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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Dacomitinib (Vizimpro) for Non-Small Cell Lung Cancer

May 31, 2019

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TABLE OF CONTENTS

DISCLAIMER ii
FUNDING ii
INQUIRIES iii
TABLE OF CONTENTS iv
1 ECONOMIC GUIDANCE IN BRIEF 1
1.1 Submitted Economic Evaluation 1
1.2 Clinical Considerations 3
1.3 Submitted and EGP Reanalysis Estimates 5
1.4 Detailed Highlights of the EGP Reanalysis 8
1.5 Evaluation of Submitted Budget Impact Analysis 10
1.6 Conclusions 11
2 DETAILED TECHNICAL REPORT 12
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 12
REFERENCES 14

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Pfizer** compared dacomitinib to gefitinib, afatinib, and erlotinib for the first-line treatment of non-small cell lung cancer (NSCLC) with an epidermal growth factor receptor (EGFR) mutation. Of note, dacomitinib is indicated for the first line treatment of adult patients with unresectable locally advanced or metastatic NSCLC with confirmed EGFR exon 19 deletion or L858R substitution mutations. The funding request is for the first-line treatment of NSCLC with an EGFR mutation.

Table 1. Submitted economic model.

Funding Request/Patient Population Modelled	The patient population in the submitted model was patients with newly diagnosed NSCLC harbouring an EGFR mutation (exon 19 deletion or the Leu858Arg mutation). The randomized controlled trial, ARCHER 1050 informed the comparison with gefitinib. Relative efficacy of agents other than gefitinib OS and PFS were informed by network meta-analysis. If the intent of the funding request is to be consistent with the Health Canada indication (i.e., specific to EGFR exon 19 deletion or Leu858Arg substitution mutations) then the population modelled is consistent with the funding request.
Type of Analysis	CEA and CUA
Type of Model	Partitioned-survival
Model Cycle Length	28 days
Comparator	In the base case, comparators are gefitinib, afatinib, and erlotinib. In scenario analysis dacomitinib was also compared to osimertinib.
Year of costs	2018
Time Horizon	15 Years
Perspective	Canadian public payer perspective
Cost of Dacomitinib *Assumed daily dose of 45mg taken orally once daily, with dose reductions to 30mg and 15mg.*	• Cost per 45mg tablet: $116.67 • Cost per 30mg tablet: $116.67 • Cost per 15mg tablet: $116.67 • Cost per day: $116.67 for 45mg, 30mg, or 15mg dose • Dose intensity: 73% • Cost per 28-day cycle: $2,384.67
Cost of Gefitinib *Daily dose of 250mg taken orally once daily.*	• Cost per 250mg tablet: $62.31 • Cost per day: $62.31 • Dose intensity: 96% • Cost per 28-day cycle: $1,674.76
Cost of Afatinib *Daily dose of 40mg taken orally once daily.*	• Cost per 20mg tablet: $73.30 • Cost per 30mg tablet: $73.30 • Cost per 40mg tablet: $73.30 • Dose intensity: 100%

	• Cost per 28-day cycle: $2,052.40
Cost of Erlotinib *Daily dose of150mg taken orally once daily.*	• Cost per 100mg tablet: $47.47 • Cost per 150mg tablet: $71.20 • Dose intensity: 100% • Cost per 28-day cycle: $1993.60
Model Structure	*The model was comprised of three health states: progression-free survival (PFS), post-progression survival (PPS), and death. Model health states were selected in accordance with the clinical pathway. The model structure is identical for all comparators, as the structure is based on disease progression. The PFS health state was defined as patients who are alive without progression of the disease, and can either be on first-line treatment or have stopped treatment. The PPS health state was defined as patients who are alive with progressive disease, who receive second- or third-line subsequent therapy, and who receive best supportive care (BSC).*
Key Data Sources	Key clinical information for dacomitinib and gefitinib: ARCHER 1050 trial (1) Clinical information for the comparison to erlotinib, afatinib, osimertinib (for scenario): Manufacturer submitted network meta-analysis (2) Drug Costs: Ontario Drug Benefit Formulary/Comparative Drug Index ((3) as cited in (4)); (4,5) Utilities: First-line treatment utility from ARCHER 1050 trial (1) Second and third-line treatment utility from (6–8) Resource Utilization: Expert opinion

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), all comparisons are appropriate.

Relevant issues identified included:

- *Effectiveness:* Although efficacy data is from a single randomized trial, PFS was significantly improved compared to gefitinib. Although Kaplan Meier survival curves cross, median survival with dacomitinib is 34.1 months compared to 26.8 months with gefitinib. This is the first randomized trial in this population to demonstrate a survival advantage – mature results from osimertinib versus gefitinib/erlotinib are pending. The key challenges with the ARCHER1050 trial include the exclusion of patients with CNS metastasis, a common problem in this patient population. This is the only randomized trial in this population to exclude CNS disease (for example, patient with CNS disease were included in the FLAURA trial [osimertinib versus gefitinib/erlotinib]). Despite this, the CGP expect that these results are still generalizable to the general population including those that present with CNS metastasis. It is unknown whether this more stringent patient selection has led to the positive survival result in this trial.
- *Safety:* Another key challenge with this study is treatment toxicity. Dacomitinib is more toxic than the currently available EGFR TKIs, with the majority of patients requiring dose reductions, dose holds or discontinuing for toxicity (1). This must be balanced against potential improvements in efficacy, as other TKIs have lower rates of dose reductions/holds, e.g. ~4% for osimertinib, ~10% for gefitinib, ~50% for afatinib. In particular, prescribers and patients should be well educated on toxicity management and additional toxicity monitoring (e.g. more frequent telephone or clinic follow up) required. If the price per tablet of dacomitinib does not change with dose intensity, there will be no impact on drug cost.
- *Burden of illness and need:* In the opinion of the clinical guidance panel members, dacomitinib as first-line therapy does yield clear clinical benefit (PFS) as first line therapy when compared with gefitinib in fit patients (performance status 0 or1) with NSCLC and EGFR-activating mutations. This would add to the current armamentarium of EGFR TKI options in this disease, and is the only EGFR TKI thus far to demonstrate a statistical survival benefit (median and hazard) when compared to gefitinib. Therefore, despite the availability of other options and the potential for higher rates of toxicity with dacomitinib, the CGP believe that there will be patients and providers that will select this as their preferred drug based on the PFS and potential survival impact.

Summary of registered clinician input relevant to the economic analysis

The CGP concluded that there is a net overall clinical benefit to dacomitinib in the initial treatment of advanced lung cancer patients with EGFR-activating mutations. This finding is based on one high quality randomized trial demonstrating compelling PFS benefit and even long-term survival benefit compared to the current standard of gefitinib. However, this is at the cost of greater toxicitity, which appears manageable and not dissimilar to that of other funded agents such as afatinib, in this setting. Clinicians suggested that dacomitinib was similar to existing treatments in terms of efficacy, safety, and tolerability; and was shown to have an improvement in PFS. The manufacturer submitted model reflected that PFS was superior to other comparators. The CGP has also recommended that if osimertinib is funded as a first-line treatment for this patient population, the majority of patients will shift to this treatment,

Summary of patient input relevant to the economic analysis

Patients considered symptoms of lung cancer, such as appetite and energy levels. They also expressed the desire to administer treatments at home, to minimize disruptions to life. Quality of life was also addressed as an important consideration for new treatments. Given that dacomitinib is a tablet to be taken orally, dacomitinib can be taken at home – similar to the existing treatments. The primary outcome of this analysis is presented as the quality adjusted life year, which theoretically incorporates quality of life. Although not explicitly considered in the manufacturer submitted model, symptoms such as appetite and energy levels are assumed to effect utility measurements, which feed into quality adjusted life year outcomes.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified clinical and economic factors that could impact the implementation:

- Comparison to afatinib
- Sequencing with other therapies, including other TKIs and immunotherapy
- Potential for drug wastage

Comparison to afatinib was generated through network meta-analysis, and sequencing with other therapies was considered in the manufacturer submitted model. In all manufacturer submitted materials, the cost of dacomitinib is $116.67/tablet, regardless of strength. In EGP re-analysis, dose intensity for dacomitinib is changed to 100%, to reflect that the cost per tablet is independent of dose. If the cost per tablet decreases with dose reductions, outcomes should be re-evaluated.

The PAG is seeking information comparing dacomitinib to osimertinib in this setting as wells as guidance on sequencing of dacomitinib and osimertinib. The submitter has included a scenario analysis in which osimertinib is a comparator, and the EGP has explored this scenario in the detailed technical report.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP estimates.

Description	Costs	ΔC (Dacomitinib vs Comparator)	Clinical Effect (QALYs)	ΔE (Dacomitinib vs Comparator)	ICER/ICUR (Dacomitinib vs Comparator)	% Change Compared to Main Analysis by Manufacturer in ICER (all Dacomitinib vs Comparator)
Main Analysis (i.e. Manufacturer Submitted Base Case Analysis, probabilistic results)						
Dacomitinib	$117,258	-	2.00 QALY	-	-	-
Gefitinib	$93,909	$23,349	1.68 QALY	0.32 QALY	$73,761/QALY	-
Afatinib	$105,016	$12,243	1.83 QALY	0.17 QALY	$73,532/QALY	-
Erlotinib	$98,714	$18,544	1.71 QALY	0.29 QALY	$65,007/QALY	-
Probabilistic EGP Re-Analysis with 100% Dose intensity for all treatments other than gefitinib, Terminal Care Costs of $9,810.33, modified second and third-line treatment baskets composition, utility of 0.87 for all treatments, incidence of AEs for afatinib from LUX-Lung 7 trial, and time horizon of 7 years						
Dacomitinib	$131,598	-	2.01 QALY	-		-
Gefitinib	$92,662	$38,521	1.67 QALY	0.34 QALY	$114,350/QALY	55.0%
Afatinib	$103,824	$27,360	1.86 QALY	0.15 QALY	$188,631/QALY	156.5%
Erlotinib	$97,039	$34,145	1.68 QALY	0.33 QALY	$103,979/QALY	60.0%

Table 3. Submitted and EGP Reanalysis estimates, gefitinib (probabilistic).

Estimate	Submitted	EGP Reanalysis
Δ E (LY)	0.471	0.411
progression-free survival (PFS)	0.410	0.399
post-progression survival (PPS)	0.061	0.012
Δ E (QALY)	0.317	0.337
First line treatment	0.297	0.340
Second line treatment	-0.018	-0.018
Third line treatment	-0.005	-0.003
Best Supportive Care	0.042	0.018
Δ C ($)	$23,349	$38,521
ICER estimate ($/QALY)	$73,761/QALY	$114,350/QALY

Table 4. Submitted and EGP Reanalysis estimates, afatinib (probabilistic).

Estimate	Submitted	EGP Reanalysis
Δ E (LY)	0.225	0.187
progression-free survival (PFS)	0.183	0.171
post-progression survival (PPS)	0.042	0.016
Δ E (QALY)	0.167	0.145
First line treatment	0.150	0.141
Second line treatment	-0.005	-0.006
Third line treatment	-0.001	-0.002
Best Supportive Care	0.023	0.012
Δ C ($)	$12,243	$27,360
ICER estimate ($/QALY)	$73,532/QALY	$188,631/QALY

Table 5. Submitted and EGP Reanalysis estimates, erlotinib (probabilistic).

Estimate	Submitted	EGP Reanalysis
Δ E (LY)	0.651	0.318
progression-free survival (PFS)	0.513	0.501
post-progression survival (PPS)	-0.162	-0.183
Δ E (QALY)	0.285	0.328
First line treatment	0.377	0.427
Second line treatment	-0.032	-0.029
Third line treatment	-0.009	-0.008
Best Supportive Care	-0.051	-0.062
Δ C ($)	$18,544	$34,145
ICER estimate ($/QALY)	$65,007/QALY	$103,979

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

Primary limitations of the manufacturer submitted model are related to drug pricing, and the survival functions fit to observed data. In the manufacturer submitted model, drug acquisition costs were calculated by multiplying the required dosage with the cost per milligram for each treatment, and subsequently adjusted for dose intensity – which significantly underestimates drug costs. The ICER was sensitive to this limitation.

In the ARCHER 1050 trial, OS curves cross at approximately three years, which is not captured in the predicted OS in the model. PFS for dacomitinib is consistently overestimated, regardless of the choice of survival curve selected. The follow-up cut-off for fit of PFS survival curves is 33 months; but, at 36 months of follow-up PFS for dacomitinib was observed to be zero. There was no possible combination of survival distributions in which PFS for dacomitinib was not overestimated.

This model relies on indirect comparisons for measures of relative efficacy in terms of PFS and OS. The comparison between dacomitinib and gefitinib is the most likely to be accurate, because gefitinib was the comparator in the ARCHER 1050 trial. Given that no loops of evidence were available for synthesis in the network meta-analysis, assessment of inconsistency was not possible. Economic outcomes based on comparisons with afatinib, erlotinib, or osimertinib should be interpreted cautiously.

Survival function extrapolation methods described in the manufacturer submitted documents are consistent with NICE guidance, and conducted appropriately. The thorough documentation reported with the network meta-analysis lends confidence to this conclusion. However, the crossing of the OS in KM curves between dacomitinib and gefitinib in the ARCHER 1050 trial is not captured in any of the predicted survival curves – possibly resulting in overestimation of OS for dacomitinib relative to gefitinib. Additionally, follow-up used to inform PFS in the model up to 33 months is used. However, follow-up data up to 36 months is available, and PFS is zero at 36 months. Therefore, extrapolation of PFS results in overestimated benefits. Economic analysis of outcomes observed during the ARCHER 1050 trial were

requested (where OS and PFS are directly informed by observed Kaplan Meier survival data), and not provided by the submitter. The manufacturer has appropriately identified that power is limited due to censoring at the end of follow-up, and a restricted means analysis based only on observed data likely fails to capture the entirety of the survival benefit. The EGP agrees that this is not a substitute for the base case analysis. However, the KM plots represent the best available estimates based on observed data during trial follow-up. Economic model outcomes based on observed data would have clarified the magnitude of observed outcomes relative to predicted outcomes for a time horizon equal to trial follow-up. Given the already identified limitations in survival curves used in this model, this limitation is significant. The model overestimates the clinical benefits of dacomitinib, and quantification of this overestimate was not possible.

1.4 Detailed Highlights of the EGP Reanalysis

Results of the EGP's reanalysis is mainly due to differences in cost, rather than efficacy of drugs. The manufacturer submitted model lacks sufficient information to alter the clinical benefits – therefore, all of the EGP reanalyses likely overestimate the efficacy of dacomitinib. Because the cost per tablet of dacomitinib does not vary with the dose required by the patient, the modification of prices to reflect dose intensity is inappropriate. In the EGP's reanalysis, dose intensity for each treatment was set to 100%. The cost for terminal care was adjusted (from $10,402.48 to $9,810.33) to reflect conversion with purchasing power parity, rather than exchange rates. Second and third line treatment basket composition was modified to reflect CGP recommendations. The time horizon was reduced to 7 years, as per CGP recommendation. Although a 10-year time horizon was seen in the osimertinib review and a 5-year time horizon was seen in the afatinib review, the 7-year time horizon was felt to be fair, given that survival is less than 5% at 7 years; and at 10-years of follow-up in the model, the only comparison left with greater than 1% of the cohort alive is osimertinib. And utility for each treatment was made equivalent to that of dacomitinib: 0.8536.

Overall the ICER is higher than was reported by the submitter. If the cost for dacomitinib differs by the strength of tablet, the costs with varying dose intensity should be re-evaluated.

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

- Dose Intensity impact on drug costs: Dose intensity for each treatment was changed to 100%. Dose intensity for gefitinib was left at 96%. Because gefitinib dose reductions result in days with no drug given, the cost for gefitinib should reflect this reduction in the number of doses given. For dacomitinib, the cost per tablet does not vary with the dose required by the patient, and modification of costs to reflect dose intensity is inappropriate.
- Second and third-line treatment baskets composition per first-line treatment: modified based on CGP recommendations (see table 26 below)
- Utility for all treatments set at 0.8536. The EGP acknowledges that these values may appear higher than normal, but note that the utilities came from the trial.
- Terminal care costs: adjusted from $10,402.48 to $9,810.33, to reflect conversion with purchasing power parity rather than exchange rates.
- Incidence of grade 3-5 adverse events associated with afatinib from LUX-Lung 7 trial, which is the same trial used in NMA to inform OS and PFS estimates. Initially, the incidence of grade 3-5 adverse events associated with afatinib was from the LUX-Lung 3 trial.
- Time horizon was decreased from 15 years to 7 years. The CGP suggests that the average survival for this patient population is 3.5 to five years. In the manufacturer submitted model, survival is less than 5% at seven years. The EGP notes that this fails to capture the crossing of OS curves between dacomitinib and gefitinib, and there is much uncertainty in the clinical benefits associated with dacomitinib. Although a 10-year time horizon was seen in the osimertinib review and a 5-year time horizon was seen in the afatinib review, the 7-year time horizon was felt to be fair, given that survival is less than 5% at 7 years; and at 10-years of

follow-up in the model, the only comparison left with greater than 1% of the cohort alive is osimertinib.

- EGP Scenario Analysis: Time horizon decreased further to 3 years, or the time at which OS curves for dacomitinib and gefitinib cross. This scenario analysis was conducted to explore the impact of OS benefits attributed to dacomitinib that were not observed in the ARCHER 1050 trial.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include unit cost of dacomitinib and each comparator, and the number of patients predicted to be eligible for each treatment. The submitter reports that a scenario analysis including osimertinib as a comparator was planned; however, Pfizer was unable to locate a reliable source for osimertinib's projected market share to inform the analysis. The submitter noted that they would include a scenario analysis if pCODR provided an estimate of market share for osimertinib. It is beyond the scope of pCODR's role to estimate market share assumptions for submitters.

One key limitation of the BIA model is related to dose intensity. In the submitted pharmacoeconomic report, the cost/mg is not consistent – regardless of dose received (either 15mg, 30mg, or 45mg), the cost per tablet is $116.67. This parameter was not able to be modified and explored by the EGP.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for dacomitinib when compared to gefitinib is $114,350/QALY. The EGP's best estimate of ΔC and ΔE for dacomitinib when compared to afatinib is $188,631/QALY. The EGP's best estimate of ΔC and ΔE for dacomitinib when compared to erlotinib is $103,979/QALY. The EGP's best estimated of ΔC and ΔE for osimertinib when compared to dacomitinib is $968,820/QALY.

- The extra cost of dacomitinib is $38,521 compared to gefitinib, $27,360 compared to afatinib, $34,145 compared to erlotinib, and -$97,297 compared to osimertinib. The main factor that influences cost outcomes is the cost for each drug, and the application of dose intensity to this cost.
- The extra clinical effect of dacomitinib is 0.34 QALY compared to gefitinib, 0.15 QALY compared to afatinib, 0.33 QALY compared to erlotinib, and -0.11 QALY compared to osimertinib. Survival functions fit to observed data, and extrapolation of these functions are the main factor that influences the difference in effectiveness.
- Outcomes are heavily reliant upon the assumption that OS of dacomitinib is superior compared to gefitinib – this was not observed in the ARCHER 1050 trial. This limitation could not be addressed adequately. Model outcomes based on observed survival outcomes from the ARCHER 1050 trial was requested from the submitter, and was not provided. Although no substitute for the base case analysis, comparison with model outcomes over the same time horizon would have clarified the magnitude of benefits attributed to dacomitinib that were not observed in the ARCHER 1050 trial.
- EGP Scenario re-analysis with a 3-year time horizon was conducted. Before three years, OS of dacomitinib was greater than gefitinib. At three years however, KM OS curves for gefitinib and dacomitinib intersect. After this point, OS with gefitinib was greater than dacomitinib. No combination of model settings could be used to circumvent this limitation.
- The manufacturer submitted model used 33 months of follow-up data, and extrapolated using survival functions. Given that PFS was zero at 36 months in the ARCHER 1050 trial, this approach likely overestimates efficacy of dacomitinib.
- Although a reduced dose intensity for dacomitinib was observed in the ARCHER 1050 trial, the cost per tablet of dacomitinib was the same regardless of the dose the patient received. Therefore, dose reductions will not result in reduced cost for dacomitinib. For gefitinib, dose reductions would have resulted in days with no drug administered, and dose reductions will result in proportional cost reductions.

Overall conclusions of the submitted model:

Primary limitations of the manufacturer submitted model are related to drug pricing, and the survival functions fit to observed data. Dose intensity is incorrectly applied to drug acquisition costs, and results in significantly underestimated costs. The crossing of the OS in KM curves between dacomitinib and gefitinib in the ARCHER 1050 trial is not captured in any of the predicted survival curves – possibly resulting in overestimation of OS for dacomitinib relative to gefitinib. Additionally, follow-up used to inform PFS in the model up to 33 months is used. However, follow-up data up to 36 months is available, and PFS is zero at 36 month. Therefore, extrapolation of PFS results in overestimation of benefits. Economic analysis of outcomes observed during the ARCHER 1050 trial were requested (where OS and PFS are directly informed by observed Kaplan Meier survival data), and not provided by the submitter. The model overestimates the clinical benefits of dacomitinib, which leads to underestimation of the ICER between dacomitinib and any comparator. Quantification of this overestimate was not possible.

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