CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Lorlatinib (Lorbrena) for Non-Small Cell Lung Cancer

January 30, 2020

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Pfizer compared lorlatinib to pemetrexed-platinum chemotherapy and best supportive care (BSC) for adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on: crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	The patient population in the submitted model are adults with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on: crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib. This is in line with the funding request.
Type of Analysis	*CUA*
Type of Model	*Partitioned-survival*
Comparator	• Pemetrexed-platinum chemotherapy • Best supportive care (defined as any concomitant medications, treatments or symptomatic therapy, excluding chemotherapy)
Year of costs	2018
Time Horizon	5 years (base-case) 3 years (scenario analysis)
Perspective	Canadian public payer perspective
Cost of lorlatinib *Assumed daily dose of 100mg taken orally once daily until progression. Dose reductions to 75 mg OD and 50 mg OD were allowed at the clinician's discretion.* ** Price Source: Pfizer PE submission*	• Cost per 25 mg tablet: $112.4443 • Cost per 100 mg tablet: $337.3333 • Recommended dose/day: 100 mg/day • Cost per day: $337.3333 • Cost per 28-day cycle: $8,958.38 • Dose intensity: Relative dose intensity (RDI) of 98.5%, as per the trial results.
Cost of Pemetrexed-platinum chemotherapy *Pemetrexed 500mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin AUC 5 or 6 (=500 mg for an average patient) administered intravenously (IV) every 3 weeks until progression with a maximum of 6 cycles (assumed body surface area of 1.74 m^2 based on EXP3B-5 group in the trial)* ** Price Source: Pemetrexed cost based on pCODR reviews of alectinib and ceritinib for second-line ALK-positive NSCLC*	Pemetrexed-cisplatin regimen • Dose of pemetrexed: 500 mg/m^2 per 21-day cycle, equal to 871.32 mg for an average person • Cost per 100 mg vial of pemetrexed: $83.18 • Cost per 500 mg vial of pemetrexed: $415.90 • Dose of cisplatin: 75 mg/m^2 per 21-day cycle, equal to 130.70 mg for an average person • Cost per 50 mg of cisplatin: $9.50

Cisplatin cost based on Reaume et al who sourced it from two Canadian Cancer Centres (Ottawa & Princess Margaret) Carboplatin cost was from IQVIA Delta PA	• Cost per 100 mg of cisplatin: $19.00 • Relative dose intensity of 98.1% based on ASCEND-5 study Pemetrexed-carboplatin regimen • Dose and cost of pemetrexed: as above • Dose of carboplatin (based on NICE TA181 and TA347): 500 mg (base-case) 750 mg (sensitivity) • Cost per 50 mg of carboplatin: $106.12 • Cost per 450 mg of carboplatin: $630.00 • Relative dose intensity of 98.1% based on ASCEND-5 study Total cost of pemetrexed-platinum chemotherapy • Relative use of carboplatin versus cisplatin: 46.15% carboplatin; 53.85% cisplatin (source: PROFILE 1014 study) • Cost per 28-day cycle: $2,578.72 (drug cost: $1,437.18; administration cost: $1,141.54)
Cost of best supportive care (BSC)	• BSC was defined as any concomitant medications, treatments or symptomatic therapy, excluding chemotherapy. • This included cost of physician services, diagnostic tests, out patient prescription drugs and home and community care in the post-progression state (=$1,222 per 28-day model cycle).
Cost of terminal care	$9,810.33 (based on Bekelman et al 2016).
Model Structure	A three state partitioned-survival model was constructed which included progression-free survival [PFS], post-progression survival [PPS] and death. Model states were selected in accordance with the clinical pathway, and the model structure is identical for all comparators. The PFS health state was defined as patients who are alive without progression of the disease. The PPS health state was defined as patients who are alive with progressive disease. The model was used to predict costs and outcomes of treatment with lorlatinib, pemetrexed-platinum chemotherapy and BSC in the target population.
Key Data Sources	<u>Effectiveness</u> *Lorlatinib:* PFS and OS curves based on a phase 2 single-arm study [Trial 1001: EXP3B-5 group]

	Pemetrexed-platinum chemotherapy: PFS based on a sponsor-conducted match-adjusted indirect comparison (MAIC) which used Trial 1001 for lorlatinib and trials ALUR and ASCEND-5 for chemotherapy. OS HR assumed to be same as PFS HR (based on NICE TA422 and supported by PROFILE 1014 study and Ou et al). *BSC:* patients enter in progressed state (so no PFS data used). HR for OS was derived from a naïve comparison to obtain a projected mean survival similar to the comparator arms in a meta-analysis of 15 RCTs reported in Wao et al. This HR was applied to lorlatinib OS curve. Drug Costs: previous pCODR reviews, and published Canadian studies Utilities: Trial 1001 using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and mapped to the 3-level EuroQol 5-dimension (EQ-5D-3L) using Longworth et al. Resource Utilization: published Canadian studies and expert opinion

1.2 Clinical Considerations

Summary of the pCODR Clinical Guidance Panel (CGP) input

- Overall, the CGP concluded that there may be a net clinical benefit for lorlatinib in the treatment of patients who progressed on previous alectinib or ceritinib or crizotinib and at least one other ALK inhibitor. Specifically,

    - Compared to doublet chemotherapy, it is not clear based on on a single phase II trial if lorlatinib is superior in terms of clinical benefits in patients who progressed on previous alectinib or ceritinib or crizotinib and at least one other ALK inhibitor. This is because of absence of direct evidence based on head-to-head Phase 3 clinical trials.

    - In the sponsor-conducted matched adjusted indirect comparison, lorlatinib had a very significant reduction in comparison to single agent chemotherapy in terms of progression-free survival, which woul align in clinical practice, some patients who were previously treated with platinum-doublet chemotherapy, but even if the comparator were doublet chemotherapy (instead of single agent), there would still likely be a benefit (though somewhat less magnitude) for lorlatinib.

    - Compared to best supportive care, the CGP concluded that lorlatinib is highly likely to provide a clinically meaningful benefit in ALK positive patients. This is based on the historic record of targeted therapy response rates translating to real patient benefit, and the difficulty of treating intracranial disease.

    - Although the meta-analysis of outcomes with no treatments reviewed by the methods team was judged to have good internal validity, CGP considered this to have little external validity to this specific subtype of driver-mutation cancer originating in lung.

- The drug appears safe based on Trial 1001, and reasonably well tolerated.

- Based on the evidence provided, it is not possible to conclude whether lorlatinib should be sequenced prior to or following doublet chemotherapy (without a randomized phase III trial). In practice and in implementation, lorlatinib would likely be used prior to doublet platinum chemotherapy in some patients, after doublet platinum chemotherapy in others, and in patients who would not ever receive or accept doublet platinum chemotherapy – similar to the patients enrolled in the clinical trial.

Relevant issues identified included:

- The response rate of 40% and intracranial response of 50%, coupled with the median duration of response of over 14 months, suggests that this drug does have the potential for a positive impact on ALK positive lung cancer patients' health. However, since evidence is based only a single arm, multiple–cohort, phase I/II trial, there is high level of uncertainty about how lorlatinib would compare with other therapies (e.g. doublet chemotherapy) in clinical practice.

- Drug safety has historically been one of the most important outcomes of a phase II trial. Serious treatment related adverse events were rare (7%), and the majority of grade3/4 events were biochemical abnormalities only (hyperlipidemia/hypertriglyceridemia), and it is expected that with increased recognition and early management this will be a manageable toxicity.

- A Matched Adjusted Indirect Comparison (MAIC) was used to answer the question of how patient outcomes compare with standard therapy. While MAIC had a reasonable framework, the caveats are that the trials cited – ALUR and ASCEND-5 – compared Alectinib and Ceritinib respectively to pemetrexed or docetaxel, but all patients had previously received the most effective chemotherapy (doublet platinum chemotherapy), whereas the current request does not require prior platinum based chemotherapy – the comparison used would bias the treatment in favour of lorlatinib and against chemotherapy. The economic model assumption that the benefit of lorlatinib versus doublet platinum chemotherapy in chemotherapy naïve patients would be the same as the benefit of lorlatinib vs docetaxel or pemetrexed monotherapy in chemotherapy pretreated patients, this assumption may not be valid.

Summary of registered clinician input relevant to the economic analysis

- Registered Clinician identified that there is an unmet need for these patients. The primary benefit of lorlatinib is that it acts as an additional line of therapy before chemotherapy for this indication. It does not replace any current treatments. Compared to lorlatinib, other treatment options (chemotherapy, immunotherapy) offer limited benefit and greater toxicity. *In the economic analysis, the toxicity profile is addressed through the costs of adverse events for each comparator and the utility values applied to each comparator treatment.*

- Chemotherapy has limited effectiveness for brain metastases. Therefore, chemotherapy is generally reserved for when ALK directed therapy has been exhausted (i.e. post progression on lorlatinib). The data from the phase II study show higher systemic and intracranial responses with lorlatinib compared to historical results of other potential options (especially chemotherapy and immune therapy). *The model included patients with brain metastases.*

- Clinicians suggest that treatment with a new ALK inhibitor like lorlatinib, that can overcome resistance to a next generation ALK inhibitor, will lead to further improvements in survival for patients. Registered clinicians noted that this type of data will take several years to mature. *The economic analysis incorporates overall survival benefit, although it acknowledges that the evidence for the survival advantage is weak.*

- Lorlatinib has a highly convenient dosing schedule for patients compared to other agents, where patients can take a single pill once daily. *Patient preference for convenient dosing was not incorporated in the economic analysis.*

- Clinician noted that in the treatment sequence lorlatinib should follow use of a next generation ALK inhibitor. *This is in line with the patient population modelled in the economic analysis.*

Summary of patient input relevant to the economic analysis

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

- Side effects: Patients and caregivers prioritize quality of life as a treatment outcome. Many patients said that side effects of lorlatinib were manageable. Patients and caregivers noted the following side effects of current therapies: neuropathy, cognitive and memory issues, increased cholesterol, edema, weight gain, mood changes, dizziness, pain, fatigue, nausea, shortness of breath, appetite loss, inability to fight infection, burning of skin and

impact to mood. Some patients required treatment to manage side effects, including counselling, anti-depressants and medication to manage depression and high cholesterol. Patients emphasized a desire for more energy and less fatigue. CGP also identified fatigue as an important side effect of treatment. *Most of these side effects, except high cholesterol were not included, in terms of costs and impact on quality of life, in the economic analysis. Only the following Grade 3/4 treatment-related adverse events experienced by at least 10% of patients in Trials 1001 and 1014 were included in the model: hypercholesterolemia, hypertriglyceridemia and neurtropenia, and were considered appropriate by CGP.*

- Improvement in survival and quality of life. *Favourable effects of lorlatinib 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 lorlatinib. Patients were inconvenienced by the need for multiple hospital visits for intravenous infusions as well as the toxicities and after effects associated with the treatment. *Impact of treatments on productivity cost was included by the sponsor in a scenario analysis conducted using societal perspective.*

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 lorlatinib which are relevant to the economic analysis:

- PAG sought clarity on eligible population for lorlatinib as the pivotal trial included several cohorts but these patients were not included in the reimbursement request
    - *Based on the funding requested, patient that are treatment-naive, ROS1 positive with any previous treatment would not be eligible to receive lorlatinib; and ALK-positive patients with disease progression following previous crizotinib only would not be eligible to receive lorlatinib (unless alectinib and ceritinib were not available). These patients were not modelled in the economic analysis; thepopulation modelled in the economic analysis was adults with ALK-positive metastatic NSCLC who have progressed on: crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib.*

- PAG sought clarification regarding flat pricing of all tablet strengths in case it becomes more costly for patients who are dispensed the lower strengths and had to adjust dose by adjusting the number of tablets.
    - *Flat pricing is not the case for lorlatinib.*

- PAG sought clarity on treatment "as long as the patient is deriving clinical benefit from therapy", treatment duration and treatment discontinuation.
    - *In the economic analysis, the base case scenario capped time on treatment to be inferior or equal to PFS; in a scenario analysis, the stopping rule was removed and treatment beyond disease progression was allowed just as in the trial. The latter approach was supported by the CGP and used in the EGP reanalysis.*

- PAG identified the oral route of administration as 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.

- *In Ontario for example, oral drugs are covered for patients age 65 and over. For those under 65, there are mechanisms to be covered (e.g. under Trillium Drug Benefit) but not all patients would be covered. This issue is not addressed in the economic analysis.*

1.3 Submitted and EGP Reanalysis Estimates

The main drivers of the cost-effectiveness results are the cost of drugs and estimates of HR for PFS and OS. Cost of the lorlatinib is based on the unit price and the duration of treatment. In sponsor's economic model, the duration of treatment is assumed to be equal to (or less than) the time to disease progression (in the base case). This is despite patients receiving lorlatinib beyond progression in sponsor's pivotal trial 1001. This assumption favours lorlatinib and reduces the incremental cost-effectiveness ratio. The CGP suggested that in clinical practice patients would likely be treated beyond progression, so this assumption is considered inappropriate. Similarly, assuming that OS HR for lorlatinib versus chemotherapy is the same as PFS HR also favours lorlatinib. As a result, in the economic analysis, patients in the lorlatinib arm have longer time to disease progression and death (and therefore greater QALYs), compared to chemotherapy and BSC. The time horizon in sponsor's base-case was 5 years (sensitivity analysis: 3 years) which was considered appropriate by the CGP and is in line with previous submissions.

The EGP reanalysis made a number of changes to the sponsor's model based on consultation with the CGP. These included: using a more plausible assumption for OS HR (=0.5; this was based on the advice of the CGP who suggested that OS HR is likely to be smaller in magnitude compared to the optimistic HR used in the sponsor's basecase, and a value of 0.5 is considered clinically plausible) for lorlatinib compared to chemotherapy, choosing an appropriate statistical distribution to extrapolate progression-free survival (i.e. generalized gamma), accounting for treatment cost beyond progression; and assuming equal proportion of patients receiving active therapy after progression.

Based on the above changes, the EGP reanalysis estimated that, for the comparison of lorlatinib versus chemotherapy and compared to the sponsor's values, the incremental QALYs decreased from 0.94 to 0.727, incremental costs increased from $125,117 to $172,479, and the resulting ICURs increased from $133,791 to$237,125, as presented in Table 2a below. Similarly, for the comparison of lorlatinib versus BSC, the EGP reanalysis evaluated that the incremental QALYs slightly increased from 1.23 to 1.25, incremental costs increased from $142,709 to $191,961, and the resulting ICURs increased from $116,003 to $153,113, as presented in Table 2b below.

The impact of each individual change in assumption is presented in Tables 3 and 4.

Table 2a. Submitted and EGP Reanalysis Estimates, lorlatinib vs chemotherapy

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	1.26	0.91
ΔE (QALY)	0.94	0.73
ΔC ($)	$125,117	$172,479
ICER estimate ($/QALY)	**$133,791**	**$237,125**

Table 2b. Submitted and EGP Reanalysis Estimates, lorlatinib vs BSC

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	1.67	1.67
ΔE (QALY)	1.23	1.25
ΔC ($)	$142,709	$191,961
ICER estimate ($/QALY)	**$116,003**	**$153,113**

The main assumptions and limitations with the submitted economic evaluation that could not be addressed in EGP reanalyses were:

- **Hazard ratio for chemotherapy based on indirect comparisons:** In the absence of direct Phase 3 evidence comparing lorlatinib with chemotherapy or best supportive care, the cost-effectiveness analysis was based on a phase II, single arm trial (Trial 1001), supported by match-adjusted indirect comparisons (MAIC) that introduces serious limitations, including the questionable assumption that relative efficacy of lorlatinib versus pemetrexed or docetaxel monotherapy is similar to pemetrexed-platinum doublet therapy (note: the CGP did not support this assumption). This led to significant uncertainty in the effectiveness estimates.

- **Hazard ratio for best supportive care (BSC):** In the absence of direct evidence for OS for the BSC arm, OS was based on a projected survival curve that was estimated to match the survival observed in comparator arms of a meta-analysis of 15 RCTs conducted in newly-diagnosed, first-line NSCLC patients (Wao et al 2013). These RCTs were not limited to the ALK-positive patient group and do not reflect patients who have failed previous treatments. This adds uncertainty to the analysis which is not accounted for in the sponsor's submission.

- **Adverse events:** The model includes only Grade 3/4 treatment-related adverse events experienced by at least 10% of patients in Trials 1001 (lorlatinib) and 1014 (chemotherapy). Other grade 3/4 AEs were not captured. Moreover, grade 1/2 adverse events, such as edema (in 41% patients) and cognitive effects (in 17% patients) were not included in the analysis. Since the two treatments, lorlatinib and chemotherapy, have different AE profiles, this can have an impact on the resulting incremental cost-effectiveness ratio, although the direction of this impact is difficult to predict given the information included in the submission.

- **Health-related quality of life:** The absence of a generic HRQoL instrument in the lorlatinib 1001 trial led to mapping of the disease-specific instrument onto the EQ-5D to derive utility values. Mapping is not a preferred approach because mapping algorithms depend on performance of econometric model, which differs between patient samples and may over or under-predict certain health states. Using mapping instead of direct utility values introduces uncertainty in the estimate of relative health benefit, and in turn the cost-effectiveness results – this is not accounted for in the sponsor's submission.

- **Cost per cycle of monitoring patients**: This was based on de Olivier (2009) which included all lung cancer patients (including those in earlier lines of treatment), starting six months after initial diagnosis (initial phase) to the terminal care stage. Since patients eligible for lorlatinib are likely to be in worse health state than the average patients in the de Olivier (2009) study, using their cost data may underestimate the maintenance cost in the model This is likely to favour the lorlatinib arm which had longer progression-free survival (and therefore longer period to incur monitoring cost); lower monitoring cost is likely to reduce the incremental cost-effectiveness ratio in favour of lorlatinib.

1.4 Detailed Highlights of the EGP Reanalysis

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

- [Issue 1]: **HR for overall survival.** Due to unavailability of data, the sponsor assumed that HR for OS was the same as HR for the PFS outcome. This assumption was argued based on comparison of crizotinib versus pemetrexed-platinum in PROFILE 1014 (a first-line treatment study) and an exploratory MAIC comparing lorlatinib to the chemotherapy arm of Ou et al. However, this is a strong assumption which unduly favours lorlatinib. The CGP did not consider there was enough evidence to support this assumption. Therefore, based on the advice of the CGP, the EGP reanalysis assessed the following three values of OS HR for chemotherapy versus lorlatinib: 0.75, 0.5 and 0.25.

- [Issue 2]: **Statistical fit for lorlatinib PFS curve.** Based on fitting statistical distributions to the KM curve of lorlatinib arm, the log-normal distribution had the lowest BIC and the generalized gamma had the lowest AIC (although the differences in AIC/BIC between these distributions were <5 points). The median PFS based on log-normal distribution (7.4 months) was greater than the median PFS observed in trial 1001 (6.9 months) which favoured the lorlatinib arm. Moreover, as acknowledged in sponsor's submission, the generalized gamma distribution fitted the tail of the observed KM curve better than the log-normal distribution. EGP reanalysis replaced log-normal with generalized gamma distribution.

- [Issue 3]: **Total time on treatment.** The submitted model assumed that treatment would stop once patients have progressed. The median time on treatment in the model was 7.4 months (equal to PFS) while median time on treatment in lorlatinib trial 1001 was 10.1 months. Therefore, the EGP reanalysis included post-progression treatment cost for lorlatinib. This reanalysis approach was supported by CGP and is in line with previous pCODR submissions.

- [Issue 4]: **Vial sharing and no wastage.** The base case in the submitted model assumed vial sharing and therefore no wastage. This is a conservative assumption. The submitted model included the option to allow potential wastage which was assessed in EGP reanalysis.

- [Issue 5]: **Subsequent treatment proportion.** The submitted model assumed that, once progressed, 52% of patients in the lorlatinib arm would receive an active subsequent therapy. The sponsor assumed that in the chemotherapy (pemetrexed-platinum) arm, after progression, 69% would receive an active subsequent therapy. This was based on consultation with Canadian experts (n=7). However, the CGP did not agree that such high proportion of post-progression patients in the chemotherapy arm would receive active systemic therapy. EGP reanalysis assumed that 50% of patients in both groups would receive subsequent treatment. CGP supported this reanalysis approach; however, this assumption had little impact on the results.

- [Issue 6]: **Utility decrement due to adverse events.** The model only included the cost impact of managing adverse events but not the quality of life impact of AEs. This is not consistent with previous pCODR submissions. CGP supported reanalysis that used a utility decrement of -0.06777 (consistent with previous pCODR submissions) for patients who experienced adverse events included in the model.

  The impact of each incremental change is presented in Tables 3 and 4.

Table 3: Lorlatinib vs. chemotherapy - detailed EGP re-analysis

	ΔC	ΔE (QALYs)	ΔE (LYs)	ICUR ($/QALY)	Δ from baseline submitted ICUR
Sponsor's base case	$125,117	0.94	1.26	$133,791	-
[1] HR for overall survival: chemotherapy vs. lorlatinib = 0.75	$113,654	0.37	0.41	$307,179	$173,388
[2] HR for overall survival: chemotherapy vs. lorlatinib = 0.50	$121,138	0.71	0.91	$171,627	$37,836
[3] HR for overall survival: chemotherapy vs. lorlatinib = 0.25	$130,014	1.10	1.50	$118,566	-$15,225
[4] Lorlatinib PFS model - generalized gamma	$137,951	0.95	1.26	$145,284	$11,493
[5] Total time on treatment for lorlatinib same as Trial 1001	$178,381	0.95	1.26	$188,411	$54,620
[6] Drug wastage allowed (i.e. no vial sharing)	$126,420	0.94	1.26	$134,980	$1,189
[7] Assume 50% of patients in both arms receive subsequent therapy after progression	$126,817	0.94	1.26	$135,500	$1,709
[8] Assume disutility of -0.06777 for ≥1 grade 3/4 AEs	$126,336	0.87	1.26	$144,982	$11,191
Best case estimate of above [2 + 4 + 5 + 7] parameters					
EGP estimate	$172,479	0.73	0.91	$237,125	$103,334
Price reduction scenarios for the best case estimate [2 + 4 + 5 + 7] parameters					

	Incremental $/QALY by lorlatinib acquisition cost discount %			
Description of Reanalysis	**0%**	**25%**	**50%**	**75%**
Submitter's Base case	$133,791	$101,464	$69,137	$36,810
EGP estimate of cost effectiveness	$237,125	$177,549	$118,371	$58,831

Table 4: Lorlatinib vs. best supportive care - detailed EGP re-analysis

	ΔC	ΔE (QALYs)	ΔE (LYs)	ICUR ($/QALY)	Δ from baseline submitted ICUR
Sponsor's base case	$142,709	1.23	1.67	$116,003	-
[1] Lorlatinib PFS model - generalized gamma	$152,052	1.24	1.67	$122,185	$6,182
[2] Total time on treatment for lorlatinib same as Trial 1001	$192,491	1.24	1.67	$155,127	$39,124
[3] Drug wastage allowed (i.e. no vial sharing)	$140,543	1.23	1.67	$114,227	-$1,776
[4] Assume 50% of patients in both arms receive subsequent therapy after progression	$140,937	1.23	1.67	$114,530	-$1,473
[5] Assume disutility of -0.06777 for ≥1 grade 3/4 AEs	$140,478	1.16	1.67	$120,634	$4,631
Best case estimate of above [1 + 2 + 4] parameters					
EGP estimate	$191,961	1.25	1.67	$153,113	$37,110
Price reduction scenarios for the best case estimate [1 + 2 + 4] parameters					

	Incremental $/QALY by lorlatinib acquisition cost discount %			
Description of Reanalysis	**0%**	**25%**	**50%**	**75%**
Submitter's Base case	$142,709	$91,429	$66,856	$42,282
EGP estimate of cost effectiveness	$153,113	$118,690	$84,213	$49,655

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 with adenocarcinoma, percentage of patients who are ALK-positive, the assumed proportion of eligible patients that would be prescribed lorlatinib if it was reimbursed, the cost of lorlatinib and its market share and the cost of alternative treatments.

The BIA was conducted from a national public payer perspective (excluding Quebec). A key limitation of the BIA is that it did not include the costs of administering treatments; this is a conservative assumption given that the use of oral lorlatinib instead of an IV regimen will reduce the cost of administration of IV regimen. Based on the advice of the CGP, the EGP conducted additional sensitivity analyses and found that assuming a higher proportion of NSCLC patients with an adenocarcinoma increased the BIA estimate.

1.6 Conclusions

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

- The EGP best estimate would likely be: $237,125/QALY. This estimate is the best estimate because it uses a more plausible assumption of overall survival advantage OS HR for lorlatinib compared to chemotherapy, conservative extrapolation for progression-free survival and accounts for treatment cost beyond progression. However *the cost-effectiveness analysis is built on indirect treatment comparisons that have serious limitations and thus lead to substantial uncertainty in the comparative effect estimates.*
- The incremental cost in the EGP best case estimate was $172,479 (compared to $125,117 in the sponsor's base-case). This higher incremental cost estimate was because of accounting for lorlatinib treatment continuation beyond progression.
- The incremental clinical effect in the EGP best case estimate was 0.73 QALYs (compared to 0.94 QALYs in the sponsor's base-case). This lower incremental QALY estimate in reanalysis was because of changing the assumption of overall survival benefit of lorlatinib compared to chemotherapy.

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

- The EGP best estimate would likely be: $153,113/QALY. As above, this estimate uses appropriate extrapolation for progression-free survival and accounts for treatment cost beyond progression. *However, this cost-effectiveness analysis is built on indirect evidence on overall survival estimates which has introduced substantial uncertainty in the comparative effect estimates.*
- The incremental cost in the best case estimate was $191,961 (compared to $142,709 in the sponsor's base-case). This higher incremental cost estimate was because of accounting for lorlatinib treatment continuation beyond progression.
- The incremental clinical effect in the best case estimate was 1.25 QALYs (which is close to the 1.23 QALYs in the sponsor's base-case).

Overall conclusion of the submitted model:

The overall structure of the economic model was appropriate. However there is considerable uncertainty around the clinical benefit of lorlatinib in terms of overall and progression-free survival in comparison to chemotherapy and best supportive care. No direct comparative evidence was available for survival estimates for comparators against lorlatinib. Trial 1001 conducted by the sponsor was a Phase 2 single arm trial; therefore, relative treatment effects were based on a match-adjusted indirect comparison for chemotherapy, and based on a broad NSCLC population for the BSC patients. Furthermore no direct comparative evidence was available for utility, and adverse events were not appropriately modelled in the economic evaluation. Varying the choice of the parametric model for PFS, assumption regarding hazard ratio for OS and time on treatment had significant impact the economic results. Thus, the best case EGP reanalysis represents more plausible estimates for cost-effectiveness analysis; however, given uncertainties in the economic analysis, the results should be interpreted with caution.

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 lorlatinib for NSCLC. A full assessment of the clinical evidence of lorlatinib for NSCLC 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.

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