CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review
# Final Economic Guidance Report

# Alectinib (Alecensaro) for Non-Small Cell Lung Cancer

**July 25, 2018**

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# FUNDING

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# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Roche** compared alectinib (Alecensaro) to crizotinib for the treatment of patients with previously untreated anaplastic lymphoma kinase (ALK)-positive advanced or metastatic non-small cell lung cancer (NSCLC).

**Table 1. Submitted Economic Model**

| | |
|---|---|
| Patient Population Modelled | Patients with previously untreated ALK+ NSCLC, locally advanced or metastatic. |
| Type of Analysis | *CUA / CEA* |
| Comparator | *Crizotinib* |
| Year of costs | *2017* |
| Time Horizon | *30 years* |
| Discounting | *1.5% for both cost and health consequences* |
| Perspective | *Government* |
| Cost of alectinib | Alectinib costs $42.17 per 150mg capsules. At the recommended dose of 600 mg BID, alectinib costs:<br>• Cost per day is $337.33<br>• Cost per 28 days is $9,445.32 |
| Cost of crizotinib* | Crizotinib costs $130.00 per 250 mg tablet. At the recommended dose of 250 mg twice daily, crizotinib costs:<br>• $260.00 per day<br>• $7280.00 per 28-days |
| Type of Model | *Partitioned-survival* |
| Model Structure | *A partitioned-survival with three mutually exclusive health states: progression-free survival (PFS), progression and death. All patients began in the PFS state. Patients could move to another state or stay in the same state at the end of each cycle (1 week).* |
| Main Analysis | *Probabilistic, 5,000 iterations* |
| Key Efficacy Data Sources | *Global ALEX trial: phase III randomized trial* |
| Key Utility Data Sources | *EuroQOL (EQ)-5D-3L collected in ALEX* |
| Key Resource Data Sources | *Various* |

** 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 (referred to as IQVIA by the submitter) DeltaPA– accessed on November 30, 2017*

## 1.2 Clinical Considerations

**According to the pCODR Clinical Guidance Panel (CGP)**, this comparison is appropriate.

- Relevant issues identified included:
  - *There is a net clinical benefit to alectinib in the treatment of ALK-positive NSCLC patients in the first line setting.*
  - *The benefits of alectinib are present regardless of the presence of CNS metastases.*

- *The difference in PFS was early and profound; alectinib was associated with earlier and more prolonged quality of life benefit.*
- *OS data in the ALEX trial was immature at the time of data analysis. With sufficient follow-up, OS could be evaluated but any benefit may be confounded by either on study cross-over or subsequent treatments outside of study.*
- *Adverse events were similar between the two treatments, despite the fact that patients on alectinib were exposed to the drug significantly longer.*
- *Without mature OS data, some clinicians may consider it premature to conclude replacing crizotinib with alectinib in the first line setting, and crizotinib should remain a valid therapeutic option. However, it would be anticipated that the majority of clinicians would favour using alectinib and prefer to give the more efficacious and better tolerated treatment as first line therapy.*
- *Crizotinib would be expected to be used first line in less than 10% of patients if alectinib were available.*
- *If alectinib were not funded first line (but available second line), physicians would be incentivized to adopt frequent monitoring for CNS progression on crizotinib in order to switch to alectinib as second line therapy earlier.*
- *First line crizotinib patients for whom crizotinib fails may be able to subsequently use alectinib and have a potentially efficacious treatment. There are to date no known subsequent efficacious targeted therapies for patients who fail on first line alectinib.*

**Summary of registered clinician input relevant to the economic analysis**
Registered clinicians identified the following benefits and harms associated with alectinib:

- Median progression-free survival by investigator was more than double in the alectinib arm compared to the crizotinib arm, which is clinically meaningful.
- The 12-month cumulative risk for brain metastases was significantly lower for alectinib compared with crizotinib. Further, the risk of development of new CNS metastases seemed to plateau at 18 months for alectinib-treated patients while the risk continue to increase for those treated with crizotinib.
- Cross-over in the trial may have contributed to similar OS rates in both trial arms, though median overall survival has not been reached.
- Similar incidence of grade 3-5 toxicities.
- No anticipation of changes in testing practice of ALK mutation with the approval of alectinib.

**Summary of patient input relevant to the economic analysis**
**Patients** considered the following, which was relevant to the economic analysis:

- increased response to treatment with the availability of alectinib
- reduction in adverse events with alectinib compared to crizotinib
- the protection from brain metastasis
- increased progression-free survival as important for both the treatment of ALK+ NSCLC.

These factors were considered in the economic analysis.

**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:

- Cost effectiveness of sequencing other targeted therapies and chemotherapies after progression on alectinib.

Enablers

- The recommended dose of 600 mg taken twice daily through 8 total tablets can be adjusted by decreasing the number of tablets.
- ALK mutation testing is currently being conducted at diagnosis to determine appropriate treatment.

Barriers

- None identified.

## 1.3 Submitted and EGP Reanalysis Estimates

**Table 2. Submitted and EGP Reanalysis Estimates (95% CI shown where appropriate)**

| Estimates | Submitted | EGP Reanalysis | Difference Between Reanalysis and Submitted numbers |
|---|---|---|---|
| ΔE (LY) | 2.23 (-1.220, 5.992) | 0.65 (-0.594, 1.875) | -1.58 |
| Progression-free | 1.493 | 1.542 | 0.049 |
| Post-progression | 0.735 | -0.891 | -1.626 |
| ΔE (QALY) | 1.62 (-0.686, 4.123) | 0.69 (0.099, 1.282) | -0.93 |
| Progression-free | 1.190 | 1.232 | 0.042 |
| Post-progression | 0.429 | -0.546 | -0.975 |
| ΔC ($) | $136,957 ($59,337, $226,093) | $124,908 ($53,646, $202,226) | -$12,049 |
| **ICER estimate ($/LY)** | **$61,305** | **$191,704** | **130,399** |
| **ICER estimate ($/QALY)** | **$84,332** | **$181,994** | **$97,662** |

Note. Difference = (Reanalysis numbers - Submitted numbers)

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

- The survival data used to inform the economic model is immature. Median progression-progression free survival and median overall survival were not reached.
- The submitted base case time horizon was 30 years which was deemed too long by the CGP for this patient population.
- In the submitted base case, it was assumed that the duration of treatment effect would be indefinite. That is, over the 30-year time horizon, the treatment effect observed in the trial period would continue.
- The best fitting curves for both progression-free and overall survival (as determined by lowest AIC/BIC) displayed plateaus towards the end of the time horizon. Parametric curves that were statistically deemed to fit less good were chosen in order to avoid the plateau.
- Immunotherapies were excluded for subsequent treatments. The CGP noted that immunotherapies warranted being included.

## 1.4 Detailed Highlights of the EGP Reanalysis

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

- Time horizon: The submitted time horizon in the base case was 30 years. The CGP noted that this time horizon was overly optimistic for this patient population. The CGP felt that at 10 years, 10% of the population would remain alive and that this was a reasonable

assumption for the time horizon. This time horizon is longer than previous NSCLC reviews in this indication as it considers that there have been advances in NSCLC treatment which have prolonged patient's survival.

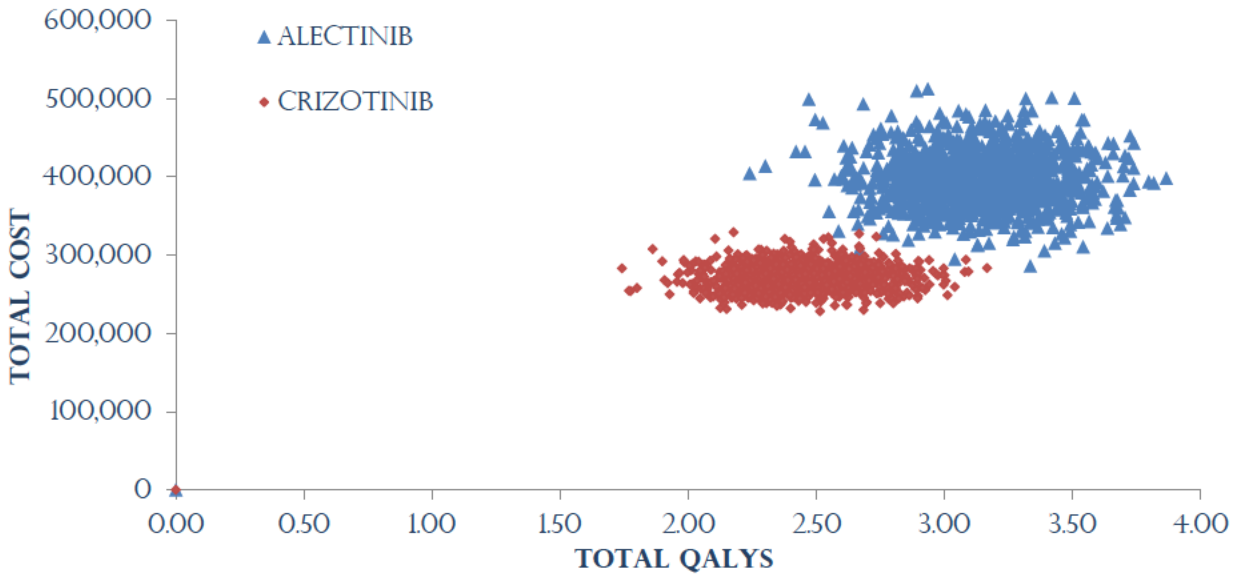
- Assessment of PFS outcomes: The protocol for the ALEX trial stated that the primary outcome (progression-free survival) would be investigator assessment. The submitted base case for the model used the option to assess outcomes by independent review committee. Though there is no one correct way to assess outcomes (it depends on the drug and disease under investigation), as the protocol stated a priori that the primary outcome would be investigator assessment, the EGP chose this method for the best case.
- Parametric curve chosen to model overall survival of alectinib: The submitted base case chose the Weibull curve in the submitted base case. This curve was the 4$^{th}$ best fitting according to AIC/BIC, however, was not chosen due to plateaus in survival in the longer term. Though the submitter stated that the parametric curves did not over-predict survival based on external data validation, the CGP disagreed and felt predicted overall survival was too optimistic. Choosing the best fitting parametric curve (exponential) reduced the predicted overall survival of alectinib by 3.5% at 4 years, which better aligned with clinical practice of CGP.
- Utility estimates in the post-progression period: In the submitted base case, the submitter chose to use a single progression utility of 0.725 (that is, for both alectinib and crizotinib). The CGP felt this was overly optimistic for progressed patients, and that patients who progress on crizotinib would have access to additional treatment options and likely have better quality of life. This is in contrast to patients progressing on alectinib who would not have other targeted treatment options available. The EGP elected to use the scenario analysis where the post-progression utility differed by treatment arm: 0.725 for 2$^{nd}$ line patients on an ALK inhibitor, 0.660 for 2$^{nd}$ or 3$^{rd}$ line patients on chemotherapy and 0.473 for 2$^{nd}$ or 3$^{rd}$ line patients on best supportive care. Further, these utilities align with previous submissions for 1$^{st}$ line NSCLC.

**Table 3. EGP Reanalysis Estimates**

| | ΔC | ΔE QALYs | ICUR (QALY) | Δ from baseline submitted ICER |
|---|---|---|---|---|
| Baseline (Submitter's best case) | $136,597 | 1.62 | $84,332 | -- |
| **Description of Reanalysis** | | | | |
| *Time horizon - 10 years* | $122,462 | 0.79 | $155,518 | $71,186 |
| *Assessment of PFS outcomes - investigator* | $137,713 | 1.63 | $84,407 | $75 |
| *Parametric curve overall survival alectinib - Exponential* | $135,936 | 0.90 | $151,472 | $67,140 |
| *Utility estimates different in post-progression period* | $136,597 | 1.33 | $102,891 | $18,559 |
| **EGP's Reanalysis for the Best Case Estimate** | | | | |
| *Best case estimate of above four parameters (95% CI)* | $124,908 ($53,646, $202,226) | 0.69 (0.099, 1.282) | $181,994* | $97,662 |

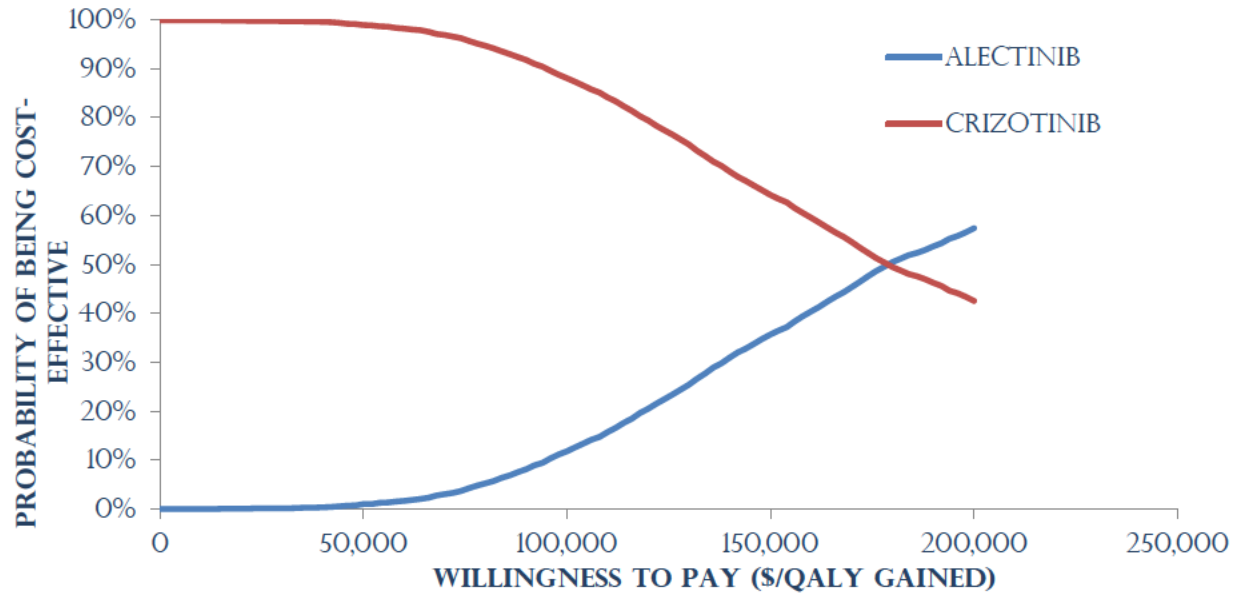
***NOTE: There is no 95% CI around a probabilistic ICER as it is derived from the mean of the incremental costs and the mean of the incremental QALYs.**

**Figure 1. CE plane of PSA results for EGP reanalysis.**




The cost-effectiveness plane for the EGP reanalysis is presented in the above figure. The mean incremental costs were $56,655 and the mean incremental QALYs were 0.25. Figure 1 highlights that there is less uncertainty in the QALYs for alectinib (blue) compared with the submitted base case.

**Figure 2. CEAC of PSA results for EGP reanalysis**




The cost-effectiveness acceptability curve is presented in Figure 2. At a willingness to pay threshold of $100,000/QALY, the probability of alectinib being cost-effective is about 12%.

## 1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include:

- The number of patients who get treated. Increasing the number of patients treated by 10% increases the 3-year budget impact by about 20%.
- The number of patients covered by public drug plans. Increasing the number of patients covered by public drug plans to 80% from what was done in the submitter BIA also increases the 3-year budget impact by about 14%.

Key limitations of the BIA model include:

- The presentation of an Ontario perspective. When the whole of Canada is considered, the budget impact is larger.
- Assumption of the number of patients would be covered by public drug plans (reimbursement programs).
- Treatment duration was based on progression-free survival, which was not reached in the global ALEX trial. Depending on the median PFS, the budget impact may be increased.

## 1.6 Conclusions

**The incremental cost-effective ratio of the EGP reanalysis for alectinib when compared to crizotinib:**

1. Would likely be: $181,984/QALY.

2. The difference in cost of alectinib is $124,808 (95% CI: $53,646, $202, 226) (ΔC). The main factors that influence ΔC among the reanalysis estimates are the time horizon (which decreases incremental costs) and the assessment of outcomes by investigator (minimally increases incremental costs).

3. The difference in clinical effect of alectinib is 0.69 (95% CI: 0.099, 1.282) (ΔE). The main factors that influence ΔE among the reanalysis estimates are the time horizon (which decreases QALYs by half) and the choice of parametric curve for overall survival for alectinib (decreases by about 40%).

4. With the EGP reanalysis, there is less uncertainty around the QALYs than what was submitted. In the submitted base case, the incremental QALYs were 1.62 (Figure 4, 95% CI: -0.686, 4.123) and in the EGP reanalysis, the incremental QALYs were 0.69 (Figure 6, 95% CI: 0.099 – 1.282). Costs were similar between the submitted base case and reanalysis (Table 20).

5. For this final EGP reanalysis, the following feature were evaluated as strengths:
   The ability to work with an functional and transparent model.

6. For this final EGP reanalysis, the following features were evaluated as weaknesses:
   Inability to identify well-fitting parametric curves based on both AIC/BIC and long-term projections.

### Summary statements

The EGP feels fairly confident that the reanalysis are sufficiently appropriate and reliable to guide decision-making. Specific issues about this economic reanalysis that pERC should keep in mind when making a recommendation include long term extrapolation of the data from immature

results. The EGP re-analysis have reduced the uncertainty in QALYs. The model structure is sound with reasonable assumptions. The majority of limitations could be addressed.

The EGP did not have any additional comments on the model structure or data inputs.

# 2 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 Lung 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 alectinib (Alecensaro) for NSCLC A full assessment of the clinical evidence of [drug name and indication] 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 information redacted from this publicly available Guidance Report.

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.

# REFERENCES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