CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Lenvatinib (Lenvima) for Differentiated Thyroid Cancer

September 20, 2016

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding Lenvatinib (Lenvima) for Differentiated Thyroid Cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding Lenvatinib (Lenvima) for Differentiated Thyroid Cancer conducted by the Endocrine Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on Lenvatinib (Lenvima) for Differentiated Thyroid Cancer, a summary of submitted Provincial Advisory Group Input on Lenvatinib (Lenvima) for Differentiated Thyroid Cancer, and a summary of submitted Registered Clinician Input on Lenvatinib (Lenvima) for Differentiated Thyroid Cancer, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the safety and efficacy of lenvatinib on patient outcomes in the treatment of for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).

Lenvatinib is an oral, multiple receptor tyrosine kinase inhibitor (TKI). Lenvatinib has a Health Canada indication for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. The recommended daily dose of lenvatinib is 24 mg taken once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan. Treatment should continue as long as there is clinical benefit.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One multicentre phase 3, double-blind, randomized controlled trial (RCT), the SELECT study, was included in this pCODR systematic review. The SELECT study randomized patients in a 2:1 ratio to receive lenvatinib or placebo and evaluated the comparative efficacy and safety of lenvatinib in patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. Patients were treated with either oral lenvatinib 24 mg once daily or placebo in 28-day cycles.

At the cut-off date (15 Nov 2013) for primary analysis, 109 (83.2%) patients randomized to the placebo arm who had disease progression confirmed by Independent Imaging Review (IIR) switched (crossed over) to an optional, open-label (OOL) lenvatinib treatment extension phase. After the primary analysis was completed, patients treated with lenvatinib who had not experienced disease progression could request to continue open-label lenvatinib at the same dose, according to the clinical judgment of the investigator.[1] Treatment continued until confirmed disease progression, development of unacceptable toxicity, or withdrawal of consent.

All patients, including those who had disease progression during the randomization phase but did not enter the OOL lenvatinib treatment extension phase and all patients who discontinued lenvatinib treatment were to be followed for survival until the time of death.

Reported patients' characteristics appeared to be similar across the two treatment groups. The ECOG performance status of most patients (95.0%) was 0 or 1 for both studies and the majority of patients (76.3%) had not received prior therapy with a TKI.

Efficacy

The primary efficacy endpoint of the SELECT study was progression-free survival (PFS). Secondary endpoints were objective response rate (ORR) and overall survival (OS). Patients in the lenvatinib group had a statistically significantly longer median PFS than those in the placebo group (18.3 versus 3.61 months), with a hazard ratio (HR) of 0.21 (99% confidence interval [CI]: 0.14, 0.31; P<0.001). The response rate was also significantly higher in the lenvatinib group than in the placebo group (64.8% versus 1.5%), with reported odds ratio (OR) of 28.87 (95% CI: 12.46, 66.86); $P < 0.001$). The median overall survival was not reached in either group at the time of primary analysis (15 Nov 2013). The criteria for reaching or not reaching the median OS were not specified. An updated analysis of OS was performed at a later cut-off date (June 15, 2014) when six of eight additional patients who were receiving placebo in the randomization phase as of 15 Nov 2013 had crossed over to the OOL lenvatinib treatment phase. The unadjusted HR for OS in this updated analysis was 0.80 (95% CI: 0.57, 1.12; P=0.1993), while adjusted HR using the rank-preserving structural failure time (RPSFT) and the resampling method (bootstrapping) showed a statistically significant difference in OS between the treatment groups in favour of lenvatinib (HR=0.53; 95% CI: 0.34, 0.82, P=0.0051). At the time of this analysis, the median follow-up period was 23.6 months in the lenvatinib arm and the median OS had not been reached while in the placebo arm the median follow-up time was 24.1 months and the median OS was 19.1 months (95% CI: 14.3, NE).

Harms

The proportion of patients who reported at least one adverse event (AE) was high in each treatment group, although higher in the lenvatinib group that the placebo group (97.3% versus 59.5%). The most commonly reported grade ≥3 treatment-related AEs (lenvatinib versus placebo) were hypertension (41.8% versus 2.3%) and proteinuria (10.0% versus 0). (Table 1).[2] Others common grade ≥3 treatment-related AE included weight loss (9.6% versus 0), fatigue (9.2% versus 2.3%), diarrhea (8.0% versus 0), and decreased appetite (5.4% versus 0). Incidence of treatment-related serious AEs was 30.3% in the lenvatinib group compared with 6.1% in the placebo group. Similarly, AEs leading to dose interruptions, dose reduction, or discontinuation of study drug occurred more frequently in the lenvatinib group than in the placebo group. Six deaths (2.3%), considered to be drug-related, occurred in the lenvatinib group during the treatment period. There was no drug-related death reported in the placebo group.[2]

Limitations

A major limitation of the SELECT is that there is uncertainty about the overall survival (OS) benefit of lenvatinib in patients with iodine refractory differentiated thyroid cancer (IR-DTC). The study was not designed to assess OS which was a secondary endpoint. At the cut-off for primary analysis and at an updated analysis seven months from the initial cut-off, the median OS was reported as not reached. Unadjusted analysis showed no statistically significant difference between lenvatinib and placebo at either point of analysis. However, a multistep statistical operation applying RPSFT model and boot

strapping approach eventually resulted in statistically significant difference in OS in favour of lenvatinib. It must be noted that the OS analysis was biased by the large proportion of patients randomized to placebo who switched to the optional open-label lenvatinib treatment phase. Another source of bias is the subsequent anticancer therapy received by patients post study, which creates uncertainty about whether the observed OS benefit was due entirely to the effect of lenvatinib.

Although the RPSFT model was applied to correct the confounding due to crossover, it required the following assumptions to be satisfied in order that the assessment on OS be valid: a) the effect of the treatment is multiplicative on time; b) the size of OS benefit is the same regardless of whether patients were randomized or crossed over to treatment and c) the benefit on OS is immediate after the treatment.[3] The bootstrapping method uses repeated sampling of the same patient pool which indicates that the same patient in a study might be sampled many times thereby providing the same OS information for the purpose of creating a suitable dataset for use in the RPSFT model. There is uncertainty around the OS benefit of lenvatinib in patients with IR-DTC and the "true" OS benefit could lie between the OS results obtained from the unadjusted analysis and OS results obtained from using the RPSFT bootstrapping method.

Further, the SELECT study did not assess patients' health-related quality of life (HRQoL).

Table 1: Highlights of Key Outcomes of the SELECT TRIAL[2]

Efficacy outcomes		
	LEN (N=261)	**Placebo (N=131)**
Median PFS (months) HR (95% CI) * p-value	18.3 0.21 (0.14, 0.31) < 0.001	3.6
Median OS (months) [a] HR (95% CI) p-value	Not reached 0.73 (0.50, 1.07) 0.103	Not reached
ORR, n (%)	169 (64.8)	2 (1.5)
Time to first objective response, months (95% CI)	2.0 (1.9, 3.5)	5.6 (1.8, 9.4)
Harms Outcome, n (%)		
Any TEAE	254 (97.3)	78 (59.5)
TEAE of Grade ≥ 3	198 (75.9)	13 (9.9)
Common treatment-related Grade ≥3, (%)		
Hypertension	41.8	2.3
Proteinuria	10.0	0
Weight loss	9.6	0
Fatigue	9.2	2.3
Diarrhea	8.0	0
Decreased appetite	5.4	0
Stomatitis	4.2	0
Nausea	2.3	0.8
TRAE SAE	79 (30.3)	8 (6.1)
TRAE Deaths	6 (2.3)	0 (0.0)
WDAE	37 (14.2)	3 (2.3)

AE = adverse event; CI = confidence interval; HR = hazard ratio; HRQoL = health-related quality of life; Len = lenvatinib; ORR = objective response rate; OS = overall survival; PFS = progression free survival; NR = not reported, TEAE =treatment emergent adverse event; TRAE = treatment-related adverse event; WDAE = withdrawal due to adverse event

*HR < 1 favours Lenvatinib

[a] At the cut-off date for primary efficacy analysis, median OS was not reached and no significant difference in OS was observed between the treatment group. OS results from a rank-preserving structural failure time (RPSFT) analysis for a potential crossover bias have been reported in Table 7. OS data from an updated (unadjusted and adjusted) analysis (June 15, 2014 data cut) are also available in Table 7.

Source: Schlumberger et al 2015,[2]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, the most important aspect of thyroid cancer to control is progression of disease, followed by fatigue, then weight gain and difficulties swallowing. Respondents reported using the following current therapies to treat thyroid cancer: levothyroxine, sorafenib or other tyrosine kinase inhibitor, vandetanib, radioactive iodine treatment, surgery, chemotherapy, external beam radiation and surveillance. Respondents who do not have experience with the drug under review expect that it will manage their disease progression and have less side effects, such as weight loss, fatigue, and pain, among others. According to Thyroid Cancer Canada, the positive effects of lenvatinib reported by respondents included: reduction in the progression of thyroid disease, reduced the effects of thyroid cancer, improved overall wellness, and decreased the side effects compared to other treatments. In contrast, the negative effects of lenvatinib reported by respondents included: increased fatigue and increased weight loss, decreased appetite, diarrhea, and high blood pressure. Thyroid Cancer Canada reported the symptoms that lenvatinib managed better than current therapy included: skin rash, pain, and maintaining a healthy appetite. Respondents also noted that lenvatinib was easy to use, in particular, lenvatinib was not a problem to swallow.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of lenvatinib:

Clinical factors:

- Unmet need for patients with refractory differentiated thyroid cancer
- High rate of serious adverse events requiring dose adjustment or dose withdrawal

Economic factors:

- Very small patient population compared to other cancers
- Percentage of patients eligible for treatment may be high

Registered Clinician Input

Overall, the clinicians providing input feel that lenvatinib fills an unmet need for patients with radioactive iodine refractory thyroid cancer. They noted that lenvatinib provides an oral treatment option for a small number of patients and believe that lenvatinib demonstrates survival benefits.

Summary of Supplemental Questions

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of lenvatinib for radioiodine-refractory DTC:

- Critical appraisal of an indirect treatment comparison of lenvatinib and sorafenib in patient with radioiodine-refractory (RR) differentiated thyroid cancer (DTC)

This section provides supporting information, which has not been systematically reviewed.

The manufacturer performed an indirect treatment analysis using the matched-adjusted indirect comparison (MAIC) method to compare lenvatinib with sorafenib. The results

suggested that treatment of patients with RR-DTC with lenvatinib was associated with statistically significantly longer median PFS than sorafenib, with HR of 0.33 (95% CI: 0.20, 0.53). In both the SELECT and DECISION trials, the median OS had not been reached in the lenvatinib or sorafenib arms at the time of the updated analyses, and the MAIC-adjusted crossover-corrected analyses showed no statistically significant difference in OS between lenvatinib and sorafenib (HR = 0.73; 95% CI: 0.40, 1.35). In the absence of a head-to-head comparison between the two drugs, the MAIC approach is a good option for comparison since individual patient data were available for the SELECT trial, whereas only published summary data were available for the DECISION trial. However, since MAIC does not have the ability to account for unreported factors which may influence the results, further studies may be needed to confirm the advantage of lenvatinib over sorafenib in the treatment of patients with RR-DTC.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for Lenvatinib for DTC

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	The majority of patients had ECOG PS of 0 or 1	95.0% and 98.5% of patients in the lenvatinib and placebo groups, respectively had ECOG PS of 0 or, with. Of 5% and 1.5% of patients in the two groups, respectively, having an ECOG PS of 2 or 3. [b]	Are the results of the trial applicable to patients with an ECOG PS of 2-3?	ECOG 2 describes patients who are "ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours". These patients were eligible for the trial, and this describes many cancer patients who receive other systemic therapies. It is reasonable to generalize the results of the trial to suitable ECOG 2 patients at the treating physician's discretion. Patients of performance status ECOG 3 are considered too functionally impaired to confidently generalize the trial results.
	Patients with certain medical conditions and medication history were excluded from the study	Patients proteinuria (≥1g/24 hours); or significant cardiovascular or gastrointestinal dysfunction, as well as patients who had received ≥2 or more therapy with TKI prior to randomization were	Are the results of the trial applicable to IR-DTC patients with such comorbidities and medication history?	No, the trial results cannot be confidently extrapolated to these patients.

Table 2: Assessment of generalizability of evidence for Lenvatinib for DTC				
Domain	**Factor**	**Evidence**	**Generalizability Question**	**CGP Assessment of Generalizability**
		excluded from the study		
	The number of patients with locally advanced IR-DTC was very small	4 (1.5%) in the lenvatinib group and none in the placebo group	Are the finding and the conclusions of the SELECT study generalizable to patients with locally advanced IR-DTC?	Yes, for patients with locally advanced IR-DTC who have exhausted local therapies, the trial results can be applied.
Intervention	Patients in the study received different daily doses of lenvatinib, driven by tolerability	The numbers (%) of patients who received the various doses them during the RCT phase are as follows: 1. 111 (42.5) –24 mg daily; 2. 30 (11.5)– 20 mg daily; 3. 66 (25.3)–14 mg daily; 4. 40 (15.3)–10 mg daily; and **5.** 14 (5.4%)– <10mg daily	PAG is seeking information on whether reduced doses would impact the benefits demonstrated in the trial with the 24mg daily dose of lenvatinib dose.	All patients started with the 24 mg dose. This was then modified according to the toxicity experience on an individual patient basis. Generally in oncology patients are treated to the maximal drug dose they can reasonably tolerate. The treatment approach reported is concordant with clinical practice and should not impact the benefits observed.
Comparator	No head-to-head comparison with an active intervention.	The submitter provided an ITC between lenvatinib and sorafenib using MAIC.	Are the results SELECT trial or the ITC enough to support the preference of one intervention over the other (lenvatinib versus sorafenib)?	Yes, although both drugs improved progression-free survival, lenvatinib was associated with a much longer PFS, higher objective response rate, and the main severe toxicity (hypertension) is usually asymptomatic for patients and treatable with medication or lenvatinib dose modification. Lenvatinib is the preferred drug.
Outcomes	The median OS was not reached at both the cut off for primary analysis and updated analysis seven months later.	Unadjusted analysis showed no statistically significant difference in OS between lenvatinib and placebo. Applying RPSFT model and bootstrapping approach to the updated analysis showed statistically significant difference in OS in favour of lenvatinib	Are the results for OS obtained by RPSFT-adjusted analysis using a bootstrapping method sufficiently certain to inform clinical decision?	The RPSFT-adjusted OS results do not prove an OS benefit for lenvatinib.

Table 2: Assessment of generalizability of evidence for Lenvatinib for DTC				
Domain	**Factor**	**Evidence**	**Generalizability Question**	**CGP Assessment of Generalizability**
	Confounding effects of crossover from placebo to OOL lenvatinib treatment, and the use of other anticancer drugs on OS	A large proportion of patients randomized to placebo switched to receive treatment with lenvatinib in OOL extension phase. Patients who experience progression but did not crossover o receive lenvatinib continued treatment with other anticancer drugs.	What is the generalizability of the OS analysis results in view of the confounding effects the crossover and the use of other anticancer drugs?	Qualitatively, the trend in OS is in the same direction as the PFS and ORR results favouring lenvatinib. This enhances the believability of an OS benefit in the absence of optional unblinding and lenvatinib treatment in placebo patients. However, this is likely of a smaller magnitude than that described by the RPSFT-adjusted analysis.
Setting	Details of setting not described	SELECT was a multicenter study involving 117 sited and several countries in Asia, Europe, and North America.	Given that differences in settings and standards of care at the various study sites are likely, what is the generalizability of the study findings to Canadian setting?	Canadian centres participated in this trial, the international nature of the trial enhances its generalizability, and there were no obvious reasons to limit generalizability of the results to Canadian patients.

ECOG PS = ECOG = Eastern Cooperative Oncology performance status; IR-DTC = iodine refractory differentiated thyroid cancer; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; OOL = optional open-label; OS = overall survival; RCT = randomized controlled trial; RPSFT = rank-preserving structural failure time; TKI = tyrosine kinase inhibitor.

[a] Although amended protocol allowed the use of both the 24 mg and 20 mg doses in the OOL phase of the study, baseline patient characteristics, previous treatments, geographical allocation, on-study placebo exposure, lenvatinib exposure in the OOL phase, as well as median follow up times varied considerably for these 2 dose regimens. Therefore, patients who received the 20-mg regimen (n=30) were considered a different population from patients who received the 24-mg regimen in both the randomization phase and the OOL lenvatinib treatment phase.[4]

[b] ECOG PS of 3 was an exclusion criterion

1.2.4 Interpretation

Differentiated thyroid cancer is increasing in incidence but is usually cured with surgery and systemic I^{131} therapy.[5] A fraction of patients develop incurable radio-iodine resistant disease (IR DTC) associated with a mortality rate of 90% within 10 years from diagnosis.[6] Cytotoxic chemotherapy may have activity but has been poorly studied, and there is no reliably effective life prolonging treatment. Although less than 200 persons die from IR DTC annually in Canada, these patients have yet to benefit from the advances in cancer drug treatment experienced by patients with more common cancers, and identification of such treatments remains a high priority for them.

Two randomized controlled clinical trials (RCTs) have been reported over the past 3 years studying agents targeting and inhibiting the vascular endothelial growth factor receptor (VEGFR) TKIs.[2,7] Both trials had a primary endpoint of progression free survival and were positive, suggestive of a class effect of these agents, however, the specific enrolment criteria and reported benefit varied. This review focuses on the results of the most recent report, the SELECT RCT, which studied lenvatinib. Lenvatinib is an oral administered inhibitor of VEGFRs 1, 2, and 3; fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor-α, RET, and KIT.[2]

The primary endpoint of SELECT was progression-free survival (PFS) which was 18.3 months with lenvatinib versus 3.6 months in the placebo arm. An overall survival primary endpoint could have displayed the benefits of lenvatinib much more clearly. However, PFS was deemed sufficient to define effectiveness for regulatory approval of the drug by the US FDA, was influenced by ethical concerns about a placebo control arm in this population, and is felt to satisfy efficacy concerns identified from pCODR patient and registered clinician input. As there is no currently funded reliably effective evidence-based treatment for IR DTC patients, the particularly extreme PFS and objective response rates of the SELECT RCT make a compelling effectiveness case.

The DECISION RCT studied another VEGFR TKI, sorafenib, in IR DTC patients and also showed PFS benefit (10.8 months compared to placebo 5.8 months); however, there were important differences in characteristics of patients treated in these two RCTs that should be considered when comparing the results. Patients in the DECISION trial were required to have radiologic evidence of progressive cancer within 14 months of study entry according to Response Evaluation Criteria in Solid Tumors (RECIST). In the DECISION trial radioactive iodine-refractoriness was defined as the presence of: 1. at least one target lesion without iodine uptake on any I^{131} scan, 2. tumours with iodine uptake and progression within 16 months of one radioactive iodine treatment; 3. tumors with iodine uptake and progression after two radioactive iodine treatments within 16 months of each other (with the last such treatment administered more than 16 months ago), or 4. cumulative radioactive iodine exposure ≥600 mCi. In the SELECT trial RECIST progression was required within 13 months, the RAI criteria 1 and 4 were the same as SELECT, however, all iodine avid patients were also required to have RECIST confirmed progression with 12 months of radio-iodine treatment. In the DECISION trial, patients with prior TKI therapy were excluded, but the SELECT trial allowed treatment with one prior TKI and 24% of randomized patients had been TKI pretreated. The consequence of these differences is enrichment of the SELECT trial with IR DTC patients with more aggressive cancers. This is reflected in the much shorter median PFS in the placebo arm of SELECT (3.6 months) compared to DECISION (5.8 months).

It is often important in cancer treatment to induce tumor shrinkage ("response") to improve symptoms or avert life-threatening organ failure. An impressive component of lenvatinib treatment in the SELECT trial was the high objective response rate observed. Nearly 65% of patients treated with lenvatinib had tumor shrinkage meeting RECIST response criteria compared with 1.5% in the placebo control arm. Of note, using the same response criteria the objective response rate with sorafenib in the DECISION trial was 12.2% (versus 0.5% with placebo).

Overall survival (OS) was a secondary endpoint in the SELECT trial. Tumor progression was confirmed by independent radiology review, and when this occurred placebo patients were offered optional open-label lenvatinib and nearly all (95.6%) chose it. This confounds the assessment of OS benefit and for OS assessment renders the SELECT trial a test of immediate versus delayed lenvatinib therapy. Notwithstanding this, a statistically unproven improvement in overall survival was observed in unadjusted (HR for death, 0.73; 95% CI, 0.50 to 1.07; P = 0.10) and adjusted overall survival analyses (RPSFT model; hazard ratio, 0.62; 95% CI, 0.40 to 1.00; P = 0.05), conducted in the primary data cut, which is somewhat impressive considering the extent of treatment contamination in the control arm. In an updated analysis, the unadjusted overall survival was still not statistically significant (HR 0.80, 95% CI, 0.57 to 1.12; *P*=0.1993), while an adjusted analysis, using a RPSFT model with a bootstrapping method, demonstrated a statistically significant difference (HR 0.53; 95% CI, 0.34 to 0.82; *P*=0.0051).

Side effects of treatment are a critical component of the effectiveness of cancer treatment and can influence health-related quality of life (HRQoL). Unfortunately HRQoL was not studied in the SELECT trial. 75.9% of patients treated with lenvatinib experienced grade 3 or higher (severe) treatment-related adverse effects compared with 9.9% of placebo treated patients. The most common of these was hypertension (41.8%) which is often asymptomatic and resulted in discontinuing drug in 1.1% of patients. Reassuringly, the typical symptomatic "class effect" adverse effects seen with VEGFR TKIs each occurred at severe levels (≥ grade 3) in less than 10% of patients treated with lenvatinib: diarrhea (8.0%), fatigue or asthenia (9.2%), decreased appetite (5.4%), decreased weight (9.6%), nausea (2.3%), stomatitis (4.2%), palmar–plantar erythrodysesthesia syndrome (3.4%), vomiting (1.9%), headache (2.7%), and dysphonia (1.1%). These rates are similar to those seen with sorafenib in the DECISION trial, with the exception of palmar–plantar erythrodysesthesia syndrome which was more common with sorafenib (≥ grade 3: 20.3%). Adverse effects were managed with symptomatic and supportive treatment and/or dose modifications. Overall 14.2% of patients discontinued lenvatinib due to adverse effects which compares favourably with sorafenib in the DECISION trial (18.8%).

On average patients received lenvatinib for over a year (median 13.8 months) and individual patient variability was reflected in a mean dose of 17.2 mg/day (starting dose 24 mg/day). 2.3% of patients in the lenvatinib group died due to adverse effects. IR DTC patients typically have had thyroidectomy with or without parathyroidectomy and require thyroxine and calcium replacement. VEGFR TKIs may affect these and regular clinical monitoring is required. The risk of arterial and venous thromboembolic effects with VEGF TKI therapy is increased and this was observed with lenvatinib (grade ≥3, 2.7% and 3.8%, respectively). An increase in skin cancers observed in the DECISION trial with sorafenib was not observed with lenvatinib presumably due to absence of B-raf inhibition.

Overall the SELECT trial provides high quality evidence supporting the benefits of lenvatinib in the patient population treated. Independent radiology review to confirm the primary endpoint of radiological progression argues against ascertainment bias. A high objective response rate and overall survival trends are concordant with benefits of lenvatinib. Adverse effects were typical of VEGFR TKI therapy. Hypertension was the most common severe side effect, is treatable, and resulted in very few patients discontinuing lenvatinib. Limitations to generalizability are those typical of most cancer trials which limit participation to patients with minimal symptoms and comorbidity and excellent organ function. Generalizability is enhanced by the participation of Canadian centres.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to lenvatinib in the treatment of iodine-refractory thyroid cancer based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in progression-free survival and objective response rate for lenvatinib compared with placebo.

In making this conclusion the Clinical Guidance Panel also considered that:

- Overall survival was a secondary endpoint and was confounded by optional treatment with lenvatinib at radiological progression in nearly all control arm patients.
- HRQoL was not studied but adverse event profiles were similar to those seen with sorafenib in another RCT in iodine-refractory thyroid cancer. Hypertension was more

common with lenvatinib but hand-foot syndrome and drug discontinuation due to adverse effects was more common with sorafenib.

- This trial with lenvatinib is the second RCT to demonstrate efficacy of VEGFR TKI therapy in this disease. In the absence of a reliably effective therapy for this relatively small group of patients with a fatal disease, there was consensus of the CGP that lenvatinib should be made available for the treatment of patients meeting the specific definitions of radio-iodine resistance used for eligibility for the SELECT RCT (see section 1.2.4 paragraph 4 above).
- For optimal management of adverse effects, practitioners prescribing lenvatinib should be experienced in the use of VEGFR TKIs in cancer therapy.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Endocrine Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Differentiated thyroid cancer (DTC) is increasing in incidence and affects an estimated 6,300 Canadians annually.[5] Most patients are cured with surgery and radioiodine therapy. However, approximately 15% of patients develop metastases typically treated initially with thyroid stimulating hormone (TSH) suppression, surgical resection, and iodine-131. Many of these patients will eventually develop incurable thyroid cancer that progresses despite iodine-131 treatment. These patients are referred to as having iodine-resistant or -refractory DTC (IR DTC). Historically, only 10% of these patients survive beyond 10 years.

2.2 Accepted Clinical Practice

IR DTC patients with biochemical progression alone (i.e. increasing serum thyroglobulin level) are not considered candidates for systemic anticancer therapies. A decision to pursue systemic therapy is guided by the symptoms associated with metastatic disease and the risk for the development of complications for example, airway compromise for local recurrence not amenable to surgery or further radiotherapy. In patients with recurrent IR DTC identified by imaging or symptoms, surgical resection is considered when feasible. Radiotherapy is usually reserved for disease that is unresectable or for palliation of pain. Chemotherapy has been poorly studied and has shown limited evidence of effectiveness in patients with IR DTC. Doxorubicin has been considered a standard of care based on US FDA approval of the drug for thyroid cancer in the 1970's. This approval was based on activity observed in single arm trials, and its effectiveness has been questioned.

Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) have been of interest based on impressive activity observed with several agents in phase II studies in patients with IR DTC. The DECISION trial showed improved progression-free survival (PFS) with sorafenib in IR DTC patients in a phase III placebo-controlled design with a primary endpoint of progression-free survival and cross-over at progression. The disease control rate observed in DECISION was 54% however, only 12% of patients had a significant (> 30%) reduction in the size of target lesions. Serious adverse events were noted in 37% of patients on sorafenib and 26% of those treated with placebo. The toxicity was consistent with previous trials conducted with VEGFR TKIs and manageable. This agent however, is not readily available in Canada due to a lack of reimbursement although patients may be funded through private insurance or provincially on a case by case basis depending on their province of residence. More recently the SELECT trial reported dramatic improvements in PFS and objective response with lenvatinib in a similarly designed phase III trial.

2.3 Evidence-Based Considerations for a Funding Population

The expected patient population in Canada for whom treatment with lenvatinib would be considered is small. There were 185 deaths from thyroid cancer in Canada in 2015. Not all patients with IR DTC are suitable candidates for treatment with lenvatinib, and not all patients with IR DTC die from their cancer.

2.4 Other Patient Populations in Whom the Drug May Be Used

VEGFR TKIs are of interest as a therapeutic option in many types of adult solid tumors and are approved for the treatment of metastatic renal cell carcinoma, hepatocellular carcinoma, gastrointestinal stromal tumors, soft tissue sarcomas, and epithelial ovarian cancer. Lenvatinib is currently not approved for use beyond IR DTC; however, as an agent in this class, it could be of interest in a variety of tumor types.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Thyroid Cancer Canada provided input on lenvatinib for the treatment of differentiated thyroid cancer and their input is summarized.

Thyroid Cancer Canada gathered information through a national online survey posted on the Thyroid Cancer Canada website between February 29, 2016 and April 22, 2016. The survey link was also given to physicians to provide to their patients. One-to-one telephone interviews were conducted by a Thyroid Cancer Canada volunteer between March 18, 2016 and April 29, 2016.

Overall, there were 21 respondents, of whom 13 completed the online survey and eight (8) participated in the one-to-one telephone interview. Of the respondents who completed the survey, four (4) were patients and caregivers who have experience with lenvatinib, and all eight (8) respondents who participated in the one-to-one telephone interview had experience with lenvatinib.

From a patient's perspective, the most important aspect of thyroid cancer to control is progression of disease, followed by fatigue, then weight gain and difficulties swallowing. Respondents reported using the following current therapies to treat thyroid cancer: levothyroxine, sorafenib or other tyrosine kinase inhibitor, vandetanib, radioactive iodine treatment, surgery, chemotherapy, external beam radiation and surveillance. Respondents who do not have experience with the drug under review expect that it will manage their disease progression and have less side effects, such as weight loss, fatigue, and pain, among others. According to Thyroid Cancer Canada, the positive effects of lenvatinib reported by respondents included: reduction in the progression of thyroid disease, reduced the effects of thyroid cancer, improved overall wellness, and decreased the side effects compared to other treatments. In contrast, the negative effects of lenvatinib reported by respondents included: increased fatigue and increased weight loss, decreased appetite, diarrhea, and high blood pressure. Thyroid Cancer Canada reported the symptoms that lenvatinib managed better than current therapy included: skin rash, pain, and maintaining a healthy appetite. Respondents also noted that lenvatinib was easy to use, in particular, lenvatinib was not a problem to swallow.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with differentiated thyroid cancer

Thyroid Cancer Canada reported that 11 respondents completed the questions about their experience with thyroid cancer. More specifically, these respondents stated the following:

- Of the aspects of thyroid cancer that were most important to control:
    - 100% of respondents said progression of disease (n=11);
    - 64% of respondents said fatigue (n=7);
    - 45% of respondents said weight gain (n=5);
    - 9% of respondents said difficulty swallowing (n=1).

- Of the ongoing symptoms that affect day-to-day life:
    - 73% of respondents said they are tired and listless (n=8);
    - 64% of respondents said they are affected emotionally (n=7);
    - 36% of respondents said they are limited from working (n=4);

- 27% of respondents said they have limits on participating in leisure activities (n=3); and
- 27% of respondents said their diet and eating habits are affected (n=3).

Thyroid Cancer Canada noted that nine (9) patients described the limitations they experience:

- unable to be physically active (78%, 7 patients)
- unable to work (56%, 5 patients)
- unable to participate in family or leisure activities (44%, 4 patients)

One (1) patient interviewed over the telephone noted that living with advanced thyroid cancer is very difficult as she felt having thyroid cancer wasn't taken as seriously as other cancers. She was told when she was diagnosed at stage 4c by health care providers that at least this was "*the good type of cancer to have*".

3.1.2 Patients' Experiences with Current Therapy for differentiated thyroid cancer

Thyroid Cancer Canada noted that eleven (11) respondents provided responses about the therapies they have used since their diagnosis to treat thyroid cancer:

Answer Choices	Responses	
Sorafenib or other Tyrokinase inhibitor (TKI)	**27.27%**	3
Nexavar	**27.27%**	3
Caprelsa	**0.00%**	0
Radioactive Iodine Treatment	**90.91%**	10
Surgery	**100.00%**	11
Chemotherapy	**18.18%**	2
External Beam Radiation	**45.45%**	5
Total Respondents: 11		

Of note, Nexavar is the brand name of sorafenib.

Eight (8) patients reported on the therapies they currently use to treat thyroid cancer:

- lenvatinib (50%, n=4)
- levothyroxine (38%, n=3)
- surveillance (13%, n=1)
- Of note, Thyroid Cancer Canada indicated that five (5) respondents skipped this question.

Two (2) respondents who were interviewed by telephone said that radioactive iodine was a temporary fix and failed, and resulted in requiring them to be treated with systemic therapy.

While on sorafenib, two (2) respondents commented that they had painful skin rashes. One (1) respondent noted that her experience with sorafenib was a very difficult journey, but her experience followed the predictable pathway of slowing the progression of the disease for the first 6-7 months, followed by a waning period up to 18 months, and then there was growth and disease progression. The respondent also reported that the gastrointestinal (GI) symptoms from previous treatments were the most difficult to manage.

One (1) respondent reported that following surgery to remove her thyroid, she was thrown into permanent menopause with no relief from symptoms that impact her quality of life. She described experiencing the following symptoms: night sweats, cold spells, headaches, and disrupted sleep as being constant.

When asked to describe how well their current therapy was seen to be controlling their thyroid cancer, nine (9) respondents reported the following:

	Excellent	Very Good	Good	Just OK	Least effective	Total
Disease progression	**44.44%** 4	**22.22%** 2	**33.33%** 3	**0.00%** 0	**0.00%** 0	9
Weight gain	**12.50%** 1	**12.50%** 1	**12.50%** 1	**25.00%** 2	**37.50%** 3	8
Fatigue	**0.00%** 0	**22.22%** 2	**22.22%** 2	**44.44%** 4	**11.11%** 1	9
Dry mouth	**12.50%** 1	**25.00%** 2	**37.50%** 3	**25.00%** 2	**0.00%** 0	8
Difficulty swallowing	**0.00%** 0	**14.29%** 1	**57.14%** 4	**14.29%** 1	**14.29%** 1	7
Emotional distress	**14.29%** 1	**14.29%** 1	**28.57%** 2	**28.57%** 2	**14.29%** 1	7

Eleven (11) patients described the following adverse events experienced with the therapies they have used:

Answer Choices	Responses	
High blood pressure	36.36%	4
Diarrhea	36.36%	4
Elevation of proteins in the urine	0.00%	0
Feel like throwing up	27.27%	3
Head pain	9.09%	1
Intense abdominal pain	0.00%	0
Joint pain	18.18%	2
Loss of appetite	36.36%	4
Low energy	100.00%	11
Muscle pain	36.36%	4
Painful, red or swollen mouth	9.09%	1
Throwing up	27.27%	3
Tingling, pain, redness and edema of hands and feet	18.18%	2
Voice disorder	36.36%	4
Weight loss	45.45%	5
Total Respondents: 11		

Three (3) respondents identified financial challenges when accessing therapies to treat thyroid cancer.

3.1.3 Impact of differentiated thyroid cancer and Current Therapy on Caregivers

Thyroid Cancer Canada reported that it received a total of 6 caregiver respondents.

Five (5) respondents identified the following caregiver issues:

- access to specialty physicians (40%, n=2)
- demands on personal time (40%, n=2)
- managing work and caregiving (40%, n=2)
- access to appropriate therapies (20%, n=1)

Six (6) respondents said current treatments affect caregivers in the following ways:

- frequent physician visits (83%, n=5)
- frequent and ongoing assessment for effectiveness (83%, n=5)
- therapies are expensive and affect income (17%, n=1)

Six (6) respondents identified the following challenges for caregivers in dealing with the adverse effects related to the current therapy a loved one is taking:

- fear of recurrence or disease progression (100%, n=6)

- fatigue (50%,n=3)
- managing diet due to painful or swollen mouth, or dry mouth/throat (17%, n=1)

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Lenvatinib

When asked about the unmet needs with current therapies they have tried, Thyroid Cancer Canada indicated that six (6) respondents reported the following:

Answer Choices	Responses	
Disease not being managed/controlled	**16.67%**	1
Weight issues	**50.00%**	3
Fatigue greater than can be managed	**33.33%**	2
Issues with appetite	**16.67%**	1
Pain	**0.00%**	0
Other (please specify)	**33.33%**	2
Total Respondents: 6		

Of note, Thyroid Cancer Canada indicated that for the two (2) respondents who responded '*other*', the unmet need was managing bowel issues and diarrhea.

One (1) respondent interviewed by telephone indicated that they will be starting lenvatinib on May 1, 2016 and anticipates that in addition to slowing disease progression, she will not have gastrointestinal (GI) issues, including loss of appetite, weight loss, diarrhea and abdominal discomfort that she had on previous treatments.

One (1) respondent said she understands it may be a similar experience as sorafenib, where she will need to balance the dose to get the positive impact, while minimizing side effects. The respondent reported that she started at 800 mg of sorafenib and had terrible side effects (mostly GI related), then was reduced to 600 mg of sorafenib.

Thyroid Cancer Canada reported that four (4) respondents who completed the online survey have experience with lenvatinib.

Respondents indicated the positive effects of lenvatinib include:

- Reduction in the progression of thyroid disease (100%, n=4)
- Reduced the effects of thyroid cancer (50%, n=2)
- Improved overall wellness (50%, n=2)
- Decreased the side effects from other treatments (50%, n=2)

Three of the four respondents who had experience with lenvatinib indicated the following negative effects of lenvatinib:

- Increased fatigue (100%, n=3)
- Increased weight loss (67%, n=2)

Three of the four respondents who have experience with lenvatinib indicated the following symptoms that lenvatinib manages better than current therapy were:

- Skin rash (100%, n=3)
- Pain (33%, n=1)
- Maintaining a healthy appetite (33%, n=1)

Weight loss, swallowing difficulties, dry mouth were not noted as either better or worse for respondents taking lenvatinib.

In terms of adverse effects with using lenvatinib, three of the four respondents who have experience with lenvatinib indicated the following:

- Increased fatigue (67%, n=2)
- Decreased appetite (67%, n=2)
- Diarrhea (67%, n=2)
- High blood pressure (33%, n=1)

All four (4) respondents who completed the online survey and have experience with lenvatinib said that lenvatinib was easy to use. One (1) respondent interviewed said that when he was having difficulty swallowing, lenvatinib was not a problem to swallow, but felt that if the pill were any bigger, he would have had an issue.

In telephone interviews, all eight (8) respondents had experience with lenvatinib. According to Thyroid Cancer Canada, respondents taking lenvatinib felt really good. Thyroid Cancer Canada noted that seven (7) respondents commented on fatigue, with two (2) respondents noting mild diarrhea, but much better than previous treatments.

One (1) respondent interviewed noted that his lymph nodes shrank dramatically since beginning lenvatinib in the fall, 2015. This respondent stated:

- "*I'm alive today because of (Lenvima). Last year, I was in rough shape, spiralling downhill very quickly in early 2015 with few options left. I'm still working full time because of this drug and very grateful that I can get it through special access.*"

Respondents also provided the following comments in the online survey about the overall impact that lenvatinib had on their health and well-being:

- "*Lenvima has literally been a life-saver. It stopped the progression of my disease last year when that progression was becoming quite serious. The only direct side effect that I can confidently attribute to Lenvima is diarrhea, which is manageable. I can still work full time.*"
- *"It has reduced bony cancerous lesions and other tumours. I believe Lenvima has given me much loved extra time but the quality of life has suffered."*
- *"Lenvima is easy to take. More energy. On current dosage, mouth sores are manageable. Better appetite."*
- *"So far pretty much stop(ped) progression of disease."*

3.3 Additional Information

None provided.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of lenvatinib:

Clinical factors:

- Unmet need for patients with refractory differentiated thyroid cancer
- High rate of serious adverse events requiring dose adjustment or dose withdrawal

Economic factors:

- Very small patient population compared to other cancers
- Percentage of patients eligible for treatment may be high

Please see below for more details.

4.1 Factors Related to Comparators

PAG noted that there is no current standard of care for the treatment of differentiated thyroid cancer that is refractory to radioactive iodine. Patients may be treated with doxorubicin based therapy, in some provinces, or receive best supportive care or palliative care.

4.2 Factors Related to Patient Population

There is a small number of patients with radioactive iodine refractory differentiated thyroid cancer. There is an unmet need for these patients, as no other treatments are widely funded for this indication, and lenvatinib will provide an oral treatment option for these patients.

PAG has concerns on the high rate of grade 3 and 4 serious adverse events and is seeking information on the impact on quality of life. In addition, PAG is seeking information on whether reduced doses would impact the benefits demonstrated in the trial with the 24mg dose.

4.3 Factors Related to Dosing

The continuous once daily dosing schedule is convenient for patients. However, PAG noted that two different strengths of capsules are required for the 24mg dose. Information provided at the time of the PAG input indicates that 10mg capsules and 4mg capsules would be available. Thus, patients would need to take two 10mg capsules plus one 4mg

capsules for the 24mg dose. PAG has some concerns that there may be the potential for dispensing error and/or dosing error with the two different strengths.

PAG noted that the Notice of Compliance issued by Health Canada includes 4mg, 10mg, 14mg and 24mg capsules. The availability of the 24mg capsules would reduce pill burden and the potential for dosing errors. However, there may be the potential for drug wastage if adverse events are experienced at the start of therapy and dose reduction is required prior to completion of the 24mg capsules.

4.4 Factors Related to Implementation Costs

Since lenvatinib is administered orally, PAG noted that chemotherapy units and chair time would not be required. This is an enabler to implementation.

Although the number of patients with radioactive iodine-refractory differentiated thyroid cancer is relatively small compared to other cancers, PAG noted there could be a significant incremental budget impact due to the number of patients who are currently not receiving treatment but would be eligible to receive lenvatinib.

Lenvatinib is a new drug and health care professionals will need to become familiar with monitoring the serious adverse events and the frequent dose adjustments.

4.5 Factors Related to Health System

Additional health care resources (including but not limited to nursing, laboratory, pharmacy, family physicians and other clinicians) are required to rigorously monitor and treat serious adverse events associated with lenvatinib. With the high incidence of serious adverse events, coordination of resources are important in obtaining baseline status, regular vigilant monitoring and management.

PAG noted that lenvatinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.6 Factors Related to Manufacturer

PAG is seeking information from the manufacturer on if and when the 14mg and 24mg capsules would be available in Canada.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Three individuals or groups of clinicians provided input:

1. Dr. Murali Rajaraman, jointly with Dr. Nathan Lamond and Dr. Stephanie Snow
2. Dr. Ralf Paschke
3. Dr. Shereen Ezzat

Their input is summarized below.

Overall, the clinicians providing input feel that lenvatinib fills an unmet need for patients with radioactive iodine refractory thyroid cancer. They noted that lenvatinib provides an oral treatment option for a small number of patients and believe that lenvatinib demonstrates survival benefits.

Please see below for details of specific input received from the registered clinicians.

5.1 Current Treatment(s) for Differentiated Thyroid Cancer

The clinicians providing input noted treatment options for recurrent or refractory thyroid cancer are very limited. Patients are typically offered additional surgery when feasible, or occasionally, additional radioactive iodine. They noted that although sorafenib is approved for the treatment of refractory thyroid cancer, sorafenib has very limited benefit with significant adverse effects and is not a funded treatment option.

5.2 Eligible Patient Population

The clinicians providing input reported that although the incidence of thyroid cancer is rising more quickly than any other cancer and the prevalence even more so, the number of cases of radioactive iodine refractory differentiate thyroid cancer who would be eligible for current targeted drug therapy is very low. They estimated that 10 to 20 percent of all patients with thyroid cancer would be eligible for treatment with lenvatinib.

5.3 Identify Key Benefits and Harms with Lenvatinib

The clinicians providing input identified the following benefits of lenvatinib:

- Oral therapy with once daily dosing schedule
- Reduction in disease progression for patients who have failed all other therapies
- Significant prolongation of disease free survival and progression free survival
- Recent analysis controlling for patient crossover from placebo to lenvatinib in the pivotal phase III trial, suggests an overall survival advantage as well

Harms identified include

- Rash, hypertension, proteinuria, fatigue, diarrhea – all of which are manageable
- Hand/foot syndrome and bone marrow suppression, which may become difficult to manage.

5.4 Advantages of Lenvatinib Over Current Treatments

The clinicians providing input consider this an unmet need, as there is no good systemic therapy option for these patients.

Dr. Rajaraman, Dr. Lamond and Dr. Snow, in their joint input, believe that lenvatinib is clinically superior to current therapies, including sorafenib. Cytotoxic drugs such as doxorubixcin have been extremely toxic to our patients with data suggesting < 10 % response rates. They stated that these cytotoxic drugs are no longer a standard option at their institution. They noted that the only other drug approved for RAI-R DTC is sorafenib, which they noted that has not been a very good option in their patients due to limited progression free survival benefit and decreased quality of life for a few months of benefit for those whose disease are incurable and treatment intent is palliative.

Dr. Ezzat felt that in the subset of patients who require TKI therapy, the choice of more agents will likely prove beneficial. This can be relevant in terms of gains where one agent's efficacy and/or adverse effects limit drug selection and/or options.

5.5 Sequencing and Priority of Treatments with Lenvatinib

Dr. Rajaraman, Dr. Lamond and Dr. Snow, in their joint input, believe that lenvatinib should be first line therapy, considering lenvatinib has much better response rate and progression free survival benefit compared to sorafenib. Additionally, considering the costs of this class of drugs, it is important to be as cost-efficient as possible when using them.

Dr. Ezzat noted that the exact position of lenvatinib relative to other agents will remain to be seen. In the absence of specific studies addressing the place in therapy of lenvatinib, the addition, and not substitution of this agent, will prove critical in managing this disease.

5.6 Companion Diagnostic Testing

There are no companion diagnostic tests required to include/exclude patients for treatment with lenvatinib.

5.7 Additional Information

Dr. Rajaraman, Dr. Lamond and Dr. Snow, in their joint input, indicated that as clinical experience continues with lenvatinib, it would be critical to track toxicities - especially hypertension and gastrointestinal toxicity. They have identified that rigorous quality of life measured would be important, as these patients are not curative and it is important to weigh any degree of quality of life detriment against a survival benefit in such patients. They believe good data in these areas are critical to individualized decision-making.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of lenvatinib (Lenvimar) on patients outcomes compared to placebo in patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (RR-DTC).

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

Critical appraisal of an indirect treatment comparison of lenvatinib and sorafenib in patient with radioiodine-refractory differentiated thyroid cancer

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 3: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized controlled trials (published and unpublished)	Adult patients (≥18 years) who had received no prior therapy with a TKI or had received one prior treatment regimen with a TKI and had measurable iodine-131–refractory, differentiated thyroid cancer, as	Lenvatinib at 24 mg per day in 28-day cycles	Placebo Sorafenib [a]	Efficacy • PFS • OS • ORR • HRQoL

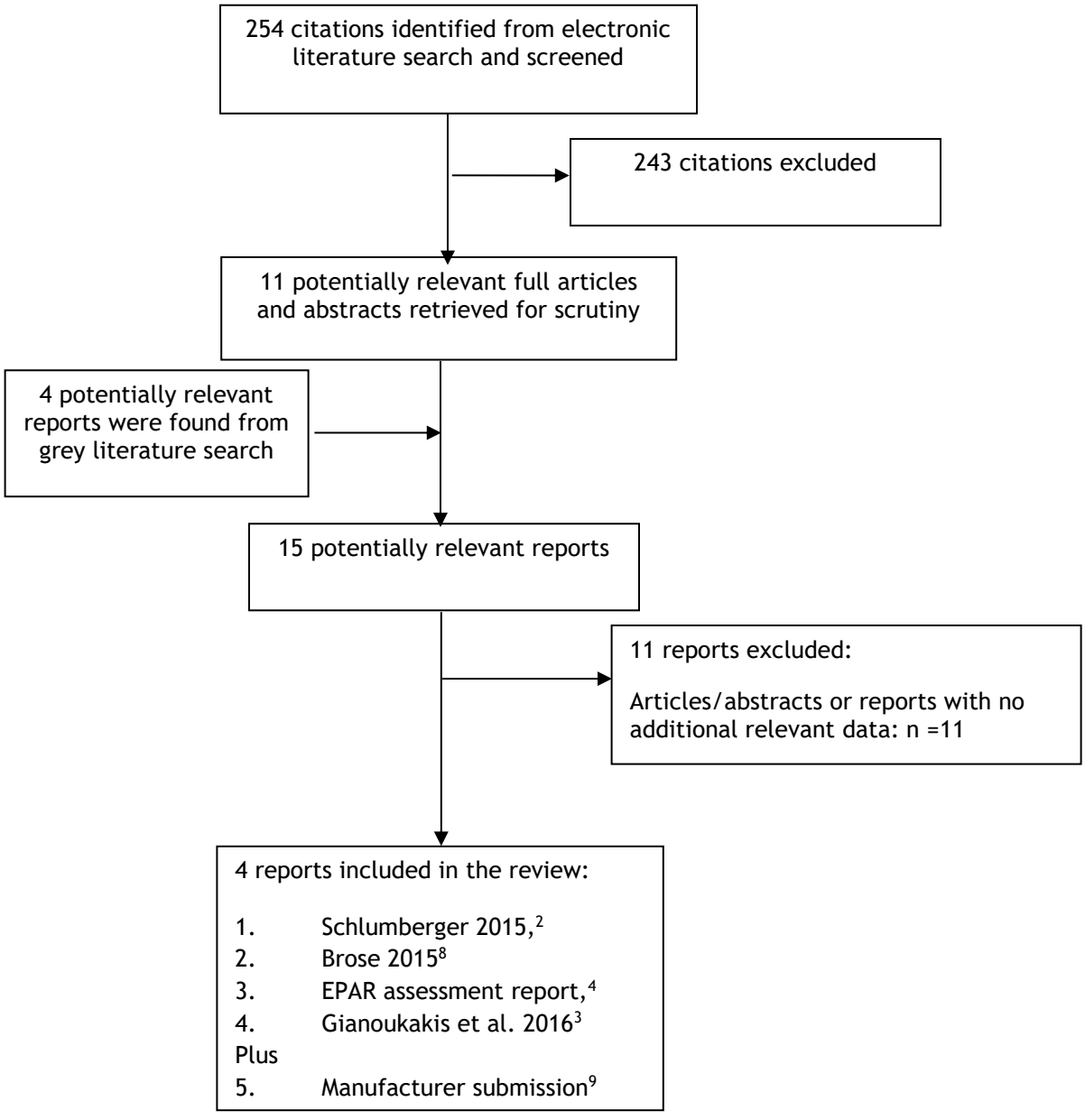
Table 3: Selection Criteria				
Clinical Trial Design	**Patient Population**	**Intervention**	**Appropriate Comparators***	**Outcomes**
	determined by at least one of the following criteria: • ≥ 1 measurable lesion without iodine uptake on any iodine-131 scan, • ≥ 1 measurable lesion that had progressed according to RECIST 1.1 criteria within 12 months after iodine-131 therapy despite iodine-131 avidity at the time of treatment, and • Radiologic evidence of progression within the previous 13 months. **Subgroups:** ○ Patients who were naïve to therapy with a TKI versus patients who had received one prior treatment regimen with a TKI ○ Patients who were ≥ 65 years old versus patients who were < 65 years old.	Each on a background of best standard care		<u>AEs</u> • Overall SAEs • Overall AEs • WDAEs • Dose reduction <u>AEs of Special Interest</u> • Hypertension • Diarrhea • fatigue/asthenia • Proteinuria • Decreased appetite • weight loss, • Nausea and • Stomatitis • Hand-and-foot syndrome
AE, adverse events; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; HRQoL, health-related quality of life; SAE, serious adverse event; TKI, tyrosine kinase inhibitor; WDAE, withdrawal due to adverse event. ** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)* *[a] Study comparing lenvatinib to sorafenib was not found. However, indirect comparison between the two drugs provided by the manufacturer has been summarized in Section 7 – SUPPLEMENTAL QUESTIONS*				

6.3 Results

6.3.1 Literature Search Results

Two hundred and fifty-four citations were identified through literature search, of which 11 were considered potentially relevant. Four potentially relevant papers were found through a grey literature search. Of these potentially relevant reports identified, four papers[2-4,8] were included and 12 studies were excluded. Reports were excluded because they were abstracts or articles based on the already included study and provided no additional relevant data. Together with the collective manufacturer submission,[9] data from a total of five reports were included in this pCODR review.

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

One clinical trial, the SELECT study met the inclusion criteria for this systematic review. The SELECT study was a multicenter, phase III, double-blind randomized controlled trials which evaluated the efficacy and safety of lenvatinib in patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (RR-DTC), compared to placebo. The characteristics of the study have been summarized in Table 4

Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Studies[2,10]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study ID: SELECT Trial; NCT01321554 or E7080-G000-303 Phase 3, double-blind, placebo-controlled, RCT; randomized in 2:1 ratio (Lenvatinib : Placebo) N = 392; n = 392 Number of centres = 150[10] Number of countries = 21 Start Date: 05 Aug 2011 Data cut-off: 15 Nov, 2013 Database lock Date: 24 Jan 2014 Funded by Eisai	<u>Key Inclusion Criteria:</u> Adult patients (≥ 18 years) with measurable, pathologically confirmed DTC, no prior therapy with TKI or had received one prior regimen of TKI, radiologic evidence of progression within the previous 13 months, and having evidence of iodine-131–refractory disease meeting the following criteria using 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 progressive 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, <u>Key Exclusion Criteria:</u> Patients with anaplastic or medullary thyroid cancer; any other malignancy within the past 24 months; any anticancer treatment 21 days before randomization; and proteinuria ≥1g/24 hours.	Intervention: Lenvatinib Comparator: Placebo	<u>Primary:</u> Progression-free Survival (PFS) <u>Secondary:</u> Overall Response Rate (ORR)

DTC = differentiated thyroid cancer; ECOG = Eastern Cooperative Oncology Group; N = number of patients randomized; n = number of patients treated; RCT = randomized controlled trial; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; TSH = thyroid-stimulating hormone; TKI = tyrosine kinase inhibitor;

a) Trials

Patients were randomized in a 2:1 ratio to receive lenvatinib or placebo. Key eligibility criteria for inclusion into the studies have been listed in Table 4. Other inclusion criteria were thyroid-hormone-suppression therapy with thyroid-stimulating hormone (TSH) levels of ≤0.50 mIU/L; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; adequately BP control (≤150/90 mmHg); and adequate renal, bone marrow, coagulation, and liver function.[10] In addition to key exclusion criterial in Table 4, patients were also excluded if they had two or more prior vascular endothelia

growth factor (VEGF) or VEGF receptor-targeted therapies; or significant cardiovascular or gastrointestinal dysfunction.[10] Randomization was stratified by age(<65 years versus ≥65 years), geographic region, and receipt or non-receipt of prior tyrosine kinase inhibitor (TKI) treatment.

The SELECT study was designed to have 90% power to detect a 75% improvement in progression-free survival (PFS) with lenvatinib versus placebo (hazard ratio for progression or death, 0.57) at a two-sided alpha level of 0.01, assuming a median PFS of 14 months in the lenvatinib group and 8 months in the placebo group.[2] At least 214 progression events or deaths in 392 enrolled patients were required for the primary analysis of PFS.[2]

b) Populations

Three-hundred and ninety-two patients were randomized on a 2:1 basis to receive lenvatinib (n=261) or placebo (n=131). The age of the patients ranged from 21 years to 89 years, with the majority (60.2%) ≥ 65 years, and median ages of 64 and 61 years in the lenvatinib and placebo groups, respectively. The demographic and disease characteristics of patients were generally similar across treatment groups at baseline (Table 5). The race of the study population was predominantly white (79.7%) with nearly half of the total population from in Europe, and one-third from North America. The majority of patients (80.4%) had less than three months of disease progression at the time of randomization. Most of the patients (76.3%) had not had prior therapy with TKI inhibitors.

Table 5: Baseline Characteristics of Randomized Patients in the SELECT Trial[2,9]

	LEN, (N = 261)	Placebo, (N = 131)
Age in years,		
Median (range) ≥ 65 years n (%)[10]	64 (27, 89) 155 (59.4)	61 (21,81) 81 (61.3)
Sex		
Male	125 (47.9)	75 (57.3)
Race, n (%)[10]		
Asian White Other	46 (17.6) 208 (79.7) 7 (2.7)	24 (18.3) 103 (78.6) 4 (3.1)
Geographical Region, n (%)		
Europe North America Other	131 (50.2) 77 (29.5) 53 (20.3)	64 (48.9) 39 (29.8) 28 (21.4)
ECOG PS n (%)		
0 or 1 2 or 3	248 (95.0) 13 (5.0)	129 (98.5) 2 (1.5)
Target Tumor size (mm), n (%)		
≤ 35 35 - 60 61 – 92 > 92	65 (24.9) 72 (27.6) 63 (24.2) 61 (23.4)	28 (21.4) 32 (24.4) 34 (26.0) 37 (28.2)
Metastatic disease Status		
Locally advanced IR-DTC	4 (1.5)	0
Metastatic IR-DTC	257 (98.5)	131 (100.0)
Site of metastatic disease >10%, n (%)		
Lung metastases	226 (86.6)	124 (94.7)
Lymph node metastases	138 (52.9)	64 (48.9)
Bone metastases	104 (39.8)	48 (36.6)
Pleural metastases	46 (17.6)	18 (13.7)
Liver metastases	43 (16.5)	28 (21.4)

Table 5: Baseline Characteristics of Randomized Patients in the SELECT Trial[2,9]		
	LEN, (N = 261)	**Placebo, (N = 131)**
Histology subtype of DTC, n (%)		
Papillary Follicular (Hürthle-cell) Follicular, (not Hürthle-cell) Poorly differentiated	132 (50.6) 48 (18.4) 53 (20.3) 28 (10.7)	68 (51.9) 22 (16.8 22 (16.8) 19 (14.5)
TKI treatment history		
TKI naïve	195 (74.7)	104 (79.4)
One prior TKI treatment	66 (25.3)	27 (20.6)
Type of therapy, n (%)		
Sorafenib	51 (19.5)	21 (16.0)
Sunitinib	5 (1.9)	3 (2.3)
Pazopanib	3 (1.1)	2 (1.5)
Other	7 (2.7)	1 (0.8)
Time from disease progression to randomization		
< 3 months ≥ 3months	215 (82.4) 46 (17.6)	100 (76.3) 31 (23.7)
TSH level (mU/L)		
≤ 0.5 > 0.5 – 2.0 > 2.0 – 5.5	226 (85.6) 25 (9.6) 10 (3.8)	120 (91.6) 10 (7.6) 1 (< 1.0)
DTC = differentiated thyroid cancer; ECOG = Eastern Cooperative Oncology Group; Len = lenvatinib; PS = performance status; THS = thyroid stimulating hormone; TKI =tyrosine kinase inhibitor		

Sources: Schlumberger et al 2015,[2] Schlumberger et al 2016 Suppl. Appendix[10]

c) Interventions

Patients were treated with either oral lenvatinib 24 mg once daily or matching placebo in 28-day cycles. Dose interruptions and incremental reductions in the dose because of toxic effects were permitted.[2] Dose reductions occurred in succession (24 mg, 20 mg, 14 mg, and 10 mg once daily) based on the previous dose level. Any dose reduction below 10 mg once daily had to be discussed with the sponsor. Patients treated with reduced dose, could not have dose increases at a later date. During the randomization phase, 111 (42.5%) of patients received 24 mg daily dose of lenvatinib, while 30 (11.5%) received 20 mg daily dose of lenvatinib. Other daily lenvatinib doses administered during the randomization phase were 14 mg, 10 mg, and <10 mg, which were given to 66 (25.3%), 40 (15.3%), and 14 (5.4%) of patients, respectively. Of the 109 patients who entered the optional open-label (OOL) extension phase, 27 had the reduced dose of 20 mg once daily. The mean lenvatinib dose was 17.2 mg per day in the double-blind phase. The median (interquartile range) duration of follow-up was 17.1 (14.8 to 20.4) months (95% confidence interval [CI]: 16.0, 17.6); in the lenvatinib group and 17.4 (14.8 to 20.4) months (95% CI: 15.9, 19.0) in the placebo group. The median duration of treatment was 13.8 months in the lenvatinib group and 3.9 months in the placebo group.

d) Outcome Measures

Efficacy outcomes

Efficacy outcomes of interest for this review include progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and health related quality of life (HRQoL). Progression-free survival, defined as the time from randomization to the first documentation of disease progression by independent radiologic review or to death, in the intention-to-treat population (ITT) was the primary efficacy outcome of the SELECT trial. Secondary end points of the study were the response rate, defined as the

best objective response (complete or partial) and OS, which was defined as the time from randomization until death from any cause. Patients' health-related quality of life was not assessed in the SELECT study. Tumor assessments were performed in a blinded manner every 8 weeks by a central imaging laboratory, according to RECIST, version 1.1 criteria.

Safety Outcomes

Patients were monitored for adverse events (AEs) throughout the study according to the National Cancer Institute Common Terminology Criteria for Adverse Events. Parameters evaluated included vital signs, electrocardiography, echocardiography, hematologic and biochemical laboratory testing, and urinalysis. Analyses of safety outcomes were based on all patients who were randomized. Adverse events were reported as overall proportions of patients who reported AEs, and according to severity. Treatment-related adverse event (TRAE), treatment-related serious AE (TRSAE), AE leading to dose interruptions or reduction, grade ≥3 AEs, and withdrawal/discontinuation due to AE of treatment (WDAE) have been reported in this review.

e) Patient Disposition

Efficacy and safety analyses were based on the ITT population which included all randomized patients. At the time of cut-off for primary analysis, 122 (46.7%) patients originally randomized to lenvatinib and 8 (6.1%) patients who were randomly assigned to placebo were continuing to receive blinded treatment. Discontinuation rates were higher in the placebo group compared to the lenvatinib group, generally driven by disease progression. However, treatment discontinuation due to AEs was higher with lenvatinib than placebo (Table 6). Data on patients who were lost to follow-up and on patients who were alive at the time of the primary analysis were censored on the latest date on which the patient was known to be alive.[2]

Table: 6 Patient Disposition at Primary data analysis date (15 Nov, 2013)

	LEN	Placebo
Randomized	261	131
Treated, n (%)	261 (100)	131 (100)
Treatment ongoing at cut-off date	122 (46.7)	8 (6.1)
Patients in placebo arm who crossed over into OOL lenvatinib	NA	109 (83.2)
Discontinued treatment during double blind Phase	45 (17.2)	4 (3.1)
Primary reason for discontinuation		
Progressive disease Adverse event Patient choice Withdrawal of consent Other	94 (36.0) 37 (14.2) 4 (1.5) 4 (1.5) 0	119 (90.8) 3 (2.3) 0 0 1 (<1.0)

NA = not applicable; Len = lenvatinib; OOL = optional open-label

Source: European Medicines Agency, 2015 - EMA/250082/2015[4]

f) Limitations/Sources of Bias

- A major limitation of the SELECT is that there is uncertainty about the overall survival (OS) benefit of lenvatinib in patients with iodine refractory differentiated thyroid cancer (IR-DTC). The study was not designed to

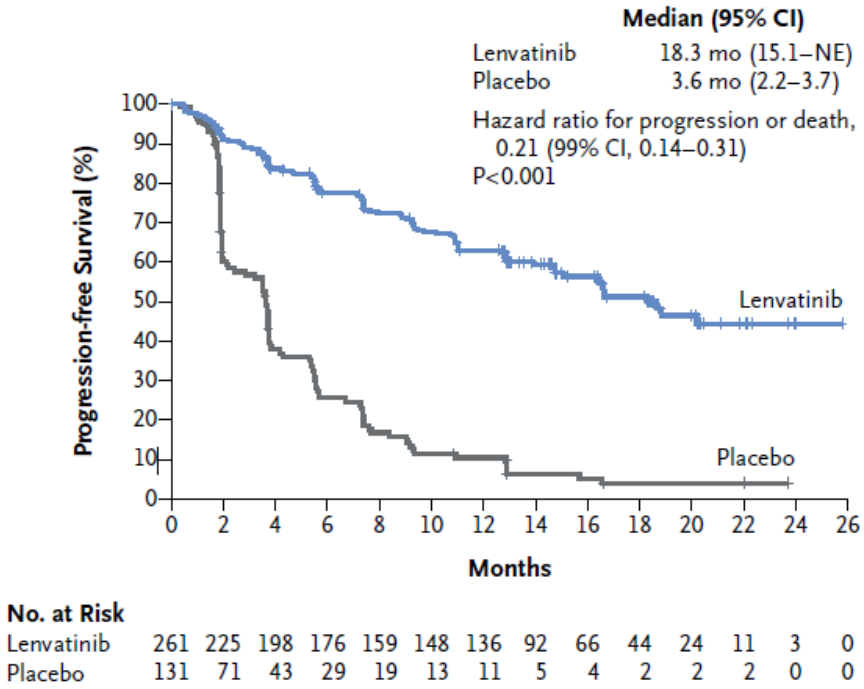
assess OS which was a secondary endpoint. At the cut-off for primary analysis and at an updated analysis seven months from the initial cut-off, the median OS was reported as not reached. Unadjusted analysis showed no statistically significant difference between lenvatinib and placebo at either point of analysis. However, a multistep statistical operation applying RPSFT model and boot strapping approach eventually resulted in statistically significant difference in OS in favour of lenvatinib. It must be noted that the OS analysis was biased by the large proportion of patients randomized to placebo who switched to the optional open-label lenvatinib treatment phase. Another source of bias was the subsequent anticancer therapy received by patients post study, which creates uncertainty about whether the observed OS benefit was due entirely to the effect of lenvatinib.

- Although the RPSFT model was applied to correct the confounding due to crossover, it required the following assumptions to be satisfied in order that the assessment on OS be valid: a) the effect of the treatment is multiplicative on time; b) the size of OS benefit is the same regardless of whether patients were randomized or crossed over to treatment and c) the benefit on OS is immediate after the treatment.[3] The bootstrapping method is normally applied in situations where data are limited, to artificially increase sample size to satisfy the normality assumptions required for statistical testing. In this case, the same patient in a study might be sampled many times thereby providing the same OS information for the purpose of creating a dataset for use applying the RPSFT model. There is uncertainty around the OS benefit of lenvatinib in patients with IR-DTC. The "true" OS benefit could lie between the OS results obtained from the unadjusted analysis and OS results obtained from using the RPSFT bootstrapping method.
- Further, the SELECT study did not assess patients' health-related quality of life (HRQoL).
- Also the exclusion criteria were restrictive and may have excluded many participants on the basis of medical conditions (e.g. ECOG PS >2, proteinuria ≥1g/24 hours; or significant cardiovascular or gastrointestinal dysfunction) and medication history (e.g. ≥2 or more prior TKI therapy). Thus the generalizability of the study findings to such IR-DTC patients who were not studied is unknown.
- This was a manufacturer-funded study.

6.3.2.1 Detailed Outcome Data and Summary of Outcome

Efficacy

Outcomes data for efficacy have been summarized in Table 7. The primary efficacy endpoint of the SELECT study was progression-free survival (PFS). Secondary endpoints were response rate (RR) and overall survival (OS). As illustrated in Figure 2, patients in the lenvatinib group had a significantly longer median PFS than those in the placebo group (18.3 versus 3.61 months), with a hazard ratio (HR) of 0.21 (99% confidence interval [CI]: 0.14, 0.31; P<0.001).



CI = confidence interval, NE = not estimable.

Figure 2: Kaplan-Meier Estimate of Progression-free Survival in the Intention-to-Treat Population. Data cut-off date: 15 Nov 2013.[2]

Reduced tumor size (the response rate) occurred in a significantly higher proportion of patients (64.8%) treated with lenvatinib than those in the placebo group (1.5%), with an odds ratio (OR) of 28.87 (95% CI: 12.46, 66.86; $P < 0.001$). The overall tumor size reduction was the sum of complete responses (CR) and partial responses (PR). The median time to response was 2.0 months (95% CI: 1.9, 3.5) for lenvatinib and 5.6 months (95% CI: 1.8, 9.4) for placebo (Table 7).

An updated analysis (data cut-off of 31 August 2015) showed that 60.2% of patients responded to lenvatinib treatment with a median duration of overall response (DOR) of 30 months (95% CI: 18.4, 35.2) compared to 2.3% of patient who responded to placebo, with a median DOR of 14.7 months (95% CI: 7.5, not evaluable [NE]).[1]

The median overall survival was not reached in either group at the time of primary analysis, and OS was not significantly different between lenvatinib and placebo (HR = 0.73; 95% CI: 0.50, 1.07; $P = 0.103$) (Figure 3). The OS outcome was potentially confounded by the large proportion of patient (83%) who switched from the placebo arm, due to disease progression, to receive lenvatinib in the optional open label (OOL) extension Phase. The rank-preserving structural failure time (RPSFT) model was used to correct the crossover effect, resulting in adjusted HR for OS of 0.62 (95% CI: 0.40, 1.00). Thus there was a trend indicating a longer survival for the lenvatinib arm versus the placebo arm, although the difference was not statistically significant (Figure 4).

However, a multistep statistical operation involving the RPSFT model and a bootstrapping approach (resampling method) eventually resulted in statistically significant difference in OS in favour of lenvatinib (HR = 0.53; 95% CI: 0.34, 0.82; *P* = 0.0051)(Figure 5). The bootstrapping method is normally applied in situations where data are limited, to artificially increase sample size to satisfy the normality assumptions required for statistical testing. In this case, the same patient in a study might be sampled many times thereby providing the same OS information for the purpose of creating a dataset for use in the RPSFT model. Further, it is uncertain whether the assumptions of the RPSFT model (listed in the Limitations section) can be satisfied in real-life clinical practice.

Therefore, taken together, there is uncertainty about the OS benefit of lenvatinib in patients with IR-DTC.

Table 7: Key efficacy outcomes of the SELECT study[2] at primary analysis

	LEN, **(N=261)**	**Placebo, (N=131)**
Median (95% CI) PFS, Months	18.3 (15, NE)	3.6 (2.2, 3.7)
HR (99% CI)for PFS	0.21 (0.14, 0.31) *P* < 0.001	
Updated median PFS, months	19.4	3.7
HR (99% CI)	0.24 (0.17, 0.35); *P*< 0.0001	
Median OS (months) [a]	Not reached	Not reached
Primary analysis		
HR (95% CI); (unadjusted)	0.73 (0.50, 1.07); *P* = 0.103	
HR (95% CI); (RPSFT-adjusted)	0.62 (0.40, 1.00); *P* = 0.051	
15 Jun 2014 data cut		
HR (95% CI); (unadjusted)	0.80 (0.57, 1.12); *P* = 0.1993	
HR (95% CI); (RPSFT-adjusted bootstrapping approach)	0.53 (0.34, 0.82)); *P* = 0.0051	
ORR, n (%)	169 (64.8)	2 (1.5)
Odds ratio (95% CI)	28.87 (12.46, 66.86); *P* < 0.001	
– CR	4 (1.5)	0 (0.0)
– PR	165 (63.2)	2 (1.5)
– SD	60 (23.0)	71 (54.2)
– Durable SD ≥ 23 weeks	40 (15.3)	39 (29.8)
Time to first OR, months (95% CI)	2.0 (1.9, 3.5)	5.6 (1.8, 9.4)
Median overall response	157 (60.2)	3 (2.3%)
Median**(95% CI)** duration of overall response, (months)	30 (18.4, 35.2)	14.7 (7.5, NE)

CI = confidence interval; CR = complete response; HR = hazard ratio; Len = lenvatinib; N.E. = not estimated; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PR = partial response; RPSFT = rank-preserving structural failure time; SD = stable disease

[a] The analysis of OS was reported both as unadjusted and as adjusted for a potential crossover bias with the use of the RPSFT model

Sources: Schlumberger et al 2015,[2] Schlumberger et al 2016 Suppl. Appendix,[10] Gianoukakis, 2016[1]

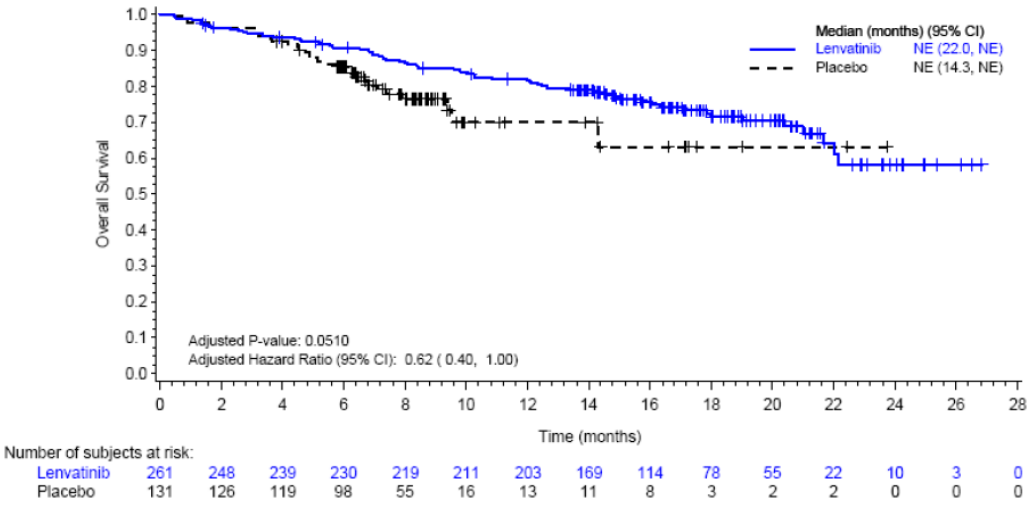
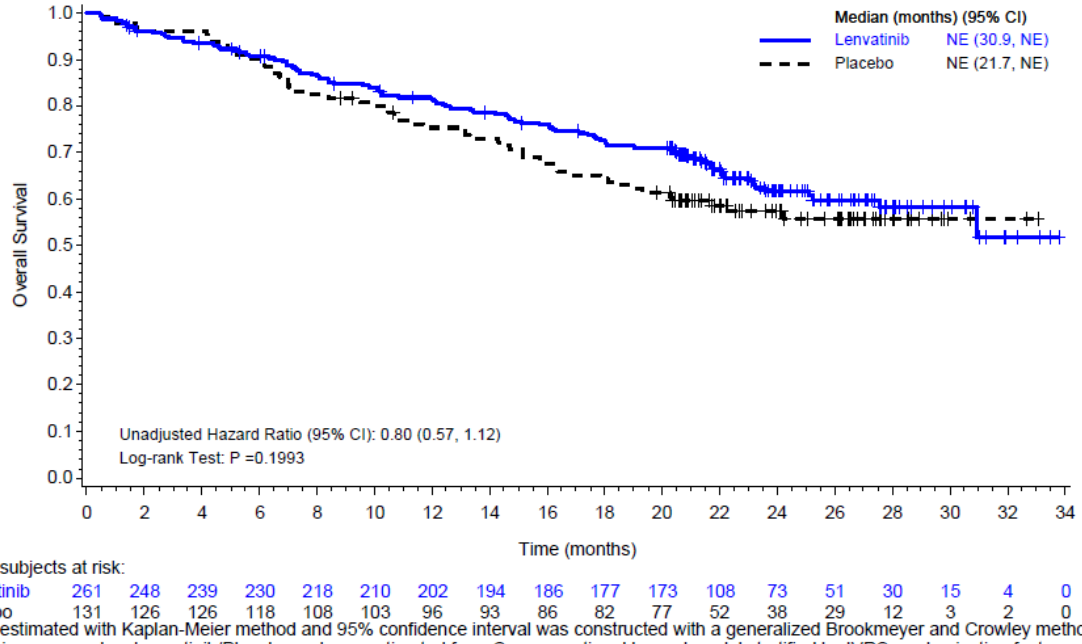


Figure 3: Kaplan-Meier Plot of Overall Survival - Unadjusted Model – Full Analysis Set. Data cut-off date: 15th November 2013)

Source: pCODR submission[9]

Figure D80.R103.303.1
Kaplan-Meier Plot of Overall Survival - Unadjusted
Full Analysis Set



Median was estimated with Kaplan-Meier method and 95% confidence interval was constructed with a generalized Brookmeyer and Crowley method.
Hazard ratio is expressed as Lenvatinib/Placebo and was estimated from Cox proportional hazard model stratified by IVRS randomization factors.
Data cutoff date is 15JUN2014

Figure 4: Kaplan-Meier Plot of Overall Survival - Unadjusted Model – Full Analysis Set. Data cut-off date: 15th June 2014)

Source: EPAR report for Lenvima, European Medicines Agency[4]

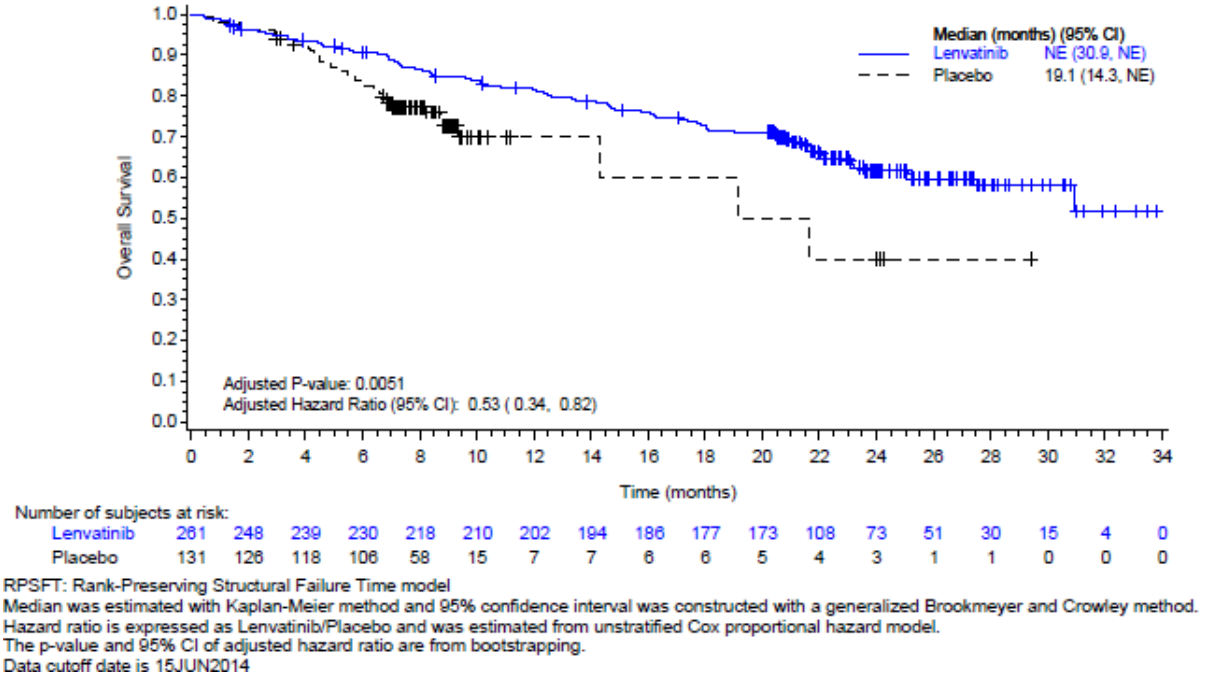


Figure 5: Kaplan-Meier Plot of Overall Survival Adjusted with RPFST Model. Data cut-off date: 15th June, 2014

Source: EPAR report for Lenvima, European Medicines Agency[4]

Quality of Life

Upon request by the Methods Team, the submitter provided an abstract for the 86th Annual Meeting of the American Thyroid Association; September 21–25, 2016, which has summarized descriptive data of patient relevant outcomes of 38 patients treated with lenvatinib. The study population was 81.6% white and the mean age was 63.3 years. The mean time since the diagnosis of RR-DTC was 3.3 years. Lenvatinib was the first-line treatment in 21.6% of the patient. Outcome measure included Functional Assessment of Cancer Therapy-General (FACT-G), and EuroQol five dimensions with five levels scale (EQ-5D-5L) scores. Overall, the FACT-G and EQ-5D-5L scores were similar among groups and slightly lower compared to normative data. Patients who received lenvatinib as first-line scored higher than those who received lenvatinib as second-line treatment in FACT-G overall domain (74.03 versus 69.92) and the EQ-5D-5L mean health utility(0.76 versus 0.71). When the EQ-5D data from 38 LEN patients were stratified by current health state, patients with the highest health utility were patients with improving disease status (mean: 0.75). All health utility index values decrease as stage of disease decreased.

It must be noted that the abstract was based on a small sample size, not peer reviewed, and the methodological quality of the observational study which reported the data could not be assessed since there was not enough information to do so.

6.3.2.2 Subgroup analysis of Efficacy outcomes

The PFS benefit associated with lenvatinib was observed in all pre-specified subgroups including age (≤65 years versus >65 years) and no prior therapy with TKI or one prior TKI treatment (Table 8). Younger patients (≤ 65 years) had a longer PFS than older patients (20.2 months versus 16.7 months). Patients with no prior TKI therapy had a longer median PFS than patients who had received prior TKI therapy (18.7 months versus 15.1 months). Treatment with lenvatinib was also associated with statistically significantly improved OS in patients >65 years of age compared to placebo (HR = 0.53; 95% CI: 0.31, 0.91; *P* =0.020).

Table 8: Analysis of PFS based on age and TKI therapy history

	Age				TKI therapy history			
	≤ 65 years		>65 years		TKI naive		One TKI therapy	
	LEN, (N=155)	Placebo (N=81)	LEN, (N=106)	Placebo (N=50)	LEN, (N=195)	Placebo (N=104)	LEN, (N=66)	Placebo (N=27)
Median PFS, Months	20.2	3.2	16.7	3.7	18.7	3.6	15.1	3.6
HR (95% CI) for PFS	0.19 (0.13, 0.27)		0.27 (0.17, 0.43)		0.20 (0.14, 0.27)		0.22 (0.12, 0.41)	
Median OS, Months	NE (22.0, NE)	NE (NE, NE)	NE (22.1, NE)	18.4 (13.3, 20.3)	NR	NR	NR	NR
HR (95% CI) for OS	0.98 (0.58, 1.66)		0.53 (0.31, 0.91)		NR		NR	
P value	0.933		0.020		NR		NR	

CI = confidence interval; CR = complete response; HR = hazard ratio; Len = lenvatinib; N.E. = not estimated; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PR = partial response; RPSFT = rank-preserving structural failure time; SD = stable disease

Sources: Schlumberger et al 2016 Suppl. Appendix,[10] Manufacturer submission 04.01_LENVIMA_PE Evaluation_Report[9]

Harms Outcomes

The proportion of patients who reported at least one adverse event (AEs) was high in each treatment group, although higher in the lenvatinib group than the placebo group (97.3% versus 59.5%). The most commonly reported treatment-related adverse events (TRAEs) were hypertension and diarrhea; occurring in 67.8% versus 9.2% and 59.4 versus 8.4% of patients in the lenvatinib and placebo groups, respectively (Table 9).[2] Others common TRAEs included fatigue (59.0% versus 27.5%), decreased appetite (50.2% versus 11.5%), weight loss (46.4% versus 9.2%) nausea (41.0% versus 13.7%), stomatitis (35.6% versus 3.8%) and proteinuria (31.0% versus 1.5%).

The most commonly reported grade ≥3 treatment-related adverse events (lenvatinib versus placebo) were hypertension (41.8% versus 2.3%) and proteinuria (10.0% versus 0) (Table 9). Others common grade ≥3 treatment-related adverse events included weight loss (9.6% versus 0), fatigue (9.2% versus 2.3%), diarrhea (8.0% versus 0), and decreased appetite (5.4% versus 0).

The overall incidence of treatment-emergent adverse events (TEAEs) or grade 3-4 TEAEs were similar in patients who were ≥65 years and those <65 years age.[4]

The incidence of treatment-related serious AEs was 30.3% in the lenvatinib group compared with 6.1% in the placebo group (Table 10). Similarly, AEs leading to dose interruptions, dose reduction, or discontinuation of study drug occurred more frequently in the lenvatinib group than in the placebo group. Six deaths (2.3%), considered to be drug-related, occurred in the lenvatinib group during the treatment period. There was no drug-related death reported in the placebo group.

As of February 12, 2016, there was an estimated 4,700 patients exposed to lenvatinib in clinical trials and post-marketing. A search of the global lenvatinib adverse event report database was performed using the MedDRA SMQs: malignant or unspecified tumours, skin neoplasms, and malignant and unspecified excluding any metastatic and disease progression terms. Thirteen cases fulfilled the search criteria. Of these 13 reports, 4 were skin cancers, 2 were haematological in origin, 1 was pre-existing, 2 were associated with an alternate more likely cause, and 4 cases were too poorly documented for medical assessment or were likely to represent metastatic disease. Only one case of cutaneous squamous cell carcinoma was considered to be possibly related to lenvatinib by the Investigator and Company. With respect to the 4 skin cancers, two were cases of squamous cell carcinoma, one was a neuroendocrine carcinoma of the skin and one was a malignant melanoma.

Table 9: Adverse events of special interest of the SELECT study[2] at primary analysis

	LEN, (N=261)		Placebo, (N=131)	
Adverse Event	**Any Grade, %**	**Grade ≥ 3, %**	**Any Grade, %**	**Grade ≥ 3, %**
Hypertension	67.8	41.8	9.2	2.3
Diarrhea	59.4	8.0	8.4	0
Fatigue/asthenia	59.0	9.2	27.5	2.3
Proteinuria	31.0	10.0	1.5	0
Decreased appetite	50.2	5.4	11.5	0
Weight loss	46.4	9.6	9.2	0
Nausea	41.0	2.3	13.7	0.8
Stomatitis	35.6	4.2	3.8	0
Pulmonary embolism*	2.7	2.7	1.5	1.5
Arterial thromboembolism	14 (5.4)	7 (2.7)	3 (2.3)	1 (0.8)
Venous thromboembolism	14 (5.4)	10 (3.8)	6 (4.6)	2 (1.5)
Hand-and-foot syndrome	31.8	3.4	0.8	0

Len = lenvatinib;
* Pulmonary embolism data are for patients with at least 1 nonfatal serious adverse event

Sources: Schlumberger et al,[2] Schlumberger et al 2016 Suppl. Appendix,[10] European Medicines Agency, 2015 - EMA/250082/2015[4]

Table10: Summary of key harms outcomes of the SELECT study[2] at primary analysis		
	LEN, (N=261)	**Placebo (N=131)**
Any TEAE, n (%)	260 (99.6)	118 (90.1)
TRAE of Grade ≥ 3, n (%)	198 (75.9)	13 (9.9)
TRSAE	79 (30.3)	8 (6.1)
TRAE Deaths	6 (2.3)	0 (0.0)
AEs leading to Dose interruption	217 (83.1)	24 (18.3)
AEs leading to Dose reduction	178 (68.2)	6 (4.6)
WDAEs	46 (17.6)	6 (4.6)
AE = adverse event; Len = lenvatinib; NR = not reported; SAE = serious adverse event; TEAE = treatment emergent adverse event; TRAE = treatment-related adverse event; TRSAE = treatment-related serious adverse event; WDAE = withdrawal due to adverse event		

Sources: Schlumberger et al,[2] Schlumberger et al 2016 Suppl. Appendix,[10] European Medicines Agency, 2015 - EMA/250082/2015[4]

6.4 Ongoing Trials

No ongoing and/or unreported trials were identified that would have met the inclusion criteria for the systematic review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of lenvatinib for radioiodine-refractory DTC

- Critical appraisal of an indirect treatment comparison of lenvatinib and sorafenib in patient with radioiodine-refractory (RR) differentiated thyroid cancer (DTC)

This section provides supporting information, which has not been systematically reviewed.

7.1 Objective

The manufacturer submitted an indirect treatment comparison (ITC) between lenvatinib and sorafenib in the treatment RR-DTC. The objective of this review is to provide a summary and critical appraisal of the manufacturer provided ITC.

7.2 Summary of Indirect Comparison Analysis

7.2.1 Rationale

Sorafenib was the first and the only other drug besides lenvatinib currently approved by Health Canada to treat RR-DTC. Sorafenib was approved based on data from the Phase 3 DECISION study while the approval of lenvatinib was based on data from the SELECT study. In the absence of a head-to-head comparison between the two drugs, the manufacturer of lenvatinib indirectly compared the key efficacy data of the SELECT and DECISION studies to assess the comparative clinical effectiveness of lenvatinib as against sorafenib for the treatment of patients with progressive RR-DTC. The clinical outcomes of the SELECT study comparing lenvatinib to placebo, and the indirect comparison on lenvatinib to sorafenib inform the economic evaluation to determine the cost-effectiveness of lenvatinib to each of those alternatives for the treatment of patients with progressive RR-DTC.

7.2.2 Method

Eligibility Criteria

The SELECT and DECISION trials were generally similar in design. Each study included patients with progressive RR-DTC. Progression was assessed based on RECIST 1.1 and RECIST 1.0 in the SELECT and DECISION studies respectively. The median age in the SELECT study was 64 (range: 27, 89) years in the lenvatinib arm and 61 (24, 82) in the placebo arm. Corresponding median age for the DECICION study was 63 (24, 83 and 63 (30, 87) for the sorafenib and placebo arms, respectively. The proportions of patients with ECOG performance status of 1 or 2 were slightly higher in the SELECT study (Table 11) but the significant of the difference is uncertain. A notable difference was that whereas the DECISION study had no patients with prior VEGF or VEGFR-targeted therapy, the population of SELECT study was made up of patients who had not previously received VEGF or VEGFR-targeted therapy, or had one prior VEGF or VEGFR-targeted therapy (Table 11). Further, the DECISION trial had data for head and neck metastatic disease but the SELECT study did not; and the SELECT study had data for metastatic disease of the brain whereas the DECISION trial did not.

Table 11: Baseline demographic and clinical characteristics in the SELECT and DECISION trials				
	SELECT Trial		DECISION Trial	
	LEN, (N = 261)	Placebo, (N = 131)	SOR (N=207)	Placebo (N=210)
Age in years,				
Median age (range), years	64 (27, 89)	61 (21,81)	63 (24, 82)	63 (30, 87)
Sex, n (%)				
Male Female	125 (48) 136 (52)	75 (57) 56 (43)	104 (50) 103 (50)	95 (45) 115 (55)
Race, n (%)[10]				
White Black or African American Asian Other 	208 (80) 4 (2) 46 (18) 3 (1) 0	103 (79) 4 (3) 24 (18) 0 0	125 (60) 6 (3) 47 (23) 0 29 (14)	130 (62) 5 (2) 52 (25) 0 23 (11)
ECOG PS n (%)				
0 1 2 3 Not available	144 (55) 101 (40) 12 (5) 1 (<1) 0	68 (52) 61 (47) 2 (2) 0 0	130 (63) 69 (33) 7 (3) 0 1 (<1)	129 (61) 74 (35) 6 (3) 0 1 (<1)
Geographical Region, n (%)				
Europe North America Other	131 (50) 77 (30) 53 (20)	64 (49) 39 (30) 28 (21)	124 (60) 36 (17) 47 (23)	125 (60) 36 (17) 49 (23)
Histology subtype of DTC, n (%)				
Papillary TC Follicular TC Other	169 (65) 92 (35) 0	90 (69) 41 (31) 0	144 (70) 50 (24) 15 (70	136 (65) 56 (27) 17 (8)
Thyroid surgery, n (%)	261 (100)	131 (100)	207 (100)	208 (99)
Locally advanced DTC, n (%)	4 (2)	0	7 (3)	7 (3)
Metastatic DTC, n (%)	257 (99)	131 (100)	200 (97)	203 (97)
Site of metastasis, n (%)				
Lung metastases Lymph node metastases Bone metastases Pleural metastases Liver metastases Head and neck Brain	226 (87) 138 (53) 104 (40) 46 (18) 43 (17) NA 9 (3)	124 (95) 64 (49) 48 (37) 18 (14) 28 (21) NA 7 (5)	178 (86) 113 (55) 57 (28) 40 (19) 28 (14) 33 (16) NA	181 (86) 101 (48) 56 (27) 24 (11) 30 (14) 34 (16) NA
Prior TKI Therapy, n (%)	66 (25)	27 (21)	NA	NA
DTC = differentiated thyroid cancer; ECOG = Eastern Cooperative Oncology Group; Len = lenvatinib; PS = performance status; THS = thyroid stimulating hormone; TKI =tyrosine kinase inhibitor				

Source: Tremblay et al 2016[11] Table 2

Interventions and Comparators

Lenvatinib was administered orally at a dose of 24 mg once daily in the morning, whereas sorafenib was administered at a dose of 400 mg twice daily (taken 12 hours apart with food, at least an hour or two hours after a meal) for a total of 800 mg daily. The median follow-up time for primary analysis in the SELECT study was 23.6 and 24.1 months for the lenvatinib and the placebo arms, respectively. For the DECISION trial the median follow-up time for primary analysis was 16.2 months. In both studies, patients in the placebo group who had disease progression were permitted to crossover to receive the study drug.

Outcomes

Progression-free survival (PFS) was the primary efficacy endpoint in both the SELECT and DECISION studies. Secondary endpoints were objective response rate (ORR) and overall survival (OS).

Analysis

Patient-level data were available for the SELECT study whereas only published summary data were available for the DECISION trial. Therefore, data from the two studies were compared using matching-adjusted indirect comparison (MAIC), a technique which allows comparison of two studies with patient-level data available for one but only aggregate data available for the other. The MAIC approach adjusts for differences in baseline characteristics. Weights were assigned to data for patients in the SELECT study so that the weighted mean baseline characteristics matched those reported for patients in the DECISION trial (Table 12). Adjusted hazard ratios (HRs) for PFS and OS were calculated using COX regression models, and used to calculate indirect HRs with 95% confidence intervals (CIs). Overall survival data were corrected for crossover using rank-preserving structural failure time (RPSFT) model.

Table12: Key Patient Characteristics Before and After Adjustment

Table13: Key Patient Characteristics Before and After Adjustment			
Characteristic	**DECISION Trial**	**SELECT Trial**	
		Without weights	**With weights**
Median age, years	63.00	62.10	63.00
Male **White**	48 70	51 77	48 70
ECOG PS, mean	0.41	0.48	0.41
Geographical Region, n (%)			
Europe **North America**	60 17	48 27	60 17
Histology- Papillary TC %	67	65	67
Metastatic DTC, %	97	99	97
Site of metastasis, n (%)			
Lung metastases **Lymph node metastases** **Bone metastases** **Pleural metastases** **Liver metastases**	86 51 27 15 14	91 46 35 15 19	86 51 27 15 14

DTC = differentiated thyroid cancer; ECOG = Eastern Cooperative Oncology Group; Len = lenvatinib; PS = performance status; THS = thyroid stimulating hormone; TKI =tyrosine kinase inhibitor

Source: Tremblay et al 2016[11] Table 3

7.3 Findings

Both lenvatinib and sorafenib demonstrated significantly improved PFS compared to placebo. Key efficacy outcomes of the SELECT and decision trials are summarized in TABLE 13. In the SELECT study, median (95% CI) PFS was 18.3 months (15.1, not estimated) for lenvatinib whereas the median PFS for sorafenib in the DECISION trial was 10.8 months (9.1, 12.9) (Table 13). Indirect treatment comparison using unadjusted and MAIC-adjusted data indicates that the risk of disease progression is significantly lower in patients treated with lenvatinib compared with those treated with sorafenib. The hazard ratio (HR) was 0.36 (95% CI: 0.22, 0.57) in unadjusted analysis and 0.33 (0.20, 0.53) in analysis with MAIC-adjusted data (Table 14).

Median OS had not been reached in the lenvatinib or sorafenib arms at the time of updated analyses. The crossover-corrected HR was 0.53 (95% CI: 0.34, 0.82) for lenvatinib versus placebo and 0.69 (95% CI: 0.49, 0.99) for sorafenib versus placebo (Table 14). Using the MAIC approach, the HR for crossover-corrected OS was 0.51 (95% CI: 0.30, 0.82) for lenvatinib versus placebo. Indirect treatment comparison crossover-corrected data showed that HR for OS was not significantly different for lenvatinib versus sorafenib (HR = 0.77; 95% CI: 0.44, 1.35). Although applying MAIC to the crossover-corrected data show a

trend of improvement in OS in favor of lenvatinib, the difference in OS between the two drugs was not statistically significant (HR = 0.73; 95% CI: 0.40, 1.35).

Table 13: Key Efficacy Outcomes in the SELECT and DECISION Trials

	SELECT Trial		DECISION Trial	
	LEN (N=261)	Placebo (N=131)	SOR (N=207)	Placebo (N=210)
Median PFS (95% CI) (months)	18.3 (15.1, NE)	3.6 (2.2, 3.7)	10.8 (9.1, 12.9)	5.8 (5.3, 7.8)
Stratified HR for PFS (99% or 95% CI) Stratified Log-Rank Test (*P* value)	0.21 (0.14, 0.31) <0.0001		0.59 (0.45, 0.76) <0.0001	
	(N=261)	(N=131)	(N=196)	(N=201)
Best OTR, n (%)				
-CR -PR	4 (1.5) 165 (63.2)	0 2 (1.5)	0 24 (12.2)	0 1 (0.5)
ORR (CR + PR) 95% CI Median Duration of Objective response (95% CI) (months)	169 (64.8) (59.0, 70.5) NE (16.8, NE)	2 (1.5) (0.0, 3.6) NE	24 (12.2) (7.6, 16.8) 10.2 (7.4, 16.6)	1 (0.5) (0.01, 2.7) NE
	(N=261)	(N=131)	(N=207)	(N=210)
Patients who went on OL active treatment, n (%)	-	109 (83.2)	61 (29.5)	157 (74.8)
Median OS (95% CI) (months)	NE (22.0, NE)	NE (20.3, NE)	NE	36.5 (32.2, NE)
Adjusted stratified HR for OS (95% CI) *P* value Unadjusted stratified HR for OS (95% CI) *P* value	0.62 (0.40, 1.00) 0.0151 0.73 (0.50, 1.70) 0.1032		Not calculated Not calculated 0.88 (0.63, 1.24) 0.24	
Death, n (%)	71 (27.2)	47 (35.9)	66 (31.9)	72 (34.3)

CI = confidence interval; CR = complete response; HR = hazard ratio; LEN = lenvatinib; NE = not estimated; OL = open-label; ORR = objective response rate; OS = overall survival; OTR = overall tumor response; PFS = progression free survival; PR = partial response; SOR = sorafenib;

Source: Tremblay et al 2016,[11] Table 3

Table 14: Comparison of PFS and OS data after matching

	LEN vs. Placebo	SOR vs. Placebo	LEN vs. SOR
PFS, HR (95% CI)			
Unadjusted trial data	0.21 (0.14, 0.31)	0.59 (0.45, 0.76)	0.36 (0.22, 0.57)
MAIC-adjusted data	0.19 (0.13, 0.29 0	NA	0.33 (0.20, 0.53)
OS, HR (95% CI)			
Unadjusted trial data	0.80 (0.57, 1.12)	0.88 (0.63, 1.24)	0.91 (0.57, 1.46)
Crossover-corrected data	0.53 (0.34, 0.82)	0.69 (0.49, 0.99)	0.77 (0.44, 1.35)
MAIC crossover-adjusted data	0.51 (0.30, 0.82)	NA	0.73 (0.40, 1.35)

CI = confidence interval; HR = hazard ratio; MAIC = matched-adjusted indirect comparison; LEN = lenvatinib; OS = overall survival; PFS = progression-free survival; SOR = sorafenib

Source: Tremblay et al 2016,[11] Table 3

7.4 Critical Appraisal of Indirect Treatment Comparison

Limitations

The main limitation of the indirect treatment comparison is that the MAIC approach does not have the ability to control for the potential for unobserved confounding bias due to factors such as differences in settings and standards of care at the various study centers of the two studies. The matching

adjustment might only ensure that the comparative outcomes of PFS and OS were unbiased by the observed and matched baseline characteristics. However, as indicated in Table 11, there were notable difference in prior TKI treatment (VEGF or VEGFR-targeted therapies), as well as metastasis disease of head and neck, and of the brain that could not be matched. Thus the generalizability of the conclusions from the indirect treatment comparison using MAIC may not extend to the category of patients who were excluded from the analysis. For the comparison of OS, the limitations in the use of RPSFT model and bootstrap approach also applied.

Strength

The MAIC approach is based on adjusted and propensity score-weighted patient data to allow for comparison of two studies when individual patient data are available for only one study. In this analysis, the population of the SELECT study was modified to align its inclusion and exclusion criteria with that of the DECISSION trial as much as possible.[11] By applying weighting to match the mean/percentage of these aligned baseline characteristics of the two studies, the MAIC approach minimizes potential biases that may be associated with using traditional indirect treatment comparison approaches to compare outcomes of two studies when individual patient data are available for only one study, whereas only published summary data are available for the other. The MAIC technique produces point estimates (i.e., HR) and 95% confidence intervals based on data adjusted to match baseline characteristics of the studies being compared.

7.5 Summary

The manufacturer performed an indirect treatment analysis using the MAIC method to compare lenvatinib with sorafenib. The results suggested that treatment of patients with RR-DTC with lenvatinib was associated with has statistically significantly longer median PFS than sorafenib with HR of 0.33 (95% CI: 0.20, 0.53). In both the SELECT and DECISION trials, the median OS had not been reached in the lenvatinib or sorafenib arms at the time of the updated analyses, and the MAIC-adjusted crossover-corrected analyses showed no statistically significant difference in OS between lenvatinib and sorafenib (HR = 0.73; 95% CI: 0.40, 1.35). In the absence of a head-to-head comparison between the two drugs, the MAIC approach is a good option for comparison since individual patient data were available for the SELECT trial, whereas only published summary data were available for the DECISION trial. However, since MAIC does not have the ability to account for unreported factors which may influence the results, further studies may be needed to confirm the advantage of lenvatinib over sorafenib in the treatment of patients with RR-DTC.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Endocrine Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on Lenvatinib (Lenvima) for Differentiated Thyroid Cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Endocrine Clinical Guidance Panel is comprised of three oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials March 2016; Embase 1974 to 2016 April 22; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

line #	Searches	Results
1	(Lenvatinib* or Lenvima* or E 7080 or E7080 or ER-203492-00 or ER203492-00).ti,ab,ot,kf,hw,rn,nm.	655
2	(942407-57-0 or 417716-92-8 or 857890-39-2 or EE083865G2 or 3J78384F61).nm,rn.	403
3	or/1-2	655
4	3 use pmez,cctr	143
5	*lenvatinib/	158
6	(Lenvatinib* or Lenvima* or E 7080 or E7080 or ER-203492-00 or ER203492-00).ti,ab,kw.	380
7	or/5-6	389
8	7 use oemezd	255
9	4 or 8	398
10	limit 9 to english language	386
11	remove duplicates from 10	265

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#4	Search #3 AND publisher [sb]	5
#3	Search #1 OR #2	125
#2	Search 942407-57-0 OR 417716-92-8 OR 857890-39-2 OR EE083865G2 OR 3J78384F61	53
#1	Search Lenvatinib OR Lenvima OR "E 7080" OR E7080 OR ER-203492-00 OR ER203492-00	125

3. **Cochrane Central Register of Controlled Trials (Central)**

   Searched via Ovid.

4. **Grey Literature search via:**

   Clinical trial registries:

   U.S. NIH ClinicalTrials.gov
   http://www.clinicaltrials.gov/

   Search: thyroid OR DTC | Lenvatinib OR Lenvima OR "E 7080" OR E7080 OR "ER-203492-00" OR "ER203492-00"

   Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
   http://www.canadiancancertrials.ca/

   Search: Lenvatinib; Lenvima; E 7080; E7080

   Select international agencies including:

   Food and Drug Administration (FDA):
   http://www.fda.gov/

   European Medicines Agency (EMA):
   http://www.ema.europa.eu/

   Search: Lenvatinib, Lenvima

   Conference abstracts:

   American Society of Clinical Oncology (ASCO)
   http://www.asco.org/
   Retrieved via Embase

European Society for Medical Oncology
http://www.esmo.org
Retrieved via Embase, except ESMO 2014

Search: Lenvatinib, Lenvima, thyroid cancer

APPENDIX B: DETAILED METHOLODGY OF LITERATURE REVIEW

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (March 2016) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were lenvatinib, Lenvima and E7080.

No filters were applied to limit the retrieval by study type. The search was limited to English-language documents, but not limited by publication year.

The search is considered up to date as of August 2, 2016.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually, limited to the past five years, for conference years not available in Embase at the time of the database search. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

All articles considered potentially relevant were acquired from library sources. A member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

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