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
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Bevacizumab (Avastin) with capecitabine **Submitted Funding Request:** In combination with capecitabine, for the first-line treatment of advanced or metastatic colorectal cancer (CRC) for patients who are not suitable for oxaliplatin or irinotecan-based therapy	
Submitted By: Cancer Care Ontario Gastrointestinal Disease Site Group	**Manufactured By:** Hoffmann-La Roche Limited
NOC Date: N/A	**Submission Date:** February 18, 2015
Initial Recommendation: July 3, 2015	**Final Recommendation:** July 21, 2015

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding bevacizumab (Avastin) in combination with a fluoropyrimidine, for the first-line treatment of patients with advanced or metastatic colorectal cancer (CRC) for whom combination chemotherapy with oxaliplatin or irinotecan is unsuitable, conditional on cost-effectiveness being improved to an acceptable level.

Funding should be for patients with ECOG performance status 0-2. Treatment should continue until unacceptable toxicity or disease progression. pERC made this recommendation because the Committee considered that there may be a net clinical benefit with bevacizumab plus capecitabine based on an improvement in progression-free survival consistent with the addition of bevacizumab in standard combination chemotherapy. Compared to capecitabine alone, bevacizumab plus capecitabine had moderate but manageable toxicities and similar overall quality of life outcomes. pERC also noted that bevacizumab plus a fluoropyrimidine aligned with patient values as there is a need for more effective treatment options for patients who cannot tolerate oxaliplatin or irinotecan-based combination chemotherapy or for whom combination chemotherapy is not suitable. Additionally, the patient population to whom this recommendation applies is small. pERC also noted that bevacizumab in combination with intravenously administered 5-fluorouracil plus leucovorin had similar efficacy and safety to bevacizumab plus capecitabine.

However, the Committee noted that bevacizumab plus capecitabine at the submitted confidential price, could not be considered cost-effective based on the Submitter's and Economic Guidance Panel's estimates of the range of incremental cost-effectiveness ratios when compared with capecitabine alone in this population.

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POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given pERC considered that there may be a net clinical benefit of bevacizumab plus a fluoropyrimidine, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of bevacizumab plus a fluoropyrimidine to an acceptable level.

Time-Limited Need for Bevacizumab Plus a Fluoropyrimidine
At the time of implementing a funding recommendation for bevacizumab plus a fluoropyrimidine, jurisdictions may consider addressing the short-term, time-limited need for bevacizumab for patients who are currently receiving first-line treatment with fluoropyrimidine monotherapy. pERC noted that this time-limited access would be for patients who otherwise meet the eligibility criteria of the MAX trial.

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SUMMARY OF pERC DELIBERATIONS

Advanced or metastatic colorectal cancer (CRC) is the second most commonly diagnosed malignancy in Canada. pERC noted that advanced or metastatic CRC is generally considered incurable and survival beyond two years is uncommon. Bevacizumab, an anti-angiogenic agent, with oxaliplatin or irinotecan-based combination chemotherapy (bevacizumab plus FOLFIRI or FOLFOX), is standard first-line therapy in the management of advanced or metastatic CRC. However, there is a small subgroup of patients, predominantly elderly patients with co-morbidities, with advanced or metastatic CRC who are not candidates for first-line treatment with oxaliplatin or irinotecan-based combination chemotherapy. These patients are currently treated with fluoropyrimidine monotherapy (e.g. capecitabine, 5-fluorouracil plus leucovorin). Based on feedback from the patient advocacy group, pERC emphasized these patients are not candidates for bevacizumab plus FOLFIRI or FOLFOX as they have been deemed unsuitable for these combination therapies and fluoropyrimidine monotherapy is the appropriate alternative option. As there are limited treatment options available for patients who cannot receive currently available combination chemotherapy in the first-line setting, pERC acknowledged the need for more effective and more tolerable treatments in this setting.

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 two open-label randomized controlled trials (AVEX and MAX) which compared bevacizumab plus capecitabine with capecitabine alone in patients with previously untreated, advanced or metastatic CRC. Patients enrolled in these trials were those whom oxaliplatin or irinotecan-based combination chemotherapy is not suitable. In addition, patients in these trials were required to have an ECOG performance status of 0-2, adequate bone marrow, renal, and hepatic function, which means they were a relatively fit population. pERC noted both the AVEX and MAX trials excluded patients with a number of contraindications to capecitabine, as well as different contraindications to bevacizumab (e.g. uncontrolled clinically significant cardiac disease), limiting the number of patients for whom bevacizumab plus capecitabine would be an option.

pERC considered that the magnitude of benefit in median progression-free survival for bevacizumab plus capecitabine compared with capecitabine alone (4.0 and 2.8 months in the AVEX and MAX trials, respectively) was statistically significant and consistent with the addition of bevacizumab to other combination chemotherapies in the first-line setting (e.g. bevacizumab plus FOLFOX or FOLFIRI). pERC noted that the review and adoption of bevacizumab with combination chemotherapy in the first-line setting occurred before pCODR came into existence. As bevacizumab with combination chemotherapy is uniformly funded across Canada, pERC considered that it would be reasonable to afford patients who are unable to tolerate irinotecan or oxaliplatin-based combination chemotherapy with bevacizumab plus a fluoropyrimidine. pERC noted that, unlike intravenously administered therapies, public coverage of oral therapies like capecitabine varies across provinces and this may lead to patients not having affordable access to capecitabine. pERC agreed with the Clinical Guidance Panel (CGP) that bevacizumab in combination with intravenously administered 5-fluorouracil plus leucovorin had similar efficacy and safety to bevacizumab plus capecitabine, which would allow all patients access to a fluoropyrimidine-based regimen.

pERC noted that quality of life (QoL) outcomes were not collected in the AVEX study. There was limited reporting of QoL in the MAX study. In the MAX study there were no significant differences for bevacizumab plus capecitabine compared to capecitabine alone in overall QoL.

pERC discussed the toxicity profile of bevacizumab plus capecitabine, noting an increase in adverse events (AEs), particularly for hand-foot skin reaction, fatigue, diarrhea, and hypertension as compared to capecitabine alone. pERC acknowledged these were expected and manageable toxicities that are well-known to be associated with bevacizumab and capecitabine. pERC discussed the significant AEs associated with bevacizumab which include proteinuria, thromboembolic events (venous and arterial), and gastrointestinal perforation. pERC noted the reported incidences of these AEs, particularly grade ≥3, were low in the AVEX and MAX trials and that there is now more than 10 years of clinical experience managing

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these AEs. After deliberating on all of these factors, pERC concluded that there may be a net clinical benefit of bevacizumab plus a fluoropyrimidine in those patients for whom oxaliplatin or irinotecan-based combination chemotherapy is not suitable.

pERC deliberated upon input from one patient advocacy group, which indicated that patients valued access to therapies that prolong survival, provide a therapeutic option that may otherwise not exist, and improve quality of life. pERC noted the unmet clinical need for the treatment of elderly patients with advanced or metastatic CRC, especially those with comorbidities. For these patients oxaliplatin or irinotecan-based combination chemotherapy is not suitable, given patients' co-morbidities and potential for serious toxicities with standard combination chemotherapy. pERC acknowledged patients valued access to therapies that provided a more tolerable, yet effective option for patients who are not eligible for the current standard of combination chemotherapy. Patients who had direct experience with bevacizumab plus capecitabine reported that their quality of life was maintained and that bevacizumab plus capecitabine had acceptable toxicities. Therefore, pERC considered that bevacizumab plus a fluoropyrimidine could be a first-line treatment option that would provide a greater clinical benefit than treatment with capecitabine alone. Overall, pERC concluded that bevacizumab plus a fluoropyrimidine aligned with patient values.

pERC also deliberated upon the cost-effectiveness of bevacizumab plus capecitabine. pERC reviewed the incremental cost-effectiveness estimates provided by both the submitter and the pCODR Economic Guidance Panel (EGP) and noted that bevacizumab plus capecitabine was not cost-effective compared with capecitabine alone in either analysis. pERC noted the EGP's estimates of the incremental cost of bevacizumab plus capecitabine were similar to those provided by the submitter. The key drivers in cost-effectiveness were the cost of bevacizumab and the method for overall survival extrapolation. pERC also appreciated that the submitter provided an economic evaluation that included both Markov and Partitioned Survival Curves model structures. This provided pERC with a deeper understanding on how the economic model structure could impact the cost-effectiveness estimates of bevacizumab plus capecitabine.

pERC discussed factors that could impact the feasibility of implementing a funding recommendation for bevacizumab plus a fluoropyrimidine. As bevacizumab is used in other treatment regimens for advanced or metastatic CRC (irinotecan or oxaliplatin-based combination chemotherapy), there is familiarity with bevacizumab and its associated adverse events. pERC agreed with the Provincial Advisory Group that the subgroup of patients for whom irinotecan or oxaliplatin is unsuitable is small and this small group may benefit from the addition of bevacizumab to capecitabine. Lastly, pERC noted that the use of bevacizumab beyond disease progression or across multiple lines of therapy was not within the scope of the current review, and would require a separate pCODR submission for further consideration.

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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 groups (Colorectal Cancer Association of Canada)
- 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 (Colorectal Cancer Association of Canada)
- the Submitter (Cancer Care Ontario Gastrointestinal Disease Site Group)

The pERC initial recommendation was to fund bevacizumab (Avastin) in combination with a fluoropyrimidine, for the first-line treatment of patients with advanced or metastatic colorectal cancer (CRC) for whom combination chemotherapy with oxaliplatin or irinotecan is unsuitable, conditional on cost-effectiveness being improved to an acceptable level

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

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the safety and efficacy of bevacizumab (Avastin) in combination with capecitabine compared to standard care options, for the first-line treatment of advanced or metastatic CRC for patients who are not suitable for oxaliplatin or irinotecan-based combination chemotherapy.

The pCODR review also provided contextual information on the efficacy and safety of bevacizumab in combination with 5-fluorouracil plus leucovorin for advanced or metastatic CRC. pERC agreed with the CGP that the use of bevacizumab in combination with 5-fluorouracil plus leucovorin yielded similar efficacy and safety results to bevacizumab plus capecitabine.

Studies included: Two high quality RCTs

The pCODR systematic review included two high-quality open-label randomized controlled trials (AVEX and MAX studies) which evaluated the efficacy and safety of bevacizumab (BEV) plus capecitabine (CAP) compared to CAP alone. Bevacizumab was administered at a dose of 7.5 mg/kg on day 1 of a 3 week schedule. Capecitabine was administered orally at a dose of 1,000 mg/m^2 or 1250 mg/m^2 (AVEX and MAX study dosing, respectively), twice daily on days 1-14 of a 3 week schedule. pERC noted that although the trial protocol reported a starting dose of 1,250 mg/m^2 for capecitabine in the MAX study, two-thirds of patients were actually dosed at 1,000 mg/m^2 of capecitabine twice daily in the BEV + CAP and CAP groups. In both the AVEX and MAX studies, the study population included patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-2.

pERC noted that the pCODR review also provided contextual information on the validity of progression-free survival as a surrogate outcome for overall survival for advanced or metastatic CRC. However, pERC could not conclude that progression-free survival is an unequivocally validated surrogate outcome for overall survival in advanced or metastatic CRC.

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Patient populations: Elderly patients, ECOG performance status mostly ≤1

Patient characteristics appeared to be balanced between the two groups in the AVEX and MAX studies. Patients had a median age of 76 and 68 years in the AVEX and MAX studies, respectively. The AVEX and MAX studies excluded patients with a history of adverse events or medical conditions that are known to be contraindications for bevacizumab as well as other serious co-morbidities. Additionally, pERC noted the majority of patients in the AVEX and MAX studies had an ECOG PS of 0 or 1 (≥91%). All of these factors may limit the applicability of the studies' results to less fit patients.

Key efficacy results: Consistent improvements in progression-free survival

Key efficacy outcomes deliberated on by pERC included progression-free survival (PFS), the primary endpoint of the AVEX and MAX studies, and overall survival (OS).

In the AVEX study, the median PFS was 9.1 and 5.1 months in the BEV + CAP and CAP groups, respectively (HR=0.53; 95%CI:0.41-0.69). pERC noted the PFS results in the AVEX study were consistent with what was also observed in the MAX study. In the MAX study, the median PFS was 8.5 and 5.7 months in the BEV + CAP and CAP groups, respectively (HR=0.53; 95%CI:0.41-0.69). pERC noted the magnitude of PFS improvement (4.0 and 2.8 months in the AVEX and MAX trials, respectively) was statistically significant and consistent with the addition of bevacizumab in other combination chemotherapy. In both the AVEX and MAX studies, there was no significant difference in OS in the BEV + CAP compared to CAP groups.

Quality of life: No significant difference in overall quality of life

Quality of life (QoL) outcomes were not collected in the AVEX study but were collected in the MAX study. Three QoL scales were used in the MAX study (Euroqol-5D, Utility Based Quality of Life Questionnaire-Cancer, and the Chemotherapy Acceptance Questionnaire). There was limited reporting of the QoL results in the MAX study. Patients in the BEV + CAP group compared to the CAP group had no significant differences in overall QoL.

Safety: Low rates of significant adverse events in both groups

pERC deliberated on the safety data available from the AVEX and MAX studies.

Treatments were generally well tolerated in both studies with similar treatment-related adverse events (TRAEs) of any grade across treatment groups. The most common TRAEs in patients treated with BEV + CAP in both the AVEX and MAX studies were hand-foot skin reaction, fatigue, diarrhea, and hypertension. The incidence of grade ≥3 proteinuria was 1.5% and 3.2% of patients in the BEV + CAP groups in the AVEX and MAX studies, respectively. In the CAP groups, grade ≥3 proteinuria did not occur in the AVEX study and occurred in 0.6% of patients in the MAX study. The incidence of grade ≥3 thromboembolic events (venous and arterial) was 11.9% and 12.1% of patients in the BEV + CAP groups in the AVEX and MAX studies, respectively. The incidence of grade ≥3 thromboembolic events was 5.1% and 7.1% of patients in the CAP groups in the AVEX and MAX studies, respectively. Finally, the rate of gastrointestinal perforation events was low: 1.0% and 1.9% of patients in the BEV + CAP groups in the AVEX and MAX studies, respectively. For the CAP groups, the AVEX study did not report a gastrointestinal perforation event while it was reported in 0.6% of patients in the MAX study.

Comparator information: Fluoropyrimidine monotherapy

The current standard of care in the first-line treatment of advanced or metastatic CRC is bevacizumab with oxaliplatin or irinotecan-based combination chemotherapy. For patients who cannot receive oxaliplatin or irinotecan, capecitabine monotherapy is commonly used and the comparator in the AVEX and MAX studies was therefore, considered appropriate.

Need: Additional treatment options for patients unable to take combination chemotherapy

Bevacizumab combined with oxaliplatin and irinotecan-based combination chemotherapies (e.g. bevacizumab plus FOLFOX/FOLFIRI) are standard first-line therapies in the management of advanced or metastatic CRC. A small proportion of patients are unable to receive oxaliplatin or irinotecan-based combination chemotherapy and would be treated with single-agent fluoropyrimidine. Therefore, there is a need for more effective therapies in this patient population.

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PATIENT-BASED VALUES

Values of patients with metastatic colorectal cancer: Need for additional treatments
pERC deliberated upon patient advocacy group input for bevacizumab in combination with capecitabine for advanced or metastatic CRC and discussed the values of patients with advanced or metastatic CRC. The most frequently reported treatment-related adverse events with current therapies, and the most difficult to control, are pain, neuropathy, diarrhea, vomiting and nausea; all of which significantly impact a patient's quality of life. pERC acknowledged that patients indicated there is a need for additional therapeutic options, particularly for the elderly patient population who are not eligible for combination chemotherapy. Patients reported a need for therapies that will increase progression-free survival and extend disease control with acceptable side effects.

pERC also acknowledged that there is considerable caregiver burden with this disease, with the most significant negative impacts being managing adverse events, providing emotional support, assuming additional unpaid work duties in the home, and the associated financial challenges.

Patient values on treatment: Disease control with acceptable toxicities
pERC noted that a small number of patients who provided input had experience with bevacizumab plus capecitabine in first-line. These patients reported adverse events with bevacizumab plus capecitabine, including tiredness, neuropathy, pain, dry skin, and nose bleeds. Patients noted their overall experience with bevacizumab with capecitabine was better than other therapies. Bevacizumab with capecitabine was able to shrink/control their colorectal cancer with overall acceptable side effects.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis
The Economic Guidance Panel assessed a cost-utility analysis comparing BEV + CAP to CAP alone for first-line treatment of advanced or metastatic CRC in patients who are not suitable for oxaliplatin or irinotecan-based combination chemotherapy. The comparison was based on the results of the AVEX study. The submitted model was a Markov model with the addition of a Partitioned survival curves model.

Basis of the economic model: Clinical and economic inputs
Costs considered in the model provided by the submitter included the cost of treatment, administration, and wastage, and the costs associated with adverse events.

The key clinical outcomes considered in the model provided by the submitter were overall survival, progression-free survival, and utilities. pERC noted that most of the appropriate factors were included in the model. However, the EGP noted that the economic model submitted was based on the AVEX study and did not include the MAX study, which may limit the applicability to a younger aged population. Furthermore, the model did not consider dose adjustments or bevacizumab with 5-fluorouracil plus leucovorin, which represent sources of uncertainty.

Drug costs: Cost of treatment
At the list price, bevacizumab costs $600.00 per 100mg vial and $2,400 per 400mg vial. At the recommended dose of 7.5 mg/kg on day 1 of every 3 weeks and assuming a 70kg weight, bevacizumab would cost $150.00 per day and $4,200.00 per 28-day course. At the submitted confidential price bevacizumab would cost $[redacted] per 100mg vial and $[redacted] per 400mg vial. (*The cost of bevacizumab is based on a confidential price submitted by the manufacturer and cannot be disclosed to the public according to the pCODR Disclosure of Information Guidelines*.)

Capecitabine costs $1.525 per 500mg tablet. Based on a 1.75m^2 average body surface and at the recommended dose of 1000 mg/m^2 twice daily on days 1-14 of every 3 weeks, capecitabine cost $6.97 per day and $195.20 per 28-day course.

Cost-effectiveness estimates: Not cost-effective at submitted price
The EGP's reanalyses estimated the extra clinical effect of BEV + CAP to be between 0.171 and 0.254 quality adjusted life-years. The factor found to have the greatest influence on the incremental cost was

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the cost of bevacizumab. The factors found to have the greatest influence on the incremental effectiveness were model type (Markov or Partitioned Survival) and survival effect of BEV + CAP.

pERC reviewed the incremental cost-effectiveness estimates provided by both the submitter and the EGP and determined that BEV + CAP was not cost-effective compared with CAP alone in either analysis. pERC noted that the incremental cost-effectiveness estimates provided by the EGP were similar to the submitter's estimates. pERC agreed with the EGP's assessment that the submitter's extrapolation of the data beyond the follow-up period in the clinical trial overestimated the overall survival benefit in favour of the BEV + CAP group. In conclusion pERC determined BEV + CAP is not cost-effective at the submitted price when compared with CAP alone.

ADOPTION FEASIBILITY

Considerations for implementation: Small population and high drug cost
pERC discussed the feasibility of implementing a funding recommendation for bevacizumab plus a fluoropyrimidine and noted the high cost of bevacizumab is a key challenge. The Provincial Advisory Group indicated that there is a familiarity with bevacizumab given its use in the first-line setting for advanced or metastatic CRC with oxaliplatin or irinotecan-based combination chemotherapy. pERC noted that the incremental budget impact for this specific recommendation is limited due to the small number of patients for whom combination chemotherapy with oxaliplatin or irinotecan is unsuitable.

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DRUG AND CONDITION INFORMATION

Drug Information	• Bevacizumab is a monoclonal antibody that targets VEGR receptors • Bevacizumab is available as 100mg and 400mg vials (25mg/mL) • The recommended dosage of bevacizumab is 7.5 mg/kg of body weight administered every 3 weeks • Capecitabine is a tumour-activated antineoplastic agent belonging to the novel fluoropyrimidine carbamate class • Capecitabine is available as 150mg and 500mg tablets • The recommended dosage of capecitabine is 1,000 mg/m^2 twice daily on days 1-14 every 3 weeks
Cancer Treated	• Advanced or metastatic colorectal cancer
Burden of Illness	• In 2014, 24,400 Canadians were diagnosed with colorectal cancer with 9,300 estimated to have died from advanced or metastatic CRC • Second and third most common causes of cancer death in Canadian males and females, respectively
Current Standard Treatment	• Fluoropyrimidine monotherapy (e.g. capecitabine, 5-fluorouracil plus leucovorin)
Limitations of Current Therapy	• Median survivals for patients with metastatic colorectal cancer are now in the 20-28 month range with current best practices • Long-term survival remains rare and cures are still not anticipated in patients with unresectable, recurrent or metastatic colorectal cancer

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

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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:

- Dr. Sunil Desai who was not present for the meeting
- Dr. Anthony Fields who was excluded from chairing and voting due to a conflict of interest
- Drs. Scott Berry, Bill Evans and Kelvin Chan who were excluded from voting due to a conflict of interest
- Jo Nanson who was the designated non-voting Patient Alternative for this meeting

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

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 bevacizumab (Avastin) with capecitabine for metastatic colorectal cancer, through their declarations, seven members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, four 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*. Hoffmann-La Roche Limited, as the primary data owner, did not agree to the disclosure of economic information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

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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