab- paclitaxel (pcodr-abraxane-mpc-fn-cgr; Sept-14) and everolimus (pcodr-afinitorab-fn-cgr; Mar-13). The Nab-paclitaxel (MPACT) trial was open-label (nab-paclitaxrel+gemcitabine vs gemcitabine alone (open label, no placebo control), The everolimus trial (BOLERO-2) was placebo controlled (everolimus + exemestane vs placebo + exemestane).
2. As reported in final pCODR economic guidance panel reports for Stivarga (pcodr_regorafenib_stivarga_resub_mcrc_in_egr, Apr-13) nab-paclitaxel (pcodr-abraxane-mpc-fn-egr, Sep-14)and everolimus for advanced breast cancer (pcodr-afinitorab-fn-egr, Mar-13)
3. Sensitivity Analysis (Stivarga mCRC Resub EGP detailed technical report).
4. Bolero 2, Central Assessment, Dec 15, 2011 Cutoff (pcodr-afinitorab-fn-cgr; Feb-13)
5. Published subsequent to pCODR recommendation: Piccart et al, 2014(1)
6. Final recommendation for everolimus did not include final OS analysis results. EGP did not provide an upper end ICER estimate.

5. The consistent incremental benefits from recent treatments are leading to extended survival and improved prognosis for mCRC patients.(2) It is imperative that Canadian mCRC patients be offered the best standard of care, as defined by local and international guidelines to achieve median overall survival outcomes that have reached 30 months of survival from diagnosis of metastatic disease in recent international studies.(3, 4) Stivarga is included in both international and local treatment guidelines for mCRC, including, despite the absence of provincial funding, some Canadian provincial therapy guidelines.(5-8)
6. Stivarga represents the only third line option for patients not eligible for anti-EGFRs. Recent evidence demonstrated that in addition to KRAS mutations other RAS mutations may also be predictive of resistance to anti-EGFRs. No PFS or OS benefit was evident with use of anti-EGFRs for tumors harboring any RAS mutation.(9) With the expanded knowledge of mutations it is now known that more than half of mCRC patients will not benefit from anti-EGFR therapy.(9) Stivarga is the only available third line option for these patients.

7. Cost Effectiveness

- Bayer's estimates ranged as low as $138K / QALY (based on CORRECT trial data) and $102K / QALY (based on CONCUR trial data).
- Bayer's base-case estimate of $158K / QALY is in the mid-range of the univariate analyses and is based on incorporation of conservative assumptions recommended by the EGP in the previous EGP review of Stivarga for mCRC.
- The EGP's best estimates are based on very conservative methods and are among the highest

estimates.

- While not meeting pCODR's undefined threshold for cost-effectiveness, Bayer wants to work with pCODR participants and the PCPA to define a risk sharing approach that ensures improved cost-effectiveness, early intervention in the management of adverse events and appropriate patient selection to optimize Stivarga's benefits.

8. Patient Based Values and Quality of Life

Bayer disagrees with pERC's statement that "regorafenib only partially aligns with patient values". Further this is inconsistent with the previous final recommendation for Stivarga in mCRC in November of 2013, which concluded:

> *"pERC noted that patients considered any extension in life meaningful, regardless of the length of this extension. Also, patients considered that an oral therapy like regorafenib could improve quality of life because patients could receive treatment at home, reducing the number of hospital visits. Therefore, considering this feedback, pERC agreed that regorafenib aligned with patient values."*

Amongst new evidence considered in the resubmission, the individual patient experiences shared by the CGP reinforce Stivarga's alignment with patient values. Patient statements included: "a less stressful life", "excellent quality of life", "it's convenient for me and my family" and "a 25% dose reduction completely resolved the toxicity issues".

9. Quality of Life Findings - Page 2 and 5; Initial Recommendation:

> "pERC noted that patients' quality of life declined from baseline to the end of treatment in both the CORRECT and CONCUR studies. These declines were similar in both the regorafenib and placebo arms of the studies. pERC considered it important to emphasize that regorafenib was unable to maintain or improve patients' quality of life, as measured in the clinical trials."

Patients entering the CORRECT trial had relatively high baseline EQ-5D utilities, demonstrating their high function status despite receiving multiple lines of therapy. Therefore, improvements in QoL in this advanced disease population would be unexpected.

In the CORRECT and CONCUR trials, clinically meaningful declines in QoL occurred primarily at the end of treatment not while receiving treatment. In the analysis of both CORRECT and CONCUR quality of life data, minimal clinically important differences (MID) in quality of life measures occurred in both arms at the end of treatment, and were most likely associated with disease progression. As shown in the time to deterioration analyses of CORRECT and CONCUR, there was a reduced the risk of HRQoL deterioration for patients treated with Stivarga, when considering the earliest event of MID decrease in HRQOL, disease progression, or death (i.e. three-component endpoint).(10, 11)

10. Feasibility of Adoption

Potential for waste due to open-product shelf-life.

The current approved in-use stability shelf-life of Stivarga is noted by the PAG as a potential adoption consideration. An S/NDS is under review at Health Canada seeking to extend the in-use stability (the time after the bottle is opened) from 28 days to 7 weeks.

Based on the above considerations, Bayer requests the recommendation be changed to fund conditional on cost-effectiveness being improved to an acceptable level.

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 within 2(two) business days of the end of the consultation period.

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

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

1. Piccart M, Hortobagyi GN, Campone M, Pritchard KI, Lebrun F, Ito Y, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2dagger. Ann Oncol. 2014 Dec;25(12):2357-62.
2. Vickers MR. Slow and steady: incremental survival improvements in advanced colorectal cancer. Oncology Exchange. 2013;12(1):4.
3. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014 Sep;15(10):1065-75.
4. Venook AP. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). ASCO Meeting Abstracts. 2014.
5. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer V.2,2015. National Comprehensive Cancer Network Inc; 2015 [cited 2014 October]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
6. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. Ann Oncol. 2014 Sep;25 Suppl 3:iii1-iii9.
7. Alberta Provincal Gastrointestinal Tumour Team. Metastatic Colorectal Cancer Clinical Practice Guideline GI-003,. June 2011 [cited 2013 Janurary]; Available from: http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-gi003-colorectal-metastatic.pdf.
8. Saskatchewan Cancer Agency. Provincial Coloretal Cancer Treatment Guidelines. Regina, Saskatchewan,2011 [updated August 2011; cited 2013 Janurary]; Available from: http://www.saskcancer.ca/Colorectal%20CPGs.
9. Sorich MJ, Wiese MD, Rowland A, Kichenadasse G, McKinnon RA, Karapetis CS. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. Ann Oncol. 2014 Aug 12.
10. Chang J, Pawar V, Grothey A, Sobrero A, Siena S, Falcone A, et al. Time to health status deterioration in regorafenib-treated patients with metastatic colorectal cancer (mCRC): a post-hoc analysis of the phase III CORRECT study. European Cancer Congress; Amsterdam, The Netherlands2013.
11. J Clin Oncol2015. A post-hoc health-related quality of life (HRQoL) analysis of patients with metastatic colorectal cancer (mCRC) in the phase III CONCUR trial; p. abstr 667.

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.cadth.ca/pcodr 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.cadth.ca/pcodr 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 by 2 (two) business days after the end of the consultation (feedback) period. 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.cadth.ca/pcodr 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.