

pCODR EXPERT REVIEW COMMITTEE (pERC) INITIAL RECOMMENDATION

The CADTH 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 reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation

Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Lenvatinib (Lenvima)

Submitted Funding Request:
For the treatment of patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory differentiated thyroid cancer

Submitted by:
Eisai Limited

Manufactured by:
Eisai Limited

NOC Date:
December 22, 2015

Submission Date:
April 18, 2016

Initial Recommendation Issued:
September 1, 2016

pERC RECOMMENDATION

pERC recommends reimbursement of lenvatinib (Lenvima) for the treatment of patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory differentiated thyroid cancer (DTC) conditional on the cost-effectiveness being improved to an acceptable level. Treatment should be for patients with a good performance status and who otherwise meet the eligibility criteria of the SELECT trial, and should continue until disease progression or unacceptable toxicity.

pERC made this recommendation because it was satisfied that compared with placebo, lenvatinib demonstrated an overall clinical benefit based on a clinically meaningful and statistically significant improvement in progression-free survival and manageable toxicities. The Committee also considered that there may be an overall survival benefit with lenvatinib compared with placebo. pERC further noted a clear unmet need for patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory DTC.

pERC also acknowledged that the use of lenvatinib aligned with patient values as it provides a treatment option to patients with an unmet need, has a manageable side effect profile, is administered as an oral therapy, and provides delay in disease progression.

However, pERC considered that, at the submitted price, lenvatinib could not be considered cost-effective compared with best supportive care.

**POTENTIAL NEXT STEPS FOR
STAKEHOLDERS**

Pricing Arrangements to Improve Cost-effectiveness

Given that pERC was satisfied that there is a net clinical benefit of lenvatinib for patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory DTC, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of lenvatinib to an acceptable level.

Evidence Collection to Determine Impact on Quality of Life and Ideal Dosage

pERC discussed the lack of quality-of-life data for lenvatinib compared with placebo in this patient population and noted that jurisdictions may want to consider evidence collection in order to better define the quality of life of patients who receive lenvatinib compared with placebo.

Given the significant number of dose reductions and dose interruptions in the primary trial, pERC noted that evidence collection may help to define the impact that lenvatinib has on quality of life of patients in order to define the optimal dose.

Risk of Significant Toxicities

pERC noted that there are risks of significant toxicities with lenvatinib compared with placebo. Therefore, the Committee noted that oncologists experienced with the administration of tyrosine kinase inhibitors (TKIs) should prescribe lenvatinib and monitor patients.

Factors Affecting Budget Impact and Adoption Feasibility

pERC noted the potential for significant wastage with lenvatinib. This is due to both the high frequency of dose reductions and interruptions in the SELECT trial and the current packaging of lenvatinib in pre-packaged blister packs that are provided in a one-month supply.

While the number of patients with DTC is small, the Committee noted that the submitted budget impact of lenvatinib may be underestimated. This is due to both an underestimation of the uptake of lenvatinib by the eligible population and an underestimation of the size of the prevalent population of patients who are currently not receiving treatment and who would be eligible to receive lenvatinib.

SUMMARY OF pERC DELIBERATIONS

DTC is a malignancy affecting approximately 6,300 Canadians annually. Between 5% and 15% of patients with thyroid cancer will present with or develop disease that is refractory to radioiodine therapy. Disease that becomes refractory to radioiodine therapy has a poor prognosis, and currently there are no effective systemic therapy options available for these patients. Each year, there are approximately 185 deaths from metastatic thyroid cancer in Canada. pERC agreed that there is a need for additional effective treatment options that improve survival and quality of life for these patients.

pERC deliberated upon one randomized controlled trial (SELECT) that compared lenvatinib to placebo in patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory DTC. The Committee noted that there was a significant improvement in the primary outcome of progression-free survival (PFS) in the lenvatinib group compared with the placebo group. pERC noted that the absolute magnitude of benefit in median PFS (14.7-month difference) and hazard ratio of 0.21 were impressive and meaningful in this patient population. The Committee also discussed the overall survival (OS) results of the trial. pERC noted that, while there was no difference in OS between the two treatment groups, the high proportion of patients in the placebo arm who crossed over to receive lenvatinib upon disease progression – more than 83% of patients – potentially confounded the OS results. The Committee noted that the updated OS results were adjusted for crossover and discussed the value and limitations of the adjustment approach. While there remains uncertainty in the magnitude of the OS benefit of lenvatinib compared with placebo, pERC noted that there is likely an OS benefit in favour of lenvatinib.

In addition to the discussion of the survival outcomes, the Committee expressed concerns regarding the lack of quality-of-life data in the SELECT study. pERC acknowledged that an observational quality of life study (n=38) was conducted in patients with radioactive-iodine-refractory DTC who received lenvatinib. Outcome measurements included Functional Assessment of Cancer Therapy-General (FACT-G), and EuroQol five dimensions with five levels scale (EQ-5D-5L) scores. However, pERC was unable to comment on the comparative impact of lenvatinib versus placebo on quality of life for patients with DTC. Maintaining or improving quality of life toward the end of life for patients with DTC was an important consideration for the Committee.

pERC also discussed the toxicity associated with lenvatinib and noted that a substantially higher proportion of patients in the lenvatinib group experienced at least one grade 3 treatment-related adverse event compared with the patients in the placebo group, including, but not limited to, hypertension, proteinuria, and diarrhea. However, the Committee noted that a substantial proportion of the grade 3 treatment-related adverse events were hypertension events, and that grade 3 hypertension is manageable and is generally asymptomatic. The Committee also noted that the majority of patients had an adverse event leading to a dose modification or interruption. However, the Committee discussed the fact that familiarity with TKIs such as sorafenib might allow for the dosing and toxicity of lenvatinib to be managed more effectively.

Overall, pERC concluded that there is an overall clinical benefit because of the clinically meaningful and statistically significant improvement in PFS and, despite uncertainty in the magnitude of OS benefit, a likely OS benefit, supported by the adjustment for crossover, in favour of lenvatinib compared with placebo. While the quality-of-life data are limited, pERC noted that there are substantial risks of adverse events associated with lenvatinib, but concluded that those adverse events are manageable. pERC noted that there is an unmet need for effective treatment for patients with refractory DTC.

pERC discussed the eligibility criteria of the SELECT trial and noted that careful selection of patients is required in order to balance the potential benefits of treatment with lenvatinib against the potential risks. Therefore, pERC agreed that the reimbursement criteria should match the eligibility criteria of the SELECT trial.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC considered input from one patient advocacy group indicating that patients value treatment options that delay progression of disease and control symptoms. pERC discussed the input from 12 patients and caregivers with experience with lenvatinib. pERC acknowledged that patients reported positive effects of delayed progression of disease, improved disease symptoms, and reduced side effects with lenvatinib. pERC noted that negative effects included symptoms of fatigue, weight loss, decreased appetite, and high blood pressure. The Committee also recognized that the oral route of administration of lenvatinib was valued by patients. Overall, pERC agreed that lenvatinib aligned with patient values, as it provides a treatment option to patients with an unmet need, has a manageable side effect profile, is administered as an oral therapy, and provides delay in disease progression.

pERC deliberated upon the cost-effectiveness of lenvatinib compared with best supportive care in patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory DTC. pERC noted that the range of the incremental cost-effectiveness ratio estimates provided by the pCODR Economic Guidance Panel (EGP) for lenvatinib compared with best supportive care were higher than the manufacturer's estimate. The Committee discussed wastage and that it could have a significant impact on the incremental cost-effectiveness of lenvatinib, based on the dose modifications and interruptions reported in the SELECT trial and the availability and pricing structure of lenvatinib in pre-packaged blister packs. pERC acknowledged that the time horizon used in the submitter's base case (10 years) may be too long and agreed with the EGP and Clinical Guidance Panel (CGP) that a seven-year time horizon is more appropriate in this disease setting. Finally, the Committee discussed the OS of lenvatinib compared with best supportive care, noting that it was a major driver of the incremental cost-effectiveness and that the uncertainty in the magnitude of the OS benefit results in a substantial amount of uncertainty in the incremental cost-effectiveness ratio estimates. The Committee noted that the EGP tried to capture this uncertainty by using the upper and lower 95% confidence interval (CI) of the crossover-adjusted estimates for OS. However, pERC noted that the true OS benefit of lenvatinib may lie between the OS estimates from the unadjusted analysis and the adjusted analysis. The Committee acknowledged that the uncertainty in the magnitude of the OS benefit introduced a large amount of uncertainty into the cost-effectiveness estimate and concluded that the true estimate of the incremental cost-effectiveness ratio is likely at, or higher than, the upper estimate of the range provided by the EGP. pERC, therefore, concluded that lenvatinib is not cost-effective compared with best supportive care in this disease setting. The Committee noted that the submitter also provided a cost-effectiveness analysis comparing lenvatinib with sorafenib; however, as sorafenib is not reimbursed in any province, pERC did not consider that comparison further.

pERC considered the feasibility of implementing a reimbursement recommendation for lenvatinib. pERC acknowledged that there is no standard of care for locally advanced or metastatic DTC refractory to radioactive-iodine and that lenvatinib would provide a new treatment option for this group of patients. pERC felt that there was the potential for significant wastage with lenvatinib, given the high prevalence of dose modifications and interruptions in the SELECT trial. The Committee also noted the clinically meaningful benefit in PFS in favour of lenvatinib that was reported in the SELECT trial, even with the reported dose reductions and interruptions of lenvatinib. However, given the significant number of dose reductions and interruptions, pERC noted that evidence collection is needed to better define the impact that lenvatinib has on the quality of life of patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory DTC in order to define the optimal dose. Furthermore, pERC noted that, due to the risks of significant toxicities with lenvatinib, oncologists with experience in the administration of TKIs should prescribe lenvatinib and monitor patients for toxicities. The Committee also discussed the limited quality-of-life data for patients who received lenvatinib and noted that jurisdictions may want to consider evidence collection in order to better define the quality of life of patients who receive lenvatinib compared with placebo. pERC noted that, although the budget impact with lenvatinib would be small due to the small number of patients with DTC, uptake would be high, as lenvatinib is an oral drug and there may be a significant prevalent population of patients who are currently not receiving treatment and who would be eligible to receive lenvatinib. In addition, the submitted budget impact analysis was from an Ontario perspective, which would only include coverage for patients aged 65 and older. Therefore, the submitted budget impact analysis may underestimate the potential budget impact of lenvatinib.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon a pCODR systematic review; other literature in the Clinical Guidance Report that provided 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); input pCODR's Provincial Advisory Group (PAG); and input from three registered individuals or groups of clinicians.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the safety and efficacy of lenvatinib (Lenvima) as compared with an appropriate comparator for the treatment of patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory differentiated thyroid cancer (DTC).

Studies included: One randomized controlled trial with 83% crossover

The pCODR systematic review included one randomized controlled trial (RCT), the SELECT trial, which compared lenvatinib plus best supportive care (n = 261) to placebo plus best supportive care (n = 131) in patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory DTC. Lenvatinib was administered orally at a dose of 24 mg (two 10 mg and one 4 mg capsules) once daily. pERC noted that 83% of patients crossed over from the placebo group to receive lenvatinib upon disease progression.

Patient populations: Majority of patients with Eastern Cooperative Oncology Group Performance Status 0 to 1

Patient characteristics appeared to be balanced between the two groups in the SELECT trial. The majority of patients (≥ 95%) had an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1. Most patients were TKI treatment naive, with 74.7% of patients in the lenvatinib group and 79.4% of patients in the placebo group having never received a TKI. More than 20% of patients in both groups had received one prior TKI treatment. Of note, 19.5% of patients in the lenvatinib group and 16.0% of patients in the placebo group were previously treated with sorafenib.

Key inclusion criteria of the SELECT trial were that patients had no prior therapy with TKI or had received one prior regimen of TKI, radiologic evidence of progression within the previous 13 months, and evidence of iodine-131-refractory disease meeting the following criteria using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1:

- At least one lesion of ≥ 1.0 cm in the longest diameter for a non-lymph node or ≥ 1.5 cm in the short-axis diameter for a lymph node
- Lesions showing evidence of progression within 12 months after iodine-131 therapy despite iodine-131 avidity at the time of treatment, or cumulative activity of iodine-131 that was > 600 mCi.

pERC noted that, while sorafenib is not reimbursed in Canada, the pCODR Clinical Guidance Report provided contextual information on sorafenib in patients with radioiodine-refractory DTC and that the CGP indicated there were differences in the eligibility criteria between the DECISION trial (sorafenib versus placebo) and the SELECT trial (lenvatinib versus placebo). In particular:

- In the SELECT trial, RECIST-defined progression was required within 13 months versus 14 months in DECISION
- In the SELECT trial, all iodine-avid patients were also required to have RECIST-confirmed progression within 12 months of radioiodine treatment versus 16 months in the DECISION trial
- In the SELECT trial, patients with one prior treatment with a TKI were included, whereas in the DECISION trial, patients who received a prior treatment with a TKI were excluded.

pERC agreed with the CGP's conclusion that these differences in eligibility criteria resulted in more patients with more aggressive cancers being included in the SELECT trial than in the DECISION trial, as evidenced by the shorter median progression-free survival (PFS) in the placebo arm of the SELECT trial (3.9 months) compared with the placebo arm of the DECISION trial (5.8 months). In discussion, pERC noted that careful selection of patients for treatment with lenvatinib is important and that the reimbursement criteria for lenvatinib should match the eligibility criteria of the SELECT trial.

Key efficacy results: Significant improvement in progression-free survival, uncertainty in magnitude of overall survival benefit in favour of lenvatinib

The primary outcome of the SELECT trial was PFS. Lenvatinib demonstrated a statistically significant improvement in PFS compared with placebo (hazard ratio [HR], 0.21; 99% CI, 0.14 to 0.31; $P < 0.001$). The median PFS was 18.3 months for the patients in the lenvatinib group, compared with 3.6 months in the placebo group. pERC noted that the absolute magnitude of benefit in median PFS (14.7-month difference) and HR were impressive and meaningful in this patient population.

Overall survival (OS) and objective response rate (ORR) were secondary outcomes in the SELECT trial. At the time of primary analysis, the median OS was not reached in either group. At an updated analysis, the median follow-up period was 23.6 months in the lenvatinib group and the median OS had not been reached, while in the placebo group, the median follow-up period was 24.1 months and the median OS was 19.1 months. The HR of death was 0.80 (95% CI, 0.57 to 1.12; $P = 0.1993$); however, the Committee noted that the trial was not powered to detect differences in OS. pERC also noted that 83.2% of patients in the placebo group crossed over to lenvatinib, which likely confounded the OS results. pERC acknowledged the results of an updated analysis of OS that was adjusted for the crossover of patients from the placebo group to receive lenvatinib. In this adjusted analysis, the HR of death for lenvatinib compared with placebo was 0.53 (95% CI, 0.34 to 0.82; $P = 0.0051$). The Committee discussed the value and the limitations of this adjustment approach, as outlined by the Methods Team. Overall pERC concluded that there is likely an OS benefit of lenvatinib compared with placebo; however, there is uncertainty in the magnitude of benefit and that the true OS benefit likely lies between the unadjusted and adjusted analysis estimates. pERC also noted that the ORR was 64.8% versus 1.5% in the lenvatinib and placebo groups, respectively (95% CI, 12.46 to 66.86). This was statistically significant ($P < 0.001$) using central assessment. pERC considered the improvement in PFS to be substantial and clinically meaningful in this patient setting and that there may be a benefit in OS in favour of lenvatinib, but that the magnitude of that benefit is uncertain.

Quality of life: Not measured in SELECT trial

Quality of life was not measured in the SELECT trial. pERC acknowledged an observational quality of life study of 38 patients with radioactive-iodine-refractory DTC treated with lenvatinib which suggested that patients with the health utility were those with improving disease status; however, the available data were limited. pERC was unable to comment on the comparative impact of lenvatinib versus placebo on quality of life.

Safety: Increased toxicity and rates of serious adverse events

Six deaths due to treatment-related adverse events (TRAEs) occurred in the lenvatinib group compared with none in the placebo group. More patients in the lenvatinib group compared with the placebo group withdrew from treatment due to an adverse event (AE) (14.2% versus 2.3%, respectively). Treatment-related serious adverse events occurred in 30.3% of patients treated with lenvatinib compared with 6.1% of patients treated with placebo. More patients in the lenvatinib group experienced at least one grade 3 or higher treatment-emergent adverse event (TEAE) compared with the patients in the placebo group (75.9% versus 9.9%, respectively). The most common grade 3 or higher TRAEs (lenvatinib versus placebo) were hypertension (41.8% versus 2.3%), proteinuria (10.0% versus 0%), and diarrhea (8.0% versus 0%). pERC discussed how the high frequency of dose modifications observed in the trial may have been a result of attempts to manage AEs. pERC noted that a clinician's familiarity with tyrosine kinase inhibitors (TKIs) such as sorafenib might allow for the dosing and toxicity of lenvatinib to be managed more effectively. The Committee also noted the high frequency of adverse events leading to dose interruptions (83.1% versus 18.3%) and dose reductions (68.2% versus 4.6%) in the lenvatinib group compared with the placebo group. Furthermore, in the lenvatinib group, the median duration of treatment (13.8 months) was shorter than the median progression-free survival (18.7 months), which might indicate that lenvatinib requires frequent monitoring and follow-up by both clinicians and patients.

Limitations: High crossover and uncertainty in overall survival

At the primary analysis of PFS, 109 (83.2%) patients in the placebo group who experienced progression subsequently enrolled in an open-label lenvatinib treatment extension phase. pERC noted that the high proportion of patients (83%) who crossed over from the placebo group to receive lenvatinib could obscure any OS difference.

The Committee discussed the statistical approach (rank-preserving structural failure time [RPSFT] model and the resampling method by bootstrapping) used to account for the effect of crossover on overall survival. pERC acknowledged the value and the limitations of this statistical method, as outlined by the Methods Team, as well as the fact that the unadjusted analysis was confounded by the high rate of crossover. pERC noted that there is likely an OS benefit of lenvatinib compared with placebo; however, there is uncertainty in the magnitude of that benefit. The Committee considered the true OS benefit to likely lie between the unadjusted and adjusted analysis estimates.

Need: No standard of care; new treatment options are required

pERC noted that there is a small number of patients with radioactive-iodine-refractory DTC, with about 185 deaths annually in Canada due to the disease. Radioactive-iodine-refractory DTC is incurable, with 90% of patients dying within 10 years of diagnosis.

pERC noted that there is currently no standard of care in Canada for the treatment of DTC that is refractory to radioactive iodine, as there are no reliable treatment options with demonstrated effectiveness for these patients. Treatment options include repeated surgery for recurrent disease, radiation therapy to manage symptoms related to bone and lung disease, and palliative care. The Committee noted that sorafenib is not reimbursed in any province. There is a need for effective treatment options in this patient population.

Registered clinician input: Very limited treatment options; small patient population

pERC noted input that was received from three registered individual or groups of clinicians. Registered clinicians expressed that treatment options for recurrent or refractory DTC are very limited. Registered clinicians also indicated that sorafenib has very limited benefit in this disease setting, has significant AEs, and is not reimbursed in Canada. pERC noted that registered clinicians felt that the number of patients who would be eligible for treatment with lenvatinib would be low and that only 10% to 20% of all patients with thyroid cancer would meet the criteria for treatment. The registered clinicians noted the following benefits of lenvatinib: an oral therapy with once-daily administration; reduction in disease progression in patients with no other treatment options; and a recent crossover-adjusted analysis of OS (SELECT trial) suggests an OS benefit in favour of lenvatinib. The following harms were also identified: rash, hypertension, proteinuria, fatigue, and diarrhea, all of which are manageable, in the registered clinicians' opinion; and hand-foot syndrome and bone marrow suppression, which may become difficult to manage. pERC also noted that the registered clinicians felt that evidence collection is required to better define the toxicities of lenvatinib, particularly hypertension and gastrointestinal toxicity, and to better define the impact that lenvatinib has on quality of life.

Comparators: Very limited treatment options; indirect comparison with sorafenib

pERC noted that the CGP and registered clinicians indicated that there are very limited treatment options in patients with radioiodine-refractory DTC. The Committee noted that, while sorafenib is not reimbursed in Canada, the pCODR Clinical Guidance Report provided contextual information on an indirect comparison of lenvatinib with sorafenib in patients with radioiodine-refractory DTC that was provided by the submitter. pERC noted the previously mentioned differences in the eligibility criteria of the SELECT and DECISION trials. In the DECISION trial, median PFS was 10.8 months with sorafenib, compared with 5.8 months with placebo (stratified HR, 0.59; 95% CI, 0.45 to 0.76; $P < 0.0001$). The median OS was not reached in the sorafenib arm compared with 36.5 months for placebo. The unadjusted HR was 0.59 (95% CI, 0.45 to 0.76) and the crossover-adjusted HR was 0.69 (95% CI, 0.49 to 0.99). pERC noted that the submitter performed an indirect comparison of lenvatinib with sorafenib using the matched-indirect comparison (MAIC) method. The Committee noted that the MAIC-adjusted PFS was statistically significantly in favour of lenvatinib (HR, 0.33; 95% CI, 0.20 to 0.53) and that the MAIC- and crossover-adjusted analysis demonstrated no statistically significant difference in OS (HR, 0.73; 95% CI, 0.40 to 1.35). However, pERC agreed with the pCODR Methods Team that the MAIC method does not have the ability to account for unreported factors that may influence the results, and that further studies would be needed to confirm the MAIC-adjusted PFS results.

PATIENT-BASED VALUES

Values of patients with differentiated thyroid cancer: Delayed progression and symptom control

pERC deliberated upon patient advocacy group input for lenvatinib for DTC and discussed the values of patients with DTC. Patients noted the most important aspects of thyroid cancer to control were progression of disease, fatigue, weight gain, and difficulty swallowing. pERC noted that patients' expectations for lenvatinib were to manage their disease progression and have fewer side effects such as weight loss, fatigue, and pain, among others. pERC acknowledged the clear unmet need expressed by patients.

Patient values on treatment: Disease control with acceptable toxicity

pERC noted that 12 patients (four respondents by online survey and eight respondents by telephone interviews) who provided input had direct experience with lenvatinib. The positive effects of lenvatinib reported by patients included reduced disease progression, reduced symptoms of thyroid cancer, improved overall wellness, and decreased side effects of treatment compared with other treatments. The negative effects of lenvatinib reported by patients included symptoms of fatigue, weight loss, decreased appetite, and high blood pressure. Patient advocacy group input indicated that lenvatinib managed symptoms of skin rash, pain, and appetite better than current therapy. Furthermore, patients appreciated that lenvatinib is orally administered and easy to use.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis in the locally recurrent or metastatic, progressive, radioactive-iodine-refractory DTC setting. The submitted model was a partitioned survival analysis. Lenvatinib was compared with best supportive care in a primary analysis and sorafenib in a secondary analysis. As sorafenib is not reimbursed in any Canadian province, the cost-utility analysis comparing lenvatinib with sorafenib was not considered further by pERC.

Basis of the economic model: Clinical and economic inputs; uncertainty in OS and health utilities

Costs considered in the model provided by the submitter included drug costs, AE costs, medical resource utilization costs, and post-progression costs. The key clinical outcomes considered in the model provided by the submitter were PFS, crossover-adjusted OS, and health state utilities. The PFS and OS efficacy data for the comparison with best supportive care were based on the SELECT trial. As quality of life data were not collected as part of the SELECT trial, utility values from a UK trial evaluating health states in radioactive-iodine-refractory differentiated thyroid cancer were applied to the model.

Drug costs: High drug cost, treatment until disease progression

Lenvatinib costs \$220.84 per 24 mg daily-dose when supplied as a carton containing six 5-day blister cards (i.e. 30-day supply). At the recommended dose of 24 mg daily and using the 24 mg daily-dose carton, lenvatinib costs \$220.84 per day and \$6,183.52 per 28-day course. pERC noted that, while the once-daily and oral route of administration should enhance patient compliance and provide ease of administration to patients, the dose reductions and interruptions reported in the SELECT trial indicate that drug wastage is likely to be an important consideration and that dose modifications may complicate the ease of administration. pERC also noted that the combination of pre-packaged 10 mg and 14 mg daily-dose cartons had a lower total price than that of the 24 mg dose carton alone.

Cost-effectiveness estimates: Not cost-effective at submitted price

pERC deliberated upon the cost-effectiveness of lenvatinib compared with placebo. pERC noted that, at the submitter's base-case estimate or the EGP's reanalysis estimates, lenvatinib could not be considered cost-effective. Furthermore, pERC discussed the incremental cost-effectiveness and that it could be higher than the EGP's upper estimate since it was based on the hazard ratio from the crossover-adjusted OS analysis and that quality of life measurements were not included in the SELECT trial. Therefore, pERC noted that uncertainty in the OS benefit and the quality of life impact of lenvatinib compared with best supportive care resulted in the greatest uncertainty in the incremental cost-effectiveness.

pERC noted that the submitter's base-case results used the crossover-adjusted estimate of the HR for OS (0.53) in order to remove the confounding effect of crossover on OS. The EGP's reanalysis used both the lower and upper boundary of the 95% CI estimate of the HR for OS (0.34 and 0.82, respectively). While pERC agreed with this adjustment, it also noted it is possible that the true OS benefit may be above the upper 95% CI HR estimate (but below the unadjusted OS analysis estimates). pERC also agreed with the EGP's decision to use a seven-year time horizon instead of a 10-year time horizon as well as the use of utility values that are adjusted for patient demographic profile. The Committee agreed with the EGP's decision to incorporate wastage, as different strength capsules were required and dose modifications were prevalent. Furthermore, pERC agreed with the adjustment of pricing such that patients were assumed to mix packs for best price value. Perhaps most importantly, pERC acknowledged the uncertainty in the magnitude of the clinical benefit with respect to OS, which led to significant uncertainty in the cost-effectiveness; however, the Committee concluded that, at the submitter's base-case estimate as well as at the EGP's reanalysis estimates, lenvatinib could not be considered cost-effective.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Small patient population; ideal dosage uncertain

pERC considered the feasibility of implementing a reimbursement recommendation for lenvatinib. pERC acknowledged that there is no standard of care for locally advanced or metastatic DTC refractory to radioactive iodine, and that lenvatinib would provide a new treatment option for this group of patients. pERC felt that there was the potential for significant wastage with lenvatinib, given the high prevalence of dose reductions and interruptions in the SELECT trial, and given the availability of lenvatinib only in pre-packaged blister packs supplied to patients in one-month supplies. The Committee also considered the impact of dose reductions and interruptions to be uncertain, as the SELECT trial had a high frequency for both, but reported a clinically meaningful benefit in PFS in favour of lenvatinib. However, given the significant number of dose reductions and interruptions, pERC noted that evidence collection is needed in order to better define the impact that lenvatinib has on the quality of life of patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory DTC in order to define the optimal dose. pERC also noted that there are risks of significant toxicities with lenvatinib and that oncologists with experience in the administration of TKIs should prescribe lenvatinib and monitor patients for toxicities. The Committee discussed the limited quality-of-life data for patients who received lenvatinib and noted that jurisdictions may want to consider evidence collection in order to better define the quality of life for patients who receive lenvatinib compared with placebo. pERC noted that, although the budget impact with lenvatinib would be small due to the small number of eligible patients, uptake would be high, as lenvatinib is an oral drug and there may be a significant prevalent population of patients who are currently not receiving treatment and who would be eligible to receive lenvatinib. In addition, the submitted budget impact was done from the perspective of Ontario Drug Benefits, thus only included costs for coverage of patients aged 65 and older. Therefore, the submitted budget impact analysis may underestimate the potential budget impact of lenvatinib.

DRUG AND CONDITION INFORMATION

Drug Information	<ul style="list-style-type: none"> • Tyrosine kinase inhibitor that blocks the receptor tyrosine kinases vascular endothelial growth factor (VEGF) receptor and platelet derived growth factor (PDGF) receptor • 4 mg and 10 mg capsules • Recommended dosage of 24 mg administered orally, once daily
Cancer Treated	<ul style="list-style-type: none"> • Differentiated thyroid cancer
Burden of Illness	<ul style="list-style-type: none"> • Differentiated thyroid cancer is a malignancy affecting an estimated 6,300 Canadians annually • Many patients with thyroid cancer will develop disease that is refractory to radioiodine therapy
Current Standard Treatment	<ul style="list-style-type: none"> • No current standard of care for patients who are refractory to radioiodine • Palliative treatment with best supportive care
Limitations of Current Therapy	<ul style="list-style-type: none"> • 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

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)	Don Husereau, Health Economist
Dr. Maureen Trudeau, Oncologist (Vice-Chair)	Dr. Anil Abraham Joy, Oncologist
Dr. Scott Berry, Oncologist	Karen MacCurdy-Thompson, Pharmacist
Dr. Kelvin Chan, Oncologist	Valerie McDonald, Patient Member Alternate
Dr. Matthew Cheung, Oncologist	Carole McMahan, Patient Member
Dr. Craig Earle, Oncologist	Dr. Catherine Moltzan, Oncologist
Dr. Allan Grill, Family Physician	Jo Nanson, Patient Member
Dr. Paul Hoskins, Oncologist	Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Kelvin Chan and Dr. Matthew Cheung, who were not present for the meeting
- Don Husereau, who was not present for the deliberations and voting due to a conflict of interest
- Jo Nanson, who was the designated non-voting patient member alternate for this meeting.

Avoidance of conflicts of interest

All members of pERC 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 lenvatinib (Lenvima) for differentiated thyroid cancer, through their declarations, six members had a real, potential, or perceived

conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

pERC 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 its 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 pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

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