pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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: **Sorafenib (Nexavar)** Treatment of patients with locally advanced or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine.	
Submitted By: **Bayer Inc.**	**Manufactured By:** **Bayer Inc.**
NOC Date: **June 17, 2014**	**Submission Date:** **December 19, 2014**
Initial Recommendation: April 20, 2015	**Final Recommendation:** **July 16, 2015**

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) does not recommend funding sorafenib (Nexavar) in patients with locally advanced or metastatic differentiated thyroid cancer progressing after treatment with radioactive iodine. The Committee made this recommendation because they were unable to conclude that there was a net clinical benefit with sorafenib compared to placebo in this population. pERC, however, recognized the clear unmet need for treatment in this setting. While a statistically significant improvement in progression-free survival was observed, pERC expressed concerns with the decline in quality of life, the rates of high grade toxicity, and uncertainty in overall survival benefit of sorafenib versus placebo. pERC acknowledged that sorafenib aligned with patient values since it provided patients with a choice in treatment. The Committee also concluded that sorafenib was not cost-effective.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

Differentiated thyroid cancer (DTC) is a malignancy affecting approximately 4,500 Canadians annually. Between 5% and 15% of patients with thyroid cancer will present with or develop disease which is refractory to radioiodine therapy. Disease which becomes refractory to radioiodine therapy has a poor prognosis and currently these patients have no effective systemic therapy options available to them. Each year, there are approximately 200 deaths from metastatic thyroid cancer in Canada. The intent of treatment for patients with DTC refractory to radioactive iodine is to prolong life and reduce symptoms from bone and lung metastases (e.g. pain, hemolysis, bone fracture, shortness of breath). pERC agreed that there is a need for additional effective treatment options that improves survival and quality of life for these patients. During the reconsideration of the initial recommendation for sorafenib, pERC reiterated the need for effective treatment options for patients at this point in their disease.

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated upon one randomized controlled trial (DECISION) which compared sorafenib to placebo in patients with locally advanced or metastatic, progressive DTC refractory to radioactive iodine. More than 70% of patients in the placebo arm crossed over to the sorafenib arm upon disease progression. The Committee noted that there was a significant improvement in the primary outcome of progression-free survival (PFS) in the sorafenib arm compared to the placebo arm. They also noted that there was no difference in overall survival between the two treatment arms, however, the median overall survival had not been reached for either arm at the time of reporting the trial results. In addition, the high proportion of crossover (early treatment switching) could potentially confound differences in overall survival. pERC noted that PFS had not been demonstrated to be a valid surrogate outcome for overall survival in DTC. During the reconsideration of the initial recommendation, pERC considered feedback from both the Provincial Advisory Group (PAG) and the submitter which noted that the absence of evidence of a correlation between PFS and OS does not mean that there is no correlation. pERC noted a proposition cannot be assumed to be true because it has not been proven false. Therefore, a lack of evidence to support or dispute the putative correlation between PFS and OS does not constitute evidence that such a correlation exists.

pERC thoroughly considered the quality of life results from the DECISION trial. Two scales were used to measure quality of life: EuroQol-5 Dimensions (EQ-5D) and the Functional Assessment of Cancer Therapy General Version 4.0 (FACT-G). pERC noted that the results were statistically significantly lower in the sorafenib arm on both scales compared to the placebo arm. pERC noted that the difference was clinically meaningful with the FACT-G scale. During the reconsideration, pERC noted the feedback from the submitter stating that one quality of life scale had barely reached the threshold for a clinically meaningful decline in quality of life. pERC noted that even though only one quality of life scale demonstrated a clinically meaningful decline in quality of life, both quality of life scales consistently demonstrated declines in quality of life. Maintaining or improving quality of life towards the end of life for patients with DTC was an important consideration for the Committee.

pERC also discussed the toxicity associated with sorafenib and noted that there were more patients in the sorafenib arm that experienced at least one grade 3 treatment-related adverse event compared to the patients in the placebo arm, including hand- foot syndrome, hypertension, and hypocalcaemia. pERC also noted that patients with DTC receiving sorafenib appear to experience more toxicity than seen in trials with patients receiving sorafenib for renal cell or hepatocellular cancer. However, the reason for this apparent increase in toxicity is unknown. Upon reconsideration of the initial recommendation, pERC referred to the Product Monograph for sorafenib and noted that the average serum concentration exposure at the same dose of sorafenib was 70% higher in patients with DTC than in patients with renal cell carcinoma (RCC) or hepatocellular carcinoma (HCC). The clinical relevance and the reason for this increase are unknown.

Differing opinions were expressed by pERC members regarding the interpretation of the statistically significant increase in PFS juxtaposed against the clinically significant reduction in quality of life. Overall, pERC was unable to conclude that there is a net clinical benefit because of the decline in the quality of life, the uncertainty in overall survival and the increased toxicity profile, even though there is an unmet need for treatment for patients with refractory DTC and a significant improvement in PFS associated with sorafenib. Again during the reconsideration of the initial recommendation, differing opinions were expressed by the Committee members. The Committee agreed there is an unmet need for effective treatment options in patients with DTC refractory to radioiodine therapy. However, after considerable discussion, the majority of the pERC members felt that there was no net clinical benefit for sorafenib due to the detriment in quality of life, the unexplained apparent increase in toxicity of sorafenib compared to other approved indications for sorafenib, and a lack of confidence in the results for overall survival.

pERC considered input from one patient advocacy group that indicated patients valued treatment options that extend survival. pERC discussed the input from two patients with experience with sorafenib. pERC acknowledged that the two patients indicated that they would be willing to manage the adverse events, however, at the same time the patients also noted that substantial adverse events impacted their activities of daily living. There were, again, differing opinions expressed by pERC members regarding the different perspectives expressed by the patient advocacy group and the two patients who had received sorafenib for thyroid cancer in contrast to the DECISION trial results that demonstrated a deterioration in quality of life on sorafenib. pERC agreed that sorafenib aligned with patient values in terms of access to treatment options. However, the majority of members concluded that the gains in disease control were offset by the significant toxicity profile and the absence of evidence of a survival gain. pERC maintained that the net benefits that were observed with sorafenib were insufficient. Upon reconsideration of the initial recommendation, pERC confirmed that, based on the patient advocacy group input which included input from two patients, sorafenib aligned with patient values.

pERC noted that the incremental cost-effectiveness estimates provided by the pCODR Economic Guidance Panel (EGP) were higher than the manufacturer's estimates. pERC favoured the EGP's re-analysis of the model provided by the manufacturer. However, pERC noted that the ICER may be even higher than the EGP's estimate given the uncertainty regarding overall survival and that the model assumes that approximately 50% of the overall survival benefit occurs in the post-progression state which is unrealistic from a clinical perspective. pERC concluded that even if there were a net clinical benefit of sorafenib in patients with DTC refractory to radioactive iodine, it would not be considered cost effective.

Finally pERC discussed the feasibility of implementing a funding recommendation for patients with locally advanced or metastatic, DTC refractory to radioactive iodine. They noted that there is no current standard of care for these patients, and that there would likely only be a small number of patients who would be eligible for treatment which the Provincial Advisory Group would view as an enabler to implementation. During the reconsideration of the initial recommendation, pERC reviewed feedback from PAG and the submitter suggesting that the recommendation could be limited to patients at the time of development of cancer related symptoms. However, pERC noted that there are no specific data on the efficacy or safety of sorafenib in symptomatic or asymptomatic patients compared to the entire trial population and, therefore, could not reasonably make a recommendation for this subgroup, again in the context of diminishing quality of life at the end of life.

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 (Thyroid Cancer Canada) and 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 (Thyroid Cancer Canada)
- the Submitter (Bayer Inc.)

The pERC initial recommendation was to not fund sorafenib in patients with locally advanced or metastatic, progressive differentiated thyroid cancer refractory to radioactive iodine.

Feedback on the pERC Initial Recommendation indicated that the manufacturer and the patient advocacy group disagreed with the initial recommendation. pCODR's Provincial Advisory Group agreed in part with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the effectiveness and safety of sorafenib (Nexavar) in combination with best supportive care (BSC) for the treatment of patients with locally advanced or metastatic, progressive differentiated thyroid cancer (DTC) refractory to radioactive iodine.

Studies included: One randomized controlled trial with >70% crossover

The pCODR systematic review included one randomized controlled trial (RCT), the DECISION trial, which compared sorafenib plus best supportive care (n=210) to placebo plus best supportive care (n=209) in patients with locally advanced or metastatic, progressive DTC refractory to radioactive iodine. pERC noted that >70% of patients crossed over from the placebo arm to the sorafenib arm upon disease progression.

Patient populations: Majority of patients with ECOG PS 0 or 1 and distant metastases

Baseline characteristics were well balanced across treatment groups. The majority of patients had an ECOG Performance Status (PS) score of 0 or 1 (~96%). Even though the study recruited patients with locally advanced disease or distant metastases, the majority of patients had distant metastases (~96%).

Key efficacy results: Significant improvement in PFS, median OS not reached

The primary outcome of the DECISION trial was progression-free survival (PFS). The median PFS was significantly longer in the sorafenib arm (10.8 months) compared to the placebo arm (5.8 months) (HR 0.59 95%CI 0.45-0.76 p<0.0001).

Overall survival and objective response rate (ORR) were secondary outcomes in the DECISION trial. Median overall survival had not been reached at the time of the updated analysis and significant differences in overall survival between the two arms were not reported. pERC noted that the high rate of crossover (treatment switching) from the placebo arm to the sorafenib arm could confound the eventual overall survival results. Objective response rate was 12.2% vs. 0.5% in the sorafenib and placebo arms respectively (95% CI: 7.0% - 16.5%). This was statistically significant (p<0.0001) using central assessment.

Quality of life: Lower scores in sorafenib arm

Two quality of life scales were used in the DECISION trial (EuroQol-5 Dimensions (EQ-5D); Functional Assessment of Cancer Therapy General Version 4.0 (FACT-G)). The quality of life scores were lower in the sorafenib arm than in the placebo arm in both scales. The FACT-G scale reported a clinically meaningful decline in quality of life for patients in the sorafenib arm. The EQ-5D scale reported a statistically significant, but not a clinically meaningful decline in quality of life for patients in the sorafenib arm

compared to patients in the placebo arm. pERC discussed at length the decline in quality of life scores in the patients receiving sorafenib. pERC questioned why the quality of life data were not reported in the publication of the DECISION trial, however, they were appreciative that these data from the trial were available in the public domain.

Safety: Increased toxicity and high rates of serious adverse events

Twelve treatment-emergent deaths occurred in the sorafenib group compared to 6 deaths in the placebo group. More patients in the sorafenib arm experienced at least one grade 3 treatment-related adverse event (TEAE) compared to the patients in the placebo arm (52.7% vs. 23.4%, respectively). For patients receiving sorafenib, about 60% experienced grade 3/4 adverse events or adverse drug reactions. Grade 3 hand- foot syndrome was reported in 20.3% of patients receiving sorafenib, and in no patients receiving placebo. In addition, grade 3 hypertension was reported in 9.7% of patients receiving sorafenib compared to 2.4% of patients receiving placebo. Grade 3 hypocalcaemia also occurred in 5.8% of patients treated with sorafenib and in <1% of patients receiving placebo. Grade 3 diarrhea was also reported in 5.3% of patients treated with sorafenib compared to 1% of patients receiving placebo. pERC noted that severe diarrhea was also reported through the patient input received by pCODR on sorafenib. pERC discussed the adverse events associated with sorafenib, and also noted that patients with DTC receiving sorafenib appear to experience more toxicity than patients receiving sorafenib for other indications. Neither pERC nor the Clinical Guidance Panel (CGP) could definitively explain the reasons for this finding. The CGP hypothesized that it could be due to the longer duration of treatment in patients with DTC compared to other cancer indications, or the possibility of lower drug clearance in this disease setting. pERC discussed the fact that treatment with sorafenib for patients with DTC is a relatively new strategy and that with more experience with DTC and sorafenib there might be potential to manage the dosing and toxicity of sorafenib more effectively.

Limitations: High crossover and uncertainty in overall survival

At the primary analysis of PFS, 150 (71.8%) of 209 placebo patients who experienced progression, subsequently enrolled in an open-label study of sorafenib. pERC noted that the high proportion of crossover (early treatment switching) could obscure any overall survival difference. pERC reviewed two statistical methods which attempt to adjust for early treatment switching, however, pERC acknowledged that an attempt was made to address the crossover, however, the Committee was unable to confidently accept the results provided in the absence of national or international guidelines on the validity of methodologies for crossover adjustment.

Comparator information: No standard of care

pERC noted that there is no current standard of care in Canada for the treatment of DTC that is refractory to radioactive iodine. Treatments options include repeated surgery for recurrent disease, radiation therapy to manage symptoms related to bone and lung disease, and palliative care.

Need: New treatment options are required

pERC noted that there is a small number of patients with radioactive iodine refractory DTC, with about 200 deaths annually in Canada due to the disease. There are no currently reliable treatment options with demonstrated effectiveness for these patients.

PATIENT-BASED VALUES

Values of patients with differentiated thyroid cancer: Seeking more treatment options

Patients with radioactive iodine refractory, locally advanced or metastatic DTC have limited treatment options. Patients living with this type of thyroid cancer are aware that their advanced disease will progress with worsening symptoms until death, and they embrace opportunities to try new treatments. pERC acknowledged the clear unmet need expressed by patients.

Patient values on treatment: Prolonged survival with acceptable toxicity

Patients have an expectation that sorafenib will extend the survival of individuals with radioactive iodine-refractory, locally advanced or metastatic DTC. Two patients provided input on their experience with sorafenib and suggested that the drug slowed down the progression of the disease, and for extending their life. pERC acknowledged that these two patients indicated that they would be willing to tolerate the

adverse events. pERC discussed the experiences of these two patients in addition to the quality of life results from the DECISION trial.

ECONOMIC EVALUATION

Economic model submitted: cost-utility analysis
pERC noted that the submitter provided a partitioned survival analysis, and that the incremental cost-effectiveness estimates provided by the pCODR Economic Guidance Panel were higher than the manufacturer's estimates. pERC favoured the EGP's reanalysis and noted that the incremental cost effectiveness ratio (ICER) may be even higher than the EGP's estimate given the uncertainty regarding overall survival and that the model assumed that approximately 50% of the overall survival benefit occurred in the post-progression state which is not realistic from a clinical perspective. pERC concluded that even if there was a net clinical benefit of sorafenib in patients with DTC refractory to radioactive iodine, it would not be considered cost effective.

Basis of the economic model: clinical and economic inputs
In the submitted analysis, the time horizon was 10 years and treatment duration was based on observed data from the clinical trial. pERC noted that the EGP decreased the time horizon to 7 years and increased the treatment duration to 18 cycles. Both changes were based on feedback from the CGP given that this is a slow growing cancer and treatment may extend beyond progression. The EGP also examined the 95% confidence intervals around the intercept of the slope for overall survival to account for the uncertainty in the extrapolation methods.

Drug costs: Cost of treatment
Sorafenib costs $46.47 per 200 mg tablet. At the recommended dose of 800 mg daily, the daily cost of sorafenib is $186 daily or $5,208 per 28 days.

Clinical effect estimates: Crossover, intercept, time horizon
The factors that most influence clinical effects are the methods used to adjust for cross-over for overall survival, the intercept of the curve for overall survival and the time horizon. These tended to inflate the potential clinical benefit of sorafenib.

Cost-effectiveness estimates: Treatment duration, post-progression survival, dose intensity
The factors that most influence cost are the treatment duration, the extrapolation curve for progression-free survival, the drug acquisition costs, and the dose intensity (which is used to calculate the drug cost per cycle).

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Small patient population
pERC considered input from the pCODR Provincial Advisory Group (PAG) which concurred with the patient perspectives and that of the CGP that there is no current standard of care for the treatment of DTC that is refractory to radioactive iodine. There is an unmet need for the small number of patients with radioactive iodine refractory DTC. PAG felt there would be minimal wastage as dosage adjustments are managed by increasing the dosing interval for sorafenib rather than changing the dose. pERC noted that the incremental budget impact would be small due to the small number of patients who would be candidates for sorafenib.

DRUG AND CONDITION INFORMATION

Drug Information	• tyrosine kinase inhibitor that blocks the receptor tyrosine kinases VEGFR (Vascular Endothelial Growth Factor Receptor) and PDGFR (Platelet Derived Growth Factor Receptor) • 200 mg tablet • Recommended dosage of 400 mg (2 x 200mg tablets) administered orally taken twice a day
Cancer Treated	• Metastatic Progressive Differentiated Thyroid Carcinoma (DTC)
Burden of Illness	• Differentiated thyroid cancer is a malignancy affecting an estimated 4,500 Canadians annually. • Between 5% and 15% of patients with thyroid cancer will present with or develop disease which is refractory to radioiodide therapy. Median overall survival for these patients is between 2 ½ and 3 ½ years.
Current Standard Treatment	• No current standard of care for patients who are refractory to radioiodine • Palliative treatment with doxorubicin (Adriamycin) or best supportive care
Limitations of Current Therapy	• No effective systemic therapy options available for patients refractory to radioiodine at the present time in Canada

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. 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. Tallal Younis, Oncologist
Dr. Kelvin Chan, Oncologist

All members participated in deliberations and voting on the initial recommendation except:
- Drs. Paul Hoskins and Sunil Desai who were not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

All members participated in deliberations and voting on the final recommendation except:

- Drs Matthew Cheung, Allan Grill, Paul Hoskins and Kelvin Chan 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 sorafenib (Nexavar) for Differentiated Thyroid Cancer, through their declarations, two members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were 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.

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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