CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Alectinib (Alecensaro) for Non-Small Cell Lung Cancer

May 4, 2017

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Hoffmann-La Roche Limited compared alectinib to pemetrexed ± cisplatin for anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) patients who have progressed on or are intolerant to crizotinib and have central nervous system (CNS) metastases.

Table [1]. Submitted Economic Model

Funding Request/Patient Population Modelled	The population was modelled based on a subgroup of patients in the NP28761 and the NP28673 trials with ALK-positive, locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib with measurable or unmeasurable CNS metastases at study start.
Type of Analysis	CEA, CUA
Type of Model	Partitioned-survival model
Comparator	Pemetrexed with and without cisplatin
Year of costs	2016
Time Horizon	10 years
Perspective	Government
Cost of alectinib	• $42.2 per 150 mg • $318.79 per day (assumed 94.5% dose intensity, base case analysis) • $2,231.5 per week (assumed 94.5% dose intensity, base case analysis)

Cost of pemetrexed ± cisplatin
 	
* Price Source: IMSB DeltaPA – current wholesaler unit price in Ontario
	Pemetrexed:
	• $99.81 per vial (100 mg), $623.72 per vial (1,000 mg)
	Cisplatin:
	• $225.75 per vial (50 mg)
	• $270 per vial (100 mg)
	Pemetrexed + cisplatin
	• No vial sharing (assume drug wastage, base case analysis)
	  ○ $53.30 per day
	  ○ $1,119.4 per 21-day cycle (pemetrexed: $623.7 + cisplatin: $495.7)
	• Perfect vial sharing
	  ○ $44.72 per day
	  ○ $939.2 per 21-day cycle (pemetrexed: $569.5 + cisplatin: $369.8)
	Pemetrexed monotherapy
	• No vial sharing (assume drug wastage, base case analysis)
	  ○ $29.70 per day

	○ $623.7 per 21-day cycle • Perfect vial sharing ○ $27.12 per day ○ $569.5 per 21-day cycle
Model Structure	The Submitter used a partition survival model with three mutually exclusive health states including progression-free survival (PFS) or pre-progression state, progressed disease (PD) and death (Figure 1 in Section 2.1 of the Technical Report).
Key Data Sources	• PFS and overall survival (OS) associated with alectinib was pooled from a subset of the full clinical populations (60%) in the NP28761 [(1)] and the NP28673 [(2)] trials. • OS patients receiving pemetrexed ± cisplatin was based on a retrospective analysis of 37 patients who enrolled in the PROFILE 1001 [(3)] expansion cohort or the PROFILE 1005 [(4)] and had received systematic therapies following progression on crizotinib. Median PFS for pemetrexed ± cisplatin was assumed to be 32% of the median OS reported in Ou et al (2014) [(5)]. • The health utility value for the alectinib pre-progression health state was derived by converting the European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC QLQ) measured in the NP28761 trial [(1)] to the EQ-5D-3L using a published conversion method [(6)]. The health utility value for the PD health state was obtained from a cross-sectional study assessing utility values of patients experience NSCLC in different mutational status in Canada [(7)]. • Resource utilization and health care costs were gathered from Canadian data sources, while unit costs were based on a single province, i.e. Ontario. For patients receiving pemetrexed ± cisplatin, pemetrexed was assumed to be discontinued at progression and cisplatin was used for 4 cycles based on Therapeutic Area Experts input. A sensitivity analysis for a situation when all patients received pemetrexed monotherapy was provided by the Submitter. • The unit cost of alectinib was provided by Roche Canada, while unit cost of pemetrexed ± cisplatin was obtained from IMSB DeltaPA (as shown in the Submitter report).

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the use of pemetrexed ± cisplatin is appropriate. If possible, the CGP considered that ceritinib (though not currently publicly funded), whole brain radiation therapy (WBRT) and best supportive care may be also clinically relevant comparators. The Submitter did not include these comparisons in the economic analysis. The CGP noted that there is a lack of efficacy evidence between alectinib and the clinically relevant comparators.

- Relevant concern raised by the CGP included a paucity of randomized clinical trials comparing alectinib to standard chemotherapy in the ALK inhibitor pretreated population.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians recognized alectinib as an efficacious and well-tolerated medication that has potential to improve clinical outcomes and quality of life. Alectinib also has potential to replace WBRT or stereotactic radiation surgery (SRS) as a second line of treatment; it can therefore relieve hospital resources allocating to chemotherapy and radiation services and improve patients health related quality of life.

The effects of alectinib on clinical outcomes including OS, PFS and quality of life were adequately addressed in the economic analysis. However, the effects of WBRT and SRS were considered only in the estimation of the cost of disease progression. The proportion of patients receiving WBRT was assumed to be smaller among patients who progress on alectinib than those receiving a standard chemotherapy. This proportion was based on input from Therapeutic Area Experts. The effects of pemetrexed ± cisplatin were taken into consideration in the estimation of cost, OS and PFS. The impact of these chemotherapy on health utility values should be investigated. The EGP performed the re-analyses by using lower utility values for patients receiving chemotherapy and those experiencing CNS metastases.

Summary of patient input relevant to the economic analysis
Patients considered the following factors important in the review of alectinib: its potential ability to replace/lessen the chance of receiving WBRT, reduction in productivity loss for patients and their caregivers due to oral administration of alectinib, improvement in lung cancer symptoms and survival, improvement in quality of life due to fewer and manageable side effects.

A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

- The submitted economic analysis explicitly considered the effect of alectinib on the chance of receiving WBRT by assuming a smaller proportion of patients receiving WBRT in the alectinib group than the standard chemotherapy group in the cost estimation. Favourable effects of alectinib on survival and quality of life were addressed by applying utility scores and measuring outcomes in QALYs.
- The model did not consider patients and caregivers time off work because the analysis adopted the perspective of the publicly funded health care system which is appropriate as per pCODR guidelines.
- The benefits of oral administration were considered in the submitted analysis by replacing the intravenous (IV) administration cost of chemotherapy to zero. However, the impact of switching from IV to oral formulation on quality of life was not included in the submitted model.

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:

- Lack of comparative and long-term safety and efficacy data.
- Choice of target population:
    - patients receiving crizotinib who have developed CNS metastasis,
    - any patients with ALK-positive NSCLC who have CNS metastasis and have previously been treated with crizotinib,
    - patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib but do not have CNS metastasis, or
    - patients with CNS metastasis and have received crizotinib first-line and subsequently treated with chemotherapy or immunotherapy
- Oral route of administration is convenient and does not incur IV administration cost. However, the number of pills required (8 capsules) per day may raise concerns of pill burden and cause medication non-adherence.
- Funding recommendation for alectinib would shift a portion of medication expenditures from the government to patients and their families in provinces where oral medications are funded in a different mechanism from intravenous cancer medications.
- Alectinib has potential to be the first-line treatment if an ongoing Phase III trial (ALEX trial) shows better outcomes in patients receiving alectinib than those receiving crizotinib.

The Submitter addressed PAG input by extrapolating long-term efficacy from two Phase II alectinib trials. The lack of comparative safety and efficacy data has not been addressed; this issue should be considered when interpreting the results of the submitted model. In the base case analysis, the Submitter focused on all ALK-positive NSCLC patients who have progressed or are intolerant to crizotinib and who have CNS metastases status at baseline. The benefit of oral route of administration and potential pill burden were adequately addressed in the submitted model given the paucity of evidence.

1.3 Submitted and EGP Reanalysis Estimates

Table [2]. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis (Range)
ΔE (LY)	1.967	0.488, 2.730
Progression-free	0.990	0.880, 0.990
Post-progression	0.977	-0.501, 1.740
ΔE (QALY)	1.436	0.416, 1.963
Progression-free	0.762	0.762, 0.762
Post-progression	0.674	-0.346, 1.201
ΔC ($)	$156,501	$185,878, $127,124
ICER estimate ($/QALY)	$108,958	$67,993, $417,128

The main assumptions and limitations with the submitted model are:

- Lack of comparative safety and efficacy between alectinib and pemetrexed ± cisplatin. The efficacy of alectinib was based on two phase II single-arm trials, while the efficacy of pemetrexed ± cisplatin was assumed to be equal to the efficacy of systemic therapies reported in a retrospective analysis of 37 ALK-positive NSCLC patients who discontinued crizotinib for at least 3 weeks [(5)]. This retrospective study, however, did not report the type of systemic therapies used, proportion of patients with CNS metastases at baseline and specific time from last dose of

crizotinib to first dose of the systemic therapy. The comparative efficacy of alectinib and pemetrexed ± cisplatin estimated by the Submitter may be influenced by difference in population and study characteristics as well as trial designs.

- PFS and OS were extrapolated from short-term trial data. Using trial data the Submitter extrapolated PFS and OS of patients receiving alectinib over a 10 year time horizon. Given the poor prognosis in this patient group and the unknown expected life expectancy of NSCLC ALK patients with brain metastases receiving alectinib after progressing on crizotinib, a shorter time horizon should be explored in a sensitivity analysis.

- The Submitter commented on the pCODR Expert Review Committee's (pERC's) Initial Recommendation that using a 3-year time horizon in the economic model for this patient population treated with alectinib is incorrect, as it falls far short of the concept of a lifetime horizon and the CADTH guidelines that recommends to consider "all relevant differences in the future costs and outcomes" (Guideline 6.1). The Submitter expressed concern that the choice of a 3 year time horizon was based on the CGP's anecdotal estimate of median survival and not on the estimate of maximum survival.

  The EGP acknowledge that the Submitter is partially correct regarding the CADTH Economic Evaluation Guideline that time horizon should capture relevant differences in the future costs and outcomes. Although the guideline suggests that "time horizon should be long enough to capture all potential differences in costs and outcomes associated with the intervention being compared", the time horizon is not solely based on an economic judgement. In fact, the most recent CADTH guideline recommends[1] 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)". In case 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 EGP and CGP acknowledge the concern of using a 3-year time horizon in the economic model by the Submitter. However, the CGP are not aware of any studies that report a maximum overall survival of 10 years in ALK positive patients with CNS metastases who have progressed on crizotinib. The time horizon used by the Submitter was driven by extrapolation results that are subject to high uncertainty. Indeed, incremental QALYs estimated beyond the trial data accounted for ~63% of incremental QALY gains over the entire time horizon. As suggested by the 4th edition of the CADTH Economic Guideline[1], "Considering whether the percentage of the estimated effect that occurs beyond the observed data is clinically realistic will help researchers to assess the suitability of the extrapolation methods. Expert judgment may be helpful in this regard" (Page 43).

  With these recommendations in mind, the CGP and EGP believe that it is reasonable to include a shorter time horizon, i.e. 3 and 5 years, in a sensitivity analysis to explore uncertainty in the extrapolation of overall survival.

- Efficacy of alectinib was pooled from two single-arm phase II trials with different population characteristics. Because both trials have different study assessment schedules and race distributions, pooling data from both trials are not appropriate. The Submitter provided the results

[1] Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa: CADTH; 2017 Mar. Available at: https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf

of additional economic evaluation based on each separate trial during the Checkpoint meeting. The economic evaluation results were within ranges of the base case analysis.

- The model estimated utilities for the progression-free (PF) health state for alectinib by mapping responses from the EORTC QLQ-C30 questionnaire reported in the NP28761 trial [(1)]. However, the Submitter reported only mean utility value (0.770) without detailed mapping methods. This utility value was slightly higher than other utility data for NSCLC patients reported in Nafee et al (2008) (PF-stable/no side effect=0.653) [(8)] and Chouaid et al (2013) (PF= 0.70) [(9)]. The utility value for progressed disease (PD) was based on Labbe et al (2016) [(7)] but the utility value used by the Submitter was slightly higher than that showed in the most recent Labbe's poster (0.69 vs 0.62) [(7)]. Moreover, the Submitter used equal utility values for patients with and without CNS metastases. This assumption was inconsistent with existing evidence cited in the submitted PE report under the Unmet Need Section suggesting that patients with CNS metastases may have shorter life expectancy and poorer quality of life compared to patients who do not develop CNS metastases.

  Due to the high uncertainty associated with the utility data, the EGP performed the re-analyses based on a range of different set of utility values reported in Nafee et al (2008)[(8)], Chouaid et al (2013) [(9)], the most recent estimates reported in Labbe et a (2016) [(7)], Matza et al (2013) [(10)] and Lester-Coll et al (2016) [(11)].

- The Submitter assumed the duration of treatments equal to PFS. This may under- or over-estimate the costs of the treatments (including alectinib and standard chemotherapy) and the incremental cost-effectiveness ratio (ICER). The EGP conducted the re-analyses by varying treatment duration of alectinib and pemetrexed ± cisplatin by 20%.

- The unit costs of pemetrexed and cisplatin used in this study were too high given the availability of their generic versions. This may overestimate the cost of pemetrexed ± cisplatin and the ICER, causing alectinib more economically attractive. The EGP conducted the re-analyses by varying the unit costs of pemetrexed and cisplatin by 25%, 50% and 75% from the base case.

  The Submitter commented on the pCODR pERC's Initial Recommendation that the submitted model used the only publicly available generic unit costs (list price) available from QuintilesIMS's Delta PA database. The EGP considers that a high unit cost of standard chemotherapy used by the Submitter are acceptable, given the limited access to generic unit cost information. However, the one-way sensitivity analysis of the unit cost of pemetrexed and cisplatin was performed to assess the impact of generic pricing of pemetrexed and cisplatin on the cost effectiveness of alectinib.

1.4 Detailed Highlights of the EGP Reanalysis

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

The EGP performed reanalyses by taking a shorter time horizon of 3 and 7 years, assuming 80% and 90% of alectinib dose intensity, varying hazard ratio of PFS vs OS by 20%, changing the duration of alectinib and pemetrexed ± cisplatin by 20%, assuming -/+ 25%, 50%, and 75% of unit cost of pemetrexed ± cisplatin, replacing utility data for pre- and post-progression health states with data reported in Labbe et al (2016) [(7)], Nafees et al (2008) [(8)] and Chouaid et al (2013)[(9)] and replacing a utility value for progression with CNS metastases with a value of 0.40 as reported by Lester-Coll et al (2016) [(11)]. Detailed description of EGP analysis is shown in Table 3. The EGP also reduced the unit cost of alectinib by 25%, 50%, and 75% of the submitted price (Table 4).

Table [3]: Detailed Description of EGP Reanalysis

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$156,501	1.436	1.967	$108,958	-
EGP Reanalyses - Lower bound					
Reducing alectinib dose intensity to 80%	$134,012	1.436	1.967	$93,301	($15,657)
Reducing alectinib dose intensity to 90%	$149,522	1.436	1.967	$104,099	($4,859)
Increasing a hazard ratio of PFS vs. OS by 20%	$155,307	1.432	1.967	$108,455	($503)
Reducing duration of alectinib treatment by 20%	$127,124	1.436	1.967	$88,506	($20,453)
Increasing duration of pemetrexed ± cisplatin by 20%	$155,043	1.436	1.967	$107,943	($1,015)
Increasing the unit cost of pemetrexed and cisplatin by 25%	$155,470	1.436	1.967	$108,241	($718)
Increasing the unit cost of pemetrexed and cisplatin by 50%	$154,439	1.436	1.967	$107,523	($1,435)
Increasing the unit cost of pemetrexed and cisplatin by 75%	$153,408	1.436	1.967	$106,805	($2,153)
Applying disutility for intravenous chemotherapy (Matza et al, 2013)[10]	$156,501	1.540	1.967	$101,607	($7,352)
Extreme case analysis: Upper bound OS for alectinib and Lower bound OS for pemetrexed ± cisplatin	$162,844	1.963	2.730	$82,958	($26,000)
Lower bound, best case based on the above lower bound scenario	$127,124	1.963	2.730	$67,993*	($40,965)
EGP Reanalyses-Upper bound					
Reducing a time horizon to 3 years	$137,150	0.873	1.163	$157,128	$48,170
Reducing a time horizon to 7 years	$155,074	1.355	1.849	$114,466	$5,507
Reducing a hazard ratio of PFS vs. OS by 20%	$157,720	1.441	1.967	$109,475	$516
Increasing duration of alectinib treatment by 20%	$185,878	1.436	1.967	$129,411	$20,453
Reducing duration of pemetrexed ± cisplatin by 20%	$157,960	1.436	1.967	$109,974	$1,015
Reducing the unit cost of pemetrexed and cisplatin by 25%	$157,532	1.436	1.967	$109,676	$718
Reducing the unit cost of pemetrexed and cisplatin by 50%	$158,563	1.436	1.967	$110,394	$1,435
Reducing the unit cost of pemetrexed and cisplatin by 75%	$159,594	1.436	1.967	$111,112	$2,153
Replacing utility of pre-progression state by Nafees et al (2008)[8]	$156,501	1.321	1.967	$118,512	$9,553
Replacing utility of pre-progression state by Chouaid et al (2013)[9]	$156,501	1.367	1.967	$114,480	$5,521
Replacing utility of post-progression by Chouaid et al (2013)[9]	$156,501	1.278	1.967	$119,363	$10,404

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Replacing utility value for CNS metastases and post-progression with Lester-Coll et al (2016) [11]	$156,501	1.172	1.967	$133,486	$24,528
Extreme case analysis: Upper bound OS for alectinib and Upper bound OS for pemetrexed ± cisplatin	$152,404	1.096	1.474	$139,054	$30,096
Extreme case analysis: Lower bound OS for alectinib and Lower bound OS for pemetrexed ± cisplatin	$154,660	1.283	1.745	$120,534	$11,575
Extreme case analysis: Lower bound OS for alectinib and Upper bound OS for pemetrexed ± cisplatin	$144,221	0.416	0.488	$346,539	$237,581
Extreme case analysis: Base case OS for alectinib and Upper bound OS for pemetrexed ± cisplatin	$148,858	0.801	1.047	$185,748	$76,789
Extreme case analysis: Lower OS for alectinib and Base case OS for pemetrexed ± cisplatin	$151,864	1.051	1.409	$144,479	$35,521
Upper bound, worst case based on the above upper bound scenario	$185,878	0.416	0.488	$417,128*	$308,170

* may not equal to ΔC/ΔQALY due to rounding

The Submitter commented on the pERC Initial Recommendation that pERC frequently cites considerable uncertainty in the Submitter's best estimate of the ICER which the Submitter argues is manufactured using implausible extreme scenarios by the EGP. For instance, the EGP used the lower 95th CI of alectinib OS with the upper 95th CI of chemotherapy OS. The probability of the two 95%CI values or more extreme occurring together is 0.025^2=0.000625. The Submitter expressed concern that the EGP cannot continue to misrepresent extreme scenarios as plausible, most likely base cases as evidence of large uncertainty to pERC.

In response to the Submitter's feedback, the EGP noted that the submitted model used OS and PFS data derived from two single-arm trials and one retrospective cohort study. Selection bias or the potential systematic differences between characteristics of participants in alectinib and standard chemotherapy groups is the key concern for the submitted PE report. The Submitter claimed that "the populations are comparable with respect to age, gender, smoking status, and ECOG performance status"; however, this claim was not supported by any formal statistical methods. The Submitter did not adjust for potential imbalances in baseline characteristics and prognostic factors between groups that are associated with survival outcomes.

Without comparative survival data and appropriate statistical adjustment for imbalances in baseline characteristics between alectinib and standard chemotherapy groups, the EGP believes that any combinations of alectinib and chemotherapy OS data is plausible.

Furthermore, the EGP is unfamiliar with the Submitter's justification regarding the probability of the two 95% CI values or more extreme occurring together. A confidence interval (CI) is interpreted as the level of confidence that the confidence interval will contain the true but unknown parameter. The CI **SHOULD NOT be interpreted as a probability** because it is not a random interval, and the unknown parameter, i.e. true OS, is constant. For example, 95% CI (3.8,

12.3) represents that we are 95% confident that the true median survival of patients receiving standard chemotherapy is between 3.8 and 12.3 months.

Table [4]. Detailed Description of EGP Reanalysis on the unit cost of alectinib

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Reducing the unit cost of alectinib by 25%	$119,860	1.436	1.967	$83,448	($25,510)
Reducing the unit cost of alectinib by 50%	$83,219	1.436	1.967	$57,938	($51,020)
Reducing the unit cost of alectinib by 75%	$46,577	1.436	1.967	$32,428	($76,531)

The Submitter commented on the pERC Initial Recommendation that the Submitter disagrees with the implausible scenario of the reanalysis by the EGP of increasing the current unit cost (list price) of alectinib by 20, 50, and 75%. It is noted that the objective of a one-way sensitivity analysis performed by the EGP was to assess the extent to which the cost-effectiveness of alectinib varies by changes in its unit costs. The results of this analysis showed that incremental cost-effectiveness ratios of alectinib were highly sensitive to its unit costs. The EGP acknowledges the Submitter's concern and therefore has removed the results of the one-way sensitivity analyses representing increases to the unit costs alectinib by 25%, 50% and 75%.

1.5 Evaluation of Submitted Budget Impact Analysis

An Ontario-specific budget impact analysis was performed to show the 3-years potential budgetary impact of alectinib, should the medication is recommended for funding for ALK-positive patients with NSCLC who have progressed following crizotinib therapy and who have CNS metastases. Methods used to estimate the budgetary impact, including study design, model, assumptions and input parameters derived from Canadian sources, are appropriate.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for alectinib when compared to usual care consisting of platinum-doublet chemotherapy (cisplatin-pemetrexed) or pemetrexed monotherapy from the perspective of Canadian health care system is between $67,993/QALY gained (lower bound) and $417,128/QALY gained (upper bound). Further analysis suggests that the estimated ICERs could be reduced to $32,428 per QALY gained if the unit cost of alectinib is reduced by 75%.

- The extra cost of alectinib is between $127,124 and $185,878. Drug and disease management costs are the main factors that influence ΔC, accounting for 91% and 9%, respectively.
- The extra clinical effect (ΔE) of alectinib is between 0.416 QALYs and 1.963 QALYs. The factors that most influence the incremental QALYs are parametric models used to fit OS and PFS data, time horizon, and utility values associated with disease free and progressed disease health states. **Furthermore, given the lack of direct comparative estimates for PFS and OS, there is a high degree of uncertainty in the estimates of extra clinical effect of alectinib. This uncertainty is not reflected in the estimates of incremental effect captured in the model and, therefore, it is also not fully captured in the EGP's range of ICER estimates.**

Overall conclusions of the submitted model:
The key and important limitation of the submitted model is a paucity of comparative efficacy of alectinib and pemetrexed ± cisplatin. The model structure is adequate and the economic evaluation is well-designed. The model captures patients' preference by incorporating health utility values associated with PFS and PD health states and performing a cost-utility analysis. Consistent with Patient and Provincial Advisory Groups inputs, the Submitter assumed that a smaller proportion of patients who progress after alectinib would receive WBRT. However, the submitted model did not incorporate the impact of having CNS metastases, receiving WBRT, and receiving IV chemotherapy on quality of life or utility values.

More importantly, efficacy data for alectinib and pemetrexed ± cisplatin were derived independently (a pooled analysis of two Phase II studies for alectinib and a retrospective cohort study for a standard chemotherapy). Actual comparative efficacy of alectinib compared to pemetrexed ± cisplatin remains unknown. Lack of head-to-head clinical trial evidence comparing the efficacy of alectinib and pemetrexed ± cisplatin may bias the estimated ICERs. Observed differences in costs and outcomes (LY and QALY) may be a result of systematic differences in baseline sociodemographic factors and NSCLC prognosis of patients. The use of data from a small retrospective analysis with limited details of study participants to estimate the OS data of patients receiving pemetrexed ± cisplatin limit the generalizability of the predicted OS data. PFS data for pemetrexed ± cisplatin group was approximated from the ratio of PFS and OS data observed in the alectinib group due to paucity of PFS data in this population.

The CGP believes that the use of a 10 year time horizon for the base case analysis is too optimistic given the poor prognosis in this patient group and the unknown expected life expectancy of NSCLC patients with CNS metastases receiving alectinib. A shorter time horizon should be explored in a sensitivity analysis.

Future head-to-head clinical trial is needed to estimate the comparative efficacy of alectinib and pemetrexed ± cisplatin. The extent to that post ALK-inhibitor immunotherapy affects incremental cost-effectiveness ratios of alectinib requires further investigation.

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 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 ALK-Positive Non-Small Cell Lung Cancer Patients Previously Treated with Crizotinib Who have Central Nervous System Metastases. 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*.

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.

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