CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Alectinib (Alecensaro) for Non-Small Cell Lung Cancer

March 29, 2018

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Roche** that compared alectinib to chemotherapy and ceritinib for in patients with Anaplastic Lymphoma Kinase (ALK) positive advanced or metastatic non-small cell lung cancer (NSCLC) that have previously been treated with crizotinib.

Table 1. Submitted Economic Model

Table 1. Submitted Economic Model	
The reimbursement request for alectinib is monotherapy for patients with ALK positive locally advanced or metastatic NSCLC who have progressed or are intolerant to crizotinib until progression or loss of clinical benefit.	The model was based on the ALUR trial and phase 2 studies (NP28761 and NP28673), all of which evaluated alectinib in patients with advanced ALK positive NSCLC who had previously progressed on crizotinib. Data from the ASCEND-5 trial and an electronic health records administrative database were used for key parameters for ceritinib.
Type of Analysis	Cost Utility Analysis
Type of Model	3 health state partitioned survival model
Comparator	1) Chemotherapy (pemetrexed or docetaxel monotherapy) 2) Ceritinib
Year of costs	*2017*
Time Horizon	*10 years*
Annual Discount Rate applied	*1.5%*
Perspective	*Government Payer*
Cost of alectinib	Alectinib costs $42.17 per 150mg capsules. The recommended dose is 600 mg BID • Cost per day is $337.36 • Cost per 28 days is $9,446.08
Cost of chemotherapy[#]	Pemetrexed costs $0.62 per mg. The recommended dose is 500mg per m^2 every 3 weeks. • Cost per 3 week cycle is $558.00 • Cost per day is $26.57 • Cost per 28 days is $744.00 Docetaxel costs $3.43 per mg. The recommended dose is 75mg per m^2 every 3 weeks. • Cost per 3 week cycle is $463.00 • Cost per day is $22.05 • Cost per 28 days is $617.00

Table 1. Submitted Economic Model	
	Assumes BSA of 1.80 m^2 Based on ALUR trial, model assumes 74% pemetrexed and 26% docetaxel utilization.
Cost of ceritinib	Ceritinib costs $52.00 per 150mg capsule. The recommended dose is 750 mg QD • Cost per day is $260.00 • Cost per 28 days is $7,280.00
Model Structure	The model was comprised of 3 health states: 1) progression free; 2) progressed disease; 3) Dead The following determine the proportion of patient that are in each of the health states every cycle. • Overall Survival • Progression Free Survival
Key Data Sources	ALUR Trial: a phase 3 RCT which compared alectinib to chemotherapy in ALK positive ALK patients previously on crizotinib: • PFS for alectinib and chemotherapy • Time on treatment for alectinib and chemotherapy • Utility values for alectinib and chemotherapy (pre-progression) • Adverse events for alectinib and chemotherapy NP28761 and NP28673: two single armed phase two trials investigating alectinib treatment in ALK positive ALK patients previously on crizotinib • OS for alectinib Ou et al.: a cohort study that investigated the impact of continuing crizotinib therapy after progressed disease in patients with advanced ALK positive NSCLC • OS for chemotherapy ASCEND-5 trial: a phase 3 RCT which compared ceritinib to chemotherapy in in ALK positive ALK patients previously on chemotherapy and crizotinib. • PFS for ceritinib (NMA with ASCEND-5 and ALUR) • Utility values for ceritinib (pre-progression) • Adverse event rates for ceritinib Flatiron Health Electronic Records database • OS for ceritinib (propensity score adjusted analysis, combining ceritinib data from database with alectinib data from phase 2 studies) Labbe et al: • Post-progression utility values for all treatments

Table 1. Submitted Economic Model	

** Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc. Quintile IMS DeltaPA- accessed on November 30, 2017 and pCODR submissions. All calculations are based on BSA = 1.8m²*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), Alectinib has demonstrated a net clinical benefit in ALK positive NSCLC patients intolerant or progressing after crizotinib. Relevant issues identified included:

- OS data in the ALUR trial was immature at the time of data analysis. Furthermore, 69% of patients in the chemotherapy arm crossed-over to receive alectinib post- progression in the trial.
- Although ceritinib, another second generation ALK TKI, has shown similar benefits compared to chemotherapy in the ASCEND 5 trial, there is no direct comparison between ceritinib and alectinib in this population. An indirect treatment comparison and network meta-analysis provided by the manufacturer suggested that alectinib was better than ceritinib for PFS, but this analysis is likely biased by uncontrolled heterogeneity in patients in these trials. Due to immaturity of OS trial data, data from two single-arm, phase 2 alectinib clinical trials and real world patient data from an electronic health record database were retrospectively analysed to indirectly compare OS and derive an estimate of treatment effect. The hazard ratio was obtained from a propensity-score adjusted analysis. The analysis suggested that alectinib was associated with prolonged OS compared to ceritinib. However, the reported estimate may be confounded since the effects of all important prognostic baseline variables were not controlled for simultaneously in the primary analysis. Overall, several limitations were identified in these indirect comparisons and should be interpreted with caution. It is the opinion of the members of the CGP that alectinib appears to have better CNS activity and appears to be better tolerated than ceritinib.
- Patients in the ALUR trial could continue on alectinib past radiologic progression, which has become the standard practice for patients with molecular drivers treated with TKIs. Many of these patients progress in one or a few sites that can be managed be local therapy such as radiation, or have asymptomatic progression not requiring intervention. In the ALUR trial, 5 (7%) patients treated with alectinib continued on alectinib past radiologic progression. The duration of treatment of alectinib is based on statistical modeling of the time to off treatment data observed in the ALUR trial.
- The results of this trial (ALUR) are likely to be relevant for the management of ALK positive NSCLC for a limited time. In a recent RCT, alectinib has demonstrated statistically significant efficacy compared to crizotinib as a first line therapy in ALK positive NSCLC. However, even if alectinib eventually becomes a funded treatment option for first line therapy, there remain significant numbers of patients who have received first line crizotinib and subsequently progressed for who alectinib after crizotinib represents a significant advance.

Summary of registered clinician input relevant to the economic analysis

Registered clinicians considered that compared to crizotinib and ceritinib, alectinib provides improvement in progression-free survival, overall response rate, duration of response, and toxicity profile; this includes patients with brain metastases. Of note, clinician input suggested that brain radiation could be delayed until CNS progression on alectinib. Compared with ceritinib, clinician input noted that alectinib following crizotinib will be able to better prevent or treat brain

metastases. *The economic model does incorporate the impact of progression free survival on both costs and QALYS. The toxicity profile is addressed through the costs of adverse events for each comparator and the utility values applied to each comparator treatment.*

Alectinib was found to be a bit more tolerable as ceritinib appears to cause more frequent transaminitis, QT prolongation, hyperglycaemia, increased amylase/lipase, and diarrhea. *Tolerability of alectinib is partially addressed as tolerability would likely impact the time to off-treatment, progression free survival and overall survival which all impact the economic results.*

Clinician input suggested that alectinib may be used for ALK+ treatment naïve NSCLC, patients who have progressed on crizotinib, or those who failed both crizotinib and ceritinib; where multiple second generation ALK inhibitors would provide the maximum number of treatment lines for patients who acquire treatment resistance. *This issue is not addressed in the economic evaluation.*

Summary of patient input relevant to the economic analysis

Patients considered the following factors important in the review of alectinib:

- Reducing the size of tumours. *This issue is not directly addressed in the economic evaluation. Though it may be indirectly addressed as the evaluation takes into account the longer overall survival and progression free survival which may be linked to the reduction of tumour size.*
- Delay or avoid permanent cognitive damage from whole brain radiation (to treat brain metastases). *The cost impact of treatment of CNS metastases is addressed in a sensitivity analysis in the economic evaluation.*
- Improvement in survival, quality of life, more manageable side effects and relief of lung cancer symptoms. *Favourable effects of alectinib on survival and quality of life were addressed in the economic model by applying utility score and measuring outcomes in QALYs.*
- Reduction in productivity loss for patients and their caregivers due to the oral administration of alectinib. *This is not considered in the economic analysis as the analysis adopted the perspective of the publicly funded health care system.*

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for alectinib which are relevant to the economic analysis:

- PAG had concerns about the additional costs to treat and manage adverse events. *The costs of treating adverse events are included in the economic evaluation.*
- PAG stated concerns that an enabler of implementation of alectinib was that dose adjustment is accomplished by adjusting the number of capsules taken and that alectinib is available only in one capsule strength. *This issue is not addressed in the economic analysis.*
- PAG sought clarity on the definition of "until loss of clinical benefit", treatment duration, and treatment discontinuation. *The economic analysis does address these issues in terms of their impact on the cost of alectinib treatment. The duration of treatment of alectinib is based on statistical modeling of the time to off treatment data observed in the ALUR trial. In the ALUR trial, patients were to remain on treatment until "loss of clinical benefit".*

- PAG raised concerns that because alectinib does is not require chair time in chemotherapy units, this may be an enabler to the implementation of alectinib. *This issue is not addressed in the economic analysis.*

1.3 Submitted and EGP Reanalysis Estimates:

The main cost drivers of the manufacturers' model were drug acquisition costs and time to off treatment. Other contributors to costs were supportive care costs and adverse event costs.

The main drivers of the clinical outcomes of the model (QALYs, Life Years) were overall survival estimates, the time horizon of the model, utility values and progression free survival estimates. Overall the approach taken in the economic evaluation was reasonable and appropriate.

Table 2: Alectinib vs. Chemotherapy submitted and EGP re-analysis

Estimates (range/point)	Submitted	EGP Reanalysis	
		Lower Estimate	Upper Estimate
ΔE (LY)	1.97	1.85	1.21
Progression-free	0.55	0.50	0.61
Post-progression	1.42	1.36	0.60
ΔE (QALY)	1.47	1.38	0.95
Progression-free	0.49	0.44	0.54
Post-progression	0.98	0.94	0.41
ΔC ($)	$123,767	$120,560	$152,170
ICER estimate ($/QALY)	$84,444	$87,357	$159,544

Table 3: Alectinib vs. Ceritinib submitted and EGP re-analysis

Estimates (range/point)	Submitted	EGP Reanalysis	
		Lower Estimate	Upper Estimate
ΔE (LY)	0.89	1.02	0.18
Progression-free	0.26	0.23	0.29
Post-progression	0.63	0.79	-0.11
ΔE (QALY)	0.68	0.77	0.20
Progression-free	0.25	0.22	0.28
Post-progression	0.44	0.55	-0.08
ΔC ($)	$46,249	$28,366	$44,150
ICER estimate ($/QALY)	$67,903	$36,935	$224,235

Table 4 presents sequential cost-effectiveness results. In sequential analysis all treatment comparators are evaluated at the same time. It helps address the question of which one of multiple comparators (i.e. more than 2) is the most cost-effective. Treatment comparators that are dominated (i.e. more costly and less effective than at least one other strategy or a combination of other strategies) are eliminated from consideration of being the most cost effective strategy. The incremental cost effectiveness ratio of moving from one non-dominated comparator to another sequentially from the least effective to the most effective strategy is then calculated.

Table 4: Sequential cost-effectiveness analysis submitted and EGP re-analysis

	Submitted	EGP Re-analysis	
		Lower estimate	Upper estimate
Alectinib	$84,444	$87,357	$224,235
Ceritinib	dominated	dominated	$142,715
Chemotherapy	reference	reference	reference

- Time Horizon: The model uses a 10 year time horizon. Using such a long time horizon can lead to erroneous predictions of long term survival based on extrapolation of trial data with limited follow-up. While the updated CADTH guideline recommends that "the time horizon of the analysis should be conceptually driven, based on the natural history of the condition or anticipated impact of the intervention (Page 31)", the guidelines also state that, in cases where that extrapolation is required to estimate long-term effect, external data sources, biology or clinical expert judgement may be used to justify the plausibility of extrapolation (Page 43). The CGP suggested using a 5 year time horizon because it is was more clinically plausible in this patient population. Therefore, a 5 year time horizon was assumed by the EGP in the re-analysis.

    - Overall Survival Estimates: Direct comparative evidence was not used to estimate and project overall survival between alectinib and its comparators (chemotherapy, ceritinib). Overall survival data from the ALUR trial could not be used because data were immature and there was high cross-over. Instead, indirect evidence from various sources was used to project OS. Phase 2 studies were used for alectinib, Ou et al was used for chemotherapy, and propensity score matched analysis was used to derive a relative risk of OS for ceritinib relative to alectinib. Overall survival projections are a big driver when estimating relative QALYs and cost-effectiveness between comparative treatments. The lack of direct evidence of comparative overall survival creates considerable uncertainty around the cost-effectiveness of alectinib compared to chemotherapy and ceritinib. It was concluded by the Methods team that the comparative efficacy estimates obtained (alectinib versus ceritinib) are likely biased due to uncontrolled heterogeneity; however, the direction and magnitude of the bias is unclear, and therefore, the estimates obtained may over or under estimate the true treatment effect associated with alectinib.

- Statistical model chosen for PFS and TTOT: The exponential statistical model had the best statistical fit for alectinib PFS and for TTOT based on AIC. However, the Gompertz model was used because the submitter indicated that it had better clinical plausibility. The statistical model chosen to extrapolate PFS and TTOT can have a large impact on cost-effectiveness results. The CADTH guidelines state that statistical fit, clinical validity and plausibility should all be considered when choosing between statistical models. However, how to weigh each criterion is somewhat arbitrary.

- The drug acquisition costs used in the model for ceritinib and chemotherapy (docetaxel, pemetrexed) were different than the costs known to pCODR. In the EGP re-analysis drug acquisition costs are based on pCODR costs.

1.4 Detailed Highlights of the EGP Reanalysis

- Time Horizon: The CGP suggested using a 5 year time horizon as it is more clinically plausible compared to the 10 years used in the submitted model. Therefore, the EGP used a 5 year time horizon in the re-analysis.

- Statistical model for PFS and TTOT for alectinib: The manufacturer's choice of a Gompertz model for PFS and Time to off treatment (TTOT) was largely based on what they cited as the plausibility of predictions. However, the exponential model had the best statistical fit to the ALUR study data for both PFS and TTOT. In the EGP reanalysis the exponential model was used to estimate PFS and TTOT over time for alectinib.

- Comparative overall survival: Only indirect, non-comparative evidence were used in the estimation of overall survival for alectinib, chemotherapy and ceritinib. This brings uncertainty to the relative overall survival for alectinib vs. chemotherapy and ceritinib. In the EGP re-analysis, the model was modified in order to specify a relative survival for chemotherapy vs. alectinib and for ceritinib vs. alectinib. Specifically, the model was run assuming a relative risk of survival of 0.75, 0.50, and 0.25 for chemotherapy vs. alectinib and ceritinib vs. alectinib.

  In addition, two extreme scenario analyses were undertaken; the best case OS scenario and the worst case OS scenario. In the best case OS scenario, the following was used: upper 95% CI of the alectinib overall survival curve. The lower 95% CI of the chemotherapy OS curve, the lower 95% of the OS hazard ratio for ceritinib vs. alectinib. In the worst case OS scenario the following was used: lower 95% CI of the alectinib overall survival curve; the upper 95% CI of the chemotherapy OS curve; the upper 95% of the OS hazard ratio for ceritinib vs. alectinib.

- The drug acquisition costs used in the model for ceritinib and chemotherapy (docetaxel, pemetrexed) were different than the costs known to pCODR. In the EGP re-analysis drug acquisition costs are based on pCODR costs.

Table 5: Alectinib vs. Chemotherapy detailed EGP re-analysis

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1. Submitter's Base case	$123,767	1.47	$84,444	
2. Change time horizon from 10 years to 5 years	$119,393	1.16	$103,036	$18,592
3. Change drug acquisition costs to be consistent with pCODR Ceritinib $67.466 per capsule Docetaxel 11.42 per mg	$124,199	1.47	$84,753	$309

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
Pemetrexed 0.83 per mg				
4. Change distribution used for PFS and TTOT to Exponential	$162,022	1.47	$109,871	$25,428
5. Assume relative overall survival for chemotherapy vs. alectinib is 0.75	$115,056	0.59	$195,917	$111,473
6. Assume relative overall survival for chemotherapy vs. alectinib is 0.50	$117,349	1.04	$112,829	$28,385
7.Assume relative overall survival for chemotherapy vs. alectinib is 0.25	$120,702	1.46	$82,859	-$1,585
8. Best case OS scenario (upper 95% Alectinib ,lower 95% chemo and ceritinib)	$131,887	1.85	$71,163	-$13,281
9. Worst case OS scenario (lower 95% Alectinib ,Upper 95% chemo and ceritinib)	$119,634	1.12	$107,011	$22,567
Lower estimate of cost effectiveness (includes changes in 2, 3, and 8)	**$120,560**	**1.38**	**$87,357**	$2,913
Upper estimate of cost effectiveness (includes changes in 2,3,4, and 9)	**$152,170**	**0.95**	**$159,544**	$75,100

Table 6: Alectinib vs. Chemotherapy, discounted costs for Alectinib

	$/QALY by alectinib acquisition cost discount %			
Description of Reanalysis	0%	25%	50%	75%
1. Submitter's Base case	$84,444	$65,686	$46,269	$26,751
Lower estimate of cost effectiveness	**$87,357**	**$67,208**	**$46,612**	**$26,737**
Upper estimate of cost effectiveness	**$159,544**	**$120,394**	**$82,032**	**$43,268**

Table 7: Alectinib vs. Ceritinib detailed EGP re-analysis

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1. Submitter's Base case	$46,249	0.68	$67,903	

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
2. Change time horizon from 10 years to 5 years	$44,735	0.48	$93,966	$26,064
3. Change drug acquisition costs to be consistent with pCODR	$26,220	0.68	$38,603	-$29,299
4. Change distribution used for PFS and TTOT to Exponential	$76,108	0.69	$110,175	$42,273
5. Assume relative overall survival for ceritinib vs. alectinib is 0.75	$48,784	0.55	$88,646	$20,744
6. Assume relative overall survival for ceritinib vs. alectinib is 0.50	$67,386	1.02	$66,311	-$1,591
7.Assume relative overall survival for ceritinib vs. alectinib is 0.25	$93,034	1.45	$64,380	-$3,523
8. Best case OS scenario (upper 95% Alectinib ,lower 95% chemo and ceritinib)	$57,475	1.18	$48,910	-$18,992
9. Worst case OS scenario (lower 95% Alectinib ,Upper 95% chemo and ceritinib)	$119,634	1.12	$107,011	$39,108
Lower estimate of cost effectiveness (includes changes in 2,3, and 8)	**$28,366**	**0.77**	**$36,935**	-$30,968
Upper estimate of cost effectiveness (includes changes in 2,3,4 and 9)	**$44,150**	**0.20**	**$224,235**	$156,333

Table 8: Alectinib vs. Ceritinib discounted costs for Alectinib

	$/QALY by alectinib acquisition cost discount %			
Description of Reanalysis	**0%**	**25%**	**50%**	**75%**
1. Submitter's Base case	$67,903	$28,857	$0	$0
Lower estimate of cost effectiveness	**$36,935**	dominant	dominant	dominant
Upper estimate of cost effectiveness	**$224,235**	$41,730	dominant	dominant

1.5 Evaluation of Submitted Budget Impact Analysis

The overall approach of the BIA appears to be reasonable and appropriate. The factors that most influence the BIA are the estimated number of patients eligible for alectinib in the next three years, the assumed proportion of eligible patients that would be prescribed alectinib if it was reimbursed and the cost of alectinib and alternative treatments. A key limitation of the BIA is that it did not include the costs of administering alectinib and alternative treatments (ceritinib, chemotherapy). The BIA was taken from an Ontario third party payer perspective. It should be noted that in Ontario, oral anti-cancer medications may not be reimbursed for patients under the age of 65. This is not necessarily the case in other provinces. In the ALUR trial the median age of patients was 57 years. Furthermore, 83% of patients in the ALUR trial were under 65 years old.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for alectinib when compared to chemotherapy is:

- Between $87,357/QALY and $159,544/QALY
- The extra cost of alectinib is between $120,560 and $152,170. Incremental costs were most impacted by drug acquisition costs.
- The extra clinical effect of alectinib is between 0.95 to 1.38 QALYs. Incremental QALYs were most impacted by overall survival estimates and time horizon.

The EGP's best estimate of ΔC and ΔE for alectinib when compared to ceritinib is:

- Between $36,935/QALY and $224,235/QALY
- The extra cost of alectinib is between $120,560 and $152,170. Incremental costs were most impacted by drug acquisition costs.
- The extra clinical effect of alectinib is between 0.20 to 0.77 QALYs. Incremental QALYs were most impacted by overall survival estimates and time horizon.

When choosing between alectinib, chemotherapy and ceritinib (sequential analysis) the cost per QALY of alectinib ranges from $87,537 to $224,235.

Overall conclusions of the submitted model:

The overall structure and much of the data used for parameter inputs the economic model were appropriate. However there is considerable uncertainty around the estimates of overall survival for alectinib and its comparators. No direct comparative evidence was used to estimate survival for alectinib, chemotherapy and ceritinib. In the ALUR trial, OS data was immature at the time of the primary analysis and there was heavy cross-over. Therefore, alectinib data from single arm phase 2 studies were used to estimate overall survival (pooled analysis), an observational study was used to estimate and project overall survival for chemotherapy, and a network meta-analysis was used to estimate the relative OS for ceritinib compared to alectinib. Furthermore no direct comparative evidence was available for the PFS, utility, TTOT or adverse event data used for ceritinib in the model.

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

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 information redacted from this publicly available Guidance Report.

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.

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.

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