pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Dacomitinib (Vizimpro) for Non-Small Cell Lung Cancer

May 31, 2019

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding dacomitinib and NSCLC. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding dacomitinib and NSCLC conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on dacomitinib and NSCLC, a summary of submitted Provincial Advisory Group Input on dacomitinib and NSCLC, and a summary of submitted Registered Clinician Input on dacomitinib and NSCLC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

As stated in the Health Canada Product Monograph, dacomitinib is a pan-human epidermal growth factor receptor (HER) (EGFR/HER1, HER2, and HER4) inhibitor, with clinical activity against mutated EGFR with deletions in exon 19 or the L858R substitution in exon 21; it is a second generation TKI that binds selectively and irreversibly to all three HER family targets thereby providing prolonged inhibition. [8]

Dacomitinib was issued marketing authorization by Health Canada 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. [8]The requested reimbursement criteria is dacomitinib for the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR-activating mutations.

The recommended dose of dacomitinib is 45 mg taken once daily until disease progression or unacceptable toxicity occurs. Dacomitinib is available in three strengths: 15 mg, 30 mg, and 45 mg. [8]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The objective of the systematic review was to evaluate the efficacy and safety of dacomitinib as a first line treatment in patients with stage IIIB/IV NSCLC with EGFR-activating mutations. Below is an overview of the information included in the systematic review.

- One randomized control trial (RCT) met the inclusion criteria for this review [1-6]. ARCHER 1050 was a phase III randomized, open labelled, two-arm, parallel arm study comparing gefitinib with dacomitinib. The eligible population was patients with newly

diagnosed (treatment-naïve) or recurrent after adjuvant or neoadjuvant treatment NSCLC that were 18 years of age or older and had have a documented EGFR mutation (exon 19 deletion or the LEU85Arg mutation). The efficacy and safety of dacomitinib is compared with gefitinib.

- The ARCHER 1050 trial was of high quality, based on the SIGN-50 quality checklist for randomized control trials[9]. The study was open label, and used appropriate randomization methods with sample sizes that were targeted for sufficient statistical power of primary outcomes. Participants and investigators were not blinded to arm allocation; however independent review was consistent with investigator assessment. Details of blinding and randomisation methods are summarized in section 6.2.8.1a.
- The study was an open-label design, which may introduce bias; however independent review was used to determine results of progression free survival, objective responses, and duration of response.
- Patients with brain metastases were excluded, potentially enriching the population of patients with better outcomes.
- The dacomitinib group had more female patients and a higher proportion of patients with an ECOG performance status of 0 than the gefitinib group.
- The ARCHER 1050 study was funded by the manufacturer of the drug of interest. The manufacturer in collaboration with the trial investigators designed the study, collected the data, and interpreted the results.
- The majority of the patient population was Asian (75% in the dacomitinib and 78% in gefitinib arms respectively). The generalisability of trial outcomes to other races may be limited; however, it is unclear what impact this may have on outcomes.

Table 1.1: Highlights of Key Outcomes

	Archer 1050	
	Dacomitinib (N=227)	**Gefitinib (N= 225)**
Progression-Free Survival, median	**14.7 (11.1-16.6)**	**9.2 (9.1-11.0)**
HR (95%CI)	**0.59 (0.47-0.74)**	
p-value	**<0.0001**	
Duration of Response, median	**15.9 (13.8-17.6)**	**9.2 (8.2-11.0)**
HR (95%CI)	**0.55 (0.42-0.71)**	
p-value	**<0.0001**	
HrQoL (Standard deviation)	**65.6 (22.2)**	**62.9 (21.4)**
Difference (95%CI)	**NR**	**NR**
Harms Outcome, n (%)	**Dacomitinib (N=227)**	**Gefitinib (N=224)**
Grade 3, Grade 4, Grade 5	**116 (51%), 5 (2%), 22(10%)**	**67 (30%), 5 (2%), 20 (9%)**
AE (any grade)	**226 (>99%)**	**220 (98%)**
TRAE	**21 (9%)**	**10 (4%)**
WDAE	**22 (10%)**	**15 (7%)**
AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, NR = not reported, SD = standard deviation, TRAE = treatment-related adverse event, WDAE = withdrawal due to adverse event ***HR < 1 favours dacomitinib [1]**		

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1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

Two patient advocacy groups provided input on dacomitinib for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations: The Ontario Lung Association (OLA) and Lung Cancer Canada (LCC).

According to OLA, patients and caregivers would like a treatment that is able to stop or slow the progression of disease, reduce the previously described symptoms of lung cancer, and improve appetite and energy levels. In addition, they would like to see a reduction in or elimination of those symptoms, along with the reduction in or elimination of inability to fight infection, burning of skin, and effect on mood. They also expressed the desire to be able to administer treatments at home, thus reducing the need for patients and caregivers to take time off work and fewer disruptions to one's day. Quality of life was also addressed as an important consideration for new treatments, with one patient stating that "if I have less than three years to live, I would like to be able to enjoy that time with my family."

According to LCC, dacomitinib is expected to perform similarly to afatinib as it is a second generation tyrosine kinase inhibitor (TKI). They also noted that there is evidence that dacomitinib is particularly effective in patients with the exon 19 deletion or exon 21 L858R substitution.

According to OLA, none of the respondents that had experience with dacomitinib had gastrointestinal issues. The LCC patient submission included reports from three patients regarding the efficacy of dacomitinib. Two patients reported stable disease, one of which was at seven months, and the third patient reported a "drastic decrease in lesion size". In contrast, one caregiver reported on the efficacy of the drug for their patient, which did not control their loved one's tumour. See Section 3 for more information.

Provincial Advisory Group (PAG) Input

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

See Section 4 for more information.

Registered Clinician Input

Two clinician input submissions were provided, one from a group of five medical oncologists from Lung Cancer Canada (LCC) and one from a single clinician from Cancer Care Ontario (CCO) who specializes in thoracic oncology.

Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitors (TKI) are considered standard of care for EGFR mutation positive (EGFR+) non-small cell lung cancer (NSCLC); this includes: gefitinib, erlotinib, afatinib. 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 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. See Section 5 for more information.

Summary of Supplemental Questions

The assessment of the network meta-analysis is included as it is relevant to the economic evaluation. The NMA was used to compare similar treatments for the economic evaluation that was conducted.

The network meta-analysis consisted of 5 RCTs that met the inclusion criteria. This allowed for the direct comparison of the outcomes between dacomitinib to gefitinib, and the indirect comparison of dacomitinib to cisplatin + pemetrexed, afatinib, erlotinib or osimertinib. The NMA found that overall, dacomitinib had a consistent trend towards improved OS and PFS compared to TKIs (afatinib, gefitinib and erlotinib. However, the credible intervals (CrI's) were wide and included the null value of 1.0.

The submitted network meta-analysis was conducted appropriately. Although an extensive search of the literature was conducted in the systematic review phase, the limited research available did not identify any closed-loops of evidence. Therefore, comparisons between dacomitinib and other agents can only be made with increasingly indirect comparisons. This results in increasingly wide credible intervals, and reduces certainty in these comparisons. Without closed loops in the network of identified evidence, no assessment of consistency could be made. The sparse evidence network also means that the impact of central nervous system metastases present in some participants in some trials at enrollment could not be fully explored. Given that the presence of these metastases was an exclusion criteria in the ARCHER 1050 trial, this may impact the validity of comparisons between dacomitinib and other agents. Additionally, the only outcomes included in the NMA were progression-free survival and overall survival.

Given the limitations in the evidence, and that relevant comparators to dacomitinib from a Canadian context included gefitinib, afatinib, erlotinib, and osimertinib, the submitted NMA is appropriate.

See Section 7 for more information.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.

Table 1.2: Assessment of generalizability of evidence for dacomitinib for NSCLC

Domain	Factor	Evidence (ARCHER 1050 trial)	Generalizability Question	CGP Assessment of Generalizability
Population	Stage of disease	Patients were eligible for participation with newly diagnosed or recurrent (minimum of 12 months disease free interval between completion of adjuvant or neoadjuvant therapy) stage IIIB/IV NSCLC	Does stage limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	These data are relevant for any EGFR mutant NSCLC patient with incurable lung cancer (stage IV or incurable III or recurrent M1 disease after adjuvant or neoadjuvant treatment).
	Performance Status	Participants had to have an ECOG status of 0-1	Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	It is important to highlight that given the toxicity of dacomitinib, only fit patients should be offered this therapy. All patients should be educated on toxicity self-management and closely followed by the health care team.
	Age	Patients were adults (>18 years of age, or>20 in Japan). The median age of participants of the dacomitinib group was 62 years, with 41% of participants being ≥65 years. Pre-specified analysis of PFS based on age were conducted.	Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?	No
	Organ dysfunction	Patients were required to have adequate renal, hepatic, and haematological function in order to enroll	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the	No

Domain	Factor	Evidence (ARCHER 1050 trial)	Generalizability Question	CGP Assessment of Generalizability
			target population	
	Metastatic Sites	Exclusion criteria included a history of brain or leptomeningeal metastases.	Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population	Yes. However the study results suggest that there is intracranial activity of dacomitinib (1 v 11 patients with CNS progression). Therefore we suggest this be considered in patients with CNS metastasis as well (treated or low volume asymptomatic after discussion with radiation oncologist).
	Ethnicity or Demographics	There were 71 Universities and medical centres from 7 countries included, and the majority of patients were Asian (77%). Progression-free survival analysis was conducted, and for patients who responded to treatment 259 (75%) of Asian patients and 72 (68%) of non-Asian patients achieved a best overall response.	The trial was conducted outside of Canada; therefore is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.	Approximately 76% of patients in this study were of Asian race. This is higher than population-based studies in Canada, however there is no evidence to suggest that there is a difference by treatment in outcomes when comparing different races. There are data to suggest that Asian patients have a better prognosis, but none to suggest that they derive greater or less benefit from EGFR TKI (similar HR in ARCHER1050. Therefore we expect the effect of dacomitinib to be similar in a Canadian population.
	Biomarkers	All patients had to have an EGFR mutation (exon 19 deletion or the Leu858Arg mutation). Both the dacomitinib and gefitinib arm had the same proportion of the	Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the	Dacomitinib is highly and similarly active in those with tumour exon 19 deletion or Leu858Arg mutations. These data should also be applied to those with other known

Domain	Factor	Evidence (ARCHER 1050 trial)	Generalizability Question	CGP Assessment of Generalizability
		exon 19 deletion (59%) and Leu858Arg mutation (41%).	trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?	sensitizing *EGFR* mutations based on current literature and clinical experience[10,11].
Intervention	Treatment Intent	First line treatment for stage IIIB/IV NSCLC.	Are the results of the treatment generalizable to an alternative treatment intent?	n/a - First line EGFR TKI should only be used in patients with *EGFR* activating mutations
	Line of therapy	First line treatment for stage IIB/IV NSCLC. All participants were excluded if they had any previous anticancer systemic treatment, or treatment with an EGFR TKI.	Are the results of the trial generalizable to other lines of therapy?	Yes
	Administration of intervention	Dacomitinib was administered orally once daily in a 28 day treatment cycles. Initial dose was 45 mg. Dose reductions were permitted, to a maximum of two dose levels (30 mg/day, then 15 mg/day. Dose reductions occurred in 150 (66%) of 227 patients in the dacomitinib group; 87 (38%) patients received a lowest dose of 30 mg/day, and 63 (28%) patients received a lowest dose of 15 mg/day.	If the dose and/or schedule is not standard, are the results of the trial relevant in the Canadian setting?	n/a - standard
Comparator	Standard of Care	The comparator was oral gefitinib.	Is this standard care in Canada? Appropriate comparator?	Yes. Afatinib is also a standard agent in the first line setting. It is unknown whether

Domain	Factor	Evidence (ARCHER 1050 trial)	Generalizability Question	CGP Assessment of Generalizability
				afatinib is similar to dacomitinib in terms of treatment outcome.
	Dose and Schedule	Gefitinib was administered orally once daily in 28 day treatment cycles. Dose was 250mg. Dose was reduced to every-other-day dosing at investigators discretion due to adverse effects. In the gefitinib group, dose reductions (every other day dosing)occurred in 18 (8%) of 224 patients	If the dose and/or schedule is not standard, are the results of the trial relevant in the Canadian setting?	Standard dose/schedule
Outcomes	Appropriateness of Primary and Secondary Outcomes	Primary outcome was progression-free survival (PFS), with secondary outcomes being: proportion of patients wo achieved an objective response; duration of response; overall survival (OS); OS at 30 months; safety assessment and patient reported outcomes.	Were the primary and secondary outcomes appropriate for the trial design?	Yes - similar to other trials in this area
	Assessment of Key Outcomes	PFS was determined by masked IRC review and defined as: the time from randomisation to the date of disease progression according to RECIST version 1.1 per masked IRC review, or death due to any cause. Objective response was defined as: best overall response of either complete response or partial response, where best overall response is the best response recorded from the start of treatment until disease progression.	If the trial used a different method of assessment than that used in Canadian clinical practice, are the results of the trial applicable to the Canadian setting?	Standard outcomes and assessment methods were used.

Domain	Factor	Evidence (ARCHER 1050 trial)	Generalizability Question	CGP Assessment of Generalizability
		Duration of response was defined as: the time form fist documentation of objective response to the date of disease progression or death. Safety was assessed based on AEs		
Setting	Countries participating in the Trial	ARCHER 1050 was conducted in 7 different countries (China, Hong Kong, Japan, South Korea, Poland, Italy and Spain), none of which were in Canada.	Is there any known difference in the practice pattern between those countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.	Subsequent therapy may differ among countries, e.g. T790M testing and access to osimertinib. However this should be resolved through the process of randomization. There was no obvious impact of race/origin on outcomes in the Mok et al NEJM 2018 paper.
	Location of the participating centres	Trials were conducted at multiple medical sites and Universities (71 total centres) in multiple counties. Details of participating study sites were not provided.	If the trial was conducted only in academic centres are the results applicable in the community setting?	Yes. Patient education regarding toxicity management is paramount with use of dacomitinib. Patients and families must be well educated to minimize toxicity and maximize supportive care interventions.
	Supportive medications, procedures, or care	More than half of patients who progressed per independent radiology central (IRC) review continued to receive study treatment after progression. There were more patient in the gefitinib arm than the dacomitinib arm that continued to receive study treatment after progression, the median duration of	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	Yes these results are still generalizable. Many patients take alternative regimens such as Traditional Chinese Medicine here in Canada as well. To date we know of no impact on outcomes.

Domain	Factor	Evidence (ARCHER 1050 trial)	Generalizability Question	CGP Assessment of Generalizability
		post-progression study treatment was slightly higher in the dacomitinib group compared to the gefitinib group, and the median post-progression survival was greater in the dacomitinib group compared to the gefitinib group. Of note, at the time of the data cut-off, more patients in the dacomitinib arm compared to the gefitinib arm were still progression-free.[32]		
Abbreviations: AE - adverse event; BSC - best supportive care; DPD - dihydropyrimidine dehydrogenase deficiency; ECOG - Easter Cooperative Group Performance ; KRAS - Kirsten Rate Sarcoma Oncogene; mCRC - metastatic colorectal cancer; OS - overall survival; PFS - progression-free survival;				

1.2.4 Interpretation

The ARCHER1050 trial establishes dacomitinib as another first-line option for EGFR TKI therapy in patients with advanced or metastatic NSCLC with activating *EGFR* mutations.

Effectiveness

The efficacy data, albeit from a single randomized trial, demonstrate significantly longer progression free survival compared with gefitinib, with median PFS of 14.7 months compared to 9.2 months with gefitinib. Although the Kaplan Meier survival curves cross, median survival with dacomitinib was 34.1 months and 26.8 months with gefitinib; therefore, representing a trend to improve overall survival.

Quality of life data 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 EORTC QLQC30) 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 2 treatment arms. Thus with the exception of worse toxicity, both agents yielded similar quality of life with some domains favouring dacomitinib and other domains favouring gefitinib.

A key challenge with the ARCHER1050 trial is 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. Despite this, we 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

The other key challenge with this study is treatment-related toxicity. Dacomitinib is the most toxic of currently available EGFR TKIs, with 66% 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 first-line osimertinib [12], 16% for gefitinib [13], and 52% for afatinib [14]. In particular, prescribers and patients should be well educated re toxicity management and additional toxicity monitoring (e.g. more frequent telephone or clinic follow up) considered.

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 (PS0 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, we believe that there will be patients and providers that will select this as their preferred drug based on the PFS and potential survival impact.

Of note, other drugs undergoing the review process may have advantages. In the event that osimertinib first-line demonstrates a similar survival benefit over gefitinib, this may be a preferred first line option for many. Then the major question that remains is whether a sequencing approach or upfront osimertinib is superior, i.e. dacomitinib first line followed by osimertinib (T790M+) or chemotherapy (T790M-) based on T790M status, versus osimertinib first line followed by chemotherapy.

Based on the current evidence, however, dacomitinib remains an important potential treatment option among first line EGFR TKIs.

1.3 Conclusions

The Clinical Guidance Panel 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 is based on 1 high quality randomized trial demonstrating compelling PFS benefit and trend in long term survival benefit in this population compared to a current standard, gefitinib. However, this is as at the cost of greater toxicity, which appears manageable and not dissimilar to that of other funded agents (e.g. afatinib) in this setting.

- The strength of the clinical results and our clinical experience leads the CGP to conclude clear net benefit from dacomitinib in this patient population. This will be an important addition to currently funded options as it is the only agent that currently (1Q 2019) demonstrates improved median survival compared to gefitinib.
- Refer to background clinical information section for the CGP's response to clinical factors related to implementation noted by PAG

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lung Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Approximately half of Canadians will be diagnosed with cancer in their lifetime. One in four Canadians will die from cancer. The most commonly diagnosed cancer in Canada is lung cancer, which is also the leading cause of cancer-related mortality, exceeding the mortality from breast, colon and prostate cancer combined [15]. The 5 year survival rate remains dismal, at approximately 15-18%. Approximately half of patients present with Stage IV or incurable disease [15].

While tobacco exposure remains the largest cause of lung cancer, a growing proportion of never smokers develop lung cancer. These cancers are often driven by specific genetic abnormalities, or genomic drivers. One of the most common drivers is activating mutations in the epidermal growth factor receptor (EGFR) gene, identified in 10-12% of all lung cancer cases and in 17% of lung adenocarcinoma [16]. Testing for *EGFR* mutations and other genomic drivers is now standard [17,18]. Optimal treatment in those with *EGFR*-mutant lung cancer is targeted therapy with EGFR tyrosine kinase inhibitors [19].

2.2 Accepted Clinical Practice

Treatment for metastatic lung cancer is palliative, aiming at the prolongation of survival while improving symptom control and quality of life. Molecular testing to identify *EGFR* mutations is standard in advanced lung cancer.

Initial therapy in the population with incurable or metastatic NSCLC with *EGFR*-activating mutations (with or without CNS metastases) is an EGFR TKI. Currently marketed agents in Canada in the first-line setting include gefitinib, afatinib and more recently osimertinib. Agents funded through provincial formularies for use in the first-line setting may include gefitinib, afatinib or erlotinib (as of 10 March 2019). These agents are all superior to chemotherapy in terms of response rate, quality of life, progression-free and quality-adjusted survival. The median duration of treatment ranges from 9 to 18 months with these agents.

Subsequent drug therapy depends on the molecular evolution of the patient's cancer. Approximately 60% of those treated with gefitinib or erlotinib develop *EGFR T790M* mutations in their tumour, conferring treatment resistance. These resistance mutations have also been described after use of second-generation EGFR TKIs afatinib and dacomitinib. Patients with acquired *EGFR T790M* mutations in their tumour may go on to receive second-line osimertinib (Health Canada approved, funded across several provinces), a third-generation EGFR TKI with activity against both classic *EGFR*-activating mutations and the *T790M* resistance mutation [20].

For those without a T790M mutation after TKI resistance, or those post-osimertinib treatment, platinum doublet chemotherapy is the standard second- or third-line option for those that can tolerate chemotherapy side effects. Third- or fourth-line therapy includes docetaxel. It should be noted that single agent PD-1 or PD-L1 inhibitors (nivolumab, pembrolizumab, atezolizumab) have minimal to no activity in patients with stage IV *EGFR* mutant lung cancer, irrespective of PDL-1 expression. [21]. At ASCO 2018, Japanese investigators presented results from a randomized trial [NEJ009] demonstrating marked improvement in survival with the addition of chemotherapy to EGFR TKI (gefitinib) versus

TKI alone [22], albeit with additional toxicity from chemotherapy. Additional studies of chemotherapy plus EGFR TKI are ongoing.

Tumour response in the CNS has been described with all EGFR TKIs. For patients with asymptomatic, low volume CNS metastasis and *EGFR* mutant lung cancer, upfront EGFR TKI or second-line osimertinib (T790M+) may be a reasonable option, with the potential to avoid or defer cranial radiation.

2.3 Evidence-Based Considerations for a Funding Population

Currently in Canada, approximately 17% of patients with advanced non-squamous lung cancer have activating *EGFR* mutations in tumour. Key considerations for selecting an oral first-line EGFR TKI in Canada include: 1) access, i.e. what is publically funded in that province; 2) survival benefit; 3) quality of life; 4) progression-free survival (PFS); 5) response rate (RR); 6) intracranial activity; 7) toxicity, dose reductions and rates of discontinuation for toxicity; and 8) subsequent therapy options.

Second and third generation TKIs have been shown to have superior PFS when compared to first generation EGFR TKIs [1,12,23]. Afatinib, despite better RR and PFS, did not improve survival when compared to gefitinib as first-line therapy in this population [13]. Survival results from the comparison of osimertinib to gefitinib are pending as of January 2018, although an interim analysis (IA) is promising albeit immature (survival hazard ratio (HR) 0.63, 95% CI 0.45-0.88, p=0.007, nonsignificant for IA) [12]. The recently published ARCHER1050 phase III trial comparing dacomitinib with gefitinib demonstrated similar RR (74.9% and 71.6%) and significantly longer PFS (HR 0.59; 95% CI: 0.47-0.74, p<0.001) [1]. Median PFS was 14.7 versus 9.2 months for dacomitinib and gefitinib respectively. With respect to the overall survival benefit, there is a trend to favour dacomitinib over gefitinib (HR 0.760, 95% CI 0.582 – 0.993, p=0.044), with median survival times of 34.1 and 26.8 months respectively. The development of CNS metastasis was less frequent for patients in the dacomitinib arm versus gefitinib (1 in dacomitinib arm, 11 in gefitinib arm).

With respect to potential bias in the ARCHER1050 study, it is the only study in this setting to exclude patients with known CNS metastasis. Up to 1/3 of patients with *EGFR* mutant lung cancer present with CNS metastases at diagnosis, and these patients may have a worse prognosis. Despite the significant improvement in the survival hazard and median survival times, the Kaplan Meier survival curves of the two study treatment arms cross at 12 months. In the first 12 months, gefitinib does not appear inferior to dacomitinib. There is a minor imbalance in demographic characteristics between arms potentially favouring dacomitinib, with more women randomized to receive dacomitinib (64.3% versus 55.6%). Female sex is a known favourable prognostic factor, but the difference is minor and otherwise the treatment arms are well balanced.

Toxicity is another key factor in the selection of first-line EGFR TKI therapy. It is currently estimated that 16% of patients discontinue or require dose reduction of gefitinib for toxicity [24], 21% for erlotinib [25], 52% for afatinib [14], 66% for dacomitinib [1] and 4% for osimertinib [12]. Thus osimertinib is the least toxic although the others have manageable toxicity (most commonly rash, diarrhea, paronychia for 2nd generation inhibitors).

2.4 Other Patient Populations in Whom the Drug May Be Used

Despite 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).

The CGP agrees that based on published literature and clinical experience, dacomitinib is expected to have major activity in patients with rare *EGFR s*ensitizing mutations in addition to those with classic tumour EGFR exon 19 deletions, exon 21 L858R point mutations [10,11].

In patients with *EGFR* mutant lung cancer that have missed the opportunity to receive first line EGFR TKI and have instead started chemotherapy, dacomitinib is appropriate subsequent second-line therapy after receiving chemotherapy.

In addition, if patients with *EGFR* mutant lung cancer have started chemotherapy as first-line therapy instead of EGFR TKI, it is appropriate to switch to EGFR TKI therapy as soon as possible with dacomitinib or other available EGFR TKIs.

It is important to recognize that failure to offer EGFR TKI therapy first-line in this patient population deviates significantly from the current standard of care. Additional efforts should be made to optimize and accelerate molecular diagnostic testing in jurisdictions where this is occurring in order to maximize patient outcomes and minimize unnecessary treatment toxicity.

Finally patients receiving first-line EGFR TKI therapy with gefitinib could be considered for a switch to dacomitinib based on the ARCHER1050 results. Similarly, patients receiving first-line erlotinib could be considered for a switch to dacomitinib, although these data are from a pooled analysis of 2 trials of pre-treated patients with *EGFR* mutant lung cancer (PFS 14.6 versus 9.6 months, no OS improvement, more rash, diarrhea with dacomitinib) [14]. However, the CGP anticipates that most clinicians will not switch between first-line TKIs before disease progression unless for reasons of toxicity.

The current data do not support a switch from agents afatinib or osimertinib first-line to dacomitinib. The CGP wishes to emphasize that indirect comparisons of efficacy among second-generation (afatinib, dacomitinib) and third-generation agents (osimertinib)should be interpreted with caution given currently available data. However, the CGP agrees that these agents have distinct toxicity profiles.

With the recent Health Canada approval of osimertinib in the first-line setting, there are varying opinions in the clinical community about whether to start with osimertinib (majority of CGP panel) or to start with second generation TKIs (dacomitinib, afatinib) with the potential to switch to osimertinib as second-line treatment if a T790M mutation is detected upon progression (~50% of patients).

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups provided input on dacomitinib for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations: The Ontario Lung Association (OLA) and Lung Cancer Canada (LCC).

The OLA provided information regarding this submission was collected during September 2018. It was obtained through feedback from a Toronto based lung health support group, made up of six members (one with lung cancer, one with IPF, and four with COPD), in addition to feedback from a patient living with lung cancer via phone interview. Data collected from Canadian residents for previous submissions to CADTH were also used to supplement this group's input submission, as well as input from a certified respiratory educator. All data gathered were from people residing in Canada.

The submission by LCC gathered their information by a survey and an environmental scan of patient forums. The former was the Faces of Lung Cancer Survey (FOLCS), conducted in August 2015, which surveyed 91 patients and 72 caregivers, all of which have or have had experience with lung cancer. Also, all of the caregivers are currently caring for, or previously cared for patients living with lung cancer. Feedback regarding dacomitinib was collected from online forums from five patients and four caregivers from the US. Patient experience with the drug was drawn from Americans because Canadian patients did not have access to dacomitinib. A summary of the population included in the environmental scan is provided in Table 3.1. The data were accessed between August and September 2018.

Table 3.1. Summary of population captured by LCC environmental scan

Patient/Caregiver	Age	Gender
Patient	50	F
Patient	47	F
Caregiver	N/A	F
Caregiver	N/A	F
Patient	54	F
Caregiver	N/A	M
Patient	67	F
Caregiver	N/A	F
Patient	60	F

From a patient perspective, 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. Patients expect new treatments to be able to be taken at home, have fewer side effects, and to improve their quality of life. It was also emphasized that improved education for general practitioners handling cancer patients, as well as for patients themselves is needed to help patients understand what to expect with a diagnosis of NSCLC.

Please see below for a summary of specific input received from the patient advocacy groups. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling,

punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Non-Small Cell Lung Cancer

The patient input submission from the OLA provided information about patient experiences with NSCLC. Patient respondents experienced the following symptoms: pain that was "*very intense at times*", shortness of breath, a cough, coughing up blood, weakness, and extreme fatigue. The patient group reported that the symptoms change frequently, lacking consistency, which can make them difficult to manage. They also described the disease as having an impact on various aspects of one's day-to-day life, from work and travelling to being social and participating in activities. This also has an effect on family and friends of those living with lung cancer, and the patient's independence, emotional well-being, and financial situation. One person described having lung cancer as having "*robbed me of my ability to do anything on my own*", while another stated "*I have lost a significant amount of weight and am tired, weak and without energy. I am no longer able to do the activities I enjoy. It is very hard to be positive and hopeful.*" The patient response emphasized the challenges of dealing with extreme fatigue and exhaustion such as the need to plan their day around managing these symptoms, as described by two additional quotes from patient respondents: *"This disease makes it hard to do day to day activities such as house cleaning, shopping and cooking. It has affected all parts of my life."* and *"Physical exertion of any kind causes my breathing to get worse."*

According to the patient input response, more information was needed to help them understand what was happening and make decisions about the next steps they needed to take. For many, they had little information about the disease (either cancer in general or lung cancer specifically), its treatment options, and the eventual prognosis in terms that would apply to them. Several people in the support group mentioned they felt rushed at appointments with doctors and would like to receive information in "easy to understand" language and a clear picture of their treatment choices. Further, patient respondents from the OLA submission spoke about issues of timeliness and heightened anxiety during this stage.

"I waited many months to see a specialist not knowing what exactly was wrong with me or what the prognosis might be."

"It took a year to finally make the diagnosis."

"The most frustrating thing for me was how long it took to get her diagnosed." (daughter of lung cancer patient)

Feelings of anxiety and/or depression with the diagnosis of lung cancer were reported by almost all of the respondents.

3.1.2 Patients' Experiences with Current Therapy for Non-Small Cell Lung Cancer

Patient respondents from the OLA group had experience with the following treatments: tiotropium bromide, glycopyrronium bromide, fluticasone propionate/salmeterol, budesonide/formoterol, roflumilast, prednisone, salbutamol, ipratropium bromide, salmeterol, indacaterol, and aclidinium bromide. One patient respondent is also undergoing radiation and chemotherapy, and another had recently (early 2018) received a

double lung transplant. The patient input submission suggested that current treatments provide some relief of symptoms of lung cancer, but are accompanied by side effects that need to be managed better, including: palpitations, dry mouth, mouth sores, vision and urinary problems, and impact on mood. The patient respondent who was undergoing radiation reported an extremely sore throat that made it difficult to swallow food. This patient submission highlighted that overall, patients would like their treatments to provide enough help that they will experience improved independence and require less assistance from others. The desire for more/increased energy was noted many times.

The OLA submission reported that many respondents expressed a desire for fewer medical appointments and reduced financial burden. Secondary costs of illness and treatments were also highlighted, including transportation to appointments and eating well for good nutrition to combat weight loss, which may include specific, costly items such as Ensure.

The LCC submission included input from a submission for osimertinib. They reported that patients who are EGFR positive consider themselves to be one of the one of the "lucky" ones *"as lucky as one can be with lung cancer,"* as one patient stated. They were able to take an oral EGFR-TKI for their first line treatment instead of chemotherapy, which is still the standard of care for the majority of NSCLC patients.

All the patients and families interviewed for the osimertinib submission reported a high quality of life on an oral targeted therapy and felt that the treatment was highly tolerable. The oral TKI therapy allowed three of the patients to go back to work. All were able to stay active, spend time with family and continue life. One person continued to go to four more years of dance competitions for his little girls. They also reported that this typical of the outcomes experienced by those on targeted therapies.

3.1.3 Impact of Non-Small Cell Lung Cancer and Current Therapy on Caregivers

The impact of NSCLC on caregivers described by the LCC and OLA submissions were similar. Caring for those living with lung cancer has an impact on various parts of life including work, finances, relationships with friends and family, and physical and leisure activities. Results from the FOCLS showed that 59% of caregivers reduced their hours at work and 8% quit their jobs. Their independence, ability to travel, and freedom to socialize were also impacted.

The emotional challenge of caring for a patient with lung cancer and seeing them suffer was also mentioned as an "overarching theme" in the OLA submission. According to the LCC submission, lung cancer only has a survival rate of 17%, which is devastating, emotionally burdensome, and even isolating for caregivers. The patient input response stated that often caregivers may feel the need to "take ownership for protecting their loved ones" thus leading to negative emotions such as anxiety, worry, depression, and psychological distress; all of which affect both the caregiver and the patient.

Lastly, the LCC submission referred to previous lung submissions that they had made, noting that oral therapies help to reduce the impact on the caregiver as treatment can be taken at home and the side effects are typically manageable, which allows patients to maintain their functional status and independence in terms of daily activities.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Dacomitinib

OLA indicated that patients and caregivers would like a treatment that is able to stop or slow the progression of disease, reduce the previously described symptoms of lung cancer, and improve appetite and energy levels. In addition, they would like to see a reduction in or elimination of those symptoms, along with the reduction in or elimination of inability to fight infection, burning of skin, and effect on mood. They also expressed the desire to be able to administer treatments at home, thus reducing the need for patients and caregivers to take time off work and fewer disruptions to one's day. Quality of life was also addressed as an important consideration for new treatments, with one patient stating that "if I have less than three years to live, I would like to be able to enjoy that time with my family."

The LCC submission presented different expectations for dacomitinib, stating that it is expected to perform similarly to afatinib as it is a second generation tyrosine kinase inhibitor (TKI). They also noted that there is evidence that dacomitinib is particularly effective in patients with the exon 19 deletion or exon 21 L858R substitution.

None of the respondents to the OLA submission had experience with dacomitinib and the LCC submission had a limited number (5 patients and 4 caregivers) of patients from the US to draw experiences from. The information is based on self-reported data obtained from online forums. The submission described the side effects as typical of epidermal growth factor receptor TKIs, which included: rashes (n = 5), diarrhea (3), mouth sores (2), itchy skin (2), fatigue (2), GI issues (1), hair loss (1), sun sensitivity (1), blisters (1), poor appetite (1), elevated liver enzymes (1), and weight loss (1). Skin-related issues were also prevalent among those taking dacomitinib, with 89% of patients reporting various issues; however, antibiotics were used to alleviate these symptoms. One caregiver respondent reported that her mother developed blisters and canker sores, making it difficult to chew her food, but said glutamine helped with these side effects. Two patients reported dose reductions to manage side effects. Lung Cancer Canada noted that for one of these patients, treatment was paused (for the patient who had elevated liver enzymes) and was restarted when it normalized. In addition, one patient respondent reported using Imodium while another had acupuncture and these were said to have helped with the symptoms related to gastrointestinal issues. LCC noted that from the patient reported outcomes in the online forum, it appeared that the side effects for dacomitinib were consistent with EGFR TKI's and were also consistent with the side effects reported in the clinical trial.

The LCC patient submission included reports from three patients regarding the efficacy of dacomitinib. Two patients reported stable disease, one of which was at seven months, and the third patient reported a "drastic decrease in lesion size". In contrast, one caregiver reported on the efficacy of the drug for their patient, which did not control their loved one's tumour.

3.3 Additional Information

A recurring theme from the patient input submission by the OLA was the lack of knowledge and understanding of the disease among patients, as well as the need for improved training for general practitioners about lung diseases to improve time to diagnosis. Patients reported anxiety and the desire to know more about their options when faced with making a decision about how to treat their cancer, as well as the need for clear

communication of these topics from clinicians. In summary, patients would like to see improved communication and education about treatment options that are presented to them.

The LCC submission also noted that first line osimertinib is still under consideration at the time of this submission and it is not yet known whether it will receive a positive recommendation. Even if it does receive a positive recommendation, LCC believes that the addition of a competitor will aid the pricing negotiations and help improve price to an acceptable level.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

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

Clinical factors:

- Comparison to afatinib
- Sequencing with other therapies, including other TKIS and immunotherapy

Economic factors:

- Potential for drug wastage

Please see below for more details.

4.1 Currently Funded Treatments

Afatinib is funded in all provinces for first line treatment. Gefitinib and erlotinib are funded in some provinces for first line treatment of NSCLC with EGFR mutations. PAG noted that the ARCHER 1050 trial compared dacomitinib to gefitinib. However, PAG is also seeking information comparing dacomitinib to afatinib, or if trial data is generalizable to afatinib.

4.2 Eligible Patient Population

In the ARCHER 1050 trial, patients were excluded if they had history of brain or leptomeningeal metastases. PAG is seeking guidance on whether patients with CNS involvement would be eligible for dacomitinib.

PAG is seeking clarity on the subgroup of patients with EGFR mutations who would be eligible for treatment with dacomitinib. PAG noted that the trial enrolled patients with Exon 19 deletion or Leu858Arg EGFR mutations.

PAG noted that some patients start chemotherapy while waiting for the results of EGFR mutation testing. Once the results are available, patients are usually switched to an EGFR TKI if they have an EGFR mutation, or some may complete their 4 cycles of chemotherapy. PAG is seeking guidance on whether patients who have started chemotherapy but have not progressed could be switched to dacomitinib, 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.

PAG is also seeking guidance on switching patients who have started therapy with gefitinib, erlotinib, or afatinib but have not progressed.

4.3 Implementation Factors

PAG is seeking clarity on the duration of treatment.

PAG noted that there are three tablet strengths and the submitted price is the same per tablet, regardless of strength. Although the availability of three different strengths is an enabler for ease of dose adjustments, this flat pricing structure would be a barrier as there would be added costs for dose modifications. There is also the potential to lead to wastage during dosage adjustments. For example, a patient on a 45 mg daily dose may be dispensed the smaller tablet strengths, to allow for the possible need of dose reductions. However, this dispensing strategy would cost more than dispensing the 45 mg tablets. There are also concerns with the potential for drug wastage for patients who may be dispensed the 45 mg tablets but do not tolerate and then have dose reduced 15 mg or 30 mg prior to finishing the amount of 45 mg tablets dispensed.

PAG noted that dacomitinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings. As such, PAG identified the oral route of administration, in which patients could easily use in the community, as an enabler. 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. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

At the time of this PAG input, osimertinib is being reviewed for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations. PAG is seeking information comparing dacomitinib to osimertinib in this setting as well as guidance on sequencing of dacomitinib and osimertinib. PAG is also seeking guidance on switching patients who have started therapy on osimertinib but have not progressed.

PAG noted that in most provinces gefitinib and afatinib are not funded in second line and beyond. In addition, in most provinces, erlotinib is funded only after chemotherapy and not funded for patients previously treated with other TKI.

4.5 Companion Diagnostic Testing

EGFR mutation testing is already available.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician input submissions were provided, one from a group of five medical oncologists from Lung Cancer Canada (LCC) and one from a single clinician from Cancer Care Ontario (CCO) who specializes in thoracic oncology. Please see below for details from the clinician input.

Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitors (TKI) are considered standard of care for EGFR mutation positive (EGFR+) non-small cell lung cancer (NSCLC); this includes: gefitinib, erlotinib, afatinib. 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 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.

5.1 Current Treatment(s) for NSCLC

The clinician input submission from LCC stated that the use of EGFR TKI has been adopted as the standard of care for EGFR+ NSCLC, as it has shown a clinical and statistically significant advantage over chemotherapy. This includes gefitinib and erlotinib, which are first generation EGFR TKIs, as well as the second generation EGFR TKI, afatinib.

According to the LCC clinician input, in Ontario, both gefitinib and afatinib are approved and available and serve as appropriate comparators to dacomitinib. It was expressed that gefitinib is an appropriate comparator as the most widely prescribed EGFR TKI in this setting, while afatinib is an appropriate comparator as the other second generation EGFR TKI. The clinician input stated that in the ARCHER 1050 study, the dacomitinib was compared to gefitinib and therefore, is an appropriate clinical trial comparator, however, in actual practice afatinib is probably more appropriate.

5.2 Eligible Patient Population

According to the LCC clinicians, testing for the EGFR mutation is routine practice for patients who have advanced non-squamous NSCLC. The mutations are detected in about 12-15% of stage 4 non-squamous NSCLC patients and are more likely in those with little to no history of smoking. The clinicians highlighted that this group of patients would form the eligible patient population, which aligns with the reimbursement request for dacomitinib. Further, the clinicians from both submissions felt that the trial criteria were appropriate and applicable in clinical practice, but the group from LCC also noted that with previously approved EGFR TKIs, a broader population is actually treated due to some restrictions in clinical trials that are less stringently applied in clinical practice. Therefore, the clinicians from LCC and CCO stated that practically all patients with stage 4 EGFR+ NSCLC would be candidates for dacomitinib, unless there was a specific patient contraindication.

The LCC submission also reported that dacomitinib does not address an unmet need as the relevant patient population has access to other EGFR TKI therapies, but it does add to the options available to clinicians and patients.

5.3 Relevance to Clinical Practice

None of the clinicians that provided input for this review had experience using dacomitinib. The LCC clinicians reported that the advanced EGFR+ NSCLC population is where they would seek to have dacomitinib as an option, although they were not aware of a particular subgroup where they could see dacomitinib as being clearly superior to existing EGFR TKIs.

Dacomitinib was described by LCC clinicians as similar in terms of efficacy, safety and tolerability, to existing treatments (gefitinib and afatinib). It was also shown to have an improvement in progression-free survival, along with an increase of side effects such as rashes and diarrhea. The LCC clinician input reported that similar findings were observed in the LUX-LUNG-7 study that compared second generation afatinib to first generation gefitinib, concluding that there is a general consensus that second generation TKIs are slightly more effective than gefitinib, but also have a slight increase in side effects. The LCC clinician input also suggested that due to these results, a second generation TKI may be offered to fitter patients. Lastly, there are no clear advantages or disadvantages for dacomitinib when compared to current options. CCO input stated that dacomitinib is more efficacious with improved survival compared to current standard.

5.4 Sequencing and Priority of Treatments with Dacomitinib

The clinicians from LCC and CCO suggested that dacomitinib would be sequenced as a first line option for stage 4 EGFR+ NSCLC. In the opinion of the LCC group, 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.

At the time of the dacomitinib was submitted for pCODR review, it was also noted that osimertinib, a first line treatment, was currently under pCODR review in this setting. The clinicians expressed that even if there is a positive funding recommendation for osimertinib, the addition of dacomitinib as a treatment option may help encourage competitive pricing for both treatments.

5.5 Companion Diagnostic Testing

As per the clinician input, companion diagnostic testing is required, however EGFR mutation testing is now routine practice, and there are no implications for new testing for this application.

5.6 Additional Information

None.

5.7 Implementation Questions

5.7.1 Osimertinib is currently being reviewed for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations. Would you use dacomitinib instead of osimertinib, or sequence before or after osimertinib?

The group from LCC indicated that for this group of patients, some physicians would use a first or second generation TKI, which may include dacomitinib, and consider switching to osimertinib as a second-line treatment if a T790M mutation is detected upon first line progression. The CCO clinician agreed that osimertinib should be used for patients with T790 mutations. The LCC clinicians also indicated that if approved, many physicians may opt to start treatment with osimertinib as first line treatment as it has "impressive progression-free survival, CNS protection, and few toxicities."

5.7.2 Would you switch patients that are currently on treatment with chemotherapy, other TKI therapy, or immunotherapy but who have not progressed to dacomitinib?

The LCC clinicians indicated that they would do so "only if a patient was on another TKI with a particular sensitivity", to determine if dacomitinib would be better tolerated. They also noted that this would be extremely rare.

5.7.3 In the ARCHER 1050 trial, patients were excluded if they had history of brain or leptomeningeal metastases. Based on your experience, would you treat patients with CNS involvement with dacomitinib?

Clinician input from the LCC group indicated that osimertinib (if approved) would be preferred over dacomitinib for patients with CNS involvement due to excellent intracranial drug penetration. According to the clinicians, first and second generation EGFR TKIs have historically been used in patients who have brain metastases that were previously controlled by radiation therapy; if osimertinib was not available, dacomitinib would be considered for patients with controlled brain metastases.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of dacomitinib or PF00299804 (trade name Vizimpro) as a first line treatment in patients with stage IIIB/IV Non Small Cell Lung Cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations. Appropriate comparators and outcomes of interest are summarized in Table 6.1 in section 6.2.1.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCT§	• Treatment naïve (including chemotherapy naïve) adult patients (≥18 years) with locally advanced/metastatic (stage IIIB/IV) or recurrent (after adjuvant or neoadjuvant treatment) NSCLC with epidermal growth factor receptor (EGFR)-activating mutations. <u>Subgroup</u>: • Type of mutation (EGFR exon 19 deletions vs. 21 L858R substitutions)	dacomitinib /VIZIMPRO / PF00299804 monotherapy	• Giotrif (afatinib) • Tarceva (erlotinib) • Iressa (gefitinib) • Tagrisso (osimertinib) • Placebo	• OS • PFS • QoL • ORR • Metastases resection rate • AE o Dose reduction • SAE • WDAE o Discontinuation rate

Abbreviations **AE** - adverse events; **BSC**- best standard care; **EGFR** = epidermal growth factor; **NSCLC** - non-small cell lung cancer; **ORR** - objective tumour response rate; **OS** - overall survival; **PFS** - progression-free survival; **RCT**- randomized controlled trial; **ROA** - route of administration; **SAE** - serious adverse events; **QoL** - quality of life; **WDAE** -withdrawal due to adverse events.

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

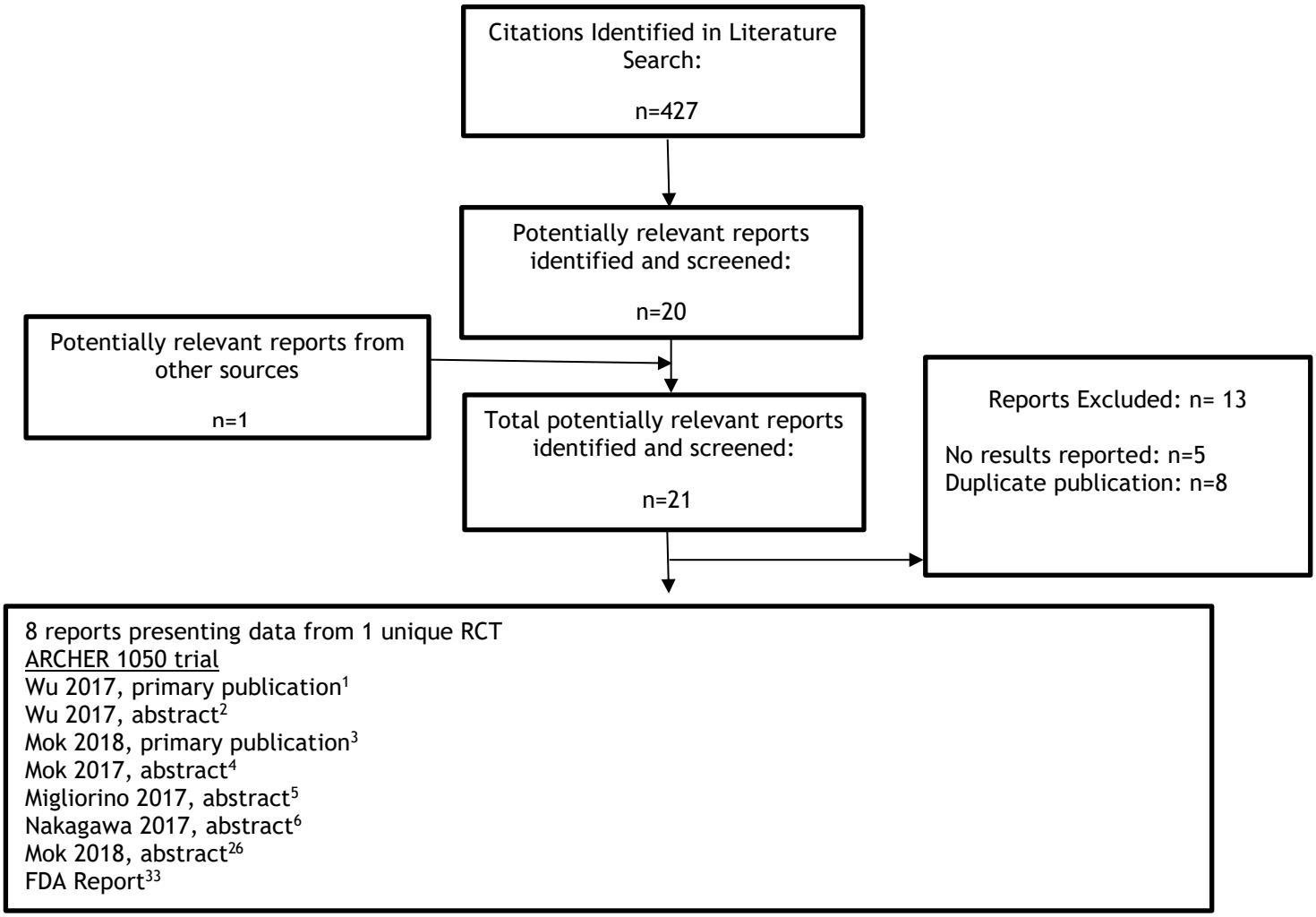
§ Includes retrospective and exploratory analyses from prospective randomized controlled trials.

6.3 Results

6.3.1 Literature Search Results

394 abstracts were identified. 20 proceeded to full text. Studies were excluded because they did not meet inclusion/exclusion criteria. Of the 20 potentially relevant reports identified, eight studies were included in the pCODR systematic review [1-6,26], all registered under Governmental Clinical Trials identifier NCT01774721[27], and 13 studies were excluded. Studies were excluded because results were not included[28-31], or they were duplicates.

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to ARCHER were also obtained through requests to the Submitter by pCODR[32]

6.3.2 Summary of Included Studies

One randomized control trial met the eligibility criteria[1-6,26,27]. Study characteristics of this trial are summarized in Table 6.2 and quality assessment results are presented in Table 6.3.

6.3.2.1 Detailed Trial Characteristics

Table 6.2: Summary of trial characteristics of included trial of dacomitinib as a first line treatment in patients with stage IIIB/IV Non Small Cell Lung Cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations.

Trial Design	Eligibility Criteria	Intervention	Comparator	Outcomes
Archer 1050 trial[1-6,26,27]				
Clinical trial NCT01774721 Ongoing trial, estimated completion date March 29, 2019 Data cut-off as of July 2016 Parallel assignment, open-label, phase 3, RCT Patient enrollment: Between May 9, 2013 and March 20, 2015 N randomized= 452 Multicentre (71 centres in 7 countries) Randomized 1:1 ratio, stratified by: •race (self-reported; Japanese *vs* Chinese *vs* other east Asian *vs* non-Asian •EGRF mutation (exon 19 deletion *vs* Leu858Arg mutation	Key Inclusion Criteria: •18≥ years of age • Histologically or cytologically confirmed newly diagnosed stage IIIB/IV or recurrent NSCLC (minimum of 12 months disease-free interval between completion of therapy and recurrence of NSCLC •Treatment naive •Presence of at least one documented EGFR mutation (Exon 19 deletion and Leu858Arg) Exclusion Criteria: •mixed histology, cytology or both (including elements of small cell or carcinoid lung cancer •atypical EGFR mutations •history of brain or leptomeningeal metastases •history of, or currently suspected, diffuse non-infectious pneumonitis or	Oral dacomitinib 45mg once daily for 28 day cycles Two dose level dose reductions were permitted for treatment-related toxicity (first dose reduction to 30mg, second to 15mg) Given until disease progression, initiation of new anticancer therapy, non-compliance, voluntary study withdrawal, death, or unacceptable toxicity	Oral gefitinib 250mg once daily in 28 day cycle If treatment interrupted for toxicity, gefitinib resumed at daily or ever-other-day dosing per investigators discretion	Primary: •PFS based on masked IRC review Key Secondary: •PFS based on investigator assessment •OR •OS •OS at 30 months Other Secondary: •Safety assessment •Patient reported outcomes •QoL •time to treatment failure •WDAE

Table 6.2: Summary of trial characteristics of included trial of dacomitinib as a first line treatment in patients with stage IIIB/IV Non Small Cell Lung Cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations.

Trial Design	Eligibility Criteria	Intervention	Comparator	Outcomes
Archer 1050 trial[1-6,26,27]				
Funded by SFJ Pharmaceuticals and Pfizer	interstitial lung disease •any previous anticancer systemic treatment of locally advanced or metastatic NSCLC •previous treatment with and EGFR TKI or other TKI •uncontrolled or substantial cardiovascular disease			

Abbreviations: AE - adverse events; BSC- best standard care; EGFR -epidermal growth factor; TKI - Tyrosine Kinase Inhibitor NSCLC - non-small cell lung cancer; OR - objective response; OS - overall survival; PFS - progression-free survival; RCT- randomized controlled trial; SAE - serious adverse events; QoL - quality of life; WDAE -withdrawal due to adverse events.

Table 6.3: Select quality characteristics of included studies of [dacomitinib in patients with NSCLC

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
Archer 1050	Dacomitinib vs. Gefitinib	Progression-free survival	440 to achieve 90% power to detect a 50% or more improvement	451	1:1 stratified by race (Japanese versus mainland Chinese versus other East Asian versus non-East Asian) and EGFR mutation status (exon 19 deletion versus the L858R mutation in exon 21)	None	Tumour assessment by independent review was masked	All randomized patients (dacomitinib n = 227, gefitinib n = 225)	NR (in progress)	193	The institutional review board or ethics committee of each participating institution approved the trial protocol. All patients provided written informed consent before enrolment.

Abbreviations: ITT - Intention-to-treat; EGFR -epidermal growth factor; NR - Not Ready

a) Trials

One randomized control trial, ARCHER 1050, was included in this review.

ARCHER 1050 was a phase III clinical trial. The trial was a randomized, open labelled, two-arm, parallel arm study comparing gefitinib with dacomitinib. The patient population were newly diagnosed (treatment naïve) or recurrent (after adjuvant or neoadjuvant treatment) NSCLC patients that were 18 years of age or

older. The randomization ratio was 1:1. Major patient inclusion and exclusion criteria are summarized in Table 6.2.

The Archer 1050 trial was a multi-centre trial, including 71 Universities and medical centres from 7 different countries (China, Hong Kong, Japan, South Korea, Poland, Italy and Spain). All patients had to have a documented EGFR mutation (exon 19 deletion or the LEU85Arg mutation) and were tested for the mutations before randomization.

Randomization was generated using a computer-generated random code assigned by a central interactive web response system (IWRD), and stratified by race and EGFR mutation. Race was stratified by self-reported "White", "Black" or "Asian". The Asian population was further stratified to "Japanese", "Chinese", or "Other east Asian".

The primary outcome for the trial was progression free survival (PFS) determined by masked independent radiological central (IRC) review. ARCHER 1050 was designed to have 90% power to detect a hazard ratio (HR) of 0.667 for dacomitinib vs gefitinib (50% or more improvement in PFS). Secondary outcomes included PFS based on investigator assessment, proportion of patients who reached objective response, overall survival (OS), OS at 30 months, safety assessment and patient outcomes including QoL), objective tumor response rate (ORR), time to treatment failure (TTF), safety based on adverse events (AEs), and disease control rate (DCR).

The ARCHER 1050 study was funded by SFJ Pharmaceuticals and Pfizer. The trial is ongoing, expected to be completed March 29, 2019. The progression-free survival data cut off is July 29, 2016, and the overall-survival data are based on a cut-off of February 17, 2017 [3].

According to the FDA report, there were protocol deviations in both in the dacomitinib group (53%) and the gefitinib group (45 %)[33] The incidence of protocol deviations were balanced: inclusion/exclusion (22% versus 19%), informed consent deviations (9% versus 11%), study treatment (17% versus 14%), lab/procedures/tests (4% versus 4%), and study procedure criteria (22% versus 19%).

b) Populations

Population characteristics for ARCHER 1050 are summarized in Table 6.4. Patient characteristics at baseline were similar between dacomitinib and gefitinib groups.

Of the 720 patients screened for eligibility in the ARCHER 1050 trial, 452 were randomized in a 1:1 ratio receiving dacomitinib (n=227) or gefitinib (n=225). The median age in the dacomitinib group was 62 years (range of 53-68 years) and in the gefitinib group 61 ear (range 54-68). The proportion of males in the dacomitinib group was 36% and 44% for gefitinib. The proportion of patients in stage IV (81%), and with the exon 19 deletion EGFR mutation (59%) were the same in both the dacomitinib arm and gefitinib arm[1].

Table 6.4: Patient Characteristics for **ARCHER 1050**[1-6,26,27]

	Dacomitinib (n=227)	**Gefitinib (n=225)**
Age, years		
Median	62 (53–68)	61 (54–68)

	Dacomitinib (n=227)	Gefitinib (n=225)
<65	133 (59%)	140 (62%)
≥65	94 (41%)	85 (38%)
Sex		
Male	81 (36%)	100 (44%)
Female	146 (64%)	125 (56%)
Race (self-identified)		
White	56 (25%)	49 (22%)
Black	1 (<1%)	0
Asian	170 (75%)	176 (78%)
Japanese	40 (18%)	41 (18%)
Chinese	114 (50%)	117 (52%)
Other east Asian	16 (7%)	18 (8%)
ECOG performance status		
0	75 (33%)	62 (28%)
1	152 (67%)	163 (72%)
Disease stage at screening		
Stage IIIB	18 (8%)	16 (7%)
Stage IV	184 (81%)	183 (81%)
Unknown*	25 (11%)	26 (12%)
Smoking status		
Never	147 (65%)	144 (64%)
Former	65 (29%)	62 (28%)
Current	15 (7%)	19 (8%)
Type of *EGFR* mutation†		
Exon 19 deletion	134 (59%)	133 (59%)
Leu858Arg	93 (41%)	92 (41%)

Reprinted from The Lancet, 18. number 11, Yi-Long Wu et al., Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial, Pages No.1454-1466, Copyright (2017), with permission from Elsevier.

c) Interventions

Trial patients received oral dacomitinib 45mg dose daily or gefitinib 250mg daily in 28 day cycles. Treatment was discontinued after progression of disease, initiation of a new anticancer therapy, unacceptable toxicities, non-compliance, withdrawal of consent or death[1]. Post-progression systemic treatment was received by 93 (41%) of patients in the dacomitinib group, and 126 (56%) of the gefitinib group. The most common post-progression treatment in both groups was pemetrexed, carboplatin, cisplatin and osimertinib. More than half of patients who progressed per independent radiology central (IRC) review continued to receive study treatment after progression. There were more patient in the gefitinib arm than the dacomitinib arm that continued to receive study treatment after progression, the median duration of post-progression

study treatment was slightly higher in the dacomitinib group compared to the gefitinib group, and the median post-progression survival was greater in the dacomitinib group compared to the gefitinib group. Of note, at the time of the data cut-off, more patients in the dacomitinib arm compared to the gefitinib arm were still progression-free.[32]

Dose reduction protocol was specified for dacomitinib and gefitinib. Patients receiving dacomitinib were allowed dose reductions for a maximum of two doses levels. The first dose reduction was to 30mg/day, and the second to 15mg/day[1]. These reductions were allowed for the treatment-related toxicity in the case of grade 3 or worse toxicity, prolonged grade 2 adverse events lasting longer than one cycle. As gefitinib is only available in 250mg doses, treatment would be interrupted for grade 3, grade 4, or intolerable grade 2 toxicity[1]. Gefitinib would be resumed at a daily, or every-other-day dosing at the investigators discretion.

d) Patient Disposition

Of the 720 patients that were assessed for eligibility, 452 were enrolled and randomly assigned to receive either dacomitinib or gefitinib. One patient assigned to the gefitinib group received no treatment and consent was withdrawn, therefore the trial population comprised of 451 patients. Median duration of dacomitinib treatment was 15.3 months and 12.0 months in the gefitinib group. At data cut-off, 66 (29%) of patients in dacomitinib group and 38 (17%) of patients in gefitinib group were still receiving treatment. Permanent discontinuation because of adverse events occurred in 22 (10%) of 227 patients in the dacomitinib group, and 15 (7%) of 224 patients in gefitinib group. Most common grade 3 adverse eves with dacomitinib were dermatitis acneiform (13.7%) and diarrhea (8.4%)[4]. Dose reductions occurred in 150 (66%) of patients in the dacomitinib group[26]. Incidence and severity of adverse events declined following dose reduction, and PFS was similar in dose-reduced and all dacomitinib treated patients [7].Temporary discontinuation occurred in 177 (78%) of the dacomitinib group, and 120 (54%) of the gefitinib group. As of February 17, 2017, there were 103 deaths in the dacomitinib group, and 117 in the gefitinib group (median follow-up time of 31.1 months and 31.4; respectively)[3]. A total of 253 patients (dacomitinib, n=113; gefitinib, n=140) received further cancer treatment following trial discontinuation. Those patients received either chemotherapy, or third generation EGFR TKIs[3].

The majority of patients treated in the dacomitinib arm and treated patients in the gefitinib arm reported concomitant drug use. The 3 most frequently reported concomitant drug treatments in the dacomitinib arm were loperamide (less than 50%), herbal preparation/Traditional Chinese Medicine (less than 30%), and dexamethasone (less than 30%). The 3 most frequently reported concomitant drug treatments in the gefitinib arm (were herbal preparation/ Traditional Chinese Medicine (less than 30%), dexamethasone (less than 30%), and paracetamol (less than 30%). Less than 20% of patients in the dacomitinib arm and in the gefitinib arm received concomitant radiation. [32].

e) Limitations/Sources of Bias

SIGN-50 quality assessment is provided in Appendix A Table A4.

The ARCHER 1050 trial was of high quality, based on the SIGN-50 quality checklist for randomized control trials[9]. The study was open label, and used appropriate randomization methods with sample sizes that were targeted for sufficient statistical power of primary outcomes. Participants and investigators were not

blinded to arm allocation, however independent review was consistent with investigator assessment. Details of blinding and randomisation methods are summarized in section 6.2.8.1a.

- The study was an open-label design, which may introduce bias; however independent review was used to determine results of progression free survival, objective responses, and duration of response.
- The number of patients with NSCLC that was after adjuvant or neoadjuvant treatment in the dacomitinib arm was 24 (11%) vs newly diagnosed NSCLC 203 (89%). The number of patients with NSCLC that was recurrent after adjuvant or neoadjuvant treatment in the gefitinib arm was 19 (8%) vs newly diagnosed 206 (96%). Trial was not stratified for newly diagnosed NSCLC and NSCLC that was recurrent after adjuvant or neoadjuvant treatment; therefore, there may be a potential effect of stage of diagnosis that is not accounted for.
- Patients without brain metastases were excluded, potentially enriching the population of patients with better outcomes. Metastases resection rate was not an outcome of the trial.
- Supportive care, therapies, or medications allowed during Archer 1050 trial were not controlled for or accounted for in analysis.
- The population of the dacomitinib group had more female patients, and a higher proportion of patients with an ECOG performance status of 0 than the gefitinib group.
- The ARCHER 1050 study was funded by the drug manufacturer. The manufacturer in collaboration with the trial investigators designed the study, collected the data, and interpreted the results.
- Population race was majority ASIAN (77%). The generalisability of trial outcomes to other races may be limited; however, it is unclear what impact this may have on outcomes.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

A gatekeeping procedure was used for hypotheses testing in a hierarchical approach to control the family-wise error rate for the analyses of the primary endpoint and key secondary endpoints of ORR per IRC review and OS. This testing began by first comparing PFS per blinded IRC review between the dacomitinib and the gefitinib arms in the ITT population with 1-sided significance level of 0.025. If the null hypothesis for the primary endpoint were rejected, then ORR per IRC review was to be tested next with a 1-sided significance level of 0.025. If the null hypothesis for ORR were rejected, then the final analysis of OS was to be tested at a 1-sided significance level of 0.025.[32]

Progression-free Survival

The primary endpoint was progression-free survival as determined by masked IRC review (defined as the time from randomisation to the date of disease progression, or death due to any cause). The median progression-free survival for dacomitinib and gefitinib were 14.7 and 9.2 months; respectively (HR=0.59, 95% CI: 0.47-0.74,

p<0.0001)[1]. Progression-free survival based on investigator assessment was consistent progression-free survival according to IRC review. Summary of Efficacy outcomes are reported in Table 6.5.

Objective Response

The proportion of patients who achieved an objective response according to masked IRC review was similar between dacomitinib and gefitinib, and investigator assessment was consistent with IRC review. The median duration of response in the dacomitinib group was 15.9 months (95% CI: 13.8-17.6), and 9.2 months (95% CI: 8.2-11) in the gefitinib group (HR: 0.55; 95% CI: 0.42-0.71; p<0.0001).

Overall Survival

Final OS analyses were conducted as of February 17, 2017. The median follow-up times for the final OS analysis were 31.1 months with dacomitinib and 31.4 months with gefitinib[3]. At that time, 103 (45.4%) deaths had occurred in the dacomitinib group, and 117 (52%) deaths in the gefitinib group. The OS was significantly longer in the dacomitinib group than the gefitinib group (HR: 0.760; 95% CI: 0.582-0.993; two-sided p-value=0.0438). The overall survival at 30 months was 56.2% in the dacomitinib group and 46.3% in the gefitinib group. The intention-to-treat population was used for this analysis (dacomitinib n= 227; gefitinib n= 225)[3]. Despite the statistically significant reported p-value when assessed on its own, due to the gatekeeping procedure applied to the outcome analysis, the results of the final OS analysis should not be considered statistically significant.

Time to Treatment Failure

Overall, 168 patients (74.0%) in the dacomitinib arm and 197 patients (87.6%) in the gefitinib arm reached a treatment failure event [32].Based on IRC review, patients in the dacomitinib group remained on treatment longer (11.1 months) than those in the gefitinib group (9.2 months) (HR-0.67; 95% CI: 0.54-0.83; p=0.0001)[1]. Results based on investigator assessment were consisted with IRC review.

Patient Reported Outcomes

Patient-reported outcomes were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), its corresponding module for lung cancer (QLQ-LC13), and the EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D). Time to deterioration was defined as the time from randomization to the first time there is a 10 point or higher increase after baseline. A 10 point or higher increase is perceived as clinically meaningful. In both the dacomitinib group and the gefitinib group, there were statistically significant improvements from baseline, with improvements seen in fatigue, pain, dyspnea, and cough [5]. There was overall improvement from baseline for pain in chest in both groups, which was greater in the dacomitinib group (mean −10·24 for dacomitinib *vs*−7·44 for gefitinib; p=0·0235). Clinically meaningful improvements were recorded for pain in chest and cough in the dacomitinib group, and in cough for the gefitinib group[5].

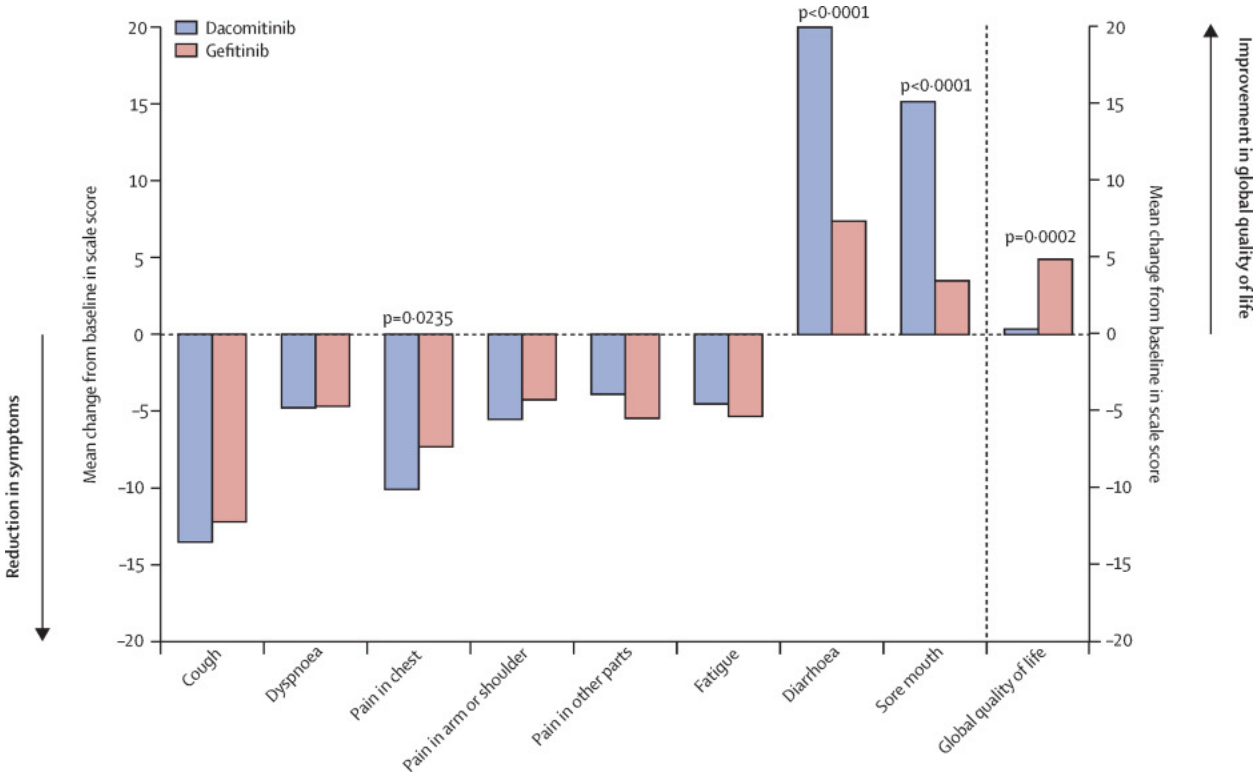


Figure 5 from Wu et al. 2017[2]: Overall change from baseline in key lung cancer-associated symptoms, fatigue, diarrhoea, sore mouth, and global quality of life
Each scale ranges from 0 to 100, with changes ≥10 points regarded as clinically meaningful. For global quality of life, higher scores indicate better global quality of life; for symptoms, higher scores indicate greater severity of symptoms. p values (unadjusted for multiple testing) are for the between-group comparison of the overall change from baseline, calculated using repeated-measures mixed-effects modelling.

Mutation comparisons

There was no difference in the number of patients achieving an objective response in the dacomitinib group (76%) and the gefitinib group (70%) for patients with the exon 19 deletion (p=0.1143). For patients with the Leu858Arg mutation, the number of patients who achieved an objective response were 73% in the dacomitinib group and 74% in the gefitinib group (p=0.5395). Detailed results for progression-fee survival, objective response rate, and duration of response by mutation can be found in Table 6.6[2].

For patients with the exon 19 deletion, the HR for OS was 0.880 (CI: 0.613-1.262; two sided p-vale = 0.4862), with a median OS of 34.1 months for the dacomitinib versus not reach for gefitinib group. For patients with the Leu858Arg mutation, the HR for OS was 0.707 (CI: 0.478-1.045; p = 0.0805), with a median OS of 32.5 months for the dacomitinib versus 23.2 gefitinib group [3].

Asian v. non-Asian and Japanese population

Subgroup analysis of Asian and non-Asian IRC review were consistent with the main analysis. 259 (75%) of Asian patients and 72 (68%) of non-Asian patients achieved a best overall response in a post-hoc exploratory analysis.

The results for the Japanese patients in the ARCHER 1050 trial are reported in a supplemental abstract in the Journal of Thoracic Oncology[6]. Progression-free survival and duration of response in Japanese population (dacomitinib n=40; gefitinib n=41) were consistent with global response.

Table 6.5: Summary of efficacy outcomes

	Archer 1050[1-6,27]	
	Dacomitinib (n=227)	Gefitinib (n=224)
Progression-Free Survival (Months)		
Median (95% CI)	14.7 (11.1-16.6)	9.2 (9.1-11.0)
Hazard Ratio (95% CI)	0.59 (0.47-0.74)	
p-value	p<0.0001	
Overall Response Rate		
n	227	225
Complete n (%)	12 (5)	4 (2)
Objective response (%)	170 (75%)	161 (72%)
p-value	p=0.4234	
Duration of Response		
Median (95% CI)	15.9 (13.8-17.6)	9.2 (8.2-11.0)
Hazard Ratio (95% CI)	0.55 (0.42-0.71)	
p-value	p<0.0001	
Overall Survival (Months)		
Median (95% CI)	34.1 (29.5-37.7)	26.8 (23.7-32.1)

	Archer 1050[1-6,27]	
	Dacomitinib (n=227)	Gefitinib (n=224)
Hazard Ratio (95% CI)	0.760(0.582-0.993)	
p-value (two sided)	p<0.0438	
Time to treatment failure (Months)		
Median (95% CI)	11.1 (9.2-14.6)	9.2 (7.6-9.4)
Hazard Ratio (95% CI)	0.67 (0.54-0.83)	
p-value (two sided)	P=0.0001	

**Conference Abstract*

Table 6.6: Progression-fee survival, objective response rate, and duration of response by EGFR mutation per IRC[2]

	Exon 19 Deletion		L858R Mutation	
	Dacomitinib (n=134)	Gefitinib (n=133)	Dacomitinib (n=93)	Gefitinib (n=92)
PFS per IRC				
Median, months (95% CI)	16.5 (11.3-18.4)	9.2 (9.1-11.0)	12.3 (9.2-16.0)	9.8 (7.6-11.1)
Hazard ratio (95% CI) 1-sided *P*value	0.551 (0.408-0.745) <0.0001		0.626 (0.444-0.883) 0.0034	
ORR per IRC				
CR, n (%)	7 (5.2)	3 (2.3)	5 (5.4)	1 (1.1)
PR, n (%)	95 (70.9)	90 (67.7)	63 (67.7)	67 (72.8)
ORR (CR + PR), n (%) (95% CI)	102 (76.1) (68.0-83.1)	93 (69.9) (61.4-77.6)	68 (73.1) (62.9-81.8)	68 (73.9) (63.7-82.5)
1-sided *P* value	0.1143		0.5395	
DoR in responders per IRC				
Median, months (95% CI)	15.6 (13.1-19.6)	8.3 (7.9-10.1)	13.7 (9.2-17.4)	7.5 (6.5-10.2)
Hazard ratio (95% CI) 1-sided *P* value	0.454 (0.319-0.645) <0.0001		0.403 (0.267-0.607) <0.0001	

CI, confidence interval; CR, complete response; DoR, duration of response; PR, partial response.

Harms

Adverse Events

Adverse events of any cause occurred in >99% of the dacomitinib group, and 98% of the gefitinib group[1]. The most commonly reported grade 3 adverse events in the dacomitinib group were dermatitis acneiform (13.7%) and diarrhea (8.4%)[4]. Deaths recoded by investigators as adverse events occurred in 22 (10%) of patients in the dacomitinib group, and 20 (9%) in the gefitinib group. Patient discontinuation because of adverse events related to study drug occurred in 22 (10%) of patients in the dacomitinib group, and in 15 (7%) of the gefitinib group [1]. Dose reductions occurred in 150 (66%) of dacomitinib group [1]. According to clinicaltrials.gov, serious adverse events of pneumonitis were reported in less than 1% of patients in the dacomitinib and gefitinib arm.[27] A summary of adverse events can be found in Table 6.7.

Table 6.7: Adverse events in Archer 1050[1]

	Dacomitinib (n=227)				**Gefitinib (n=224)**			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Any adverse event	83 (37%)	116 (51%)	5 (2%)	22 (10%)	128 (57%)	67 (30%)	5 (2%)	20 (9%)
Diarrhoea	178 (78%)	19 (8%)	0	1 (<1%)	123 (55%)	2 (1%)	0	0
Paronychia	123 (54%)	17 (7%)	0	0	42 (19%)	3 (1%)	0	0
Dermatitis acneiform	80 (35%)	31 (14%)	0	0	64 (29%)	0	0	0
Stomatitis	91 (40%)	8 (4%)	0	0	39 (17%)	1 (<1%)	0	0
Decreased appetite	63 (28%)	7 (3%)	0	0	54 (24%)	1 (<1%)	0	0
Dry skin	60 (26%)	3 (1%)	0	0	38 (17%)	0	0	0
Weight decreased	53 (23%)	5 (2%)	0	0	36 (16%)	1 (<1%)	0	0
Alopecia	52 (23%)	1 (<1%)	0	0	28 (13%)	0	0	0
Cough	48 (21%)	0	0	0	41 (18%)	1 (<1%)	0	0
Pruritus	44 (19%)	1 (<1%)	0	0	28 (13%)	3 (1%)	0	0
ALT increased	42 (19%)	2 (1%)	0	0	69 (31%)	19 (8%)	0	0
Conjunctivitis	43 (19%)	0	0	0	9 (4%)	0	0	0
Nausea	40 (18%)	3 (1%)	0	0	48 (21%)	1 (<1%)	0	0

	Dacomitinib (n=227)				Gefitinib (n=224)			
AST increased	42 (19%)	0	0	0	72 (32%)	9 (4%)	0	0
Rash	30 (13%)	10 (4%)	0	0	24 (11%)	0	0	0
Palmar-plantar erythrodysesthesia syndrome	31 (14%)	2 (1%)	0	0	7 (3%)	0	0	0
Pain in extremity	31 (14%)	0	0	0	26 (12%)	0	0	0
Dyspnoea	25 (11%)	4 (2%)	1 (<1%)	0	24 (11%)	4 (2%)	0	2 (1%)
Asthenia	24 (11%)	5 (2%)	0	0	25 (11%)	3 (1%)	0	0
Constipation	29 (13%)	0	0	0	31 (14%)	0	0	0
Mouth ulceration	28 (12%)	0	0	0	13 (6%)	0	0	0
Maculopapular rash	18 (8%)	10 (4%)	0	0	26 (12%)	1 (<1%)	0	0
Upper respiratory tract infection	25 (11%)	3 (1%)	0	0	28 (13%)	0	0	0
Musculoskeletal pain	24 (11%)	2 (1%)	0	0	28 (13%)	0	0	0
Dermatitis	21 (9%)	4 (2%)	0	0	8 (4%)	1 (<1%)	0	0
Insomnia	23 (10%)	1 (<1%)	0	0	33 (15%)	0	0	0
Anaemia	20 (9%)	2 (1%)	0	0	11 (5%)	5 (2%)	0	0
Chest pain	22 (10%)	0	0	0	32 (14%)	0	0	0
Hypokalaemia	11 (5%)	9 (4%)	2 (1%)	0	9 (4%)	4 (2%)	0	0
Vomiting	18 (8%)	2 (1%)	0	0	29 (13%)	0	0	0
Back pain	18 (8%)	0	0	0	34 (15%)	1 (<1%)	0	0
Pustular rash	6 (3%)	8 (4%)	0	0	3 (1%)	0	0	0
Hypertension	10 (4%)	3 (1%)	0	0	6 (3%)	4 (2%)	0	0
Disease progression	0	0	0	8 (4%)	0	0	0	11 (5%)
Pleural effusion	1 (<1%)	5 (2%)	0	0	4 (2%)	1 (<1%)	0	1 (<1%)
Lymphocyte count decreased	0	5 (2%)	0	0	2 (1%)	0	0	0
Abnormal hepatic function	2 (1%)	0	0	0	3 (1%)	4 (2%)	0	0

Reprinted from The Lancet, 18. number 11, Yi-Long Wu et al., Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial, Pages No.1454-1466, Copyright (2017), with permission from Elsevier.

6.4 Ongoing Trials

No ongoing clinical trials investigating dacomitinib as a first line met the eligibility criteria of this review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question/assessment was identified during development of the review protocol as relevant to the pCODR review of dacomitinib for NSCLC:

- Critical appraisal of the manufacturer-submitter network meta-analysis of RCTs to examine the comparative clinical efficacy of dacomitinib versus its relevant TKI comparators (afatinib, erlotinib, gefitinib, osimertinib, and erlotinib in combination with bevacizumab) for the first-line treatment of EGFR mutation positive NSCLC.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of Network Meta-Analysis

7.1.1 Objective

The assessment of the network meta-analysis is included as it is relevant to the economic evaluation. The NMA was used to compare similar treatments for the economic evaluation that was conducted, as there are no available direct comparisons of dacomitinib to other EGFR TKI drugs (except gefitinib, described in RCT in Section 6). Similar treatments to dacomitinib for the treatment of NSCLC include afatinib, erlotinib, gefitinib and osimertinib. These comparison treatments were included in the NMA, along with cisplatin+pemetrexed.

7.1.2 Findings

The Submitter aimed to assess the relative efficacy of EGFR TKI's by conducting a systematic literature review (SLR) and network meta-analysis (NMA) in order to inform an economic model regarding the use of dacomitinib as a first line treatment for NSCLC. Both the SLR and NMA focuses only on TKI monotherapies (with the exception of erlotinib in combination with bevacizumab), patients with the EGFR mutation and treats chemotherapy as individual treatment.

Methods:

A detailed systematic review was provided by the submitter. The SLR was conducted in order to identify potential studies that would be included in the NMA. A NMA feasibility assessment was performed to identify feasibility of performing and NMA among identified trials based on similarity of study, patient, and intervention characteristics and outcomes. A base case network (BC) was used to assess efficacy of dacomitinib with other first line TKI therapies, along with 2 sensitivity analysis networks. Additionally, subgroup analysis was performed defined by ethnicity (Asian and non-Asian), and presence of EGFR mutations (deletion 19 and L858R mutations).

A total of 15 RCT's met the inclusion criteria for the SLR. Five of these trials were used to develop the BC, with the remaining trials used for the sensitivity analysis networks. The BC network meta-analysis consisted of 5 RCT's that met the inclusion criteria. This allowed for the direct comparison of the outcomes between dacomitinib to gefitinib, and the indirect comparison of dacomitinib to cisplatin+pemetrexed, afatinib, erlotinib or osimertinib. The NMA found that overall, dacomitinib had a consistent trend (Credible Interval's were wide and included the null value of 1.0) towards improved OS and PFS compared to TKIs (afatinib, gefitinib and erlotinib.

Figure 7.1 Base Case Network diagram. This network included five trials: ARCHER 1050, ENSURE, LUX-Lung 6, LUX-Lung 7 and FLAURA[1,12,23,34,35].

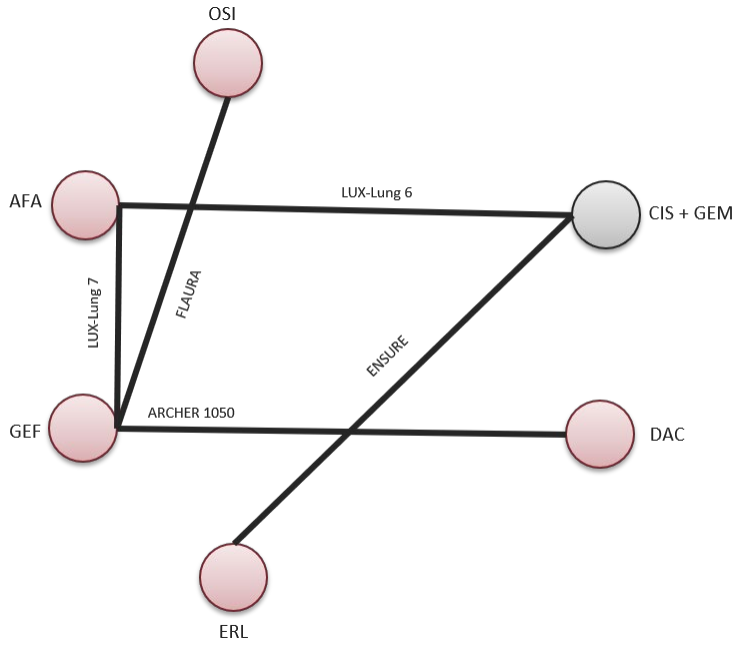
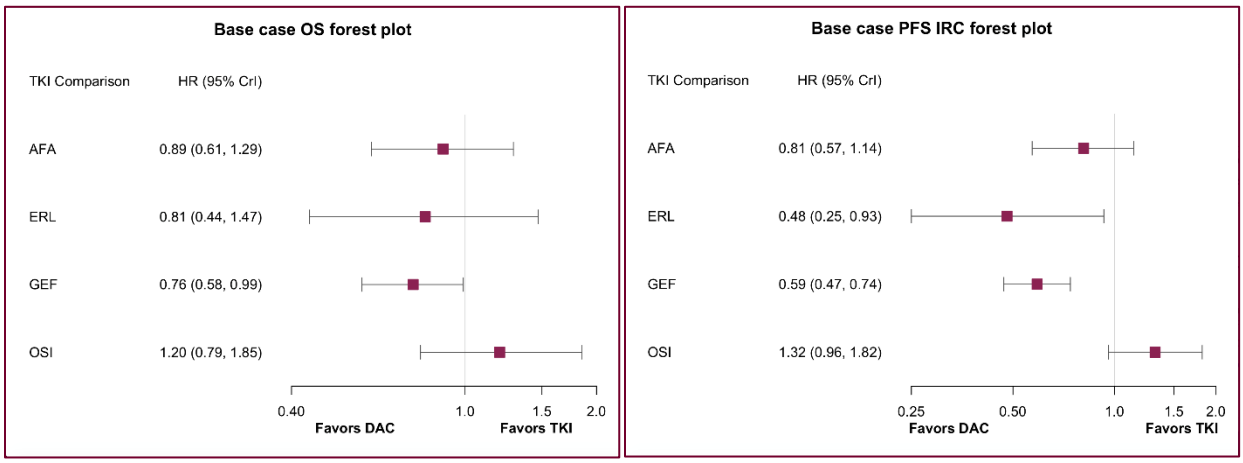


Figure 7.2. Forest plot of OS (left) and PFS (IRC; right) hazard ratios and 95% CrIs for DAC versus each TKI in the BC network.



7.1.3 Summary

The submitted network meta-analysis was conducted appropriately. Although an extensive search of the literature was conducted in the systematic review phase, the limited research available did not identify any closed-loops of evidence. Therefore, comparisons between dacomitinib and other agents can only be made with increasingly indirect comparisons. This results in increasingly wide credible intervals, and reduces certainty in these comparisons. Without closed loops in the network of identified evidence, no assessment of consistency could be made. The sparse evidence network also means that the impact of central nervous system metastases present in some participants in some

trials at enrollment could not be fully explored. Given that the presence of these metastases was an exclusion criteria in the ARCHER 1050 trial, this may impact the validity of comparisons between dacomitinib and other agents. Additionally, the only outcomes included in the NMA were progression-free survival and overall survival.

Given the limitations in the evidence, and the requirement that dacomitinib is compared to gefitinib, afatinib, erlotinib, and osimertinib, the submitted NMA is appropriate.

Table 6.8 ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	Yes.
2. Are any critical interventions missing?	No.
3. Are any relevant outcomes missing?	Yes. NMA only includes Progression-free survival and Overall survival determined by IRC or investigator assessment (which ever was available). Other quantitative outcomes not included in NMA are duration of follow-up, objective response, quality of life toxicity results. The data for these outcomes were extracted in Archer 1050, LUX-Lung 6, LUX-Lung 7, ENSURE and FLAURA trials for the systematic review.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes. Search strategy included RCT's (as well as systematic reviews of RCT's and meta-analysis of systematic literature review of RCT's). Multiple data bases were searched: Medline, Embase, Cochrane, Econ Lit and Bibliography screening.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes.
7. Is it apparent that poor quality studies were included thereby leading to bias?	No. Quality appraisal was conducted for included RCT trials.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	No. Both OS and PFS were reported in 5 trials included for base case network
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Yes. Only 3 of the 5 trials report data for non-Asian subgroups, and differences in baseline characteristics exist between trials for percentage of males, as well as ECOG scores. Follow-up times were discordant across trials. In the LUX-Lung 7 trial and the FLAURA trial, there were participants with brain metastases. In the ARCHER 1050 trial, the presence of brain metastases was an exclusion criteria. In the ENSURE trial, no participants had brain metastases. And the proportion of participants with brain metastases in the LUX-Lung 6 trial was not reported.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Subgroup analyses were conducted between populations defined by ethnicity (Asian vs. non-Asian) and by EGFR mutation to establish if these were effect modifiers. Differences in the presence of brain metastases in trial participants were not addressed.
Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Yes.
If both direct and indirect comparisons are available for pairwise contrasts (i.e.	Not applicable. There are no closed-loops

Table 6.8 ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†	
ISPOR Questions	**Details and Comments‡**
closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	
In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable
With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	Subgroup analyses were conducted between populations defined by ethnicity (Asian vs. non-Asian) and by EGFR mutation to establish if these were effect modifiers. Differences in the presence of brain metastases in trial participants were not addressed.
Was a valid rationale provided for the use of random effects or fixed effect models?	Yes. Both random-effects and fixed models were run; however, it was decided to only report fixed effects model since there was only one trial per comparison.
If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable
If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Not applicable
Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes.
Are the individual study results reported?	Yes.
Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Yes; however it should be noted that there were no closed-loops as none of the included trials presented the same pairwise comparison as another. Therefore, comparisons between some interventions can only be made with increasingly indirect comparisons.
Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes.
Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes.
Is the impact of important patient characteristics on treatment effects reported?	Yes.
Are the conclusions fair and balanced?	Yes.
Were there any potential conflicts of interest?	Yes. The NMA was funded by the submitter.
If yes, were steps taken to address these?	Unclear
† Jansen et al. Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report. ‡Bolded comments are considered a weakness of the ITC.	

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lung Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on dacomitinib for NSCLC. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH 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 Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Lung Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

Literature Search Methods

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials August 2018, Embase 1974 to 2018 September 24, Ovid MEDLINE(R) ALL 1946 to September 24, 2018

#	Searches	Results
1	(dacomitinib* or Vizimpro* or PF-00299804-03 or PF-00299804 or pf00299804 or pf 299804 or pf299804 or pf 299 or pf299 or 5092U85G58 or 2XJX250C20).ti,ab,ot,kf,kw,hw,rn,nm.	1163
2	1 use medall	165
3	1 use cctr	64
4	2 or 3	229
5	*dacomitinib/	186
6	(dacomitinib* or Vizimpro* or PF-00299804-03 or PF-00299804 or pf00299804 or pf 299804 or pf299804 or pf 299 or pf299).ti,ab,kw,dq.	618
7	5 or 6	633
8	7 use oemezd	420
9	8 not conference abstract.pt.	208
10	4 or 9	437
11	remove duplicates from 10	269
12	8 and conference abstract.pt.	212
13	limit 12 to yr="2013 -Current"	147
14	11 or 13	416
15	limit 14 to english language	399

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#3	Search #1 AND #2	3
#2	Search publisher [sb]	529665
#1	Search "PF 00299804" [Supplementary Concept] OR dacomitinib* [tiab] OR Vizimpro* [tiab] OR PF-00299804 [tiab] OR PF-00299804-03 [tiab] OR pf00299804[tiab] OR pf	186

Search	Query	Items found
	299804[tiab] OR pf299804[tiab] OR pf 299[tiab] OR pf299[tiab] OR 5092U85G58[rn] OR 2XJX250C20[rn]	

3. Cochrane Central Register of Controlled Trials (Central)
   Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Vizimpro/dacomitinib

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Vizimpro/dacomitinib, non-small cell lung cancer (NSCLC)

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

ESMO
https://oncologypro.esmo.org/Meeting-Resources

Search: Vizimpro/dacomitinib - last 5 years

Detailed Methododolgy

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (Aug 2018) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was dacomitinib.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of March 7, 2019.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health - clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Table A4: Sign-50 Quality Assessment

Section 1: Internal validity ARCHER 1050		
1.1	The study addresses an appropriate and clearly focused question.	Yes ✓ No ☐ Can't say ☐
1.2	The assignment of subjects to treatment groups is randomised.	Yes ✓ No ☐ Can't say ☐
1.3	*An adequate concealment method is used.*	Yes ☐ No ✓ Can't say ☐

1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	Yes ☐ No ✓ Can't say ☐
1.5	The treatment and control groups are similar at the start of the trial.	Yes ✓ No ☐ Can't say ☐
1.6	The only difference between groups is the treatment under investigation.	Yes ✓ No ☐ Can't say ☐
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes ✓ No ☐ Can't say ☐
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	70.9% - dacomitinib 83.1% - gefitinib
1.9	*All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).*	Yes ✓ No ☐ Can't say ☐ Does not apply ☐
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Yes ☐ No ☐ Can't say ✓ Does not apply ☐

SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	*How well was the study done to minimise bias?*	High quality (++) ✓ Acceptable (+) Low quality (-) Unacceptable – reject 0
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Yes
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes

Source: Methodology checklist 2: controlled trials. Edinburgh (GB): Scottish Intercollegiate Guidelines Network (SIGN); 2018: https://www.sign.ac.uk/assets/checklist_for_controlled_trials.doc. Accessed 2018 Oct 30.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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