pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Dacomitinib (Vizimpro) Submitted Reimbursement Request: For the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer with epidermal growth factor receptor-activating mutations.	
Submitted By: Pfizer Canada Inc.	Manufactured By: Pfizer Canada Inc.
NOC Date: February 26, 2019	Submission Date: September 19, 2018
Initial Recommendation: April 4, 2019	Final Recommendation: May 31, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	• Cost per 45 mg, 30 mg, or 15 mg tablet: $116.67 • Cost per day: $116.67 for 45 mg, 30 mg, or 15 mg dose • Cost per 28-day cycle: $3,266.76 for 45 mg, 30 mg, or 15 mg daily dose

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

* If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends the reimbursement of dacomitinib for the first-line treatment of adult patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) with confirmed epidermal growth factor receptor (EGFR) (exon 19 deletion or exon 21 L858R substitution) mutations with a good performance status, if the following condition is met:

- cost-effectiveness being improved to an acceptable level.

Treatment should continue until unacceptable toxicity or disease progression.

pERC made this recommendation because it was satisfied that compared with gefitinib there is a net clinical benefit of dacomitinib, based on a statistically significant and clinically meaningful improvement in progression-free survival (PFS), a manageable but not insignificant toxicity profile, and no significant detriment in quality of life. However, the committee's assessment of net clinical benefit was tempered by the lack of evidence demonstrating a statistically significant improvement in overall survival (OS). Dacomitinib aligned with the patient values of being an effective treatment option that has a demonstrated improvement in PFS and is an oral therapy that can be taken at home.

pERC concluded that, at the submitted price, dacomitinib cannot be considered cost-effective compared with gefitinib, and noted several limitations in the submitted economic model. In addition, pERC also concluded that, at the submitted price, dacomitinib cannot be considered

	cost-effective compared with afatinib or erlotinib due to the uncertainty in the indirect comparison between dacomitinib and these agents.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness of Dacomitinib** Given that pERC concluded that there is a net clinical benefit with dacomitinib for unresectable locally advanced or metastatic NSCLC with confirmed EGFR (exon 19 deletion or exon 21 L858R substitution) mutations, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and affordability of dacomitinib compared with other EGFR tyrosine kinase inhibitors (TKIs). **Factors Affecting Dosage and Dose Wastage** pERC noted the potential for significant wastage with dacomitinib due to both the high frequency of dose reductions and the non-linear (flat) pricing of the different tablet strengths. Both of these, combined, have cost implications due to the possibility of a dose adjustment prior to the patient completing the strength initially provided. **Optimal Sequencing of Dacomitinib and Other Therapies** pERC noted that there is no clinical trial evidence to inform the optimal sequencing of dacomitinib and other treatments now available for the treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations. Upon implementation of dacomitinib reimbursement, pERC recognized that collaboration among provinces to develop a common approach for treatment sequencing would be of value. **Time-Limited Need for Patients Currently on Treatment With a First- or Second-Generation EGFR TKI or Chemotherapy** When implementing a reimbursement recommendation for dacomitinib, jurisdictions may wish to consider addressing the time-limited need for this treatment in patients currently receiving targeted agents or chemotherapy in the first-line setting and who have not experienced disease progression. pERC noted that this time-limited access should be for patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations (exon 19 deletion or exon 21 L858R substitution) and who would otherwise meet the eligibility criteria outlined in this Recommendation. **Please note:** Provincial Advisory Group questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

In Canada, an estimated 28,400 new cases and 20,800 deaths occurred in 2016 from lung cancer, which has a five-year survival rate of 18%. The treatment decision regarding advanced or metastatic NSCLC is typically dependent on the presence or absence and type of driver mutation status of patients. Current estimates of the incidence of the EGFR mutation range from 10% to 15% in Western populations. In patients with Asian backgrounds, the incidence can increase to 30% to 40%. pERC noted that about 2,000 Canadian patients would present in this setting per year. Two common mutations, a deletion in exon 19 (exon 19 del) or a point mutation in exon 21 (L858R), account for almost 90% of EGFR gene mutations. For patients with an EGFR mutation, treatment regimens consist of oral targeted therapies such as afatinib, gefitinib, and erlotinib. Despite the efficacy of EGFR TKIs observed in patients with advanced NSCLC, resistance emerges in the majority of patients. Although treatment options are available in this setting, pERC concluded that there is a continued need for more effective and tolerable treatments for patients who harbour EGFR mutations. pERC also noted that it recently made a recommendation for osimertinib in a similar patient population; however, this drug is not currently publicly funded in any Canadian jurisdiction.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on the results of one randomized controlled trial (RCT), ARCHER 1050, which compared dacomitinib with gefitinib in patients with locally advanced or metastatic NSCLC with confirmed EGFR (exon 19 deletion or exon 21 L858R substitution) mutations. pERC discussed the hierarchical approach to hypothesis testing in the ARCHER 1050 study design whereby the hypothesis testing would be assessed in the following order: PFS assessed first, as the primary outcome. If the PFS was statistically significant in favour of dacomitinib, then the next outcome assessed would be the overall response rate (ORR), and if ORR was statistically significant in favour of dacomitinib, then OS would be assessed next. pERC noted that dacomitinib demonstrated a statistically significant and clinically meaningful improvement in PFS compared with gefitinib; however, there was no statistically significant difference between the treatment arms for ORR. pERC acknowledged that while the *P* value for OS was less than 0.05, given the a priori statistical analysis plan, the OS results cannot be considered statistically significant.

pERC discussed the proportion of patients experiencing grade 3, 4, or 5 adverse events in the ARCHER 1050 study. Members noted that the rate of grade 3 adverse events was notably higher in the patients receiving dacomitinib compared with gefitinib. The most common adverse events were dermatologic reactions and diarrhea. The committee also discussed that patient-reported outcomes were assessed as a secondary outcome in the ARCHER 1050 study. Members noted that there was an improvement in chest pain in the patients receiving dacomitinib compared with baseline, but concluded overall that quality of life was likely similar in both treatment arms despite the increased rates of toxicity in the patients receiving dacomitinib. Overall, pERC was satisfied that there is a net clinical benefit of dacomitinib compared with gefitinib based on a statistically significant and clinically meaningful improvement in PFS, manageable but not insignificant toxicity, and no detriment in quality of life.

In addition to the ARCHER 1050 study, the submitter also provided a network-meta-analysis (NMA) that compared dacomitinib with gefitinib, afatinib, erlotinib, osimertinib, and cisplatin in combination with pemetrexed. pERC noted that the network meta-analysis (NMA) found that dacomitinib had a consistent trend toward improved OS and PFS compared with the other TKIs (afatinib, gefitinib, and erlotinib). However, pERC also acknowledged the limitations of the NMA, including the heterogeneity of the patient populations in the studies included (e.g., inclusion/exclusion of patients with central nervous system [CNS] metastases), and the uncertainty in the results of the NMA due to the wide credible intervals that included the null value of 1.0, limiting their confidence to draw conclusions from the results of the NMA.

pERC deliberated on input from two patient groups and noted that patients with advanced NSCLC often have a high symptom burden and value treatments that can stop or slow progression of the disease and reduce or eliminate symptoms. pERC also recognized that the patient groups noted that patients would value treatments that could be administered at home because it would be less disruptive to the routines

of patients and their caregivers, who may otherwise need to take time away from work (and other commitments) for treatment. pERC concluded that dacomitinib aligns with the values of being a treatment that could slow disease progression, and it is an oral treatment that can be administered at home. pERC also noted that dacomitinib may reduce symptoms such as chest pain, while acknowledging the considerable toxicity profile of dacomitinib.

pERC deliberated on the input received from registered clinicians, noting that it aligned with the interpretation and conclusion of the CGP. Of note, both the registered clinicians and CGP felt that it would likely be appropriate to generalize the use of dacomitinib to patients with CNS metastases, even though patients with brain metastases were excluded from the ARCHER 1050 study. pERC discussed that, despite the exclusion of patients with EGFR mutant NSCLC with CNS metastases at baseline, it is presumed that dacomitinib would also be effective in this population (without symptoms or with previously treated CNS metastasis).

pERC discussed the cost-effectiveness of dacomitinib compared with gefitinib, afatinib, and erlotinib. As mentioned previously, indirect evidence was required to compare dacomitinib with afatinib and erlotinib. The results of the cost-effectiveness analysis of dacomitinib compared with afatinib and erlotinib need to be interpreted with caution due to the limitations in the NMA. pERC agreed with the Economic Guidance Panel (EGP) that the PFS for dacomitinib in the submitted economic model was overestimated, because the results of the ARCHER 1050 study indicated that by 36 months all patients had progressive disease, and yet all of the parametric curves (modelled curves) used in the economic model extrapolated PFS beyond 36 months. Similarly, pERC also agreed with the EGP regarding the limitations in the submitted model because of the inaccurate assumption that the OS for dacomitinib was superior to gefitinib in the ARCHER 1050 trial (i.e., the crossing of the OS in KM curves between dacomitinib and gefitinib in the ARCHER 1050 trial was not captured in any of the predicted survival curves, therefore, possibly resulting in overestimation of OS for dacomitinib). pERC discussed that the submitter assumed that a lower dose intensity would result in a lower cost, however, the EGP countered that given that the price per tablet is the same regardless of tablet strength this would not lower the cost. While pERC agreed with the EGP that the flat pricing would not have an impact on the cost for dose reductions, however there will be a reduction in cost for patients who temporarily discontinue treatment. pERC discussed the challenge with the model in that it did not allow separation of dose reductions from temporary discontinuations, and as a result, it was unclear if both temporary discontinuations and dose reductions were included in the aggregate cost savings. Finally, pERC also agreed with the EGP's reanalysis using a shorter time horizon (seven years versus 15 years). Therefore, pERC concluded that dacomitinib could not be considered cost-effective at the submitted price.

pERC deliberated on the feasibility of implementing a reimbursement recommendation for dacomitinib. The committee discussed the flat pricing of dacomitinib (i.e., the same price per tablet regardless of tablet strength) and noted the potential for considerable wastage with this pricing strategy, especially in this patient population where there is a high proportion of patients who have their dose reduced due to the toxicity profile of dacomitinib. pERC discussed the budget impact analysis provided by the submitter and noted that it was difficult to draw conclusions from the submitted analysis because it remains unclear how dacomitinib will be utilized in relation to relevant treatments. However, pERC acknowledged the challenges of modelling the budget impact of TKIs; in particular, members noted that pERC had recently issued a recommendation for osimertinib for a similar patient population, but osimertinib is not currently publicly funded in Canada, therefore making assumptions regarding market share difficult to estimate. pERC also noted that the public reimbursement of other oral TKIs (afatinib, gefitinib, and erlotinib) is not consistent across all of the jurisdictions. As well, pERC acknowledged that in provinces where oral and intravenous cancer drugs have different methods of reimbursement, provincial reimbursement policies also act as a barrier to access. Finally, pERC also discussed that there is no evidence to guide the sequencing of available agents subsequent to first-line dacomitinib.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy groups: Ontario Lung Association and Lung Cancer Canada
- input from two clinician input submissions: one from five medical oncologists from Lung Cancer Canada, and one from a single clinician from Cancer Care Ontario (CCO)
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- a single clinician from CCO
- PAG
- the submitter: Pfizer Canada Inc.

The pERC Initial Recommendation was to conditionally recommend the reimbursement of dacomitinib for the first-line treatment of adult patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) with confirmed epidermal growth factor receptor (EGFR) (exon 19 deletion or exon 21 L858R substitution) mutations with a good performance status, if cost-effectiveness is improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that the manufacturer, registered clinician, and PAG agreed with the Initial Recommendation and supported early conversion. However, in its feedback, PAG requested that pERC review the eligible patient population for dacomitinib, which required pERC to reconsider its recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate dacomitinib as a first-line treatment in patients with stage IIIB/IV NSCLC with EGFR mutations.

Included study: Phase III randomized, open-labelled study comparing dacomitinib with gefitinib

One randomized control trial was included in this review. ARCHER 1050 was a phase III randomized, open-labelled, two-arm, parallel-arm study comparing dacomitinib with gefitinib.

The pCODR review also provided contextual information on a network meta-analysis (NMA) that consisted of five randomized control trials. This allowed for the direct comparison of the outcomes between dacomitinib and gefitinib, and the indirect comparison of dacomitinib with cisplatin in combination with pemetrexed, afatinib, erlotinib, and osimertinib.

Patient population: Treatment-naive adult patients with EGFR mutation and no brain metastases

The patient population was patients with newly diagnosed or recurrent NSCLC (minimum of 12 months' disease-free interval between completion of adjuvant or neo-adjuvant therapy and recurrence of NSCLC) that were treatment-naive, 18 years of age or older, and had a documented EGFR mutation (exon 19 deletion or the L858R mutation). Patients with a history of brain metastases were excluded from the ARCHER 1050 trial.

Key efficacy results: Statistically significant improvement in PFS

The ARCHER 1050 study was designed with a hierarchical approach to hypothesis testing whereby the testing was designed as follows: first progression-free survival (PFS) was assessed, as the primary outcome, between dacomitinib and gefitinib. If the PFS was statistically significant in favour of dacomitinib, then the next outcome assessed would be overall response rate (ORR). If ORR was statistically significant in favour of dacomitinib, then overall survival (OS) would be assessed next.

The median PFS for dacomitinib and gefitinib was 14.7 and 9.2 months, respectively (hazard ratio = 0.59, 95% confidence interval, 0.47 to 0.74; *P* < 0.0001). PFS based on investigator assessment was consistent with PFS according to IRC review. The ORR was not statistically significant for patients receiving dacomitinib compared with gefitinib (75% versus 72%; *P* = 0.42, respectively). The median OS was 34.1 months versus 26.8 months for dacomitinib versus gefitinib. pERC acknowledged that while the *P* value for OS was less than 0.05, given the a priori statistical analysis plan, the OS results cannot be considered statistically significant.

The NMA found that overall, dacomitinib had a consistent trend toward improved OS and PFS compared with tyrosine kinase inhibitors (TKIs) (afatinib, gefitinib, and erlotinib). However, pERC also acknowledged the limitations of the NMA, including the heterogeneity of the patient populations in the studies included (e.g., inclusion/exclusion of patients with central nervous system metastases) and the uncertainty in the results of the NMA due to the wide credible intervals that included the null value of 1.0, limiting members' confidence to draw conclusions from the results of the NMA.

Patient-reported outcomes: Overall no detriment in quality of life

Quality of life data from the ARCHER 1050 study demonstrated significant improvement in chest pain with dacomitinib from baseline (*P* = 0.0235). Otherwise symptom control was similar in both treatment arms. Diarrhea and sore mouth (measured by the European Organisation for Research and Treatment of Cancer core quality of life questionnaire) were significantly worse with dacomitinib (more than 10 points higher, *P* = 0.0001). Global quality of life favoured gefitinib (*P* = 0.0002) but was not clinically different (< 5 points) between the two treatment arms.

Limitations: Patient with brain metastases excluded

The ARCHER 1050 trial did not include patients with brain metastases, which differed from some other trials of drugs in similar patient populations. This limitation could have potentially enriched the patient population in the ARCHER 1050 trial, and limits its generalizability to the real-world setting. Also, this limitation impacted the strength of the NMA because the inclusion or exclusion of patients with brain metastases varied in the trials included in the NMA. Other limitations of the ARCHER 1050 trial included a possible imbalance in patient characteristics between the trial arms (including gender and ECOG status), and the open-label design; however, independent review was used to determine results of PFS, ORR, and duration of response.

Safety: Toxicity management education and monitoring of toxicity important due to considerable toxicity profile

The ARCHER 1050 trial reported more grade 3 adverse events in the dacomitinib arm compared with the gefitinib arm (51% versus 30%, respectively). The most common adverse events were dermatologic reactions and diarrhea. The Clinical Guidance Panel (CGP) noted that the rate of dose reductions in the ARCHER 1050 study (66%) was higher than dose reductions with other TKIs, and needs to be weighed against possible improvements in efficacy. The CGP stated that prescribers and patients should be well educated regarding toxicity management and additional toxicity monitoring (e.g., more frequent telephone or clinic follow-up) should be considered.

Need and burden of illness: Dacomitinib is another treatment option

As noted by the CGP, the most commonly diagnosed cancer in Canada is lung cancer, and it is also the leading cause of cancer-related mortality. Treatment decisions regarding advanced or metastatic NSCLC are typically dependent on the presence or absence and type of driver mutations. Current estimates of the incidence of the EGFR mutation range from 10% to 15% in Western populations. In patients with Asian backgrounds, the incidence can increase to 30% to 40%. pERC noted that about 2,000 Canadian patients would present in this setting per year. Dacomitinib provides another treatment option for these patients.

Registered clinician input: Dacomitinib would be another option

Both clinician groups stated that practically all patients with stage 4 EGFR+ NSCLC would be candidates for dacomitinib, unless there was a specific patient contraindication. Dacomitinib was described by LCC as similar in terms of efficacy, safety and tolerability, to existing treatments (gefitinib and afatinib), as well as showing improved progression-free survival. CCO input stated that dacomitinib is more efficacious with improved survival compared to the current standard. As per the clinician input, it was suggested that dacomitinib would be sequenced as a first line option for stage 4 EGFR+ NSCLC. In their opinion, the new treatment of dacomitinib would be another option, but not a replacement of existing treatments unless there was a clear competitive

advantage in terms of cost. Companion diagnostic testing is required, however EGFR mutation testing is now routine practice, and there are no implications for new testing for this application. Clinician input indicated that osimertinib (if approved) would be preferred over dacomitinib for patients with CNS involvement due to excellent intracranial drug penetration.

PATIENT-BASED VALUES

Patient experience with NSCLC: Symptoms have significant impact on day-to-day lives
Pain, weakness, and extreme fatigue are among the challenging symptoms patients with NSCLC have to deal with, which have a significant impact on their day-to-day lives. Treatments for this type of cancer include a variety of steroids and inhalers, radiation and chemotherapy, or even a lung transplant; however, the current treatments only provide some relief of symptoms, are costly, and have undesirable side effects. This disease has an impact on those caring for persons living with lung cancer as well, posing a financial and emotional burden.

Patient values on treatment: Stop or slow disease progression, reduce symptoms, improvement in quality of life
Patients with advanced NSCLC often have a high symptom burden. Patients and caregivers would like a treatment that can stop or slow progression of the disease and reduce or eliminate symptoms. pERC also recognized that the patient groups noted that patients would value treatments that could be administered at home because it would be less disruptive to the routines of patients and their caregivers, who may otherwise need to take time away from work (and other commitments) to receive treatment. Patients also expressed concern about rising costs of drugs and argued that marketplace competition will help maintain a sustainable healthcare system.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis
The cost-effectiveness and cost-utility analysis submitted to pCODR by the manufacturer compared dacomitinib with gefitinib, afatinib, and erlotinib for the first-line treatment of patients with NSCLC with an EGFR mutation.

Basis of the economic model: Three health states: PFS, post-progression survival, and death
The model was comprised of three health states: PFS, post-progression survival, and death. Model health states were selected in accordance with the clinical pathway. The model structure was identical for all comparators, as the structure was 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 post-progression survival 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.

Drug costs: Non-linear (flat) pricing of dacomitinib
The cost of dacomitinib per tablet is the same regardless of tablet strength.

Cost of dacomitinib *Assumed daily dose of 45 mg taken orally once daily, with dose reductions to 30 mg and 15 mg.*	• Cost per 45 mg tablet: $116.67 • Cost per 30 mg tablet: $116.67 • Cost per 15 mg tablet: $116.67 • Cost per day: $116.67 for 45 mg, 30 mg, or 15 mg dose • Dose intensity: 73% • Cost per 28-day cycle: $2,384.67 (at 73% dose intensity)
Cost of gefitinib *Daily dose of 250 mg taken orally once daily.*	• Cost per 250 mg tablet: $62.31 • Cost per day: $62.31 • Dose intensity: 96% • Cost per 28-day cycle: $1,674.76 (at 96% dose intensity)

Cost of afatinib *Daily dose of 40 mg taken orally once daily.*	• Cost per 20 mg tablet: $73.30 • Cost per 30 mg tablet: $73.30 • Cost per 40 mg tablet: $73.30 • Dose intensity: 100% • Cost per 28-day cycle: $2,052.40
Cost of erlotinib *Daily dose of 150 mg taken orally once daily.*	• Cost per 100 mg tablet: $47.47 • Cost per 150 mg tablet: $71.20 • Dose intensity: 100% • Cost per 28-day cycle: $1,993.60

Cost-effectiveness estimates: Overestimation of PFS in model, underestimation of dose intensity

pERC discussed the cost-effectiveness of dacomitinib compared with gefitinib, afatinib, and erlotinib. As mentioned previously, there was only indirect evidence to compare dacomitinib with afatinib and erlotinib. The results of the cost-effectiveness of dacomitinib compared with afatinib and erlotinib need to be interpreted with caution due to the limitations in the NMA. pERC agreed with the Economic Guidance Panel (EGP) that the PFS in the submitted economic model was overestimated because the results of the ARCHER 1050 study indicated that by 36 months all patients had progressed disease, and yet all of the parametric curves (modelled curves) used in the economic model extrapolated PFS beyond 36 months. Similarly, pERC also agreed with the EGP regarding the limitations in the submitted model because of the inaccurate assumption that the OS for dacomitinib was superior to gefitinib in the ARCHER 1050 trial. pERC discussed that the submitter assumed that a lower dose intensity would result in a lower cost, however, the EGP countered that since the price per tablet is the same regardless of tablet strength this would not lower the cost. While pERC agreed with the EGP that the flat pricing would not have an impact on the cost for dose reductions, there will be a reduction in cost for patients who discontinue treatment temporarily. Finally, pERC also agreed with the EGP's reanalysis using a shorter time horizon (seven years versus 15 years). Therefore, pERC concluded that dacomitinib could not be considered cost-effective at the submitted price.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Wastage and non-linear pricing

pERC deliberated on the feasibility of implementing a reimbursement recommendation for dacomitinib. Members discussed the flat pricing of dacomitinib (i.e., the same price per tablet regardless of tablet strength) and noted the potential for considerable wastage with this pricing strategy, especially in this patient population where there is a high proportion of patients who have their dose reduced. pERC discussed the budget impact analysis provided by the submitter and noted that it was difficult to draw conclusions from the submitted analysis because it remains unclear how dacomitinib will be utilized in relation to relevant treatments. In particular, pERC noted that it had recently issued a recommendation for osimertinib for a similar patient population, but osimertinib is not currently publicly funded in Canada. Finally, pERC also discussed that there is no evidence to guide the sequencing of available agents subsequent to first-line dacomitinib.

For other considerations for implementation, refer to Appendix 1: CADTH Pan-Canadian Oncology Drug Review Expert Review Committee Responses to Provincial Advisory Group Implementation Questions.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Drs. Kelvin Chan and Marianne Taylor, who were not present for the meeting
- Dr. Anil Abraham Joy, who was excluded from voting due to a conflict of interest
- Daryl Bell, who did not vote due to his role as a patient member alternate.

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Matthew Cheung, Dr. Anil Abraham Joy, and Dr. Kelvin Chan, who were not present for the meeting
- Daryl Bell, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of dacomitinib for patients with non-small cell lung cancer with epidermal growth factor receptor mutations, through their declarations, six members had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is also seeking information comparing dacomitinib with afatinib, or if trial data are generalizable to afatinib	• The submitted network-meta-analysis (NMA) compared dacomitinib with afatinib, erlotinib, osimertinib, and cisplatin in combination with pemetrexed. Dacomitinib had a consistent trend toward improved OS and PFS compared with the other TKIs. However, the uncertainty in the results of the NMA due to the wide credible intervals that included the null value of 1.0, limit the confidence to draw conclusions on the results of the NMA. • It is unknown whether afatinib is similar to dacomitinib in terms of treatment outcome.
• Eligibility for dacomitinib in patients with CNS metastases	• Despite the exclusion of patients with EGFR mutant NSCLC with CNS metastases at baseline, it is presumed that dacomitinib would also be effective in this population (without symptoms or with previously treated CNS metastasis).
• Eligibility for dacomitinib in patients with EGFR mutations	• Only patients with confirmed EGFR exon 19 deletion or exon 21 L858R substitution mutations were eligible for the ARCHER 1050 trial; however, pERC discussed that it was reasonable to generalize the results of the ARCHER 1050 study to patients with other known sensitizing EGFR mutations. • Upon reconsideration, pERC discussed the feedback from PAG and acknowledged the difference in the recommended eligibility for dacomitinib compared to osimertinib in the first line setting. pERC noted the dacomitinib and osimertinib trials included patients with EGFR exon 19 deletion or exon 21 L858R substitution mutations and excluded patients with other known sensitizing EGFR mutations. pERC agreed that EGFR exon 19 deletion or exon 21 L858R substitution mutations account for the majority of EGFR mutations in NSCLC. pERC also noted that opinions with respect to the eligible patient population differed between the Clinical Guidance Panel for osimertinib and dacomitinib. Ultimately, pERC concluded that eligibility for dacomitinib should be restricted to patients with EGFR exon 19 deletion or exon 21 L858R substitution mutations to align with the final recommendation of osimertinib (issued January 4, 2019).
• Eligibility for dacomitinib in patients who have started chemotherapy but have not progressed, or if dacomitinib could be given second line at the time of disease progression for those who completed first-line chemotherapy that was started before the results of EGFR mutation status were known	• When implementing a reimbursement recommendation for dacomitinib, jurisdictions may consider addressing the time-limited need for this treatment in patients currently receiving a targeted agent or chemotherapy in the first-line setting and who have not experienced disease progression. pERC noted that this time-limited access should be for patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations and who would otherwise meet the eligibility criteria outlined in this Recommendation. • pERC noted that there is no evidence to use dacomitinib in the broader EGFR population as a second-line treatment option for patients who complete first-line treatment with chemotherapy and have disease progression.
• Eligibility for dacomitinib in patients who have started therapy with osimertinib, gefitinib, erlotinib, or afatinib but have not progressed	• If a patient is intolerant to another TKI but has not progressed, it is reasonable to switch to dacomitinib.

• Clarity of duration of treatment	• Treatment should be until disease progression or unacceptable toxicity (in the ARCHER 1050 trial the median treatment duration was 15.3 months).
• Sequencing of dacomitinib with other treatments	• There is no clinical trial evidence to inform the optimal sequencing of dacomitinib and other treatments available for the treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations. Upon implementation of dacomitinib reimbursement, pERC recognized that collaboration among provinces to develop a common approach for treatment sequencing would be of value.

PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.