CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Lenvatinib (Lenvima) for Differentiated Thyroid Cancer

September 20, 2016

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Eisai Limited compared Lenvatinib to Best Supportive Care (primary analysis) and Lenvatinib to Sorafenib (secondary analysis) for patients with Iodine-131-Refractory Differentiated Thyroid Cancer.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Patients with locally recurrent or metastatic, progressive Radioactive iodine-Refractory Differentiated Thyroid Cancer. Patient with progressive Iodine-131-Refractory Differentiated Thyroid Cancer. Patients 18+ years, willing and able to provide consent, had ECOG performance 0 to 2 with measurable pathologically confirmed DTC, and had disease progression within the prior 13 months.
Type of Analysis	CUA: Cost Utility Analysis
Type of Model	Partitioned Survival Model
Comparator	Best supportive care (primary analysis) – based on the control arm of the SELECT trial. Sorafenib (secondary analysis)
Year of costs	2016 Canadian Dollars
Time Horizon	10 years (base case)
Perspective	Public payer (base case) using Ontario Ministry of Health and LT Care as exemplar. (Societal perspective built into model)
Cost of Lenvatinib	• Trial dose is 24mg per day at $220.84 per day and $6,183.52 per 28-day cycle • Dose reductions incorporated in proportions corresponding to trial • 20 mg per day at $164.64 per day and $4,609.92 per 28-day cycle • 14 mg per day at $110.42 per day and 3,091.76 per 28-day cycle • 10 mg per day at $71.64 per day and $2,005.92 per 28-day cycle • 8 mg per day at $77.56 and $2,171.68 per 28-day cycle • 4 mg per day at $38.78 and $1,085.84 per 28-day cycle
Cost of Supportive Care (Maintenance of TSH levels; control of pain at metastatic sites; management of associated skeletal events; treatment of	• Costs of BSC incorporated into each arm of the model, considered costs associated with progressive disease;

hypocalacaemia; monitoring of localized AE).	• No systemic therapy post-progression (base case) – doxorubicin in sensitivity analysis.
Cost of Sorafenib	• Sorafenib costs $46.47 for 200 mg. At the recommended dose of 800 mg per day, sorafenib costs $185.88 per day and $5,204.64 per 28-day cycle
Model Structure	Partitioned Survival Model with four States: • Stable, • Response (sub-state of stable), • Progressive (post-progression), • Death. Transitions between health states occur monthly (every 30.4 days). Treatment assumed to continue until disease progression. Uses clinical trial data directly instead of estimated transition probabilities like Markov. Possible bias in favour of treatments that impact disease progression, with moderate survival.
Key Data Sources	OS and PFS data from SELECT trial for lenvatinib vs. BSC; OS and PFS data from DECISION trial and Tremblay match-adjusted indirect comparison (MAIC) for lenvatinib vs sorafenib; Data from literature for utilities. Utility data from a published study (Fordham et al. 2015). Utility values collected from 100 members of the general public in the UK. Utility of stable disease is 0.87. Response to therapy is +0.04. Progression is -0.35. AE also decrease utility.

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The primary comparator is Best Supportive Care, which in this case is appropriate, as no other treatment for this disease is currently funded in Canada. A secondary comparison to Sorafenib was discussed as providing some contextual guidance, despite Sorafenib not currently being funded through any Canadian formulary.

Relevant issues identified included:
The SELECT trial design (cross-over) and outcomes (median OS not reached for treatment group) presents challenges in estimating the true benefits of Lenvatinib. The challenge carries forward to the economic evaluation.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Reanalysis Estimates

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	1.01	1.03
Progression-free	NA	NA
Post-progression	NA	NA
ΔE (QALY)	0.84	0.84
Progression-free	NA	NA
Post-progression	NA	NA
ΔC ($)	105,783	147,380
ICER estimate ($/QALY)	126,235	176,281
Note: NA=not available.		

The ICER would be improved with a better pricing structure, and/or better packaging for patients, and/or reliance on patients to be able to mix the available pack appropriately.

The main assumptions and limitations with the submitted economic evaluation were:

The economic model is based on data from the SELECT clinical trial. A median overall survival was not reached in the clinical trial for the Lenvatinib arm, and the trial allowed cross-over. Both of these present challenges to the economic model. The cross-over means that the true benefits of the trial drug are difficult to isolate. The OS benefit is uncertain, the unadjusted HR in the updated analysis (June 2014) was 0.80 (95% CI: 0.57, 1.12; *P*=0.1993). When the analysis is adjusted for cross over the estimated HR (0.53) has a relatively large confidence interval (0.34 to 0.82; *P*=0.0051).

Overall the model is well developed. An economic model cannot be executed without assumptions and extrapolation. In this case, there does not appear to be a systematic effort to make all assumptions in favour of the drug. The assumptions appear reasonable, and limitations related to modeling cannot be avoided.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP considered the following areas in re-estimation: overall survival hazard ratio estimates (using confidence intervals, time horizon in the base case is set at 10 years, which does not reflect the reality of most patients; pricing structure is unusual (see below), utility values used by the manufacturer are conservative, wastage is not incorporated at all into the model.

The EGP made the following changes to the submitted economic model:

- **Overall Survival:** Given the outcomes of the clinical trial, progression free survival data are available, but overall survival data needed to be estimated using modeling (median overall survival for the Lenvatinib arm was not reached, and the trial allowed for cross-over). The HR outcome is uncertain and the estimated confidence interval for the adjusted HR is (0.34 – 0.82). The economic model was re-estimated using the lower and upper values of the confidence interval. Even this may under estimate the full degree of uncertainty as the original trial adjusted results {HR 0.62 (95% CI: 0.40, 1.00)} and unadjusted results{ HR=0.80

(95% CI: 0.57, 1.12)} from the second data cut show non-significant higher upper boundaries to the confidence interval.

- **Time Horizon**: The model assumes a 10 year time horizon. This was judged as long relative to the reality of the disease. The re-estimation assumes a 7 year time horizon for two reasons: (i) closer to the reality of the disease; and (ii) same time horizon used in the discussions of Sorafenib.
- **Wastage**: The economic model does not account for wastage in the base case. In an attempt to account for this, the re-estimation assumes that all patients purchase the full daily dose of 24 mg using the compliance pack (see issue 3). Some of these patients may use a reduced dose.
- **Pricing Structure**: Pricing structure is based on compliance packaging. Using the appropriate compliance package can be more costly than using multiple lower strength compliance packages to achieve the required dose. Patients may be more likely to take the appropriate dosage, when they purchase the compliance pack (24 mg) rather than purchasing and mixing two packs (14 mg and 10 mg), even though the latter combination has a lower price. The reestimation assumes that patients can mix the 10mg+14mg packs ($182.06) and use in place of the 24mg pack ($220.84); and they mix two 10mg packs ($143.64) to take in place of the 20mg pack ($165.64). The price of the combination is lower than the price of the large pack.
- **Utilities:** Utilities from a British vignette study (published) are used. The study provides two sets of utilities, adjusted for patient demographic profile and not adjusted. The unadjusted values are used in the economic report. The reestimation uses the adjusted values.

Table 3: Detailed Description of EGP Reanalysis

One-way and multi-way sensitivity analyses

Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICUR
Submitted results (after check-point reanalysis)	105,783	0.84	1.01	126,235	
Changed HR using the confidence interval lower value HR=0.34	112,532	1.23	1.82	91,203	-35,032
Changed HR using the confidence interval upper value HR=0.0.82	101,484	0.53	0.41	191,828	65,593
Time horizon changed from 10 years to 7 years.	101,504	0.75	0.85	135,287	9,052
Wastage – All patients assumed to purchase full dose.	150,410	0.84	1.01	179,490	53,255
Pricing – Patients assumed to mix packs for best price value.	95,322	0.84	1.01	113,752	-12,483
Utilities – Adjusted utility values are used.	105,783	0.90	1.01	117,019	-9,216
Seven year time horizon and full wastage; HR = 0.53 (EGP best estimate)	**147,380**	**0.84**	**1.03**	**176,281**	**50,046**
Seven year time horizon and full wastage; HR = 0.34 (EGP range – low value)	**151,706**	**1.13**	**1.62**	**133,980**	**7,745**
Seven year time horizon and full wastage; HR = 0.82 (EGP range – high value)	**143,233**	**0.49**	**0.33**	**294,275**	**168,040**

The ICER is uncertain given the uncertainty surrounding the overall survival HR. The EGP's best estimate of the ICER estimates varies between $133,980 and $294,275 using the two ends of the HR confidence interval. Within this range, the best estimate would likely be $176,281, if the time horizon is changed to 7 years and wastage is built into the model, and the HR=0.53 estimate is used; this is higher than what the submitter reported by approximately $50,046 per QALY. Wastage takes the form of patients purchasing the full dose, even when actually using a reduced dose. The ICER can be improved by a better pricing structure. As submitted, the price of 24 mg of lenvatinib is lower if a combination of a 10 mg pack and a 14 mg pack is purchased, as opposed to a 24 mg pack.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include estimated number of patients, drug prices, dosing, and estimated market share.

Re-estimations are:

Drug Prices – The new assumption is made that patients can mix the 10mg+14mg packs ($182.06) and use in place of the 24mg pack ($220.84); and they mix two 10mg packs ($143.64) to take in place of the 20mg pack ($165.64). The price of the combination is lower than the price of the large pack.

Market Share – The new assumption is made that Lenvatinib, being the only new treatment option, captures a substantially larger share of the market. 70% are assumed in the re-analysis. The budget impact approximately doubles.

Dosing – The new assumption is made that all patients purchase the 24mg dose (even though they may not all take the full 24mg dose). The budget impact increases by approximately 20%.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for Lenvatinib when compared to best supportive care:

- Ranges from $133,980/QALY to $294,275/QALY
- Within this range, the best estimate would likely be: $176,281/QALY if the model allows for full wastage and a time horizon of 7 years and uses the HR=0.53 estimate.
- The ICER values are driven primarily by assumptions about the clinical benefit of Lenvatinib (HR values).
- The extra cost of Lenvatinb is between $143,233 and $151,706. Changes to HR are not strong drivers of costs. Changes to the time horizon are a strong driver of cost.
- The extra clinical effect of Lenvatinib is between 0.49 and 1.13 QALY. Changes to the HR value for OS (highest, lowest value of the confidence interval) have the greatest effect on the QALY.

Overall conclusions of the submitted model:

- The nature of the clinical data creates a challenge for the precise estimation of the economic impact. Not reaching a median overall survival during the trial, and the cross-over feature introduce uncertainty into the estimation of the overall survival advantage. This carries forward in the estimation of the ICER.
- The model is well developed and makes reasonable assumptions with respect to the above (the uncertainty regarding overall survival outcomes). The EGP noted that four HR estimates and their confidence intervals are available (first versus second data cut, adjusted versus unadjusted values), yet the submitted model uses the most favourable HR estimates.

- The submitted model is estimated for a 10 year time horizon. The EGP modification is to a seven year time horizon, as per the advice of the CGP. This greatly increases the ICER.
- The submitted model does not account for waste and assumes dose reductions in the patient population in the same proportions as the trial population. Allowance for full wastage increases the ICER.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Endocrine Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of Lenvatinib (Lenvima) for Differentiated Thyroid Cancer. A full assessment of the clinical evidence of Lenvatinib (Lenvima) for Differentiated Thyroid Cancer is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR 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 Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.