pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Osimertinib (Tagrisso) for Non-Small Cell Lung Cancer

January 4, 2019

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

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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 osimertinib (Tagrisso) for non-small cell lung cancer. 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 osimertinib (Tagrisso) for non-small cell lung cancer 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 osimertinib (Tagrisso) for non-small cell lung cancer, a summary of submitted Provincial Advisory Group Input on osimertinib (Tagrisso) for non-small cell lung cancer, and a summary of submitted Registered Clinician Input on osimertinib (Tagrisso) for non-small cell lung cancer, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of osimertinib for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations. The appropriate comparators for osimertinib are erlotinib, gefitinib or afatinib.

Osimertinib has a Health Canada approval for the first-line treatment of patients with locally advanced (not amenable to curative therapies), or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (either alone or in combination with other EGFR mutations).

Osimertinib is an oral, potent, and selective tyrosine kinase inhibitor (TKI) which irreversibly binds both EGFR sensitizing mutations (EGFRm) and T790 resistance mutation (T790M) but has limited activity against wild-type EGFR. The recommended dose for osimertinib is 80mg per day until disease progression or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence[1,2]

One randomized controlled trial, FLAURA, was identified that the met eligibility criteria of this review. FLAURA was a phase III, randomized (1:1 ratio), double blind, intervention-control trial that compared osimertinib to standard-EGFR TKI (gefitinib or erlotinib) in patients with previously untreated EGFR mutation–positive (exon 19 deletion [Ex19del] or L858R) advanced NSCLC. The primary objective was to assess the efficacy of osimertinib compared with standard EGFR-TKI as measured by progression-free survival (investigator-assessed). FLAURA was funded by AstraZeneca and designed by the principal investigators and AstraZeneca.

Patients enrolled in FLAURA met the following key criteria:

- Male or female, aged at least 18 years (with the exception of Japan, at least 20 years);

- Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy;
- The tumour harbours one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations; and
- World Health Organization Performance Status of 0 to 1.

The FLAURA trial is ongoing, and data related to the primary PFS analysis and secondary endpoints (including interim OS analysis) have been published using a data cut-off of June 12, 2017. Of note, only one analysis of the primary endpoint (PFS) was planned (approximately 359 events of progression or death in a total of 530 randomly assigned patients, which would provide at least 90% power to detect a hazard ratio of 0.71 at a two-sided alpha level of 5%).

At the time of the analysis, 71 (26%) of patients on the standard therapy group had not yet progressed or died.

Of the patients that discontinued study treatment (n=138, n=213 respectively), 82 patients in the osimertinib group and 129 patients in the standard EGFR-TKI group received second line treatment, which included: EGFR-TKI, PD-1/PD-L1, non-platinum chemotherapy, platinum-based chemotherapy, other targeted therapy, or anti-VEGF. Some patients also received third line treatment in the form of EGFR-TKI, PD-1/PD-L1, non-platinum chemotherapy, other targeted therapy, or anti-VEGF. A total of 29 patients received EGFR-TKIs as subsequent therapy post osimertinib. Of note, 55 patients (out of 277) in the standard EGFR-TKI group received osimertinib: 48 patients received osimertinib on crossover (17%) and 7 (3%) patients received osimertinib outside of the trial as second-line treatment. It is important to mention that crossover (which was permitted in the trial - after disease progression) did not impact the primary endpoint, PFS, because patients crossed over after disease progression.

Overall, the FLAURA trial was well-conducted. The randomization procedure, method of allocation concealment, and double-blind design were carried out appropriately. The treatment groups were well balanced. There was transparent reporting of the disposition of patients through the trial, and outcome analyses were performed according to the intent-to-treat principle. The statistical analysis plan (SAP) of the trial specified the number of efficacy analyses to be performed on the primary outcome and the key secondary outcome, and used a hierarchical statistical testing strategy to adjust for multiplicity in testing the primary outcome (PFS) and key secondary outcomes (OS and CNS PFS). Sensitivity analyses related to the primary outcome were performed to account for ascertainment bias, evaluation-time bias, and attrition bias and were consistent with the primary PFS analysis.

However, the following limitations should be considered when interpreting the results:

- Given that the interim OS analysis results were immature at the time of the data cut-off and did not reach formal statistical significance for the interim analysis, OS data should be interpreted with caution.
- As well, because of the hierarchical statistical testing strategy, CNS PFS could not be formally tested for statistical significance and the P value for the statistical analyses was then classed as nominally significant and therefore, reported results related to CNS PFS should be interpreted with caution.
- The quality of life (QoL) results were only available in poster form and have not been fully peer-reviewed. The assessment of patient-reported QoL is limited as currently presented and may not fully capture the QoL experience of all patients in the trial. Furthermore, QOL was not considered in the hierarchical statistical testing strategy and should therefore be considered exploratory. As a result, QoL data should be interpreted with caution.

- Lastly, the exclusion of afatinib from the comparator group is a study limitation. Although the publication noted that at the time of the trial initiation, afatinib was not widely used nor was it made available as a global standard-of-care EGFR-TKI.

A summary of key results can be found in *Table 1.1 Highlights of Key Outcomes*.

Table 1.1: Highlights of Key Outcomes

	FLAURA	
	Osimertinib (n=279)	Standard EGFR-TKI (n=277)
Analysis	Final primary analysis (PFS), interim OS analysis	
Data cute-off date	June 12, 2017	
Median follow-up in months (range)	15.0 (0-25.1)	9.7 (0-26.1)
Patients remaining on treatment, n (%)	141(51)	64(23)
Primary Outcome - PFS by investigator assessment		
PFS events, total patients (%)	136(49)	206(74)
Median PFS, months (95% CI)	18.9(15.2-21.4)	10.2 (9.6 -11.1)
HR (95% CI, p-value)	0.46 (0.37-0.57) *P*<0. 001	
Sensitivity Analysis - PFS by blinded independent central review		
PFS events, total patients (%)	137(49)	198(71)
Median PFS, months (95% CI)	17.7(15.1- 21.4)	9.7(8.5-11.0)
HR (95% CI, p-value)	0.45 (0.36-0.57) *P*<0.001	
Key Secondary Outcomes		
Secondary outcome - OS		
No. OS events, total patients(%)	58(21)	83(30)
Median OS, months (95% CI)	NC (NC)	NC (NC)
HR (95% CI, p-value)	0.63 (0.45-0.88) *P*=0.007†	
Secondary outcome - HRQoL		
• Key symptoms (dyspnoea, chest pain, fatigue and appetite loss) improved from baseline until randomized treatment discontinuation, but of these only cough in the osimertinib group was clinically relevant (i.e., decrease of 10.14, which favours osimertinib). There were no significant differences (i.e., P <0.05) between treatment groups, with the exception of chest pain where the estimated treatment difference (osimertinib minus standard care EGFR-TRI) was -2.96 (95% CI: -5.47-0.47), P= 0.021 (adjusted mean chest pain scores for the osimertinib were -2.96 lower than the comparator group) (recall: a higher score on the symptom scale representing an increased level of symptomatology/problems). • The proportion of patients with clinically relevant improvements at any time until randomized treatment discontinuation was similar for the key symptoms in both treatment groups. • In terms of mean changes from baseline in global health and functioning, there were no clinically meaningful improvements in QLQ-C30 Global health status, Physical functioning, Role functioning, Emotional functioning, Cognitive functioning and Social functioning. • With regard to time to deterioration of key lung cancer symptoms, the median time from randomization to the first recorded clinically relevant deterioration of key lung cancer symptoms was similar between the two treatment groups.		
Harms Outcome, n (%)	**Osimertinib (n=279)**	**Standard EGFR-TKI (n=277)**
Adverse Events (any grade)	273(98)	271(98)
Grade ≥3 Adverse Events	95(34)	124(45)
Serious Adverse Events	60(22)	70(25)
Withdrawal Due to Adverse Event	36(13)	50(18)
Fatal Adverse Events	6(2) ‡	10(4) ‡
CI=confidence interval; HR=hazard ratio; EORTC=European Organisation for Research and Treatment of Cancer; HRQoL=health-related quality of life; NC=could not be calculated; OS=overall survival; PFS=progression-free survival; QLQ-C=Quality of Life Questionnaire- Cancer; QLQ-LC=Quality of Life Questionnaire-Lung Cancer *HR < 1 favours osimertinib † Not statistically significant. A *P* value of less than 0.0015 was required for statistical significance in the interim analysis of overall survival.		

	FLAURA
‡Osimertinib group: pneumonia, respiratory, tract infection, cerebral infarction, myocardial infarction, pulmonary embolism, and intestinal ischemia in 1 patient each; and standard EGFR-TKI group: sepsis in 2 patients; pneumonia in 1; endocarditis in 1; cognitive disorder and pneumonia in 1; peripheral-artery occlusion in 1; dyspnea in 1; hemoptysis in 1; diarrhea, gastrointestinal hemorrhage, respiratory failure, and circulatory collapse in 1; and "death" [the adverse event was not further specified] in 1. ¯A difference in score of at least 10 points was considered clinically relevant, corresponds to a moderate or greater change in patient reported quality of life. Key symptoms (cough, dyspnoea, chest pain, fatigue and appetite loss; defined as a decrease in score from baseline of ≥ 10 at two consecutive assessments ≥ 21 days apart) and time to symptom deterioration (defined as time from randomization until the date of the first clinically relevant symptom deterioration or death from any cause).	

Sources[1-5]

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

Lung Cancer Canada (LCC) highlighted the great physical and emotional burden lung cancer patients face compared to other cancers; lung cancer patients experience high symptom burden, the most common of which was reported to be fatigue. Fatigue was reported to be a very debilitating symptom of lung cancer, greatly interfering with patient's daily activities and quality of life. LCC commented on stigma that is specifically associated with patients of lung cancer and their families. For example, quotes provided by LCC indicate that caregivers feel the need to advocate for their loved one's condition to others.

Brain metastasis was mentioned to be a factor greatly impacting a lung cancer patient's prognosis. While LCC did not have specific patient input regarding brain metastasis and osimertinib, they did provide data from a previous submission on alectinib for ALK positive patients and mentioned that no evidence was available to suggest that symptoms related to treatment for brain metastasis would differ between patients with different types of lung cancer. Patients reported feelings of fear and anxiety surrounding treatments for brain metastasis, such as radiation, due to the potentially permanent side effects.

Patient's responses to osimertinib were positive; patients commented on the effectiveness of osimertinib and the speed by which they showed signs of improvement. Patients commented on the significant reduction of their tumour, some even showing signs of reduction after their first scan. LCC indicated that use of osimertinib in the second-line setting showed favourable responses. Patients reported managing side effects such as fatigue and change in appetite with naps, or consumption of smaller meals and varying the types of foods eaten. Overall, the symptoms from osimertinib were manageable, and osimertinib allowed patient's to continue to enjoy life activities, and adopt a sense of hope.

Please see Section 3 below for more details.

Provincial Advisory Group (PAG) Input

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 immunotherapies.

Economic factors:

- High drug cost and flat pricing of tablets

Please see Section 4 below for more details.

Registered Clinician Input

Clinicians providing input reported that osimertinib was superior to current first line standard of care gefitinib and erlotinib in the FLAURA trial in terms of PFS, duration of response and initial survival data, and also showed improvements in efficacy over afatinib. It was also noted that safety and tolerability were comparable to other first line options. One additional benefit noted was the efficacy of osimertinib in patients with brain metastases. Clinicians noted that having osimertinib available to patients may prevent some patients from undergoing brain radiotherapy, which can poorly affect quality of life. In terms of sequencing, clinicians indicated that osimertinib would replace gefitinib, erlotinib and afatinib as the first line treatment option, specifically for the patient population with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. It was noted that in patients with less common EGFR mutations, clinicians may still want to use the other first line treatment options. It was also noted by some clinicians that if osimertinib was given in the first line, it is not clear how subsequent treatment with tyrosine kinase inhibitors (TKIs) would affect the patient. In another clinician input, it was stated that treatment with osimertinib should be followed by chemotherapy with platinum and pemetrexed chemotherapy. The clinicians providing input reported that EGFR mutation testing is a standard of care upon diagnosis and that no additional diagnostic testing is required.

Please see Section 5 below for more details.

Summary of Supplemental Questions[6-8]

The objective of the supplemental question/assessment was to summarize and critically appraise the methods and findings of a manufacturer-submitted indirect treatment comparison (ITC) of osimertinib versus afatinib for advanced/metastatic EGFR mutation-positive NSCLC patients.

In an ITC, a common comparator is required to form a link between the treatments of interest. The FLAURA trial compares osimertinib to standard EGFR-TKI (erlotinib or gefitinib), therefore, the common comparator used in the ITC was standard EGFR-TKI. However, the relative effect of osimertinib was only found compared to erlotinib and gefitinib combined; in other words, separate results (osimertinib versus erlotinib and osimertinib versus gefitinib) were not reported nor pre-specified in the study's analysis plan. As a result, a fundamental assumption of the ITC was that gefitinib and erlotinib are equivalent in efficacy and with this assumption, the common comparator used in the ITC became standard EGFR-TKI (erlotinib and/or gefitinib). As such, in this ITC, the network of evidence consisted of the FLAURA trial (osimertinib versus standard EGFR-TKI [erlotinib or gefitinib]) and the LUX-Lung 7 trial (afatinib versus gefitinib).

According to the submitter, the results of the ITC suggest that osimertinib improved both PFS and OS compared to afatinib in the overall population (patients with EFGR mutation positive NSCLC receiving treatment at first line) and for each subgroup (CNS metastases, EGFR mutation type and ethnicity). Overall, there is moderate uncertainty in the reported ITC results. The following considerations should be taken into account when interpreting the results of the ITC:

- A fundamental assumption of the ITC was that erlotinib is of equivalent efficacy to gefitinib. According to the CGP, it was a reasonable assumption that erlotinib and gefitinib are of equivalent efficacy in the EFGR mutation setting, however erlotinib is considered to be more toxic than gefitinib.
- More transparent reporting would have been helpful; as many details related to the Methods of the Indirect Comparison were lacking (See Section 7.1.3 for details). Missing details related to the methodology of the ITC made it difficult to perform a comprehensive assessment of the ITC. More transparent reporting and better adherence to the best practice for the conduct of ITC would have been appreciated to fully critically appraise the ITC and may have reduced uncertainty.
- It was appropriate to use the Bucher method.
- The ITC considered the following relevant outcomes: OS and PFS but not health related quality of life (HRQoL). However, the purpose of the ITC was to inform the cost-effectiveness analysis and therefore, HRQoL is relevant outcome that was not considered in the ITC.
- There was a systematic difference in the reporting of disease stage (a treatment effect modifier) across the different treatment comparison in the network; there were more patients with advanced stage NSCLC in the LUX-Lung 7 trial compared to the FLAURA trial (96.6% versus 82% with Stage IV NSCLC). The ITC report noted this systematic difference and explained that results for this subgroup (disease stage) was not presented and therefore could not be investigated further.
- As well, the submitter noted that treatment switch is a source of trial heterogeneity and addressed that treatment switching in both studies was relatively low, but that in the absence of adjusted results, treatment switching may be a limitation of the ITC.
- The ITC was prepared for AstraZeneca. This ITC is not published and as a result, has not been fully peer-reviewed.
- CGP acknowledged the ARCHER 1050 trial of dacomitinib versus gefitinib could have contributed to the ITC but understand that dacomitinib is still in the pipeline for approval

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 Section 6.

Table 1.2: Assessment of generalizability of evidence for osimertinib (first-line NSCLC)

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	WHO performance status	Patients with a WHO performance status of 2 or greater were excluded from the FLAURA trial WHO 0: n=228/556 (41%) WHO 1: 327/556 (59%) Missing data: n=1/556 (<1%)	Do the trial results apply to patients with a WHO performance status of 2 or greater? If so, why?	While the study included only patients with performance status (PS) 0-1, the results would be generalized to include PS 2 patients as well, in keeping with the current use of first-line EGFR TKI. This in keeping with the current use of first line EGFR TKI. There is a higher likelihood of response to an EGFR TKI than chemotherapy and a more favourable safety profile, further justifying the use of osimertinib in ECOG 2 patients.
	EFGR mutations	The funding request is for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations. The FLAURA trial included patients with Exon 19 deletion or 21 substitution mutations either alone or in combination with other EGFR mutations.	Do the trial results apply to patients that do not have Exon 19 deletion or 21 substitution mutations, but have other EGFR mutations?	No. However, with patients that have baseline T790M, the results may apply, but it is expected that these patients would also have exon 19 deletion or/and 21 substitution.
	Locally advanced NSCLC	Patient with locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy were included in the trial. 95% of patients had metastatic NSCLC, 5% of patients had locally advanced NSCLC.	Do the trial results apply to patients with locally advanced NSCLC?	The CGP agree that the results of the FLAURA trial should apply to any patient with locally advanced disease not amenable to radical or curative treatment approaches
	Age	The ages of patients in the osimertinib group were between 26 and 85, whereas the ages of patients in the standard EGFR-TKI group were between 35 and 93. However, the median age was the same in both groups (64 years old).	Are the baseline characteristics of the trial similar to what we would expect in the Canada?	The CGP confirmed that baseline characteristics are similar to those expected in Canada (e.g. smoking status, performance status), with the exception of fewer Asian patients than in the FLAURA trial.
Intervention		If dose reductions were needed, patients with a starting dose of 80mg osimertinib had a reduced dose of 40mg osimertinib; patients with a starting dose of 150 mg of erlotinib had a reduced dose of 100 mg of erlotinib; and no dose reduction was allowed for patients receiving gefitinib because the starting dose of 250 mg was the lowest dose available.	Is this typically the dose modification practice in Canada?	The CGP noted that dose reduction of gefitinib was not allowed in the trial, as there is only one pill size. In clinical practice though, clinicians may choose to change the dose schedule in order to achieve a dose reduction ie dose patients on two out of every three days, or every second day

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Comparator	Afatinib	The FLAURA trial compared osimertinib to standard EGFR-TKI (gefitinib or erlotinib). Afatinib was not a standard EGFR-TKI included in the comparator group. In an unpublished indirect treatment comparison, the Submitter concluded that afatinib and gefitinib are of equivalent efficacy.	Are afatinib and gefitinib of similar efficacy?	While limitations exist in the use of network meta-analysis, an indirect comparison, it is the opinion of he CGP that afatinib and gefitinib are of similar efficacy but that afatinib has greater toxicity.
Outcomes	Short-term survival data	Overall survival data were immature at the interim OS analysis (data cut-off June 19, 2017). The median survival for each group could not be calculated since data were 25% mature at the time of the data cut-off. The hazard ratio for death was 0.63 (95% CI, 0.45-0.88), *P*=0.007 and not considered statistically significant.	Is the overall survival data reflective of longer term survival?	While OS data are immature, the available data suggest that first-line therapy with osimertinib may improve overall survival. As the results are not yet considered statistically significant based on the trial statistical plan, further follow up of these data are needed to provide more certainty.
Setting	Trial centres	The trial (n=556) was conducted in 132 sites in 29 countries, including Canada. Notably, the majority of patients in the FLAURA trial (62%) were recruited from Asian countries (China, Japan and other Asian) In an abstract by Cho et al., a total of 322 Asian patients were enrolled in Asian sites (Chinese n=46, Japanese n=120, and other Asian n=156).	Do the trial results apply to patients from Canadian centres? Are different treatment practices expected in Asian countries which may impact the generalizability of the overall trial results in Canada?	The CGP note that EGFR mutations occur almost twice as frequently in Asian populations than in Canadian patients. This would explain the large proportion of Asian patients in the FLAURA trial. However, the approach to the treatment of patients with EGFR mutated NSCLC does not differ according to ethnicity and the results of FLAURA are generalizable to the Canadian population.
Abbreviations: CGP=clinical guidance panel; CI=confidence interval; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; OS=overall survival; TKI=tyrosine kinase inhibitor; WHO=World Health Organization				

Sources[1,9,10]

1.2.4 Interpretation

Burden of Illness and Need

Identification of molecular abnormalities driving the development and growth of NSCLC has drastically changed the approach to the diagnosis and treatment of advanced and metastatic NSCLC.[11] Molecular profiling has become the standard of care in patients with non-squamous NSCLC. Molecularly defined subgroups of non-squamous NSCLC, such as tumors with activating mutations of the *EGFR* gene, or translocations of the *ALK* and *ROS1* genes, are now preferentially treated with oral tyrosine kinase inhibitors (TKIs) targeting the respective molecular abnormality. These targeted therapies are associated with improved efficacy (higher ORR, longer PFS) and better tolerability than platinum-based chemotherapy that would otherwise be the standard of care. Multiple trials have also consistently demonstrated Improvements in quality of life favouring the targeted therapies.

Mutations of the *EGFR* gene represent the most common targetable molecular abnormality in patients with NSCLC. The estimated frequency among Canadian patients with NSCLC tumors containing *EGFR* mutations is approximately 17%.[12] First-line therapy with either the first generation EGFR TKIs gefitinib,[13-16] or erlotinib,[17,18] or the second generation TKI afatinib,[19,20] have been the standard of care for the last decade. However, resistance to first and second generation EGFR TKIs emerges in the majority of patients. The most frequent mechanism of resistance, occurring in 50-60% of patients, is the development of a T790M resistance mutation.[21]

Osimertinib, a third generation EGFR TKI, has activity against both the sensitizing and T790M resistance mutations. Initial development of osimertinib was undertaken in patients who developed a T790M mutation on first or second generation EGFR TKIs.[22] Subsequently, the AURA 3 trial compared osimertinib with cisplatin and pemetrexed chemotherapy, in patients with NSCLC known to have developed a T790M mutation.[23] Higher ORR, longer PFS and improvements key lung cancer symptoms including appetite loss, cough, shortness of breath, dyspnea and fatigue were observed in patients randomized to osimertinib. Significantly improved efficacy was also observed in patients with central nervous system metastases randomized to osimertinib.

Effectiveness

Given the observed efficacy of osimertinib against both sensitizing and resistance *EGFR* mutations, the FLAURA trial evaluated osimertinib in the first-line setting. Patients (n=556) with advanced NSCLC with common *EGFR* mutations (exon 19 del and L858R), were randomized to standard first generation EGFR TKI (gefitinib 250mg or erlotinib150mg daily) versus osimertinib 80mg daily. These are appropriate standard options which are reflective of international practice. The primary outcome, PFS, was significantly improved for patients randomized to osimertinib versus standard EGFR TKI (median PFS 18.9m vs 10.2m, HR 0.46 (95%CI 0.37-0.57). Overall survival data were immature, but favoured patients randomized to osimertinib (median OS not reached in either group, HR 0.63, 95%CI 0.45-0.88). The CGP noted that a high benchmark was placed for significance in OS at the interim analysis. No significant differences were observed in ORR (80% vs 75%, p=0.24), although the median duration of response was much longer for patients randomized to osimertinib (17.2m vs 8.5m). No significant changes in QoL scores (EORTC QLQ30) were observed from baseline to treatment discontinuation. Similarly, there were no clinically meaningful differences between groups, in lung cancer symptom scores from baseline to treatment discontinuation, with the exception of cough (favouring osimertinib). The improvement in PFS was observed across all baseline variables examined including sex,

age, race, smoking history, presence of CNS metastases at baseline, performance status, and type of *EGFR* mutation.

Safety
The most common adverse events observed in the FLAURA trial were rash, diarrhea, dry skin, paronychia, stomatitis and decreased appetite. Patients randomized to standard EGFR TKI experienced more diarrhea, more elevation of liver enzymes (ALT and AST), whereas more QT prolongation was observed in patients randomized to osimertinib. The incidence of serious adverse events was similar between the two groups. More patients in the standard EGFR TKI arm withdrew from treatment because of adverse events (18%vs 13%)

Other Considerations
FLAURA was generally a well conducted randomized clinical trial, without major methodological issues. The primary analysis for PFS was conducted with slightly fewer events than planned for in the sample size. However, the effect size was much larger than anticipated. Therefore, the results support the use of osimertinib over gefitinib or erlotinib for patients with advanced NSCLC containing either exon 19 del or L858R *EGFR* mutations. While the study included only patients with performance status (PS) 0-1, the results would be generalized to include PS 2 patients as well, in keeping with the current use of first-line EGFR TKI. The challenge though, in interpretation of the FLAURA data, reflects the choice of the standard therapy arm. Afatinib, a second generation EGFR TKI, is another choice of first-line therapy for *EGFR* mutated NSCLC in Canada. The Lux-Lung 7 trial demonstrated that afatinib was marginally more effective than gefitinib.[14] The results of a network meta-analysis provided by the Submitter suggest that osimertinib is more effective than afatinib (PFS HR 0.59, 95%CI 0.43-0.83; OS HR 0.73, 95%CI 0.48-1.12); however, the results should be interpreted with caution given the methodologic limitations. While dacomitinib is currently not licensed in Canada, results of an RCT comparing dacomitinib and gefitinib (ARCHER1050) demonstrated improved PFS and for patients treated with dacomitinib versus gefitinib.[41] Available data do not allow for comparison of osimertinib with dacomitinib, although this agent is currently not in use in Canada.

Advanced and metastatic NSCLC represents a major population health problem in Canada. Despite the fact that *EGFR* mutated NSCLC represents only 17% of NSCLC cases, this still represents approximately 1800-2000 cases annually. Improving the outcome of treatment for these patients remains a priority for clinicians. Input from clinicians, as well as patient advocacy group (LCC) identify that osimertinib represents a more effective treatment option for *EGFR* mutated NSCLC. While treatment options exist already for this group of patients, osimertinib offers improved efficacy over gefitinib and erlotinib, as well as afatinib through indirect comparison. The use of first-line osimertinib would eliminate the need for repeat biopsies (liquid or solid) and T790M mutation testing in patients progressing on standard first-line EGFR TKI. The Clinical Guidance Panel agrees that osimertinib should be considered as first-line therapy for advanced and metastatic NSCLC with exon 19 del and L858R *EGFR* mutations, PS 0-2.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit from osimertinib as first-line therapy in advanced / metastatic NSCLC patients with tumors containing common *EGFR* mutations (exon 19 del, L858R). This is based on a substantial improvement in PFS with

osimertinib compared to gefitinib or erlotinib (median PFS 18.9m vs 10.2m, HR 0.46 (95%CI 0.37-0.57).

In making this conclusion the Clinical Guidance Panel also considered that:

- While the results are not yet mature, data from the FLAURA trial also suggest that first-line therapy with osimertinib may improve overall survival and delay the progression of CNS metastases. These results are not yet considered statistically significant based on the trial statistical plan and further follow up of these data are needed to provide more certainty to these conclusions.
- The results of a network meta-analysis provided by the Submitter suggest that osimertinib is more effective than afatinib; however, the results should be interpreted with caution given the methodologic limitations. Both osimertinib and standard EGFR TKI have favourable toxicity profiles in comparison to platinum-based chemotherapy.
- While there are no clear contraindications to osimertinib therapy, caution should be exercised in patients with known QTC prolongation.
- There are no clear quality of life differences between osimertinib and standard EGFR TKI. However, patients randomized to osimertinib had more improvement in cough. The assessment of patient-reported QoL is limited as currently presented and may not fully capture the QoL experience of all patients in the trial.
- Based on the CGP's opinion, for patients who start platinum-based chemotherapy and are subsequently found to have an exon 19 del, or L858R *EGFR* mutation, osimertinib should be considered as first *targeted* therapy for advanced or metastatic NSCLC
- Based on the CGP's opinion, patients currently receiving gefitinib, afatinib, or erlotinib as first-line therapy for advanced/metastatic NSCLC should be allowed to switch over to osimertinib, so long as there has been no progression of their disease
- The FLAURA trial allowed treatment beyond progression and many patients did receive treatment beyond progression. Patients receiving osimertinib, who have evidence of disease progression according to RECIST1.1 criteria, who have evidence of ongoing clinical benefit and have not progressed symptomatically, should be allowed to continue osimertinib. If next scheduled imaging demonstrates further disease progression, then osimertinib should be discontinued.
- Current data do not support therapy with gefitinib, erlotinib or afatinib in patients with disease progression on osimertinib.
- While the FLAURA trial included only patients with performance status (PS) 0-1, the results would be generalized to include PS 2 patients as well, in keeping with the current use of first-line EGFR TKI.
- This therapy is valued highly by clinicians and patients. The CGP note that up to 2000 patients with advanced and metastatic *EGFR* mutated NSCLC could benefit from the implementation of first-line osimertinib therapy.

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

Lung cancer represents the second most common cause of cancer among both men and women in Canada, but the largest cause of death from cancer. In 2016, there were approximately 28,400 new cases of lung cancer and 20,800 deaths from lung cancer.[25] About 85% of these cases would be classified as Non-Small Cell Lung Cancer (NSCLC). Approximately 50% of NSCLC patients have stage IV disease at the time of presentation, with another 25-30% presenting with locally advanced stage III disease.[26] Only 20-25% of patients present with early stage disease amenable to surgical resection. The incidence of NSCLC rises with age and the median age at diagnosis is 70 years. Given the high proportion of patients presenting with advanced stage, it is not surprising that the expected five year survival is only 18%.[25]

Molecular profiling studies have identified a diverse spectrum of molecular alterations (gene mutations, translocations, increased gene copy number and protein overexpression) among NSCLC patients with adenocarcinoma histology (approximately half of NSCLC cases).[11] Oncogenic drivers are identified in as many as 50-60% of patients with adenocarcinoma, of which the most common targetable alterations are activating mutations of the epidermal growth factor receptor (EGFR) gene. These occur in about 17% of western populations and 30-40% of patients of Asian background. Two common mutations, a deletion in exon 19 (exon 19 del), or a point mutation in exon 21 (L858R), account for almost 90% of EGFR gene mutations. A multitude of other mutations, occurring in exons 18-21 of the EGFR gene locus, together form a group of uncommon EGFR mutations.

2.2 Accepted Clinical Practice

The complexity of treatment decision-making in advanced and metastatic NSCLC has increased greatly over the last two decades. Historically, all patients were treated using the same algorithm. First-line therapy consisted of a platinum-doublet with cisplatin or carboplatin in combination with gemcitabine, vinorelbine, paclitaxel, or docetaxel. [27] Maintenance therapy was not routinely recommended and patients well enough to receive further therapy at the time of disease progression would be offered docetaxel,[28] pemetrexed[29] and/ or erlotinib.[30] In the last decade different algorithms have emerged for patients with squamous and non-squamous histologies.[31] Patients with squamous histology are commonly treated with a platinum agent plus gemcitabine, or paclitaxel.[32] Patients with non-squamous histology most commonly are treated with platinum plus pemetrexed,[31] generally followed by maintenance pemetrexed therapy.[33] While data support the combination of carboplatin, paclitaxel plus bevacizumab,[34] this combination has not been widely adopted in Canada because of the high cost of bevacizumab and marginal improvements in efficacy. Nevertheless, available data would suggest that only one in three patients receive systemic therapy and the rate of treatment declines with advancing age.[26,35]

More recent advances in the management of advanced NSCLC have arisen as a result of greater understanding of the molecular growth factors important in lung cancer proliferation. One representative study from the Lung Cancer Mutation Consortium (LCMC) undertook molecular profiling of 1007 lung adenocarcinomas.[11] Oncogenic drivers were found in 64% of cases. Commonly observed gene mutations included *KRAS* (25%), *EGFR*

(17%) and *ALK* (8%). Mutations occurring in 1-2% of patients included *ERBB2*, *BRAF*, *MET*, *NRAS*, *MEK* and *ROS1*. Therapeutic options for several of these oncogenic driver mutations have demonstrated superior efficacy to standard chemotherapies and have dramatically changed the treatment paradigms for advanced NSCLC. Oral targeted therapies directed at the tyrosine kinase domain of the *EGFR*, *ALK* and *ROS1* genes have all shown higher objective response rates (ORR), improved progression free survival (PFS) and improved quality of life compared to standard chemotherapy options and have been incorporated into treatment algorithms. Molecular profiling of lung adenocarcinomas for *EGFR* mutations and *ALK* translocations is now routinely performed at the time of initial lung cancer diagnosis. Molecularly targeted therapies such as gefitinib,[16,36] afatinib,[19,20] crizotinib[37] and alectinib[38] are now the preferred initial therapy in NSCLC patients with these molecular abnormalities.

Mutations of the *EGFR* gene represent the most common targetable molecular abnormality among patients with advanced NSCLC. Multiple randomized clinical trials (RCTs) have been conducted comparing an EGFR TKI with standard platinum-based therapy in patients with tumors known to have an *EGFR* mutation, or with clinical characteristics associated with *EGFR* mutated NSCLC (Table 1). Data from nine RCTs comparing first-line therapy with an EGFR TKI (gefitinib, erlotinib, afatinib, or icotinib) with platinum-based chemotherapy demonstrate consistent findings.[13-20,36,39] Higher ORR was observed in all trials, with significant reductions in the risk of disease progression (HR ranged from 0.16 to 0.61). Quality of life, when measured, favoured patients receiving an EGFR TKI over chemotherapy in all trials. Individually, none of these trials demonstrated significant improvements in overall survival (OS). However, a post hoc combined analysis of the Lux Lung 3 and 6 trials demonstrated significant improvements in OS for patients with exon 19 del mutations randomized to afatinib compared with chemotherapy (Lux Lung 3 HR 0.54, 95%CI 0.36-0.79, Lux Lung 6 HR 0.64, 95%CI 0.44-0.94). No difference in OS was observed for patients with L858R mutations (Lux Lung 3 HR 1.30, 95%CI 0.80-2.11, Lux Lung 6 1.22, 95%CI 0.81-1.83).[40]

Two additional trials compared a second generation EGFR TKI (afatinib, dacomitinib) with a first generation EGFR TKI (gefitinib, erlotinib).[6,41] Both trials demonstrated significant improvements in PFS for a second versus first generation EGFR TKI. Patients randomized to afatinib had a significantly higher ORR and PFS compared with gefitinib, although the absolute improvement in PFS was relatively small. In contrast, the ARCHER1050 trial found that dacomitinib improved both PFS and OS compared with a first generation EGFR TKI.[24]

Despite the high efficacy of EGFR TKIs observed in advanced NSCLC patients with tumors harbouring an *EGFR* mutation, resistance emerges in the majority of patients. The most common mechanism of resistance to first and second generation EGFR TKIs arises from the development of a second mutation in exon 20 (T790M).[21,42] Osimertinib, a third generation EGFR TKI with activity against both sensitizing and T790M resistance mutations, was shown to have high ORR (~60%) in previously treated patients with tumors that developed a T790M mutation.[22] An RCT (AURA 3) of second-line therapy with osimertinib, or cisplatin and pemetrexed, in NSCLC patients known to have developed T790M mutations, demonstrated superior efficacy for second-line osimertinib.[23] Higher ORR (80% vs 76%) and significantly longer (10.1m vs 4.4m, HR 0.30, 95%CI 0.23-0.41) were observed in patients randomized to osimertinib compared with cisplatin and pemetrexed. Osimertinib also demonstrated significantly greater activity for central nervous system (CNS) metastases. It has been approved by Health Canada as second-line therapy in patients who have developed a T790M mutation on a first or second generation EGFR TKI. However, this requires either a tissue or liquid biopsy to demonstrate the presence of the resistance mutation.

Given the long PFS observed in the AURA 3 trial, the activity against both sensitizing and resistance *EGFR* mutations, and the high observed activity in patients with CNS metastases, the FLAURA trial evaluated osimertinib versus gefitinib or erlotinib in the first-line setting. Patients (n=556) were randomized to osimertinib 80mg daily versus a first generation EGFR TKI (gefitinib 250mg daily, or erlotinib 150mg daily). PFS was significantly prolonged in patients randomized to osimertinib versus a first generation EGFR TKI (median PFS 18.9m vs 10.2m, HR 0.46, 95%CI 0.37-0.57). ORR was higher for osimertinib (80% vs 76%) but this was not statistically significant. However, the median duration of response was significantly longer for osimertinib (17.2m vs 8.5m). Similar efficacy was seen in patients with, or without CNS metastases. OS data was immature at the time of the initial analysis.

The FLAURA trial demonstrated that initial therapy with osimertinib in patients with advanced NSCLC with common *EGFR* mutations (exon 19 del and L858R) resulted in superior PFS compared with a first generation EGFR TKI. Second-line osimertinib was not mandated in the control arm. However, approximately half of patients randomized to a first generation EGFR TKI, who went on to receive further therapy at the time of progression, received osimertinib. There are no direct comparisons of osimertinib to a second generation EGFR TKI. Nevertheless, first-line therapy with osimertinib in advanced NSCLC with common *EGFR* mutations appears to represent a new treatment option.

Significant improvements in OS have been observed in trials of immune checkpoint inhibitors in the first and second-line setting of advanced NSCLC.[43-45] However, these data are less applicable to the group of *EGFR* mutated NSCLC. They were excluded from the trials of first-line pembrolizumab.[45] Subgroup analyses of trials of second-line immune checkpoint inhibitors failed to demonstrate improved OS compared with docetaxel in patients with *EGFR* mutated NSCLC.[43,44] Therefore immune checkpoint inhibitor therapy is not a competing strategy for first or second-line therapy with osimertinib.

Patients with advanced NSCLC		
Line of Therapy	[Subgroup by mutation positive]	[Subgroup by mutation negative]
1st-Line	First or second generation EGFR TKI	NA
Maintenance	First or second generation EGFR TKI	NA
2nd-Line	Osimertinib	Platinum-based chemotherapy with maintenance pemetrexed
3rd Line	Platinum-based chemotherapy with maintenance pemetrexed	Docetaxel
4th Line	Docetaxel	Immune checkpoint inhibitor (nivolumab, pembrolizumab [if PD-L1 >1%] or atezolizumab)
5th line	Immune checkpoint inhibitor (nivolumab, pembrolizumab [if PD-L1 >1%] or atezolizumab)	

Table 1: Summary of RCTs comparing and EGFR TKI with platinum-based chemotherapy, or another EGFR TKI

Trial	Intervention	ORR	PFS	Quality of Life
IPASS[16] Mut + Mut -	Gefitinib vs carboplatin and paclitaxel	71% vs 47% 1% vs 23%	HR 0.48 (95%CI 0.36-0.64) HR 2.85 (95%CI 2.05-3.98)	More patients on gefitinib reported improvements in QoL scores (FACT-L).

Trial	Intervention	ORR	PFS	Quality of Life
First Signal[13] Mut + Mut -	Gefitinib vs cisplatin and gemcitabine	85% v 38% 26% vs 52%	HR 0.54 (95%CI 0.27-1.1) HR 1.42 (95%CI 0.82-2.5)	Significant improvement in physical role and social domains of QoL in favour of gefitinib.
NEJ002[14,36]	Gefitinib vs carboplatin and paclitaxel	74% vs 31%	10.8mvs 5.4m, HR 0.32 (95%CI 0.24-0.44)	Not evaluated
WJTOG 3405[15]	Gefitinib vs cisplatin and docetaxel	62% vs 32%	6.3m vs 9.2m, HR 0.49 (95%CI 0.34 – 0.71)	Not evaluated
Optimal[18]	Erlotinib vs carboplatin and gemcitabine	83% vs 36%	13.1m vs 4.6m, HR 0.16 (95%CI 0.10-0.26)	Significant improvement in total FACT-L and LCS scores for patients randomized to erlotinib compared with chemo
EURTAC[17]	Erlotinib vs platinum-doublet	58% vs 15%	9.7m vs 5.2m, HR 0.37 (95%CI 0.25-0.54)	Not evaluated
Lux Lung 3[19]	Afatinib vs cisplatin and pemetrexed	56% vs 23%	11.1m vs 6.9m, HR 0.58 (95%CI 0.43-0.78)	Significantly longer time to deterioration in cough, dyspnea for patients on afatinib. More improvement in dyspnea and shortness of breath
Lux Lung 6[20]	Afatinib vs cisplatin and gemcitabine	67% vs 27%	11.0m vs 5.6m, HR 0.28 (95%CI 0.20-0.39)	More improvements in cough, dyspnea and pain for patients on afatinib. Significantly longer time to deterioration in cough, dyspnea and pain.
CONVINCE[39]	Icotinib vs cisplatin and pemetrexed		11.2m vs 7.9m, HR 0.61 (95%CI 0.43-0.87)	Not evaluated
Lux Lung 7[6]	Afatinib vs gefitinib	70% vs 56%	11.0m vs 10.9m HR 0.73 (95%CI 0.57-0.95)	No difference between treatment arms in EG-5D scores
ARCHER1050[41]	Dacomitinib vs gefitinib/erlotinib	75% vs 72%	14.7m vs 9.2m, HR 0.59 (95%CI 0.47-0.74)	Dacomitinib associated with more improvement in chest pain (-10.2 vs -7.4, p=0.23). Other lung cancer symptom scores similar. More diarrhea and sore mouth with dacotitinib
AURA 3[23]	Osimertinib vs cisplatin and pemetrexed	71% vs 31%	10.1m vs 4.4m, HR 0.30 (95%CI 0.23-0.41)	Significant improvements in appetite loss, cough, chest pain, dyspnea and fatigue favouring osimertinib over chemo

2.3 Evidence-Based Considerations for a Funding Population

There are approximately 28,800 new cases of lung cancer annually in Canada.

- Proportion of NSCLC (85%) 24,480
- Proportion with locally advanced or metastatic disease (75%) 18,360
- Proportion with adenocarcinoma (60-70%) 11,016-12,852
- Proportion with *EGFR* mutation (17%) 1872-2184

Based on the above assumptions, there are between 1872 and 2184 patients with advanced NSCLC with tumors harbouring an *EGFR* mutation. The number treated will likely be lower, as some of these patients may not be detected because of inadequate tissue for molecular testing, some may not be well enough for treatment and some may choose not to have therapy.

2.4 Other Patient Populations in Whom the Drug May Be Used

Osimertinib is only indicated in patients with NSCLC known to have tumors with an EGFR mutation. The inclusion criteria for the FLAURA trial were limited to performance status ECOG 0 and 1. However, physicians are likely to extrapolate the data to patients with poor performance status, as well. The FLAURA trial included only patients with the common EGFR mutations (exon 19 del and L858R). First-line therapy would be limited to this patient population, although there is some risk that physicians might extrapolate the data to patients with uncommon EGFR mutations. However, they represent a small population of patients.

In the second-line setting, osimertinib is only indicated in patients known to have developed a T790M mutation. This group represents 50-60% of patients with tumors containing an EGFR mutation. ORR's were seen in early clinical trials of osimertinib among patients with T790M negative tumors. There is some risk of off label use in this group of patients.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Patient input regarding osimertinib (Tagrisso) for the treatment of patients with non-small cell lung cancer (NSCLC) was provided by Lung Cancer Canada (LCC). LCC obtained information through a survey, the Faces of Lung Cancer Survey, and an environmental scan. The Faces of Lung Cancer Survey, conducted in August 2015, was sent across Canada, resulting in responses from 91 patients, all of whom either have or have had lung cancer, and 72 caregivers, who were caring for, or had previously cared for patients living with lung cancer at the time the survey was completed. Through May 2018, patient forums were used as sources to conduct environmental scans and data mining; all information obtained was from patients receiving osimertinib as first-line therapy. In addition to the survey and environmental scan, information from a literature review was also conducted to inform sections of their submission; this literature review was in fact updated from previous submissions to pCODR. Moreover, information from previous pCODR submissions was used to inform sections of their submission. For instance, to illustrate quality of life of patients using first-line TKI therapies, details from their submission in 2015 for osimertinib for second-line EGFR T790M were included here; as well, to illustrate the impact of brain metastases, details from their submission for alectinib for ALK-positive NSCLC were also included here.

LCC highlighted the great physical and emotional burden lung cancer patients face compared to other cancers; lung cancer patients experience high symptom burden, the most common of which was reported to be fatigue. Fatigue was reported to be a very debilitating symptom of lung cancer, greatly interfering with patient's daily activities and quality of life. LCC commented on stigma that is specifically associated with patients of lung cancer and their families. For example, quotes provided by LCC indicate that caregivers feel the need to advocate for their loved one's condition to others.

Brain metastasis was mentioned to be a factor greatly impacting a lung cancer patient's prognosis. While LCC did not have specific patient input regarding brain metastasis and osimertinib, they did provide data from a previous submission on alectinib for ALK positive patients and mentioned that no evidence was available to suggest that symptoms related to treatment for brain metastasis would differ between patients with different types of lung cancer. Patients reported feelings of fear and anxiety surrounding treatments for brain metastasis, such as radiation, due to the potentially permanent side effects.

Patient's responses to osimertinib were positive; patients commented on the effectiveness of osimertinib and the speed by which they showed signs of improvement. Patients commented on the significant reduction of their tumour, some even showing signs of reduction after their first scan. LCC indicated that use of osimertinib in the second-line setting showed favourable responses. Patients reported managing side effects such as fatigue and change in appetite with naps, or consumption of smaller meals and varying the types of foods eaten. Overall, the symptoms from osimertinib were manageable, and osimertinib allowed patient's to continue to enjoy life activities, and adopt a sense of hope.

Please see below for a summary of specific input received from LCC. 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 this type of cancer

LCC states that lung cancer patients face a lower likelihood of surviving at least five years compared to other types of cancer; only 14% of males and 20% of females with lung cancer achieve a five-year survival, lagging behind other cancers (Canadian Cancer Statistics 2017). Lung cancer also results in more deaths than breast, prostate and colorectal cancers combined (Canadian Cancer Society 2017).

From LCC's submission for second-line osimertinib conducted in 2015, the following information was extracted: LCC mentioned that the sample of respondents for the osimertinib 2015 submission was younger than the average lung cancer patient, physically active and non-smokers, which led to many feelings of shock at diagnosis. For example, the sample included two families in their 40's with an infant or young children, two long distance runners, a competitive tennis player, a five-year kickboxer, and a doctor in the Canadian Armed Forces. The doctor, identified as Dr R stated that they "thought it would be more likely that [they] would be killed by a bomb in Afghanistan than by lung cancer." Another patient stated, "you've been given an expiration date that is really close."

LCC posited that lung cancer patients face the highest symptom burden compared to all other cancer patients. LCC provided statistics from a US study stating that a high proportion of patients experienced lung the following cancer symptoms: fatigue (100%), loss of appetite (97%), shortness of breath (95%), cough (93%), pain (92%), and blood in septum (63%). Specifically, loss of appetite, cough, pain and shortness of breath were found to be significant quality of life predictors (Lyer et al. Support Cancer Care, 2014). According to a Canadian survey of patients with advanced lung cancer, two-thirds of lung cancer patients felt their symptoms interfered with daily activities, and 27% of patients expressed "frequent" or "constant" feelings of anxiety or worry (Patel et al. Proc ASCO 2003; Zawisza et al. WCLC 2013). Rates of depression were reported to be between 16% and 50% among lung cancer patients, which LCC stated was higher than rates of cancers for other sites (Aass et al. 1997, Hopwood et al. 2000; Akechi et al. 1998). Financial hardship was reported by 41% of patients in the Canadian study of patients with advanced lung cancer. The majority of patients (69%) also reported feeling that their disease had a significant negative impact on those close to them. LCC also mentioned feelings of stigma associated with patients of lung cancer, related to negative attitudes regarding smoking; however none of the patients interviewed for the 2015 osimertinib for second-line submission were currently smoking or had never smoked.

3.1.2 Patients' Experiences with Current Therapy

LCC mentioned that patients who are EGFR positive are considered one of the "lucky" ones, as they have the option of an oral EGFR-TKI as first-line treatment instead of chemotherapy, which stands as the current standard of care for most lung cancer patients. The current standards of care for patients with EGFR-positive lung cancer as LCC states, are erlotinib, afatinib, or gefitinib. Compared to other cancers, LCC indicated an unmet need in effective treatment options for lung cancer patients in the first line setting,

LCC provided information taken from the second-line osimertinib submission, which highlighted patients' tolerability to oral targeted therapies and relatively high quality of life. LCC mentioned that patients were able to continue to stay active and spend time with family while on targeted oral therapies. One patient even mentioned that when afatinib was no longer working for them, they were surprised as they were continuing to remain physically active and could not physically feel a decline in their health. LCC mentioned

that results from the 2015 osimertinib for second-ling submission was in line with clinical evidence and quality of life analyses documented in the PASS, OPTIMAL, and LUX-LUNG 3-6 trials (Mok TS et al, N Engl J Med. 2009; Zhou et al, Lancet Oncol. 2011; Sequist LV et al, J Clin Oncol. 2013; Wu YL et al, Lancet Oncol. 2014).

Brain metastases place an additional burden on lung cancer patients, as it significantly negatively impacts their prognosis. While there is currently no oral therapy for EGFR-positive patients with brain metastasis, LCC posited that early data show promising results for the effect of osimertinib against brain metastasis. Current treatments for patients with brain metastasis include chemotherapy or radiation. LCC emphasizes the important role osimertinib can play in this space, as other available treatments are considered unfavourably by patients, such as stereotactic radiation, which patients have to be eligible for, or, whole brain radiation (WBR), which involves risk of permanent cognitive damage. LCC provided information taken from their previous submission for alectinib for second-line ALK positive lung cancer with brain metastasis, mentioning that there is currently no evidence to suggest that patients who are EGFR positive lung cancer experience different side effects from radiation than patients with other types of cancer. For the alectinib submission it was noted that patients reported fear and anxiety due to long term and potentially permanent side effects, including memory loss, seizures, headaches, and changes to hair growth including hair loss. Patients even reported feelings of thanks and gratefulness when they were told they did not have to undergo radiation.

3.1.3 Impact on Caregivers

An emphasis was placed by LCC on feelings of discrimination that burden both patients and family members of lung cancer. Caregivers expressed the need to justify and advocate for their loved one's lung cancer diagnosis due to the stigma associated with lung cancer. The daughter of a lung cancer patient stated, "I was putting together pictures for Dad's funeral and the person at the photolab asked what they are for. I explained and then felt I had to rush to add, "But he didn't smoke", before she could even ask. It was maddening that he was continuing to be judged even after he passed." "I still find that I have to justify by husbands disease to others. He was healthy, athletic and never smoked. He was still running regularly when he went to he doctor for spot at the back of his eye. It turned out to be lung cancer. That was 2011 and he was 40. Our first (children) were 5 and 7." The previous quote was provided by the wife of a lung cancer patient, who was able to be "Superman" to their daughters for another four years while on osimertinib.

Caregivers of patients with lung cancer face additional stress due to the late diagnosis of lung cancer. The majority of lung cancer diagnoses occur in stage IV (Statistics Canada, Canadian Centre Registry) where the demands of caregiving are highest and most stressful. The resulting demands of caregiving also place high financial burden, as caregivers are forced to take time off work resulting in the loss of income of two individuals within a household. The burden of financial matters can be especially burdensome for younger lung cancer patients.

The experienced symptoms and quick decline of patients are also sources of distress to caregivers. Fatigue and lack of energy was stated to be the most common symptom experienced by lung cancer patients, and happens also to be the symptom most difficult to manage and with the greatest impact on quality of life on both patients and caregivers; pain, concentration or memory issues and nausea were also symptoms as being difficult to manage, after fatigue. The rapid progression of the disease was reported by the Faces of Lung Cancer Report to be the most common source of stress for caregivers of lung cancer patients.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations with Osimertinib

Overall, LCC stated that patient's experiences with osimertinib were positive, as it worked quickly and effectively, was effective against brain metastases, showed manageable side effects and allowed patients to remain hopeful and return to their lives.

Five patients who were using osimertinib first-line all reported tumour shrinkage; one patient reported over 50% reduction of his tumour, saying that the primary tumour was almost gone, and that his "oncologist says it does not even quality as a nodule at this point, more like scar tissue." Four of these five patients receiving osimertinib as first-line experienced significant tumour reduction. LCC mentioned many of these patients expressed that osimertinib worked fairly quickly, observing significant results after their first scan; "After nearly 6 weeks on Tagrisso as my first line treatment (did not have T790 mutation) CT scan revealed significant reduction in initial mass that was over 6 cm (lower right lobe collapsed lower lung) and several tumours scattered throughout left lung now almost non-existent."

LCC stated that osimertinib has only received FDA approval in the first-line setting as of April 2018, making assessment of durability of treatment somewhat difficult. However, LCC stated that durability of osimertinib in the second-line setting was favourable for some patients, with one patient even saying that they had been using osimertinib for 41 months.

Based on information provided by both patients and caregivers, a total of eight patients who received osimertinib as first-line reported brain metastases prior to the beginning of their treatment. Four of the eight patients with brain metastases treated with stereotactic radiation or whole brain radiation (WBR) before they began treatment with osimertinib. The remaining four patients were only treated with osimertinib and showed signs of shrinkage, which LCC mentioned was significant, as treatment with osimertinib allows for avoidance of WBR, and is associated with permanent cognitive side effects.

According to LCC, the most commonly reported side effects of osimertinib were fatigue (n=9) and a change in appetite (n=8) (Table 2). Many patients reported few side effects, and said that of the side effects experienced, they were mostly manageable. *"At the end of the day, I am very tired but I am still able to work full-time."* Patients reported napping as a way to manage their fatigue. A few patients reported that symptoms of fatigue were experienced only during the beginning of their treatment. One of the caregivers expressed concern about the fatigue her father experienced, since he slept all day at the beginning of his treatment with osimertinib. However, LCC reported that symptoms of fatigue were not as severe a week into the caregiver's father's treatment, the caregiver said her father had been "out fishing all day!", decreased appetite was managed by consuming smaller meals, and by trying different types of food.

Table 2: Side Effects of Osimertinib As Reported by Patients

Side effect	No
Fatigue	9
Increase/decreased appetite	8
Muscle cramping	3
Leg/back/arm pain	3
Cough	2
Runny nose	2
Rash	2

Side effect	No
Heart burn	2
Throat irritation	1
Mouth sores	1
Diarrhea	1
Nausea	1
Chest pain	1
Dry skin	1

Based on input from forums, LCC reported that tumour shrinkages reflected great feelings of hope among patients. LCC posited that patients appeared to be able to continue to participate in life activities, and take part on hobbies such as fishing

3.3 Additional Information

LCC provided positive feedback regarding pCODR submission method that allows manufacturers to file for a drug submission before receiving approval from Health Canada. LCC stated that this method reduces delays in access to drugs for Canadians, particularly for lung cancer which has a very low five year survival rate. However, LCC did mention that due to the early submission of osimertinib to pCODR, obtaining patient responses for this review was difficult, as the main trial is double-blinded and currently ongoing, therefore patient's drug status is not yet known.

LCC also mentioned that previously lung cancer patents did not have many treatment options that were tolerable and which allowed patients to return to their lives; with targeted molecular therapies, the paradigm of lung cancer treatments is shifting. Previously, osimertinib was reviewed for patients in the second-line with a T790M mutation. As indicated by LCC, approximately 50% of patients present with the T790M mutation, therefore only half of patients would be eligible for osimertinib in the second line. LCC highlighted that with the current review, all patients who are EGFR positive will be eligible for osimertinib, regardless of their T790M mutation status.

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 immunotherapies.

Economic factors:

- High drug cost and flat pricing of tablets

Please see below for more details.

4.1 Currently Funded Treatments

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

4.2 Eligible Patient Population

PAG is seeking clarity on the subgroup of patients with EGFR mutations who would be eligible for treatment with osimertinib. PAG noted that the trial enrolled patients with EGFR exon 19 deletions or exon 21 (L858R) substitution 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 osimertinib, or if osimertinib 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 information on the mean duration of treatment.

PAG noted that the cost of 40mg tablet and 80mg tablet is the same and identified that flat pricing of the two strengths is a barrier to implementation.

4.4 Sequencing and Priority of Treatments

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. PAG indicated that in next steps for stakeholders, provinces would collaborate to align funding of sequencing of therapies (including immunotherapy). PAG identified that moving the currently funded first generation TKI (gefitinib, afatinib, erlotinib) to second line after failure of osimertinib would likely not be considered in the absence of data to inform benefit.

4.5 Companion Diagnostic Testing

EGFR mutation testing is already available.

4.6 Additional Information

Osimertinib was previously reviewed and recommended for locally advanced or metastatic EGFR T790M mutation–positive NSCLC after progression on EGFR TKI.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Three clinician inputs were provided: one from an individual oncologist and two group inputs.

Clinicians providing input reported that osimertinib was superior to current first line standard of care gefitinib and erlotinib in the FLAURA trial in terms of PFS, duration of response and initial survival data, and also showed improvements in efficacy over afatinib. It was also noted that safety and tolerability were comparable to other first line options. One additional benefit noted was the efficacy of osimertinib in patients with brain metastases. Clinicians noted that having osimertinib available to patients may prevent some patients from undergoing brain radiotherapy, which can poorly affect quality of life. In terms of sequencing, clinicians indicated that osimertinib would replace gefitinib, erlotinib and afatinib as the first line treatment option, specifically for the patient population with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. It was noted that in patients with less common EGFR mutations, clinicians may still want to use the other first line treatment options. It was also noted by some clinicians that if osimertinib was given in the first line, it is not clear how subsequent treatment with tyrosine kinase inhibitors (TKIs) would affect the patient. In another clinician input, it was stated that treatment with osimertinib should be followed by chemotherapy with platinum and pemetrexed chemotherapy. The clinicians providing input reported that EGFR mutation testing is a standard of care upon diagnosis and that no additional diagnostic testing is required.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for this Type of cancer

The clinicians providing input reported that current standards of care for treating patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations are: erlotinib, afatinib, and gefitinib. It was noted that erlotinib is not funded for first line treatment in Ontario.

5.2 Eligible Patient Population

The clinicians providing input indicated that the patient population in the trial and the inclusion and exclusion criteria applied are relevant and meet the needs in clinical practice. Clinicians specified that osimertinib would be prescribed to EGFR positive non-small cell lung cancer (NSCLC) patients who are stage IIIB or IV with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2 in the first line setting. It was noted that in clinical practice, some patients present poorer ECOG PS than allowed in the trial, and that due to the ability of osimertinib to penetrate the blood-brain barrier into the central nervous system, patients with brain metastases (of any ECOG PS) should be able to receive this treatment. Clinicians reported that osimertinib proved to be superior to gefitinib and erlotinib in the FLAURA trial in terms of PFS, duration of response and initial survival data. It was indicated that in clinical practice, EGFR positive NSCLC tumour are highly responsive to targeted therapies, with a significant response in patients with an ECOG PS of 2 or above. It was reported by the clinicians providing input that it is likely that this therapy would be offered to most patients with EGFR positive advanced NSCLC.

5.3 Relevance to clinical Practice

Clinicians indicated that there are first line options currently available to the specified patient population, but osimertinib is superior in terms efficacy compared to erlotinib, gefitinib, afatinib. Clinicians also indicated that osimertinib is comparable in terms of safety and tolerability to the current first line options listed above. It was noted that progression free

survival was approximately doubled with osimertinib compared to standard EGFR TKIs from the FLAURA trial. One clinician input stated: "as not everyone who received current standard first line therapy would actually receive osimertinib in the second line, this also guarantees access to the best current drug for all eligible patients." Based on the trial, clinicians also indicated that osimertinib is associated with fewer side effects (such as rash and diarrhea) than standard EGFR TKIs. It was indicated that an important benefit of osimertinib is its efficacy against brain metastases. Clinicians indicated that some patients receive brain radiotherapy as treatment, which can be harmful to the patient and cause permanent cognitive impairments, and could be avoided due to the neuroprotective advantage of osimertinib over other EGFR TKIs. It was noted that this would allow patients to maintain a high quality of life. Clinicians felt that superiority with osimertinib was demonstrated through a substantially longer PFS as well as improved CNS activity, and because the initial survival superiority looked promising.

One clinician input made note of the European Lung Cancer Congress in Geneva Switzerland where similar improvements in quality of life were found with frontline osimertinib treatment for patients with advanced EGFR-mutant non–small cell lung cancer (NSCLC), as well as a clinically meaningful improvement in cough, when compared with the standard of care EGFR TKIs according to the phase III FLAURA trial.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The clinicians providing input reported that currently patients with EGFR positive NSCLC patients are treated with either gefitinib, erlotinib or afatinib in the first line setting. It was noted that in the second line setting, osimertinib is only indicated in T790M mutation positive patients, which would encompass about 50-60% of the patients who progress on first or second generation EGFR TKI. In one clinician input, it was noted that in the trial, "osimertinib in the first line yielded a median PFS of 19 months and that it could be argued that for patients who ultimately develop a T790M mutation, using osimertinib first line or second line will not affect the combined median PFS for first and second line therapy." The input went on to say, "However, for those who do not develop a T790M mutation, there is a definite improvement in the medians PFS." It was also stated that osimertinib in the first line setting would, for the majority of patients with one of the two common EGFR mutations (exon 19 deletion or exon 21 L858R; compromising 90% of the EGFR mutations), replace gefitinib, afatinib and erlotinib. In addition, it was stated that based on LUX-Lung 3 and 6 trials, afatinib showed benefit in those with uncommon EGFR mutations, and that this is the only trial to demonstrate activity in these mutations. It was then stated that in those with Exon 19, 20 or 21 deletions, clinicians may choose to use afatinib in the first line setting.

In one clinician input, it was reported that the sequencing is complicated because if a patient received osimertinib in the first line and then progressed, it is not clear if any of the other older TKIs will have any efficacy. It was noted that it is not clear if patients would do better by having one of the current first line drugs up front and then osimertinib, compared to using osimertinib

up front. It was stated that even though the drug is superior in a head to head trial with older drugs, it may not be the best strategy.

Another clinician input reported that osimertinib should be used in first line to be followed by chemotherapy with platinum and pemetrexed chemotherapy.

5.5 Companion Diagnostic Testing

The clinicians providing input reported that EFGR mutation is currently a standard of care in Canada upon diagnosis and that osimertinib (in the first line setting) does not require an additional diagnostic.

It was noted that use of osimertinib would reduce biomarker testing. It was stated, "Some patients, currently treated with first or second generation EGFR TKIs in the first line, cannot easily access T790M mutation testing on progression for a variety of reasons (inter-provincial differences with access, clinical contraindications to further biopsy, or CNS only progression). So upfront osimertinib would, in addition to the benefits described, allow patients and clinicians to avoid timely and expensive additional testing."

5.6 Additional Information

No additional comments.

6 SYSTEMATIC REVIEW

6.1 Objectives

The primary objective of this review is to evaluate the efficacy and safety of osimertinib for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations.

One supplemental question/assessment relevant to the pCODR review and to the Provincial Advisory Group was identified and is outlined in section 7:

- Critical appraisal of the manufacturer-submitted indirect treatment comparison (ITC) of osimertinib versus afatinib for advanced/metastatic EGFR mutation-positive NSCLC patients.

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 Table 6.1 Selection Criteria. 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 or unpublished RCTs	Treatment-naïve patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations <u>Subgroups of Special Interest</u> - CNS metastases - EGFR mutation type	Osimertinib monotherapy	Erlotinib Gefitinib Afatinib	**Overall survival** PFS PFS2 Time to CNS progression ORR Duration of response Disease control rate **HRQoL** **Adverse events** SAEs WDAEs <u>Adverse Events of Special Interest</u> - QTc Interval Prolongation - Interstitial Lung Disease - Left Ventricular Dysfunction and Cardiomyopathy - Keratitis - Diarrhea - Skin toxicity
CNS=central nervous system; EGFR=epidermal growth factor receptor; HRQoL=health-related quality of life; NSCLC=non-small cell lung cancer; ORR=objective response rate; PFS=progression-free survival; RCT=randomized controlled trial; SAE=serious adverse event; WDAE=withdrawals due to adverse event				

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

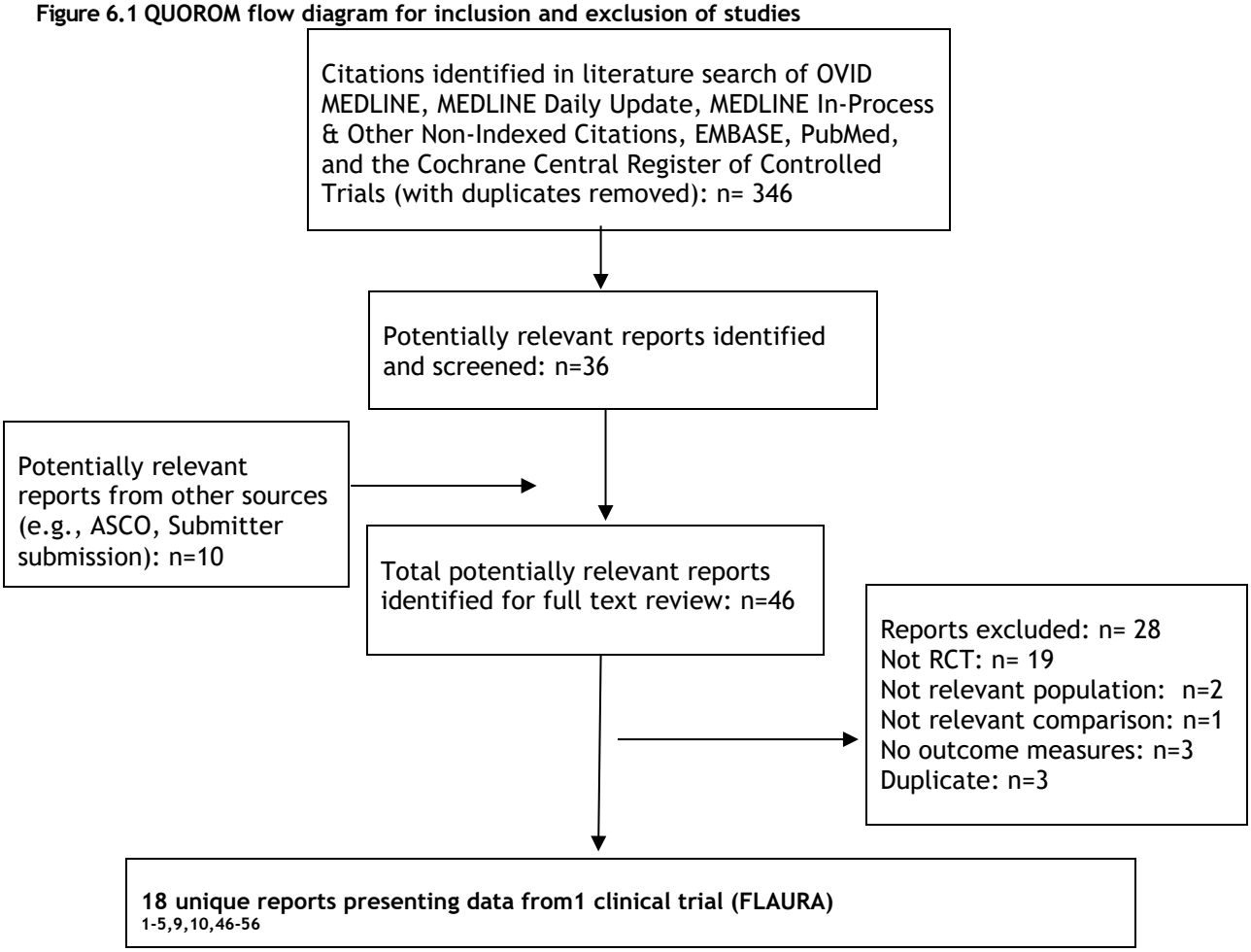
† CGP acknowledge that dacomitinib, although not available in Canada, may be an upcoming relevant comparator in this setting.

6.3 Results

6.3.1 Literature Search Results

Of the 46 potentially relevant reports identified, one study was included in the pCODR systematic review[1-5,9,10,46-56] and 28 studies were excluded. Studies were excluded because they were not RCT, not relevant comparator, no outcome measures or duplicate.

Figure 6.1 QUOROM flow diagram for inclusion and exclusion of studies



Note: Additional data related to FLAURA were also obtained through requests to the Submitter by pCODR.[7]

6.3.2 Summary of Included Studies

One trial, FLAURA, was identified to have met eligibility criteria of this review. Characteristics of the trial are summarized in Table 6.2: *Summary of Trial Characteristics of the Included Studies* and specific aspects of the trial quality are summarized in Table 6.3: *Select quality characteristics of included studies of osimertinib in patients with NSCLC* and Table A3: *Critical appraisal of the FLAURA trial using SIGN-50 Methodology Checklist 2: Controlled Trials*. Detailed trial characteristics and outcome data related to the FLAURA trial are described below.

6.3.2.1 Detailed Trial Characteristics.

a) Trial[1,3]

FLAURA was a phase III, randomized (1:1 ratio), double blind, intervention-control trial that compared osimertinib to standard-EGFR TKI (gefitinib or erlotinib) in patients with previously untreated EGFR mutation–positive (exon 19 deletion or L858R) advanced NSCLC. The primary objective was to assess the efficacy of osimertinib compared with standard EGFR-TKI as measured by progression-free survival (investigator-assessed). The trial was conducted in 132 sites in 29 countries (patients were enrolled in 29 of these 30 countries: Australia, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, France, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, Malaysia, Philippines, Poland, Portugal, Romania, Russian Federation, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, Unites States of America, and Vietnam). A summary of trial characteristics can be found in Table 6.2: *Summary of Trial Characteristics of the Included Studies*.

Funding

FLAURA was funded by AstraZeneca and designed by the principal investigators and AstraZeneca. AstraZeneca was responsible for the collection and analysis of the data and had a role in data interpretation.

Eligibility criteria[2]

Patients enrolled in FLAURA met the following key criteria:

- Male or female, aged at least 18 years (with the exception of Japan, at least 20 years);
- Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy;
- The tumour harbours one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations; and
- World Health Organization Performance Status of 0 to 1.

For a more detailed list of key eligibility criteria used in the trial refer to *Table 6.2: Summary of Trial Characteristics of the Included Studies*.

Outcomes[1,3]

The primary outcome of the trial was progression-free survival (PFS) by investigator assessment, according to RECIST v1.1. Sensitivity analyses were performed to address biases (ascertainment, evaluation-time, and attrition); most notably, a sensitivity analysis of progression-free survival was performed using data from blinded independent central review of RECIST assessments. In addition to the above PFS analyses, the following subgroup PFS analyses were conducted:, sex, race, age, smoking history, known or treated CNS metastases at entry, baseline WHO performance status, EGFR mutation at randomization, EGFR mutation by circulating tumour DNA, and centrally confirmed EGFR mutation.

Overall survival, health-related quality of life, and safety were secondary outcomes. Other secondary outcomes included objective response rate (ORR), duration of response (DoR), disease control rate (DCR), and depth of response, all by investigator assessment, according to RECIST v1.1. Second progression-free survival (PFS2) and time to subsequent treatments were exploratory endpoints.

Tumor assessments were performed at baseline, every 6 weeks (±1 week) for 18 months, followed by every 12 weeks (±1 week) until disease progression. Of note, baseline brain imaging was required only in patients with known or suspected CNS metastases, and with follow-up imaging in patients with confirmed CNS metastases.

Randomization, Sample Size, and Statistical Analyses[1-3,54,55]

Patients were centrally randomized in a 1:1 ratio to osimertinib or standard-EGFR TKI (gefitinib or erlotinib) using Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). Patients were stratified at randomisation based on EGFR mutation (Ex19del or L858R) and race (Asian or Non-Asian).

Approximately 359 events of progression or death from 530 randomized patients were required to achieve 90% power to detect a hazard ratio of 0.71 at a two-sided alpha-level of 5%; this represented an improvement in median progression-free survival from 10 months to 14.1 months assuming exponential data distribution and proportional hazards. Of note, the protocol highlighted that once 530 patients were recruited globally, and additional recruitment in mainland China would include up to 120 Chinese patients to facilitate a China-only analysis dataset. It is important to note that the results related to this analysis are not included in this report, as it included China-only patients.

There were two notable amendments to the trial protocol:

- Amendment 1 (April 13, 2015), patients randomized to receive standard EGFR-TKI were permitted to cross over to receive open label osimertinib, if they had confirmed progression by blinded independent central review and post progression documentation of T790M-positive mutation status; and
- Amendment 2 (September 24, 2015), the defined sample size for randomization was reduced from 650 to 530 patients because of updated statistical assumptions which was based on the recent results of a phase I study (D5160C00001).

Also, there were notable changes to the planned analyses (final SAP version 3.0 Feb 2017) which are not reflected in the final protocol (Edition 3, Sep 2015):

- Change in the alpha spending for overall survival, which was requested by the FDA; and
- T790M progression-free survival removed from the testing hierarchy and replaced with CNS progression-free survival. According to AstraZeneca, CNS progression-free survival was considered to be more clinically relevant than T790M progression-free survival subgroup analysis, which was based on new emerging data since the final protocol.

The Statistical Analysis Plan was updated to reflect the above Amendments (1 and 2) and changes to the planned analyses and can be found in the final SAP version 3.0 Feb 2017.

Of note, only one analysis of the primary endpoint (PFS) was planned. Two analyses of overall survival were planned: one interim at the time of PFS and a final OS analysis (when the OS data was approximately 60% mature [approximately 318 deaths]).

The statistical analysis plan specified that a multiple testing strategy was used to control for type I error rate. This meant that progression-free survival, overall survival and CNS progression-free survival were tested in this sequential order and if any previous analysis in the sequence was not statistically significant, then significance testing of the subsequent endpoints would not be performed.

All efficacy analyses, including all secondary outcomes, were performed in the intent-to-treat (ITT) population. Safety assessments were performed in all patients who received at least one dose of randomly assigned treatment.

Patient reported outcomes were assessed using the EORTC-QLQ-C30 and the EORTC- QLQ-LC13 questionnaires. The EORTC QLQ-C30 measures overall quality of life and different aspects of patient function. It consists of questions grouped into five multi-item functional scales (physical, role, cognitive, emotional, and social); three multi-item symptom scales (fatigue, pain, and nausea and vomiting); a two-item global health-related quality-of-life scale; 5 single items assessing dyspnoea, loss of appetite, insomnia, constipation, diarrhoea which are symptoms commonly reported by cancer patients; and one item on the financial impact of the disease. The EORTC QLQ-LC13 is a disease specific module that complements the EORTC QLQ-C30 and it evaluates different aspects of lung cancer symptoms and side-effects from chemotherapy and radiotherapy. It consists of questions assessing cough, hemoptysis, dyspnea, site specific symptoms, sore mouths, dysphagia, peripheral neuropathy, and alopecia and pain medication. Both questionnaires are considered to be valid and reliable patient report outcomes instruments. In the updated statistical analysis plan (final SAP version 3.0 Feb 2017), clinically meaningful changes in EORTC QLQ-C30 and EORTC QLQ-LC13 were removed as part of the planned analyses and no rationale for this change was given. However, in a poster by Leighl et al. clinically meaningful changes in EORTC QLQ-C30 and EORTC QLQ-LC13 are presented and are reported in this review.

The FLAURA trial is ongoing, and data related to the primary PFS analysis and secondary endpoints (including interim OS analysis) have been published using a data cut-off of June 12, 2017

According to the European Medicines Agency, non-adherence to a protocol-required procedure was the most frequent important protocol deviation; this included (but was not limited to):

- Missing RECIST assessment for efficacy (67 patients overall has single missed assessments)
- RECIST scan performed outside of the visit window and on more than 2 occasions (27 patients overall)
- Baseline tumour RECIST assessments was performed more than 28 days before randomisation (15 patients overall)
- Tumour assessment methods and procedures was not compliant with protocol or RECIST v1.1 (14 patients overall)

Including patients who did not meet eligibility criteria was the second most frequent protocol deviation; this included (but was not limited to):

- No confirmation that the tumour harboured Ex19del or L858R (7 patients overall)
- No pathological confirmation that the patient had an adenocarcinoma of the lung (5 patients overall)
- Patient was not treatment-naïve for locally-advanced or metastatic NSCLC (3 patients overall); these patients received prior treatment for advanced cancer.

- Additional information on randomization, required sample size, statistical assumptions, and other indicators of trial quality are detailed in *Table 6.3: Select quality characteristics of included studies of osimertinib in patients with NSCLC* and *Table A3: Critical appraisal of the FLAURA trial using SIGN-50 Methodology Checklist 2: Controlled Trials*.

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: FLAURA (NCT02296125) **Characteristics:** Phase III, randomized (1:1 ratio), double-blind, intervention-control **Sample size:** N= 556; osimertinib n= 279, Standard EGFR-TKI (gefitinib or erlotinib) n=277 **Locations:** 132 sites in 29 countries (including Canada) (patients were enrolled in 29 of these 30 countries: Australia, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, France, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, Malaysia, Philippines, Poland, Portugal, Romania, Russian Federation, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, Unites States of America, and Vietnam) **Patient Enrolment:** December 2014 - March 2016 **Primary analysis data cut-off:** June 12, 2017 (final primary PFS + interim OS) **Actual primary completion:** June 19, 2017 **Estimated study completion:** June 28, 2019 **Funding:** AstraZeneca	<u>Key Inclusion Criteria:</u> - Male or female, aged at least 18 years; 20 years for Japan. - Pathologically confirmed adenocarcinoma of the lung. Patients with mixed histology are eligible if adenocarcinoma is the predominant histology. - Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy. - The tumour harbours one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations. - Provision of an unstained, archived tumour tissue sample for central analysis of EGFR mutation status. - Treatment-naïve for locally advanced or metastatic NSCLC and eligible to receive first-line treatment with gefitinib or erlotinib. - Prior adjuvant and neo-adjuvant therapy is permitted (chemotherapy, radiotherapy, investigational agents) - World Health Organization Performance Status of 0 to 1 with no clinically significant deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks. - At least one lesion, not previously irradiated and not chosen for biopsy <u>Key Exclusion Criteria:</u> - Treatment with any of the following: o Prior treatment with any systemic anti-cancer therapy for locally advanced/ metastatic NSCLC including chemotherapy, biologic therapy, immunotherapy, or any investigational drug. o Prior treatment with an EGFR-TKI. o Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study drug. o Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug. o Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of study drug) medications or herbal supplements known to be potent inducers of cytochrome P450 (CYP) 3A4. o Treatment with an investigational drug within five half-lives of the compound or any of its related material, if known. - Any concurrent and/or other active malignancy that has required treatment within 2 years of first dose of study drug. - Any unresolved toxicities from prior systemic therapy (e.g., adjuvant chemotherapy) greater than CTCAE grade 1 at the time of starting study drug with the exception of alopecia and grade 2, prior chemotherapy-induced neuropathy. - Spinal cord compression, symptomatic and unstable brain metastases, except for those patients who have completed definitive therapy, are not on steroids, have a stable neurologic status for at least 2 weeks	<u>Intervention</u> osimertinib (80 mg once daily) <u>Comparator</u> standard EGFR-TKI - gefitinib (250 mg once daily) or - erlotinib (150 mg once daily)	<u>Primary:</u> - progression free survival (PFS) <u>Secondary:</u> - PFS in patients with (1) positive (or negative) pre-treatment T790M mutation, (2) EGFRm+ Ex19del or L858R, (3) EGFRm+ Ex19del or L858R detectable in plasma-derived circulating tumour deoxyribonucleic acid (ctDNA) - Objective Response Rate (ORR) - Duration of Response (DoR) - Disease Control Rate (DCR) - Depth of response - Overall survival (OS) - Health related quality of life (change from baseline EORTC QLQ-C30 and LC13) - Patient Satisfaction (CTSQ-16) - Safety <u>Exploratory:</u> - Second progression-free survival (PFS2) - Time to subsequent treatments

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	after completion of the definitive therapy and steroids. - Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol; or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). - Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of AZD9291. - Any of the following cardiac criteria: o Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 ECGs. o Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG. o Any factors that increase the risk of QTc prolongation or risk of arrhythmic events. - Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD. - Inadequate bone marrow reserve or organ function.		
For full details, refer to Protocol for: Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113-25. DOI: 10.1056/NEJMoa1713137			

Source: Protocol for: Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113-25. DOI: 10.1056/NEJMoa1713137[1,2]

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

Study	FLAURA
Treatment vs. Comparator	osimertinib vs. standard EGFR-TKI (gefitinib or erlotinib)
Primary outcome	Investigator assessed progression-free survival
Required sample size	530 Approximately 359 events of progression or death from 530 randomized patients were required to achieve 90% power to detect a hazard ratio of 0.71 at a two-sided alpha-level of 5%. At the time of the data cut-off, 342 events of progression or death occurred; this is 17 fewer events required. Despite this small difference (17 fewer required, 342 events instead of 359 events) and the fact that the results are statistically significant, it is unlikely that this difference had an impact on the findings of the trial.
Sample size	556
Randomization method	Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS), stratified
Allocation concealment	Yes
Blinding	Yes. Of note, following independent central confirmation of progression, the patient may then be unblinded to establish randomized treatment. If randomized to standard EGFR-TKI treatment arm, the patient may be a candidate to receive open-label osimertinib. Patients who have been unblinded prior to central confirmation of progression were not able to receive open-label osimertinib.
ITT Analysis	Yes
Final analysis	Yes
Early termination	No

Ethics Approval	Yes

Abbreviations: EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; ITT=intent to treat

Source: Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113-25. DOI: 10.1056/NEJMoa1713137; Protocol for: Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113-25. DOI: 10.1056/NEJMoa1713137[1,2]

b) *Populations*[1,9,10]

Patient randomization occurred between December 2014 and March 2016. During this period, a total of 556 patients were randomized; 279 were allocated to osimertinib and 277 were allocated to standard EGFR-TKI (gefitinib or erlotinib). Overall, baseline characteristics of patients were well balanced. However, the median age was the same in both groups (64 years old).

The majority of patients had metastatic disease and about 20% of patients had CNS metastasis. Most patients were Asian, never smokers, and had a WHO performance status of 1 at the time of trial entry. Refer to *Table 6.4: Baseline characteristics of patients included in the FLAURA trial*.

Table 6.4: Baseline characteristics of patients included in the FLAURA trial

Characteristic	Osimertinib (N=279)	Standard EGFR-TKI (N=277)
Age — yr		
Median	64	64
Range	26–85	35–93
Male sex — no. (%)	101 (36)	105 (38)
Race — no. (%)†		
White	101 (36)	100 (36)
Asian	174 (62)	173 (62)
Other	4 (1)	4 (1)
Smoking status — no. (%)		
Never	182 (65)	175 (63)
Current	8 (3)	9 (3)
Former	89 (32)	93 (34)
WHO performance status — no. (%)‡		
0	112 (40)	116 (42)
1	167 (60)	160 (58)
Missing data	0	1 (<1)
Histologic type — no. (%)		
Adenocarcinoma	275 (99)	272 (98)
Other§	4 (1)	5 (2)
Overall disease classification — no. (%)		
Metastatic¶	264 (95)	262 (95)
Locally advanced‖	14 (5)	15 (5)
Missing data	1 (<1)	0
Metastases — no. (%)		
Visceral metastases**	94 (34)	103 (37)
CNS metastases††	53 (19)	63 (23)
EGFR mutation type at randomization — no. (%)		
Exon 19 deletion	175 (63)	174 (63)
L858R	104 (37)	103 (37)
EGFR mutation type by central test — no. (%)‡‡		
Exon 19 deletion	158 (57)	155 (56)
L858R	97 (35)	90 (32)
No mutation detected, invalid test, or no or inadequate sample	24 (9)	32 (12)

Characteristic	Osimertinib (N=279)	Standard EGFR-TKI (N=277)
EGFR-TKI comparator — no. (%)		
Gefitinib	NA	183 (66)
Erlotinib	NA	94 (34)

* No formal comparison between the two groups was performed for baseline characteristics. CNS denotes central nervous system, EGFR-TKI epidermal growth factor receptor tyrosine kinase inhibitor, and NA not applicable. Percentages may not total 100 because of rounding.
† Race was reported by the patient. The category of "other" includes black, American Indian, and Alaska Native.
‡ The World Health Organization (WHO) performance status of 0 indicates that the patient is fully active and able to carry out all predisease activities without restrictions, and a WHO performance status of 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work.
§ Five patients (two in the osimertinib group and three in the standard EGFR-TKI group) had large-cell carcinoma; three patients (one in the osimertinib group and two in the standard EGFR-TKI group) had adenosquamous carcinoma; and one patient (in the osimertinib group) had a carcinoid tumor.
¶ The patient had any metastatic site of disease.
‖ The patient had only locally advanced sites of disease.
** Visceral metastases were determined programmatically from baseline data for which the disease site was described as adrenal, ascites, brain or CNS, gastrointestinal, genitourinary, hepatic (including gallbladder), liver, other CNS, pancreas, peritoneum, or spleen. Also included were other metastatic sites, such as those occurring in the eye and thyroid, as identified as extrathoracic visceral sites by AstraZeneca physicians.
†† CNS metastases were determined programmatically from baseline data for the CNS lesion site, medical history, surgery, or radiotherapy.
‡‡ A patient could have more than one type of mutation.

Source: New England Journal of Medicine. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. Soria JC, Ohe Y, Vansteenkiste J, et al., 378(2):113-125. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.Table 1.Page 4.[1]

c) Interventions[1,54]

In the FLAURA trial, patients were either randomized to receive osimertinib or standard EGFR-TKI (erlotinib or gefitinib). Patients in the osimertinib group received osimertinib at a dose of 80 mg once daily and patients in the standard EGFR-TKI group received gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily. The type of standard EGFR-TKI was determined at the site/country level. Of note, afatinib was not a standard EGFR-TKI included in the comparator group in the FLAURA trial. According to the authors of the publication, at the time the trial was conducted, afatinib was not widely used nor had it been made available international as the standard EGFR-TKI.

Treatment was given until disease progression, development of unacceptable side effects, or withdrawal of consent. Treatment beyond disease progression was allowed as long as the investigator judged that there was continued clinical benefit. A total of 91 patients (67%) in the osimertinib group and 145 patients (70%) in the standard EGFR-TKI group remained on treatment beyond investigator assessed RECIST progression and the median duration of continued treatment was 8 weeks compared with 7 weeks respectively. As noted previously, Protocol Amendment 2 allowed patients in the standard EGFR-TKI group to cross over to open-label osimertinib after confirmation of objective disease progression (by blinded independent central review) and post-progression documentation of T706M-postitive mutation status. In total, 48 patients in the standard EGFR-TKI group crossed over to receive osimertinib.

Dose modification[2,3]

In the event of dose modifications due to treatment toxicity, dose interruption was required prior to dose reduction. If dose reductions were needed, patients with a starting dose of 80mg osimertinib/comparator matching placebo had a reduced dose of 40mg osimertinib/comparator matching placebo; patients with a starting dose of 150 mg of erlotinib/osimertinib matching placebo had a reduced dose of 100 mg of erlotinib/osimertinib matching placebo; and no dose

reduction was allowed for patients receiving gefitinib because the starting dose of 250mg was the lowest dose available.

In total, 70 patients (25%) in the osimertinib group and 66 patients (24%) in the standard EGFR-TKI group experienced adverse events leading to dose interruptions. In the osimertinib group the dose interruptions were driven mostly by QT prolongation (8 patients), decreased appetite (7 patients), diarrhea (7 patients), and pneumonia (5 patients); while in the standard EGFR-TKI group the dose interruptions were driven mostly by alanine aminotransferase increase (18 patients), aspartate aminotransferase increase (12 patients), QT prolongation (6 patients) and dermatitis acneiform (5 patients). Adverse events leading to dose reduction were experienced by 11 patients (4%) in the osimertinib group and 15 patients (5%) in the standard EGFR-TKI group; these were mainly due to QT prolongation and skin disorders. Adverse events leading to treatment discontinuation occurred in 37 patients (13%) in the osimertinib group compared to 49 patients (18%) in the standard EGFR-TKI group.

Duration of Treatment[1]

The median duration of treatment was 16.2 months (0.1 to 27.4 months) for the osimertinib group and 11.5 months (0 to 26.2 months) for the standard EGFR-TKI group.

Concomitant medication[7]

Some concomitant medication and other treatment were restricted during the study, for complete details refer to FLAURA protocol. Concomitant medication necessary for the patient's safety and well-being were given at the discretion of the investigator.

The majority of patients received concomitant medications during the study. Proton pump inhibitors were given as concomitant medication (27.6% in the osimertinib group and 29.2% in the EGFR-TKI group) as well as glucocorticoids (22.6%, 21.7% respectively); these were well balanced between treatment groups.[7]

Source: CSR from Submitter. Non-disclosable.

d) Patient Disposition[1,3]

The disposition of patients throughout the FLAURA trial is summarized in *Figure 6.2: Patient Disposition*. All patients randomized into each arm received at least one dose of study treatment. At the time of the data cut-off, 49% of patients (138/279) in the osimertinib group compared with 77% (213/277) of patients in the standard EGFR-TKI group had discontinued study treatment. Discontinuation of study treatment was due to disease progression, adverse events, patient decision, severe protocol non-compliance, or other.

Of note, 48 patients in the standard EGFR-TKI group crossed over to receive open-label osimertinib; and of these patients, 18 discontinued osimertinib because of: disease progression, adverse events, patient decision, or other.

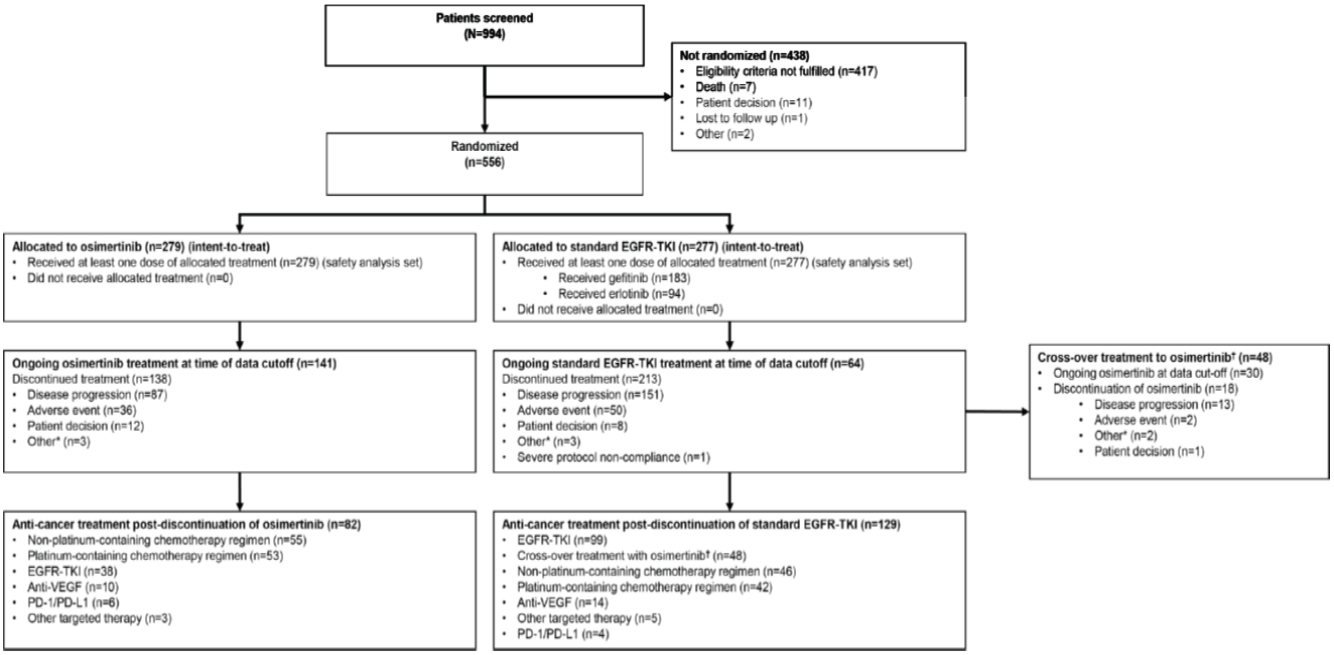
Subsequent anti-cancer therapies[1-3,54]

Subsequent anti-cancer therapies received by patients after discontinuation of study treatment are summarized in *Table 6.5: Subsequent anti-cancer therapy regimens*. Of those patients that discontinued study treatment (n=138, n=213 respectively), 82 patients in the osimertinib group and 129 patients in the standard EGFR-TKI group received second line treatment, which included: EGFR-TKI, PD-1/PD-L1, non-platinum chemotherapy, platinum-based chemotherapy, other targeted therapy, or anti-VEGF. Some patients also received third line treatment in the form of EGFR-TKI, PD-1/PD-L1, non-platinum chemotherapy, other targeted therapy, or anti-VEGF. A total of 29 patients received EGFR-TKIs as subsequent therapy post osimertinib. Of note, 55 patients

(out of 277) in the standard EGFR-TKI group received osimertinib: 48 patients received osimertinib on crossover (17%) and 7 (3%) patients received osimertinib outside of the trial as second-line treatment. It is important to mention that crossover did not impact the primary endpoint, PFS, because patients crossed over after RECIST-defined progression.

As an exploratory analysis of post-progression outcomes, time to first subsequent therapy and time to second subsequent therapy was explored. The median time from randomization to first subsequent therapy or death was in favour of osimertinib (23.5 months compared with 13.8 months; with a hazard ratio of 0.51 (95%CI: 0.40 to 0.64, *P* <0.0001)). The median time to second subsequent therapy or death was not calculate for patients in the osimertinib group and was 25.9 in patients in the standard EGFR-TKI group (hazard ratio of 0.60, 95% CI: 0.45 to 0.80, *P* =0.0005).

Figure 6.2: Patient Disposition



EGFR, epidermal growth factor receptor; PD1, programmed cell death; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

* Any reason not specifically recorded; for example, subject died.

† Crossover patients are patients that crossed over and received at least one dose of open-label osimertinib.

Source: New England Journal of Medicine. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. Soria JC, Ohe Y, Vansteenkiste J, et al., 378(2):113-125. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Figure S1. Page 18.[3]

Table 6.5: Subsequent anti-cancer therapy regimens (including crossover osimertinib)

	Number (%) of patients[a]	
Classification/ATC dictionary text	Osimertinib (N=279)	SoC (N=277)
First post-treatment anti-cancer therapy (including cross-over osimertinib)		
Discontinued randomised study treatment	138 (49.5)	213 (76.9)
First post-treatment anti-cancer therapy	82 (29.4)	129 (46.6)
No post-treatment anti-cancer therapy	56 (20.1)	84 (30.3)
Ongoing randomised study treatment	141 (50.5)	64 (23.1)
First post-treatment anti-cancer therapy		
EGFR-TKI	29 (10.4) [21.0]	97 (35.0) [45.5]
PD1/PDL1	3 (1.1) [2.2]	2 (0.7) [0.9]
Non-platinum chemotherapy	50 (17.9) [36.2]	27 (9.7) [12.7]
Platinum-based chemotherapy	48 (17.2) [34.8]	26 (9.4) [12.2]
Other targeted therapy	2 (0.7) [1.4]	3 (1.1) [1.4]
Anti-VEGF	7 (2.5) [5.1]	4 (1.4) [1.9]
Second post-treatment anti-cancer therapy		
Second post-treatment anti-cancer therapy	24 (8.6)	39 (14.1)
Only 1 post-treatment anti-cancer therapy	58 (20.8)	90 (32.5)
Second post-treatment anti-cancer therapy		
EGFR-TKI	10 (3.6) [7.2]	14 (5.1) [6.6]
PD1/PDL1	2 (0.7) [1.4]	1 (0.4) [0.5]
Non-platinum chemotherapy	11 (3.9) [8.0]	19 (6.9) [8.9]
Platinum-based chemotherapy	4 (1.4) [2.9]	16 (5.8) [7.5]
Other targeted therapy	1 (0.4) [0.7]	2 (0.7) [0.9]
Anti-VEGF	3 (1.1) [2.2]	6 (2.2) [2.8]

[a] The number of patients is shown with percentages calculated as the proportion of patients in the FAS and secondly (between brackets) as the proportion of patients who discontinued randomised study treatment.
The first post-treatment anti-cancer therapy was the first treatment started on or after the last dose date of randomised study treatment. The second post-treatment anti-cancer therapy was the second treatment started on or after the last dose date of randomised study treatment.
Patients with no post-treatment anti-cancer therapy had discontinued randomised study treatment without starting any other post-treatment anti-cancer therapy.

Source: European Public Assessment Report (EPAR): Tagrisso (osimertinib). London (GB): European Medicines Agency; 2018: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/004124/WC500251570.pdf Accessed 2018 Jun 1. Table 16 Page 46[54]

e) Limitations/Sources of Bias[1,2]

Overall, the FLAURA trial was well-conducted. The randomization procedure, method of allocation concealment, and double-blind design were carried out appropriately. The treatment groups were well balanced, with the exception of age range; however, the median age was the same in both groups. There was transparent reporting of the disposition of patients throughout the trial, and outcome analyses were performed according to the intent-to-treat principle. The statistical analysis plan (SAP) of the trial specified the number of efficacy analyses to be performed of the primary outcome and the key secondary outcome, and used a hierarchical statistical testing strategy to adjust for multiplicity in testing the primary outcome (PFS) and key secondary outcomes (OS and CNS PFS). Sensitivity analyses related to the primary outcome were performed to account for ascertainment bias, evaluation-time bias, and attrition bias and were consistent with the primary PFS analysis.

However, the following limitations should be considered when interpreting the results:

- Given that the interim OS analysis results were immature at the time of the data cut and did not reach formal statistical significance for the interim analysis, OS data should be interpreted with caution.
- As well, because of the hierarchical statistical testing strategy, CNS PFS could not be formally tested for statistical significance and the P value for the statistical analyses was then classed as nominally significant. Therefore, reported results related to CNS PFS should be interpreted with caution.
- The QoL results were only available in poster form and have not been fully peer-reviewed. The assessment of patient-reported QoL is limited as currently presented and may not fully capture the QoL experience of all patients in the trial. Furthermore, QOL was not considered in the hierarchical statistical testing strategy and should therefore be considered exploratory. As a result, QoL data should be interpreted with caution.
- Lastly, the exclusion of afatinib from the comparator group is a study limitation. Although the publication noted that at the time of the trial initiation, afatinib was not widely used nor was it made available as a global standard-of-care EGFR-TKI.

For the complete assessment of the FLAURA trial, refer to *Table A3: Critical appraisal of the FLAURA trial using SIGN-50 Methodology Checklist 2: Controlled Trials.*

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Overall Survival – Secondary Outcome[1]

As noted previously, OS was a secondary outcome, and two analyses of overall survival were planned: one interim at the time of PFS and a final OS analysis (when the OS data was approximately 60% mature [approximately 318 deaths]).

At the interim OS analysis, overall survival data were immature (25% maturity; hazard ratio of 0.63 [95% CI, 0.45–0.88] *P*=0.007). As a result, the median OS was not estimable in either group. A P value of less than 0.0015 was required for statistical significance in the interim analysis of overall survival. Refer to *Figure 6.3: Progression-Free Survival and Overall Survival* for the Kaplan-Meier curve and estimates and *Table 6.6 Secondary Endpoints* for percentage of patients alive at 6, 12 and 18 months.

No subgroup analysis (for OS) was pre-specified in the statistical analysis plan nor was any subgroup analysis (for OS) performed.

Progression-Free Survival – Primary Outcome[1]

Progression-free survival was defined as the time from randomization to objective disease progression or death (from any cause in the absence of progression, irrespective of withdrawal from the trial or treatment with another anticancer therapy before progression) and was determined by the investigator assessment. As mentioned previously, (1) PFS was the primary outcome, only one analysis of the primary endpoint (PFS) was planned, (2) a sensitivity analysis of progression-free survival was performed using data from blinded independent central review of RECIST assessments, and (3) pre-specified subgroup analyses were also conducted for the following subgroups:

- sex (male vs. female)
- race (Asian vs. non-Asian)
- age at screening (<65 years vs. ≥65 years)
- CNS metastases status at entry (yes vs. no)
- smoking history
- baseline WHO performance status
- pre-treatment T790M status
- EGFR mutation (exon 19 deletion vs. L858R)
- EGFR mutation-positive by ctDNA,
- Centrally confirmed EGFR mutation).

In terms of overall investigator assessed PFS, there is a statistically significant difference in progression-free survival in favour of the osimertinib group (hazard ratio for disease progression or death, 0.46; 95% CI, 0.37 to 0.57; *P*<0.001).The median progression-free survival was 18.9 months in the osimertinib group compared with 10.2 months in the standard EGFR-TKI group. Refer to *Figure 6.3: Progression-Free Survival and Overall Survival* for the Kaplan-Meier curve and estimates. According to the EMA, there was a greater proportion of patients treated with osimertinib were alive and progression-free at 6 months, 12 months, and 18 months compared to those treated with SoC (6 months: 88.4% [95% CI: 83.9, 91.7] versus 75.2% [95% CI: 69.5, 79.9]; 12 months: 68.2% [95% CI: 62.3, 73.5] versus 42.3% [95% CI: 36.3, 48.2]; and 18 months: 50.9% (95% CI: 44.5, 57.0] versus 24.4% [95% CI: 19.2, 30.0]).

Results from the sensitivity analysis (blinded independent central review-assessed PFS) and all pre-defined subgroup analyses were consistent with those for primary PFS analysis (investigator-assessed PFS). Refer to *Figure 6.4 Progression-free survival assessed by blinded independent central review* for the Kaplan-Meier curve and estimates.

Figure 6.3: Progression-Free Survival and Overall Survival

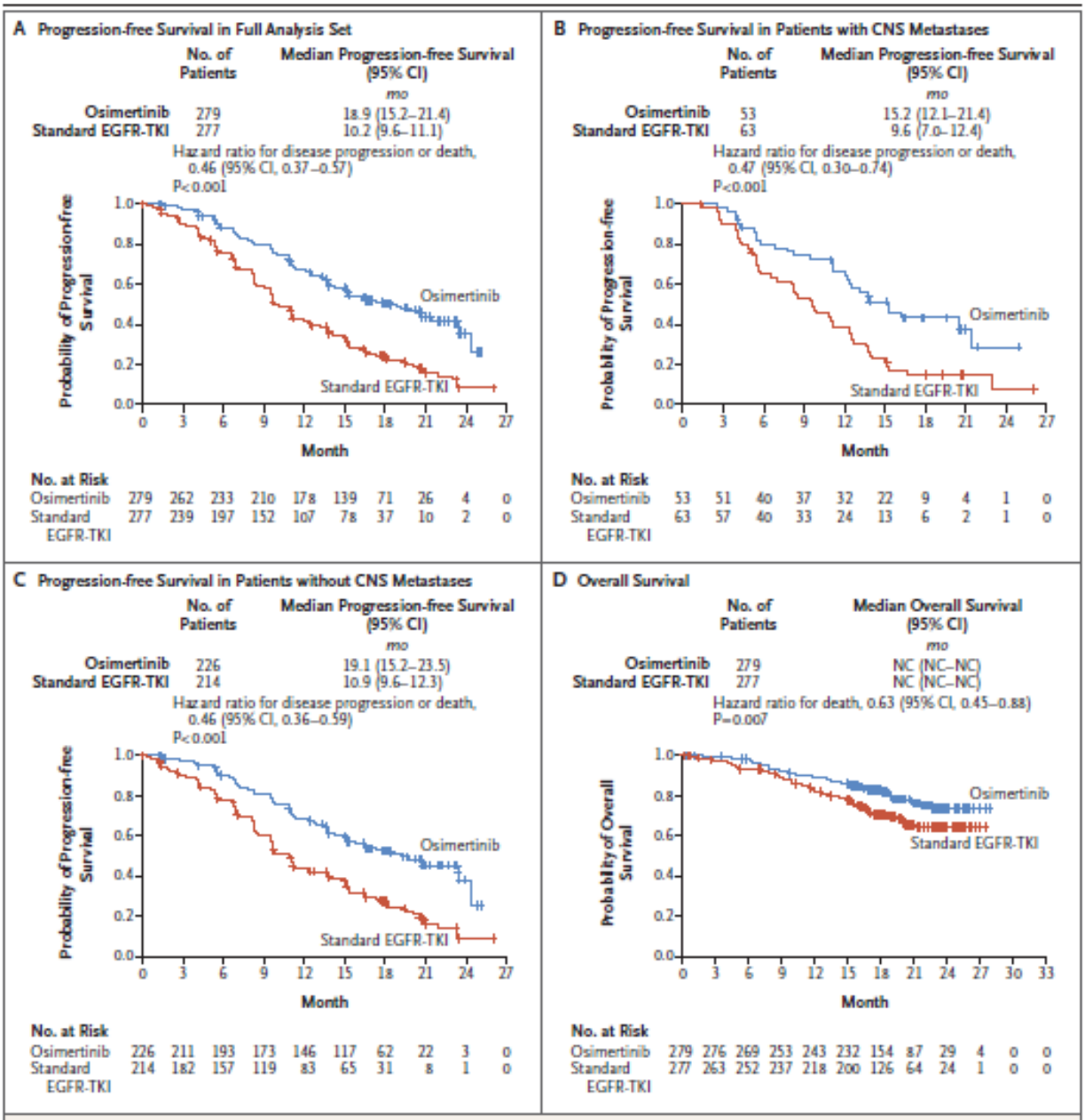


Figure 1. Progression-free Survival and Overall Survival.

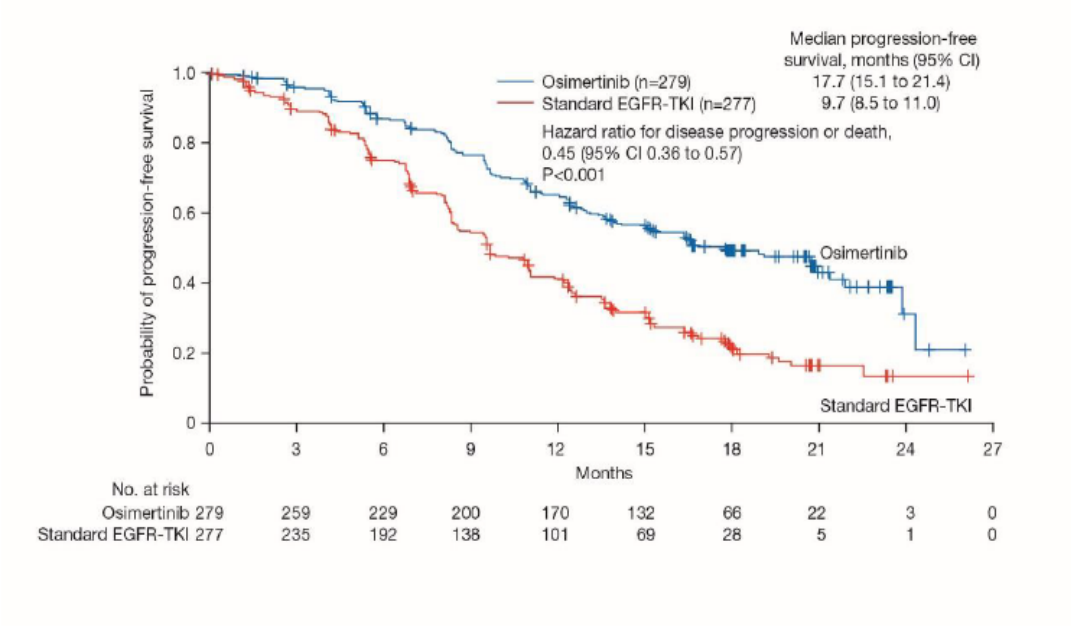
Shown are Kaplan–Meier estimates of the duration of progression-free survival in the full analysis set as assessed by investigators (Panel A), in patients with known or treated central nervous system (CNS) metastases at trial entry (Panel B), and in patients without known or treated CNS metastases at trial entry (Panel C). Also shown are Kaplan–Meier estimates of overall survival (Panel D). Censored data are indicated by tick marks. For the analysis of progression-free survival, data for patients who had not had a progression event or had not died at the time of the analysis were censored at the time of their last assessment (according to Response Evaluation Criteria in Solid Tumors) that could be evaluated. For the analysis of overall survival, data for any patients who were not known to have died at the time of the analysis were censored at the last recorded date that the patient was known to be alive. CI denotes confidence interval, EGFR-TKI epidermal growth factor receptor tyrosine kinase inhibitor, and NC could not be calculated.

Note: A P value of less than 0.0015 was required for statistical significance in the interim analysis of overall survival.

Source: New England Journal of Medicine. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. Soria JC, Ohe Y, Vansteenkiste J, et al., 378(2):113-125. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Figure 1. Page 6.[1]

Figure 6.4: Progression-free survival assessed by blinded independent central review.

Censored data are indicated by tick marks. For progression-free survival analysis, patients who had not progressed or died at the time of analysis were censored at the time of their last evaluable RECIST assessment.



CI, confidence interval; RECIST, response evaluation criteria for solid tumors

Source: New England Journal of Medicine. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. Soria JC, Ohe Y, Vansteenkiste J, et al., 378(2):113-125. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Figure S2. Page 19.[1]

Progression-Free Survival 2 – Exploratory Outcome[3]

Time from randomization to second progression (PFS2) was defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the primary efficacy variable of PFS or date of death after starting subsequent anti-cancer therapy. PFS2 was an exploratory outcome.

At the time of data cut-off, 26% of patients on osimertinib and 38% of patients on standard EGFR-TKI had second progression events after the start of subsequent therapy or died (hazard ratio of 0.58 [95% CI 0.44 to 0.78], *P*<0.001). Of note, the median PFS2 was not calculable (NC) (95% CI 23.7 to NC) for the osimertinib group and 20.0 months (95% CI 18.2 to NC) for the standard EGFR-TKI group.

Other Secondary Outcomes[1]

In terms of objective response rate, 80% of patients in the osimertinib group compared to 76% of patients in the standard EGFR-TKI group had at least 1 visit response of complete response (n=7, n=4 respectively) or partial response (n-216, n=206 respectively).

With regard to duration of response, the median duration of response was 17.2 months in the osimertinib group compared with 8.5 months in the standard EGFR-TKI group.

Lastly, with respect to disease control rate, 97% of patients in the osimertinib group and 92% in the standard EGFR-TKI group had a best overall response of complete response, partial response, or stable disease at least 6 weeks prior to any progressive disease. For more details refer to *Table 6.6.1 Secondary Endpoints*.

Table 6.6 Secondary Endpoints

End Point	Osimertinib (N= 279)	Standard EGFR-TKI (N= 277)
Type of response — no. (%)†		
Complete	7 (3)	4 (1)
Partial	216 (77)	206 (74)
Stable disease for ≥6 wk	47 (17)	46 (17)
Progression	3 (1)	14 (5)
Death	0	5 (2)
Could not be evaluated	6 (2)	7 (3)
Objective response rate — % of patients (95% CI)	80 (75–85)	76 (70–81)
Disease-control rate — % of patients (95% CI)‡	97 (94–99)	92 (89–95)
Time to response§		
No. of weeks — median (95% CI)	6.1 (6.0–6.1)	6.1 (NC–NC)
≤6 wk after first dose — no./total no. (%)	154/223 (69)	148/210 (70)
≤12 wk after first dose — no./total no. (%)	193/223 (87)	180/210 (86)
≤18 wk after first dose — no./total no. (%)	199/223 (89)	196/210 (93)
Duration of response¶		
No. of months — median (95% CI)	17.2 (13.8–22.0)	8.5 (7.3–9.8)
Range	0–23.8	0–24.9
Percent of patients with continued response at 12 mo (95% CI)	64 (58–70)	37 (31–44)
Percent of patients with continued response at 18 mo (95% CI)	49 (41–56)	19 (13–26)
Percent of patients with continued response at 24 mo (95% CI)	NC (NC–NC)	5 (1–16)
Overall survival‖		
No. of months — median (95% CI)	NC (NC–NC)	NC (NC–NC)
Percent of patients alive at 6 mo (95% CI)	98 (96–99)	93 (90–96)
Percent of patients alive at 12 mo (95% CI)	89 (85–92)	82 (77–86)
Percent of patients alive at 18 mo (95% CI)	83 (78–87)	71 (65–76)

* Efficacy analyses included all randomly assigned patients (full analysis set). CI denotes confidence interval, and NC could not be calculated.
† Tumor responses were assessed by the investigators according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.
‡ The disease-control rate is the proportion of patients who had a complete response, a partial response, or stable disease lasting at least 6 weeks before any disease-progression event.
§ The time to tumor response was calculated with the use of the Kaplan–Meier method from the date of randomization to the date of the first documentation of a partial or complete response. Per the protocol, RECIST assessments occurred every 6 weeks (±1 week) for 18 months, then every 12 weeks (±1 week) until disease progression.
¶ The duration of response was calculated with the use of the Kaplan–Meier method from the date of the first documented response until the date of documented disease progression or death in the absence of disease progression.
‖ Overall survival was calculated from the date of randomization to the date of death due to any cause.

Source: New England Journal of Medicine. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. Soria JC, Ohe Y, Vansteenkiste J, et al., 378(2):113-125. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Table 2. Page 8.[1]

CNS Metastases - *Subgroups of Special Interest*[1,49,53,54]

According to the trial publication, among all patients in the trial, events of CNS progression were reported in 6% of patients in the osimertinib group and 15% in the standard EGFR-TKI (n=17, 42 respectively).

Given the hierarchical statistical testing strategy, no formal test for statistical for progression-free survival in patients with CNS metastases (CNS PFS) could be performed (since OS did not reach formal statistical significance); the P value for the statistical analyses was then classed as nominally significant. CNS PFS was defined as the time from randomization to CNS progression or death by any cause. Select CNS metastases analyses are reported below.

For context, CNS analyses included different sets of patients: 1) CNS MTS, 2) cFAS by CNS BICR and 3) cEFR by CNS BICR (applicable to results related to response only). CNS MTS refers to patients with CNS metastases status at baseline based on investigator assessment, whereas, CNS BICR refers to CNS patients identified by blinded independent central review. cFAS is defined as patients with measurable and non-measurable CNS metastases at baseline, whereas, cEFR is defined as patients with measurable CNS metastases at baseline. The results presented below will only include CNS BICR: cFAS and cEFR.

It was reported that 200 patients had a baseline brain scan (36%)). With respect to the cFAS by CNS BICR dataset (n=128), there were 18 patients with CNS PFS events compared to 30 patients (in favor of osimertinib). The hazard ratio for CNS PFS was 0.48 (95%CI: 0.26 to 0.86, *P* = 0.014 [nominally statistically significant]). The median CNS PFS was not reached (95% CI 16.5 month to not calculable) for patients in the osimertinib group and 13.9 months (95% CI: 8.3 to not calculable) for patients in the standard EGFR-TKI group. Among the 128 patients, the confirmed objective response rate was 57.4% for patients in the osimertinib group and 40.3% for patients in the standard EGFR-TKI group. With respect to the cEFR by CNS BICR dataset (n=41), the confirmed objective response rate was 77.3% for patients in the osimertinib group and 63.2% for patients in the standard EGFR-TKI group. For more details, refer to *Table 6.6.2 Efficacy of CNS in cFAS and cEFR analysis set by CNS BICR*.

The European Medicines Agency also highlighted that regardless of the CSN lesion status at study entry (CNS metastases yes/no), patients in the osimertinib group demonstrated an efficacy benefit over patients in the standard EGFR-TKI group, as well, there were fewer patients with new CNS lesions in the osimertinib group compared to the standard EGFR-TKI group .

Table 6.6.2 Efficacy of CNS in cFAS and cEFR analysis set by CNS BICR

	Number (%) patients			
	cFAS (N=128)		cEFR (N=41)	
	Osimertinib (n = 61)	SoC (n = 67)	Osimertinib (n = 22)	SoC (n = 19)
CNS progression-free survival				
No. (%) patients with CNS PFS events (CNS progression or death)[a]	18 (29.5)	30 (44.8)	-	-
Median CNS PFS (months) (95% CI)[b]	NC (16.5, NC)	13.9 (8.3, NC)	-	-
Hazard ratio (95% CI)[c]	0.48 (0.26, 0.86)		-	
2-sided p-value	0.014[d]		-	
CNS progression-free survival by number of CNS lesions at baseline				
No. of patients with 1-3 CNS lesions at baseline	47	49	-	-
No. (%) patients with CNS PFS events (CNS progression or death)[a]	11 (23.4)	21 (42.9)	-	-
Median CNS PFS (months) (95% CI)[b]	NC (16.6, NC)	13.9 (9.7, NC)	-	-
No. of patients with >3 CNS lesions at baseline	14	18	-	-
No. (%) patients with CNS PFS events (CNS progression or death)[a]	7 (50.0)	9 (50.0)	-	-
Median CNS PFS (months) (95% CI)[b]	16.5 (7.5, NC)	8.3 (4.0, NC)	-	-
CNS objective response rate				
No. (%) patients with CNS response	40 (65.6)	29 (43.3)	20 (90.9)	13 (68.4)
ORR, % (95% CI)[e]	65.6 (52.3, 77.3)	43.3 (31.2, 56.0)	90.9 (70.8, 98.9)	68.4 (43.5, 87.4
CNS confirmed objective response rate				
No. (%) patients with CNS response	35 (57.4)	27 (40.3)	17 (77.3)	12 (63.2)
ORR, % (95% CI)[e]	57.4 (44.1, 70.0)	40.3 (28.5, 53.0)	77.3 (54.6, 92.2)	63.2 (38.4, 83.7)
CNS duration of response[f]				
Median CNS DoR (months) (95% CI)[b]	NC (11.9, NC)	14.4 (7.0, 18.7)	15.2 (4.1, NC)	18.7 (4.2, 18.7)
Patients remaining in response >6 months	30 (75.0)	16 (55.2)	15 (75.0)	6 (46.2)
Patients remaining in response >12 months	16 (40.0)	8 (27.6)	8 (40.0)	4 (30.8)
CNS duration of response for confirmed responses				
Median CNS DoR (months) (95% CI)[b]	NC (11.9, NC)	14.4 (8.3, 18.7)	NC (8.5, NC)	18.7 (4.2, 18.7)
Patients remaining in response >6 months	30 (85.7)	16 (59.3)	15 (88.2)	6 (50.0)
Patients remaining in response >12 months	16 (45.7)	8 (29.6)	8 (47.1)	4 (33.3)
CNS disease control rate				
DCR% (95% CI)	90.2 (79.8, 96.3)	83.6 (72.5, 91.5)	95.5 (77.2, 99.9)	89.5 (66.9, 98.7)

cEFR = central nervous system evaluable-for-response analysis set; cFAS = central nervous system full analysis set.

a Progression events that did not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) were censored and therefore excluded from the number of events.

b Calculated using the Kaplan-Meier method.

c The HR was calculated from a Cox proportional hazards model with a factor for treatment. The CI was calculated using profile likelihood. An HR <1 favours osimertinib.

d nominally statistically significant.

e The CIs were calculated using Clopper-Pearson exact method for binomial proportions.

f Duration of response is the time from first documentation of CR/PR until the date of progression or death in absence of disease progression. Responses required confirmation at least 4 weeks after the criteria for first response were met.

DCO1: 12 June 2017

Source: European Public Assessment Report (EPAR): Tagrisso (osimertinib). London (GB): European Medicines Agency; 2018: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/004124/WC500251570.pdf Accessed 2018 Jun 1. Table 31.Page 66[54]

EFGR Mutation Type - *Subgroups of Special Interest*[3]

EFGR mutation type was among the pre-specified subgroups analyses performed for progression-free survival. It is important to note that the pre-specified subgroup analyses were only designed to be supportive of the primary analysis of progression-free survival and thus, no adjustment to the significance level was made. Below are certain EFGR mutation type analyses reported.

In patients with Exon 19 deletion, the median progression-free survival for the osimertinib group was 21.4 months compared with 11.0 months in the standard EGFR-TKI group (hazard ratio for disease progression or death, 0.43 [95% CI 0.32-0.56], *P*<0.001). In patients with L858R (21 substitution), the median progression-free survival for the osimertinib group was 14.4 months compared with 9.5 months in the standard EGFR-TKI group (hazard ratio for disease progression or death, 0.51 [95% CI 0.36-0.71], *P*<0.001).

***Quality of Life*[5]**

All randomized patients were asked to complete the QLQ-C30 (at baseline and followed by every 6 weeks) and the QLQ-LC13 (at baseline, then weekly for 6 weeks, and followed by every 3 weeks).

Leighl et al. noted that item scores range from 0 to 100, with higher functional scores representing a higher ('better') quality of life or level of functioning, and a higher score on the symptom scale representing an increased level of symptomatology/problems. It was stated that a difference in score of at least 10 points was considered clinically relevant, which was believed to correspond to a moderate or greater change in patient-reported quality of life. So, symptom improvement rates were defined as a decrease in score from baseline of at least 10 at two consecutive assessments at least 21 days apart. Key endpoints presented in the poster included changes in cough, dyspnoea, chest pain, fatigue and appetite loss. Leigh et al. assessed improvements in key symptoms (defined as a decrease in score from baseline of ≥ 10 at two consecutive assessments ≥ 21 days apart) and time to symptom deterioration (defined as time from randomization until the date of the first clinically relevant symptom deterioration or death from any cause).

According to Leighl et al, compliance rate with completing the both questionnaires was above 70% at most of the time points in both treatment groups. Baseline mean QLQ-LC13 scores and QLQ-C30 scores were similar among patients in the osimertinib and the standard EGFR-TKI groups. Although, according to Leigh et al., patients in FLAURA trial reported clinically relevant lower scores for Dyspnoea (i.e., ≥ 10 points) and clinically relevant higher scores for Role functioning and Cognitive functioning compared to the EORTC reference population (recall: higher functional scores representing 'better' quality of life or level of functioning, and a higher score on the symptom scale representing an increased level of symptomatology/problems).

According to Leighl et al, key symptoms (dyspnoea, chest pain, fatigue and appetite loss) improved from baseline until randomized treatment discontinuation, but of these only cough in the osimertinib group was clinically relevant (i.e., decrease of 10.14, which favours osimertinib). There were no significant differences (i.e. *P*<0.05) between treatment groups, with the exception of chest pain where the estimated treatment difference (osimertinib minus standard care EGFR-TRI) was -2.96 (95% CI: -5.47-0.47), *P*= 0.021 (adjusted mean chest pain scores for the osimertinib were -2.96 lower than the comparator group) (recall: a higher score on the symptom scale

representing an increased level of symptomatology/problems). Refer to Table 6.7 for more details.

Leighl et al. also noted that the proportion of patients with clinically relevant improvements at any time until randomized treatment discontinuation was similar for the key symptoms in both treatment groups. Refer to Figure 6.5 for more details.

In terms of mean changes from baseline in global health and functioning, there were no clinically meaningful improvements in QLQ-C30 Global health status, Physical functioning, Role functioning, Emotional functioning, Cognitive functioning and Social functioning. Refer to Figure 6.6 for more details.

With regard to time to deterioration of key lung cancer symptoms, the median time from randomization to the first recorded clinically relevant deterioration of key lung cancer symptoms was similar between the two treatment groups. Refer to Figure 6.7 for more details.

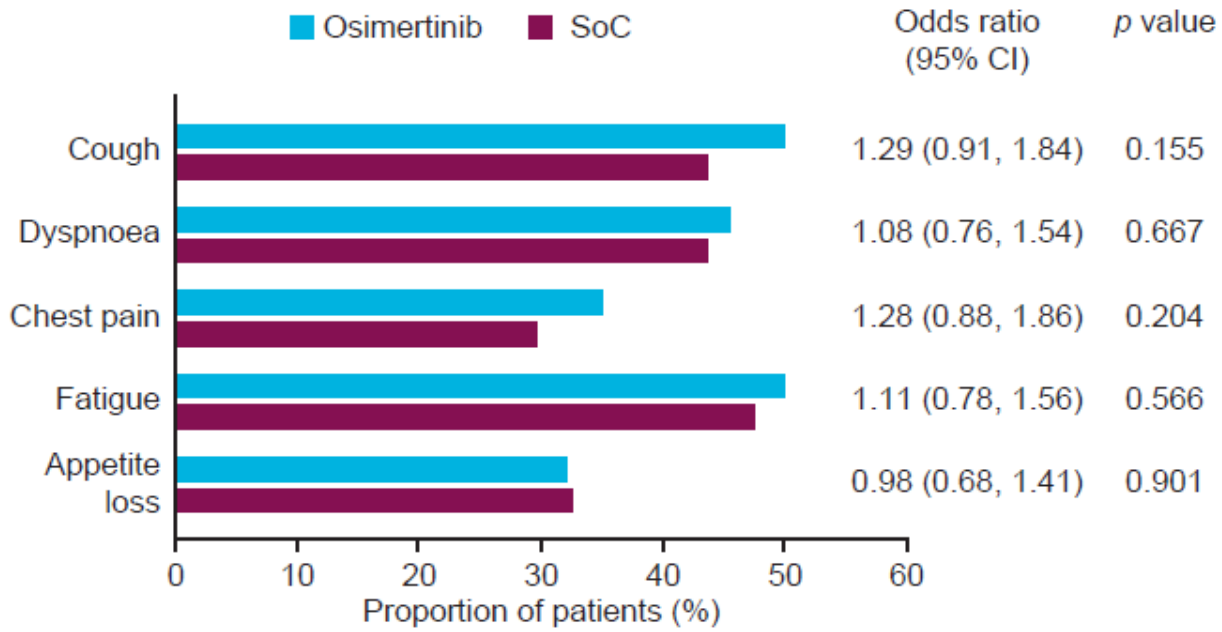
Table 6.7: Changes in key patient-reported symptom scores over time from baseline until randomization treatment discontinuation, assessed using MMRM analysis*

Symptom	Treatment	Adjusted mean (95% CI)	Estimated treatment difference[b] (95% CI)	*p* value
Cough	Osimertinib	**–10.14** (–12.12, –8.16)	–1.96 (–4.83, 0.91)	0.180
	SoC	–8.18 (–10.25, –6.10)		
Dyspnoea	Osimertinib	–3.19 (–4.92, –1.47)	–1.99 (–4.45, 0.47)	0.113
	SoC	–1.20 (–2.95, 0.54)		
Chest pain	Osimertinib	–6.84 (–8.58, –5.10)	–2.96 (–5.47, –0.45)	0.021
	SoC	–3.88 (–5.69, –2.07)		
Fatigue	Osimertinib	–3.30 (–5.45, –1.16)	0.01 (–3.22, 3.25)	0.993
	SoC	–3.32 (–5.68, –0.95)		
Appetite loss	Osimertinib	–5.81 (–8.24, –3.39)	–1.46 (–5.08, 2.15)	0.427
	SoC	–4.35 (–7.04, –1.66)		

[a]Treatment, visit and treatment by visit interaction were fitted as fixed effects in the model; patient fitted as a random effect. Compound symmetry was used as the covariance structure for all models.
[b]Osimertinib minus SoC.
CI, confidence interval; MMRM, mixed-effects model for repeated measures; SoC, standard of care.

Source: Leighl NB, Karaseva N, Nakagawa K, et al. Patient-reported outcomes from FLAURA: osimertinib versus standard of care epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) in patients with EGFR-mutated advanced non-small cell lung cancer (poster 139PD). Poster presented at: 8th European Lung Cancer Conference (ELCC); 2018 April 11–14; Geneva, (Switzerland); 2018. Table 3.[5] Full-text conference poster provided by AstraZeneca Canada Inc.

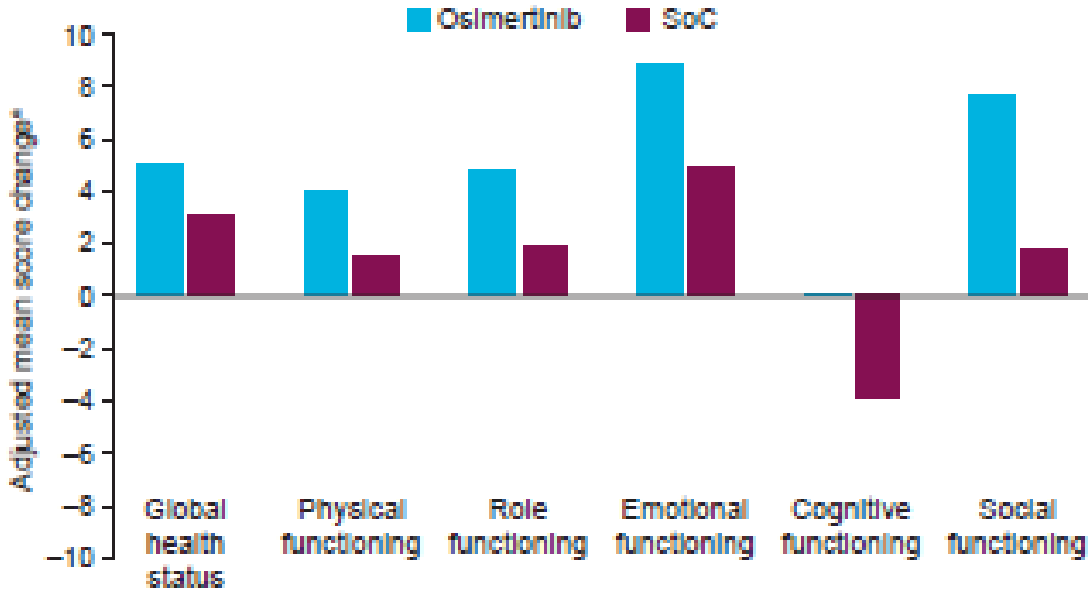
Figure 6.5 Proportion of patients with improvement in key symptoms



[a]Symptom improvement rate was based on a decrease in score from baseline of ≥ 10 at two consecutive assessments ≥ 21 days apart.
CI, confidence interval; SoC, standard of care.

Source: Leighl NB, Karaseva N, Nakagawa K, et al. Patient-reported outcomes from FLAURA: osimertinib versus standard of care epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) in patients with EGFR-mutated advanced non-small cell lung cancer (poster 139PD). Poster presented at: 8th European Lung Cancer Conference (ELCC); 2018 April 11–14; Geneva, (Switzerland); 2018. Figure 2.[5] Full-text conference poster provided by AstraZeneca Canada Inc.

Figure 6.6: Changes from baseline in global health and functioning scores over time from baseline until randomization treatment discontinuation, assessed using MMRM analysis*

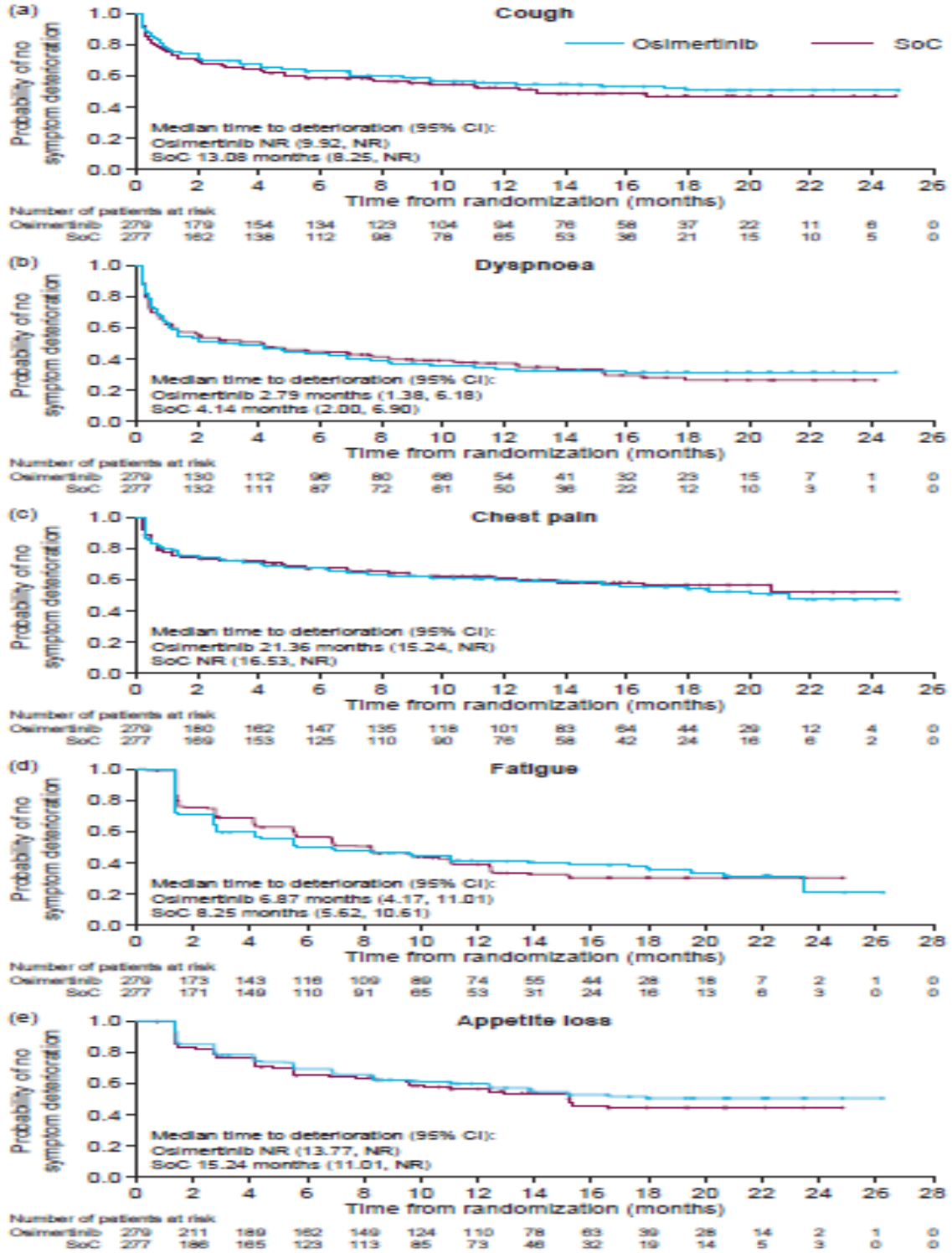


	Global health status	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning
Estimated difference:	2.06	2.43	2.91	**3.88**	**3.94**	**6.82**
95% CI:	−0.85, 4.98	−0.20, 5.06	−0.58, 6.40	1.22, 6.53	1.22, 6.67	12.88, 8.97
	$p = 0.165$	$p = 0.070$	$p = 0.102$	$p = 0.004$	$p = 0.006$	$p < 0.001$

*Treatment, visit and treatment by visit interaction were fitted as fixed effects in the model; patient fitted as a random effect. Compound symmetry was used as the covariance structure for all models.
CI, confidence interval; MMRM, mixed-effects model for repeated measures; SoC, standard of care.

Source: Leighl NB, Karaseva N, Nakagawa K, et al. Patient-reported outcomes from FLAURA: osimertinib versus standard of care epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) in patients with EGFR-mutated advanced non-small cell lung cancer (poster 139PD). Poster presented at: 8th European Lung Cancer Conference (ELCC); 2018 April 11–14; Geneva, (Switzerland); 2018. Figure 3.[5] Full-text conference poster provided by AstraZeneca Canada Inc.

Figure 6.7: Time to deterioration of key patient-reported symptoms*



*Time to symptom deterioration was defined as the time from randomization until the date of the first record of clinically relevant deterioration (increase in symptom scale score of ≥ 10 points from baseline) or death (from any cause).
CI, confidence interval; NR, not reached; SoC, standard of care.

Source: Leighl NB, Karaseva N, Nakagawa K, et al. Patient-reported outcomes from FLAURA: osimertinib versus standard of care epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) in patients with EGFR-mutated advanced non-small cell lung cancer (poster 139PD). Poster presented at: 8th European Lung Cancer

Conference (ELCC); 2018 April 11–14; Geneva, (Switzerland); 2018. Figure 4.[5] Full-text conference poster provided by AstraZeneca Canada Inc.

Harms Outcomes[1]

A summary of safety outcomes in the FLAURA trial is provided in *Table 6.8: Key harms outcomes, Table 6.9: Adverse events* and *Table 6.10: Most common possibly casually-related adverse events (as assessed by the investigator) reported in at least 10% of patients treated with osimertinib or standard EGFR-TKI*.

Adverse Events[1,54]

Safety assessments were performed in all patients who received at least one dose of randomly assigned treatment; this included 279 patients in the osimertinib group and 277 patients in the standard EGFR-TKI group. Overall, the majority of patients reported adverse events of any grade (98% in each group). Rash or acne (58% in the osimertinib group and 78% in the standard EGFR-TKI group), diarrhea (58% and 57%, respectively), and dry skin (36% in each group) were the most commonly reported adverse events. For more detail, refer to *Table 6.9: Adverse events*.

The most common adverse events that were considered by the investigator to be possibly related to study treatment were: rashes and acnes, diarrhea, dry skin, paronychia, stomatitis, decreased appetite, pruritus, aspartate, aminotransferase elevation, and alanine aminotransferase elevation. For more details, refer to *Table 6.10: Most common possibly casually-related adverse events (as assessed by the investigator) reported in at least 10% of patients treated with osimertinib or standard EGFR-TKI*.

In terms of cardiac effects, changes in QT interval occurred in 10% of patients in the osimertinib group (29/279) compared with 5% of patients in the standard EGFR-TKI group (13/277); the majority of which were grade 1 or 2 and there were no fatal cases of torsades des pointes or prolongation of the QT interval in either group. Cardiac failure SMQ was reported in 4% of patients in the osimertinib group and 2% of patients in the standard EGFR-TKI group, while cardiomyopathy SMQ was reported in 4% and 2% of patients respectively. With respect to interstitial lung disease, adverse events of interstitial lung disease occurred in 4% of patients in the osimertinib group (11/279) compared to 2% patients in the standard EGFR-TKI group (6/277) and no fatal events of interstitial lung disease were reported in either group. In terms of left ventricle dysfunction, 8 patients in the osimertinib group and 3 patients in the standard EGFR-TKI group had a ≥10%-point decrease from baseline to an LVEF value <50%. Lastly, the grouped term keratitis was reported less than 1% of patients receiving osimertinib and less than 2% of patients receiving standard EGFR-TKI.

Adverse events of grade 3 or greater were reported in 34% of patients in the osimertinib group (95/279) compared with 45% of patients in the standard EGFR-TKI group (124/277).

Serious Adverse Events[1]

Serious adverse events were reported in 22% of patients in the osimertinib group (60/279) and 25% of patients in the standard EGFR-TKI group (70/277). Of note, a serious event of QT interval prolongation was reported in 1 patient in the osimertinib group and serious events of interstitial lung disease were reported in 6 patients in the osimertinib group and 4 in the standard EGFR-TKI group.

Adverse events leading to death were reported in 2% of patients in the osimertinib group (6/279) and 4% of patients in the standard EGFR-TKI group (10/277). Of note, none of the adverse events

leading to death were considered related to osimertinib; however one adverse event leading to death (diarrhea) was considered related to standard EGFR-TKI.

Withdrawal Due to Adverse Events[1]

In terms of withdrawal due to adverse events, a total of 13% (36/279) of patients in the osimertinib group discontinued treatment due to adverse event compared with 18% (50/277) of patients in the standard EGFR-TKI group.

Table 6.8: Key harms outcomes

Harms Outcome, n (%)	Osimertinib (n=279)	Standard EGFR-TKI (n=277)
Adverse Events (any grade)	273 (98)	271 (98)
Grade ≥3 Adverse Events	95(34)	124 (45)
Serious Adverse Events	60(22)	70(25)
Withdrawal Due to Adverse Event	36(13)	50(18)
Fatal Adverse Events	6(2) †	10(4) ‡

† Osimertinib group :pneumonia, respiratory, tract infection, cerebral infarction, myocardial infarction, pulmonary embolism, and intestinal ischemia in 1 patient each
‡ Standard EGFR-TKI group: sepsis in 2 patients; pneumonia in 1; endocarditis in 1; cognitive disorder and pneumonia in 1; peripheral-artery occlusion in 1; dyspnea in 1; hemoptysis in 1; diarrhea, gastrointestinal hemorrhage, respiratory failure, and circulatory collapse in 1; and "death" [the adverse event was not further specified] in 1.

Source: Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113-25. DOI: 10.1056/NEJMoa1713137; Protocol for: Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113-25. DOI: 10.1056/NEJMoa1713137; RA MALINGAM, S., et al.2017 Annals of Oncology 2017 28 (Supplement 5)(v635[1-3]

Table 6.9: Adverse events

Table 3. Adverse Events.*

Adverse Event	Osimertinib (N=279)					Standard EGFR-TKI (N=277)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)									
Any adverse event	273 (98)	34 (12)	144 (52)	83 (30)	6 (2)	271 (98)	22 (8)	125 (45)	103 (37)	11 (4)
Rash or acne†	161 (58)	134 (48)	24 (9)	3 (1)	0	216 (78)	110 (40)	87 (31)	19 (7)	0
Diarrhea	161 (58)	120 (43)	35 (13)	6 (2)	0	159 (57)‡	116 (42)	35 (13)	6 (2)	0
Dry skin†	100 (36)	87 (31)	12 (4)	1 (<1)	0	100 (36)	76 (27)	21 (8)	3 (1)	0
Paronychia†	97 (35)	52 (19)	44 (16)	1 (<1)	0	91 (33)	55 (20)	34 (12)	2 (1)	0
Stomatitis	80 (29)	65 (23)	13 (5)	1 (<1)	1 (<1)	56 (20)	47 (17)	8 (3)	1 (<1)	0
Decreased appetite	56 (20)	27 (10)	22 (8)	7 (3)	0	52 (19)	25 (9)	22 (8)	5 (2)	0
Pruritus	48 (17)	40 (14)	7 (3)	1 (<1)	0	43 (16)	30 (11)	13 (5)	0	0
Cough	46 (16)	34 (12)	12 (4)	0	0	42 (15)	25 (9)	16 (6)	1 (<1)	0
Constipation	42 (15)	33 (12)	9 (3)	0	0	35 (13)	28 (10)	7 (3)	0	0
Nausea	39 (14)	28 (10)	11 (4)	0	0	52 (19)‡	32 (12)	19 (7)	0	0
Fatigue	38 (14)	21 (8)	15 (5)	2 (1)	0	33 (12)	23 (8)	8 (3)	2 (1)	0
Dyspnea	35 (13)	24 (9)	10 (4)	1 (<1)	0	20 (7)‡	8 (3)	8 (3)	3 (1)	0
Anemia	34 (12)	19 (7)	12 (4)	3 (1)	0	25 (9)	18 (6)	4 (1)	3 (1)	0
Headache	33 (12)	26 (9)	6 (2)	1 (<1)	0	19 (7)	12 (4)	7 (3)	0	0
Vomiting	31 (11)	25 (9)	6 (2)	0	0	29 (10)	22 (8)	3 (1)	4 (1)	0
Upper respiratory tract infection	28 (10)	16 (6)	12 (4)	0	0	18 (6)	9 (3)	9 (3)	0	0
Pyrexia	28 (10)	27 (10)	1 (<1)	0	0	11 (4)	8 (3)	2 (1)	1 (<1)	0
Prolonged QT interval on ECG	28 (10)	11 (4)	11 (4)	5 (2)	1 (<1)	11 (4)	6 (2)	3 (1)	2 (1)	0
Aspartate aminotransferase elevation	26 (9)	18 (6)	6 (2)	2 (1)	0	68 (25)	38 (14)	18 (6)	12 (4)	0
Alopecia	20 (7)	17 (6)	3 (1)	0	0	35 (13)	31 (11)	4 (1)	0	0
Alanine aminotransferase elevation	18 (6)	11 (4)	6 (2)	1 (<1)	0	75 (27)	31 (11)	19 (7)	21 (8)	4 (1)

* Listed are adverse events that were reported in at least 10% of the patients in any group. Safety analyses included all the patients who received at least one dose of a trial drug (safety analysis set). Some patients had more than one adverse event. ECG denotes electrocardiography.
† This category represents a grouped term for the event. If a patient had multiple preferred-term events within a specific grouped-term adverse event, then the maximum grade (according to the Common Terminology Criteria for Adverse Events) across those events was counted.
‡ In the standard EGFR-TKI group, there were two patients who had missing data on grade, one with diarrhea and one with nausea. In addition, there was one patient with grade 5 diarrhea and one patient with grade 5 dyspnea.

Source: New England Journal of Medicine. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. Soria JC, Ohe Y, Vansteenkiste J, et al., 378(2):113-125. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Table 3. Page 10.[1]

Table 6.10: Most common possibly casually-related adverse events (as assessed by the investigator) reported in at least 10% of patients treated with osimertinib or standard EGFR-TKI

Table S7. Most common possibly causally-related adverse events (as assessed by the investigator) reported in at least 10% of patients treated with osimertinib or standard EGFR-TKI

Adverse events by preferred term*	Osimertinib (n=279)					Standard EGFR-TKI (n=277)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
	Number (percent)									
Rashes and acnes†	152 (54)	125 (45)	24 (9)	3 (1)	0	205 (74)	105 (38)	81 (29)	19 (7)	0
Diarrhea	138 (49)	105 (38)	27 (10)	6 (2)	0	142 (51)	105 (38)	31 (11)	5 (2)	0
Dry Skin†	93 (33)	80 (29)	12 (4)	1 (<1)	0	92 (33)	70 (25)	19 (7)	3 (1)	0
Paronychia†	91 (33)	48 (17)	42 (15)	1 (<1)	0	84 (30)	52 (19)	30 (11)	2 (1)	0
Stomatitis	69 (25)	57 (20)	11 (4)	1 (<1)	0	45 (16)	36 (13)	8 (3)	1 (<1)	0
Decreased appetite	33 (12)	15 (5)	13 (5)	5 (2)	0	29 (10)	16 (6)	11 (4)	2 (1)	0
Pruritus	43 (15)	36 (13)	6 (2)	0	0	38 (14)	26 (9)	12 (4)	0	0
Aspartate aminotransferase elevation	22 (8)	15 (5)	5 (2)	2 (1)	0	57 (21)	31 (11)	16 (6)	10 (4)	0
Alanine aminotransferase elevation	17 (6)	11 (4)	5 (2)	1 (<1)	0	62 (22)	23 (8)	16 (6)	19 (7)	4 (1)

EGFR, epidermal growth factor receptor, TKI, tyrosine kinase inhibitor

* Adverse events occurring in 10% or more of patients in any group are listed. Safety analyses included all patients who received at least one dose of trial drug (safety analysis set). Some patients had more than one adverse event.

†This category represents a grouped term for the event. If a patient had multiple preferred-term level events within a specific grouped term adverse event, then the maximum grade across those events was counted.

Source: New England Journal of Medicine. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. Soria JC, Ohe Y, Vansteenkiste J, et al., 378(2):113-125. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Table S7. Page 32[3]

6.4 Ongoing Trials

Apart from the FLAURA trial, no other ongoing trial met the inclusion criteria for this review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question/assessment was identified as relevant to the pCODR review of osimertinib in NSCLC:

- Critical appraisal of the manufacturer-submitted indirect treatment comparison (ITC) of osimertinib versus afatinib for advanced/metastatic EGFR mutation-positive NSCLC patients.[7]

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

7.1 Critical Appraisal of Indirect Treatment Comparison of Osimertinib versus Afatinib[7,57]

7.1.1 Objective

The objective of this section was to summarize and critically appraise the methods and findings of the manufacturer-submitted ITC of osimertinib versus afatinib for advanced/metastatic EGFR mutation-positive NSCLC patients.

7.1.2 Findings

The following were reasons for which this critical appraisal was necessary:

- Afatinib is a relevant comparator;
- No available direct comparison of osimertinib to afatinib; and
- The manufacturer-submitted an economic evaluation which included afatinib as a comparator.
- Of note, the results of the ITC were not used in the pharmacoeconomic model, rather the Submitter provided this ITC as supplemental material.

7.1.3 Summary

ITC Methods

The submitter's objective was to perform an ITC of osimertinib versus other relevant options for EGFR mutation-positive NSCLC patients.

The following were the ITC inclusion criteria:

- Population - studies that had study population exclusively of patients with EGFR mutation-positive NSCLC patients receiving treatment at first line.
- Treatments – compare osimertinib with other EGFR-TKIs including afatinib, erlotinib and gefitinib.
- Endpoints – overall survival and progression-free survival (investigator assessed). Independent assessed progression free survival was considered in a scenario analysis.
- Study design – the systematic literature review included both RCTs and non-randomized study designs, but the ITC required only evidence from RCTs, therefore studies from non-randomized designs were excluded from the ITC.

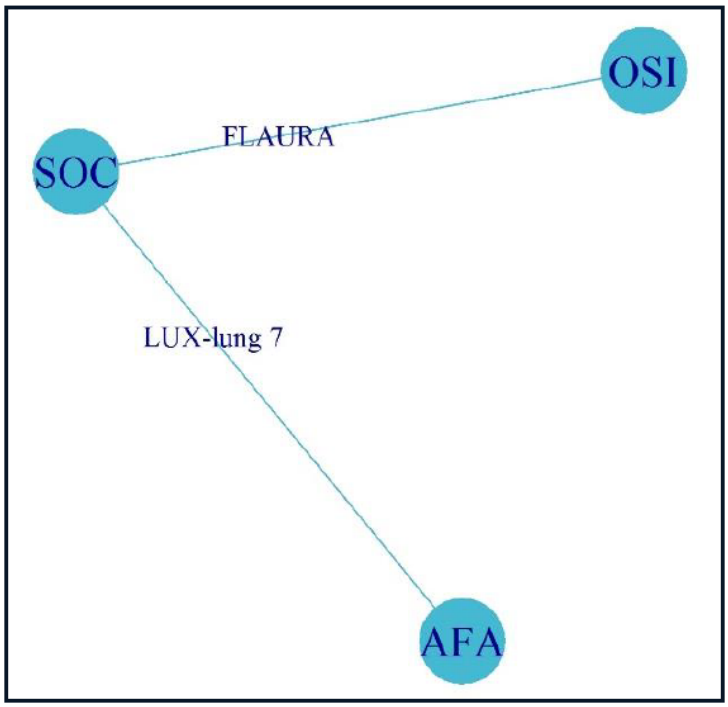
In an ITC, a common comparator is required to form a link between the treatments of interest. The FLAURA trial compared osimertinib to standard EGFR-TKI (erlotinib or gefitinib), therefore, the common comparator used in the ITC is standard EGFR-TKI. However, the relative effect of osimertinib was only found compared to erlotinib and gefitinib combined; in other words, separate results (osimertinib versus erlotinib and osimertinib versus gefitinib) were not reported nor pre-specified in the study's analysis plan. As a result, a fundamental assumption of the ITC was that gefitinib and erlotinib are equivalent in efficacy and with this assumption, the common comparator used in the ITC became standard EGFR-TKI (erlotinib and/or gefitinib). According to the CGP, it was a reasonable assumption that erlotinib and gefitinib are of equivalent efficacy in the EGFR mutation set ting, however erlotinib is considered to be more toxic than gefitinib.

ITC Results[7]

From the submitter's systematic literature search, three head-to-head RCTs of EGFR-TKIs (ARCHER 1050, LUX-Lung 7, and CTONG 0901) in addition to the FLAURA study were identified. CTONG 0901 (erlotinib versus) gefitinib was not considered in the ITC because the study reduces to a single arm when the erlotinib and gefitinib arms are combined. The ARCHER 1050 study was not considered because dacomitinib is not currently licensed for first-line treatment and therefore was not considered a relevant comparator. Therefore, the network of evidence only consisted of the FLAURA trial (osimertinib versus standard EGFR-

TKI [erlotinib or gefitinib])[1] and the LUX-Lung 7 trial (afatinib versus gefitinib)[6] See Figure 1: ITC analysis – network of evidence for the network of evidence.

Figure 1: ITC analysis – network of evidence



Key: AFA, afatinib; OSI, osimertinib; SOC, standard of care (gefitinib/erlotinib).

Source: Figure provided by AstraZeneca Canada Inc. in the pCODR Submission[7]

The submitter compared the following patient characteristics to address any heterogeneity: age, gender, race, central nervous system metastases, disease stage, smoking status and EFGR mutation type. The submitter noted that baseline characteristics were similar, with the exception of disease status and explained that results for this subgroup (disease stage) was not presented in the publication and therefore could not be investigated further. As well, the submitter noted that treatment switch was a source of trial heterogeneity and addressed that treatment switching in both studies was relatively low, but that in the absence of adjusted results, treatment switching may be a limitation of the ITC.

For the ITC comparing osimertinib and afatinib, the submitter used the Bucher method. As previously noted, the outcomes of interest were progression-free survival (investigator assessed) and overall survival. As well, the following sensitivity analyses were performed for progression-free survival: CNS metastases (patients with metastases versus patients without metastases), EGFR mutation type (exon 19 deletions versus exon 21 L858R), and ethnicity (non-Asian versus Asian). The submitter noted that subgroup analysis could not be performed for OS, since OS data were not available for the FLAURA trial.

According to the submitter, the results of the ITC suggest that osimertinib improved both PFS and OS compared to afatinib in the overall population (patients with EFGR mutation positive NSCLC receiving treatment at first line) and for each subgroup (CNS metastases, EGFR mutation type and ethnicity) (refer to Table 7.1 *Results of Indirect Treatment Comparison, Osimertinib versus Afatinib*).

Table 7.1 Results of Indirect Treatment Comparison, Osimertinib versus Afatinib

Osimertinib Versus Afatinib	Hazard Ratio (95% Confidence Interval)
Investigator assessed PFS	0.59 (0.43-0.82)
Overall survival	0.73 (0.48-1.12)
SCENARIO ANALYSIS	
Independent assessed PFS	0.62 (0.44-0.87)
SUBGROUP ANALYSIS	
EGFRm: Exon 19 deletion	0.57 (0.37-0.87)
EGFRm: L858R (21 substitution)	0.72(0.43-1.21)
Race: Asian	0.72(0.47-1.11)
Race: Non-Asian	0.47(0.28-0.80)
CNS metastasis: Yes	0.62(0.29-1.34)
CNS metastasis: No	0.62(0.43-0.90)
Abbreviations: CNS=central nervous system; EGFRm=epidermal growth factor receptor mutation; PFS=progression-free survival;	

Source: Information provided by AstraZeneca Canada Inc. in the pCODR Submission[7]

ITC Critical Appraisal

The credibility of the manufacturer-submitted ITC was assessed in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparison. Details and commentary with respect to the manufacturer-submitted ITC for each item in the ISPOR Task Force Questionnaire to Assess the Relevance snd Credibility of a Network Meta-Analysis can be found in *Table 7.2*.

ITC Conclusions

As mentioned above, according to the submitter, the results of the ITC suggested that osimertinib improved both PFS and OS compared to afatinib in the overall population (patients with EFGR mutation positive NSCLC receiving treatment at first line) and for each subgroup (CNS metastases, EGFR mutation type and ethnicity).
Overall, there is moderate uncertainty in the reported ITC results.
The following considerations should be taken into account when interpreting the results of the ITC:

- A fundamental assumption of the ITC was that erlotinib is of equivalent efficacy to gefitinib. If one believes erlotinib and gefitinib are of equivalent efficacy, then there is a network to indirectly compare osimertinib to afatinib. The FLAURA trial compares osimertinib to standard EGFR-TKI (erlotinib or gefitinib), while LUX-Lung 7 compares afatinib to gefitinib. With the assumption that erlotinib is equivalent to gefitinib, the common comparator used in the ITC is standard EGFR-TKI (erlotinib and/or gefitinib). However, if one does not believe that erlotinib and gefitinib are of equivalent efficacy then this indirect comparison is not valid. According to the CGP, it was a reasonable assumption that erlotinib and gefitinib are of equivalent efficacy in the EGFR mutation setting, however erlotinib is considered to be more toxic than gefitinib.
- More transparent reporting would have been helpful; as the submitted ITC did not fully adhere to the best practices for the conduct of ITC, as well as the CADTH Guidelines for Reporting Indirect Comparisons. For instance, many details related to the Methods of the Indirect Comparison were missing (i.e. 3.1 - provide literature search strategy, including publication dates for inclusion, database used, keywords, and relevant medication Subject

Headings (mesh) terms; 3.4 specify doses included for each treatment, 3.6 – Describe study selection process: report this using Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flow diagram; 3.7 outline methods of quality assessment of literature that met the inclusion criteria). These missing details related to the methodology of the ITC made it difficult to perform a comprehensive assessment of the ITC. More transparent reporting and better adherence to the best practice for the conduct of ITC would have been appreciated to fully critically appraise the ITC and may have reduced uncertainty.

- It was appropriate to use the Bucher method.
- The ITC considered the following relevant outcomes: OS and PFS but not health related quality of life (HRQoL). However, the purpose of the ITC was to inform the cost-effectiveness analysis and therefore, HRQoL is relevant outcome that was not considered in the ITC.
- There was a systematic difference in the reporting of disease stage (a treatment effect modifier) across the different treatment comparison in the network; there were more patients with advanced stage NSCLC in the LUX-Lung 7 trial compared to the FLAURA trial (96.6% versus 82% with Stage IV NSCLC). The ITC report noted this systematic difference and explained that results for this subgroup (disease stage) was not presented and therefore could not be investigated further.
- As well, the submitter noted that treatment switch is a source of trial heterogeneity and addressed that treatment switching in both studies was relatively low, but that in the absence of adjusted results, treatment switching may be a limitation of the ITC.
- The ITC was prepared for AstraZeneca. This ITC is not published and as a result, has not been fully peer-reviewed.

Table 7.2 ISPOR Task Force Questionnaire to Assess the Relevance snd Credibility of a Network Meta-Analysis Applied to the Manufacturer-Submitted Indirect Treatment Comparison

Relevance

		Strength	Weakness	Can't answer		
				Not reported	Insufficient information	Other reason*
1	Is the population relevant?	Yes	No			
2	Are any critical interventions missing?	No	Yes			
3	Are any relevant outcomes missing?	No	Yes			
4	Is the context (e.g., settings and circumstances) applicable to your population?	Yes	No			

Comments

1. Yes, the population is relevant. The population is patients with EGFR mutation-positive NSCLC receiving treatment as first line.
2. No critical interventions missing. The objective of the ITC was to compare osimertinib with other EGFR-TKIs including afatinib, erlotinib and gefitinib.
3. Yes, in part. The ITC considered the following relevant outcomes: OS and PFS. However, the purpose of the ITC was to inform the cost-effectiveness analysis and therefore, health-related quality of life would have been another relevant outcome that was not considered in the ITC.
4. Yes, this context is applicable to the funding population. The year when the studies included in the ITC were performed is recent. Afatinib is funded intervention in Canada for this patient population.

Abbreviations: EGFR=epidermal growth factor receptor; ITC=indirect treatment comparison; NSCLC=non-small cell lung cancer; OS = overall survival; PFS=progression-free survival; TKI= tyrosine kinase inhibitor

* Other reasons can include insufficient training of the assessor. Please specify in the comments section.

3. Can't answer (not reported) if it is apparent that poor quality studies were included, since summary information on key study characteristics of each RCT such as methods of randomization, treatment allocation, concealment, blinding of the outcome assessor and drop out were not reported.
4. No, it is not likely that bias was induced by selective reporting of outcomes in the studies. The Methods team performed a "check" to identify whether any of the selected studies did not report some of the outcomes of interest and were therefore not included in some of the network meta-analyses of the different end points. The selected study did report the outcomes of interest (OS and PFS). The Methods Team performed a "check" on the reasons studies were excluded and not eligible studies were excluded only because the outcome of interest. However, the study selection process using Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flow diagram would have been useful.
5. Yes, there was a systematic difference in treatment effect modifier reported across the different treatment comparison in the network, disease stage. Baseline characteristics were reported as similar (age, gender, race, CNS metastasis, smoking status and EGFR mutation type), with the exception of disease status. There were more patients with advanced stage NSCLC in the LUX-Lung 7 trial compared to the FLAURA trial (96.6% versus 82% with Stage IV NSCLC). The ITC report noted this systematic difference and explained that results for this subgroup (disease stage) was not presented and therefore could not be investigated further.
6. Cannot answer (not reported/insufficient information) if these imbalances in effect modifiers across the different treatment comparisons were identified prior to comparing individual study results. This is unclear; greater detail in the methodology of the systematic literature review and ITC process would have been helpful.

Abbreviations: CNS=central nervous system; ITC=indirect treatment comparison; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; RCT=randomized controlled trial

* Other reasons can include insufficient training of the assessor.

** To help answer this specific item, one can think of the following sub-questions:

-Did the search strategy target randomized controlled trials between all interventions of interest?

-Were multiple databases searched (e.g. MEDLINE, EMBASE, Cochrane Central Registry of Trials)?

-Would review selection criteria admit all randomized controlled trials of interest (if identified by the literature search)?

Credibility

Evidence base used for the indirect comparison or network meta-analysis

		Strength	Weakness	Can't answer			
					Not reported	Insuff. infor-mation	Other *
1	Did the researchers attempt to identify and include all relevant randomized controlled trials?**	Yes	No			(Insuff. information)	
2	Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes	No				(Other *)
3	Is it apparent that poor quality studies were included thereby leading to bias?	No	Yes		(Not reported)		
4	Is it likely that bias was induced by selective reporting of outcomes in the studies?	(No)	Yes				
5	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?	No	(Yes)				
6	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?	Yes	No	Not applicable	(Not reported)	(Insuff. information)	
Overall judgment (Strength / Neutral / Weakness)							

1. There was "Insufficient information" related to the researcher's attempt to identify and include all relevant RCTs. Although the systematic literature review of the ITC included only RCTs, the specific details of the search strategy were not reported (i.e., search terms, databases used in the search).
2. The ITC assumes that erlotinib and gefitinib are of equivalent efficacy. If one believes that erlotinib is equivalent to gefitinib, then there is one network comparing osimertinib to afatinib. This is a fundamental assumption of the ITC. The FLAURA trial compares osimertinib to standard EGFR-TKI (erlotinib or gefitinib), while LUX-Lung 7 compares afatinib to gefitinib. With the assumption that erlotinib is equivalent to gefitinib, the common comparator used in the ITC is standard EGFR-TKI (erlotinib and/or gefitinib). However, if one does not believe that erlotinib and gefitinib are of equivalent efficacy, then this indirect comparison is not valid.

Abbreviations: EGFR=epidermal growth factor receptor; ITC=indirect treatment comparison; NSCLC=non-small cell lung cancer; RCT=randomized controlled trial; TKI= tyrosine kinase inhibitor

* Other reasons can include insufficient training of the assessor.

** To help answer this specific item, one can think of the following sub-questions:

-Did the search strategy target randomized controlled trials between all interventions of interest?

-Were multiple databases searched (e.g. MEDLINE, EMBASE, Cochrane Central Registry of Trials)?

-Would review selection criteria admit all randomized controlled trials of interest (if identified by the literature search)?

Analysis

		Strength	Weakness	Can't answer			
					Not reported	Insuff. infor-mation	Other *
7	Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Yes	No -> Fatal flaw				
8	If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Yes	No	Not applicable			
9	In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Yes	No	Not applicable			
10	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? **	Yes	No				
11	Was a valid rationale provided for the use of random effects or fixed effect models?	Yes	No				
12	If a random effects model was used, were assumptions about heterogeneity explored or discussed? ***	Yes	No	Not applicable			
13	If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed? ***	Yes	No	Not applicable			
Overall judgment (Strength / Neutral / Weakness/ Fatal flaw)							

7. Yes, a Bucher adjusted indirect comparison was performed.
8. Not applicable not a closed loop analysis.
9. Not applicable, not a closed loop analysis.
10. No, attempt to minimize this bias with the analysis was not made. There were imbalances in the disease stage, however subgroup analysis related to disease stage could not be further investigated since results were not presented for disease stage. Methods Team noted that a meta-regression and models with inconsistency could not have been performed /not applicable.
11. Not applicable, random effects or fixed effect model was not used for the network. The ITC report simply stated that "*upon the available evidence base, we concluded the most appropriate analysis to meet the primary objective would be indirect comparison using the Bucher method*". The Bucher method was appropriate.
12. Not applicable. A random effects model was not used.
13. Yes, heterogeneity between the two study populations was considered and subgroup analyses were performed (where data were available). A meta-regression was not possible given the number of includes studies for the pairwise comparison and subgroup analysis.

Abbreviations: ITC=indirect treatment comparison

* Other reasons can include insufficient training of the assessor.
** In the absence of inconsistency and absence of differences in effect modifiers across comparisons, this item is scored "yes." If there are inconsistencies or systematic differences in effect modifiers across comparisons, this item will be scored "yes" if models are used that capture the inconsistency, or meta-regression models are used which are expected to explain or adjust for inconsistency/bias.
*** If a valid rationale for the fixed effect model was provided, state "not applicable."

Reporting Quality & Transparency

		Strength	Weakness	Can't answer		
				Not reported	Insufficient information	Other reason*
14	Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes	No			
15	Are the individual study results reported?	Yes	No			
16	Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Yes	No			
17	Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes	No			
18	Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes	No			
19	Is the impact of important patient characteristics on treatment effects reported?	Yes	No			
Overall judgment (Strength / Neutral / Weakness)						

14. Yes, a graphical or tabular representation of the evidence network is provided (in the form a table, the studies included along with the intervention in the columns and observed results with each intervention of each study in the cells are provided. Although, additional details related to each trial (study design, eligibility criteria, sample size, methods of randomization, treatment allocation, concealment, blinding of the outcome assessor and drop out) would have been useful.
15. Yes, individual study results are reported.
16. Not applicable, not a closed loop and therefore there is no direct evidence (osimertinib versus afatinib).
17. Yes, all pairwise contrasts are reported along with measures of uncertainty (i.e., 95% confidence interval).
18. Not applicable.
19. Yes, the effect of important patient characteristics on treatment effects is reported; subgroup analyses were performed (where data were available, i.e., CNS metastases, EGFR mutation type and ethnicity).

Abbreviations: CNS=central nervous system; EGFR=epidermal growth factor receptor

* Other reasons can include insufficient training of the assessor. Please specify in the comments section.

Interpretation

		Strength	Weakness	Can't answer		
				Not reported	Insufficient information	Other reason*
20	Are the conclusions fair and balanced?	Yes	No			◯
Overall judgment (Strength / Neutral / Weakness)						
20. Given the above assessment, there is uncertainty in the results of the ITC. Refer to earlier sections for additional notes and considerations for when interpreting ITC results.						

* Other reasons can include insufficient training of the assessor.

Abbreviations: CNS=central nervous system; EGFR=epidermal growth factor receptor; ITC=indirect treatment comparison; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; RCT=randomized controlled trial; TKI= tyrosine kinase inhibitor

Conflict of Interest

		Strength	Weakness	Can't answer		
				Not reported	Insufficient information	Other reason*
21	Were there any potential conflicts of interest?**	No	◯ Yes			
22	If yes, were steps taken to address these?***	Yes	No	◯	◯	
Overall judgment (Strength / Neutral / Weakness)						
21. The ITC was prepared for AstraZeneca, the submitter for this pCODR submission. 22. Can't answer (Not reported / Insufficient information) details related to steps taken to address any potential conflicts of interest. Details related to conflicts of interest were not report (other than that the ITC was prepared for AstraZeneca). It unlikely, given that the ITC report is not from a public source, that the ITC is has been peer reviewed.						

Abbreviations: ITC=indirect treatment comparison; pCODR= pan-Canadian Oncology Drug Review

* Other reasons can include insufficient training of the assessor.

** Conflicts of interest may exist when an author (or author's institution or employer) has financial or personal relationships or affiliations that could influence (or bias) the author's decisions, work, or manuscript.

*** To help answer this specific item, one can think of the following:
In order to address potential conflicts of interest, all aspects should be noted, including the specific type and relationship of the conflict of interest, and the publication should be peer-reviewed. The contribution of each author should be clearly noted to document full disclosure of activities. Also, a fair and balanced exposition, including the breadth and depth of the study's limitations, should be accurately discussed.

Reprinted from: Value Health 17(2):157-173, Jansen JP, Trikalinos T, Cappelleri JC, et al. Supplement to: 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, 157-173, Copyright 2014 with permission from Elsevier.[57]

8 COMPARISON WITH OTHER LITERATURE

No additional information relevant to the review was identified.

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 osimertinib (Tagrisso) for advanced or metastatic lung cancer. 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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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. 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

1. Literature search via OVID platform

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

#	Searches	Results
1	(osimertinib* or Tagrisso* or mereletinib* or AZD9291 or AZD-9291).ti,ab,ot,kf,kw,hw,rn,nm.	1837
2	(3C06JJ0Z2O or RDL94R2A16).rn,nm.	93
3	or/1-2	1837
4	Carcinoma, Non-Small-Cell Lung/	47993
5	(NSCLC or NSCLCs).ti,ab,ot,kf,kw,hw.	102633
6	((lung cancer* or lung carcinoma* or lung neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,ot,kf,kw,hw.	148611
7	(lung adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,ot,kf,kw,hw.	48250
8	((bronchial cancer* or bronchial carcinoma* or bronchial neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,ot,kf,kw,hw.	485
9	(bronchial adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,ot,kf,kw,hw.	253
10	((pulmonary cancer* or pulmonary carcinoma* or pulmonary neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,ot,kf,kw,hw.	54
11	(pulmonary adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,ot,kf,kw,hw.	4923
12	((lung cancer* or lung carcinoma* or lung neoplasm*) adj2 (large cell or squamous cell)).ti,ab,ot,kf,kw,hw.	8119
13	((bronchial cancer* or bronchial carcinoma* or bronchial neoplasm*) adj2 (large cell or squamous cell)).ti,ab,ot,kf,kw,hw.	111
14	((pulmonary cancer* or pulmonary carcinoma* or pulmonary neoplasm*) adj2 (large cell or squamous cell)).ti,ab,ot,kf,kw,hw.	32
15	or/4-14	208248
16	3 and 15	1568
17	16 use medall	365
18	16 use cctr	65
19	*osimertinib/ or (osimertinib* or Tagrisso* or mereletinib* or AZD9291 or AZD-9291).ti,ab,kw,dq.	1389
20	exp Non Small Cell Lung Cancer/	111081
21	(NSCLC or NSCLCs).ti,ab,kw.	102424
22	((lung cancer* or lung carcinoma* or lung neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,kw.	139437
23	(lung adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw.	32960
24	((bronchial cancer* or bronchial carcinoma* or bronchial neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,kw.	485
25	(bronchial adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw.	251

26	((pulmonary cancer* or pulmonary carcinoma* or pulmonary neoplasm*) adj2 (nonsmall cell or non-small cell)).ti,ab,kw.	54
27	(pulmonary adj2 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw.	4903
28	((lung cancer* or lung carcinoma* or lung neoplasm*) adj2 (large cell or squamous cell)).ti,ab,kw.	4881
29	((bronchial cancer* or bronchial carcinoma* or bronchial neoplasm*) adj2 (large cell or squamous cell)).ti,ab,kw.	111
30	((pulmonary cancer* or pulmonary carcinoma* or pulmonary neoplasm*) adj2 (large cell or squamous cell)).ti,ab,kw.	32
31	or/20-30	207496
32	19 and 31	1203
33	32 use oemezd	788
34	33 and conference abstract.pt.	375
35	limit 34 to yr="2013 -Current"	375
36	limit 35 to english language	375
37	33 not conference abstract.pt.	413
38	17 or 37	778
39	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1087156
40	Randomized Controlled Trial/	966006
41	exp Randomized Controlled Trials as Topic/	272061
42	"Randomized Controlled Trial (topic)"/	145821
43	Controlled Clinical Trial/	553949
44	exp Controlled Clinical Trials as Topic/	283058
45	"Controlled Clinical Trial (topic)"/	9468
46	Randomization/	172820
47	Random Allocation/	190216
48	Double-Blind Method/	399583
49	Double Blind Procedure/	150042
50	Double-Blind Studies/	257640
51	Single-Blind Method/	73091
52	Single Blind Procedure/	31401
53	Single-Blind Studies/	74488
54	Placebos/	326252
55	Placebo/	325420
56	Control Groups/	112508
57	Control Group/	112412
58	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3798979
59	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	743840
60	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2655
61	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2476093

62	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	91735
63	allocated.ti,ab,hw.	166561
64	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	104739
65	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	21899
66	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	842
67	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	9889
68	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	15931
69	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	119810
70	or/39-69	5472812
71	36 and 70	116
72	38 and 70	143
73	18 or 72	208
74	limit 73 to english language	207
75	remove duplicates from 74	175
76	71 or 75	291

2. Literature search via PubMed

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

Search	Query	Items found
#15	Search #1 AND #12 AND #13 Filters: English	31
#14	Search #1 AND #12 AND #13	32
#13	Search publisher[sb]	518709
#12	Search #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	81855
#11	Search (pulmonary cancer*[tiab] OR pulmonary carcinoma*[tiab] OR pulmonary neoplasm*[tiab]) AND (large cell[tiab] OR squamous cell[tiab])	274
#10	Search (bronchial cancer*[tiab] OR bronchial carcinoma*[tiab] OR bronchial neoplasm*[tiab]) AND (large cell[tiab] OR squamous cell[tiab])	242
#9	Search (lung cancer*[tiab] OR lung carcinoma*[tiab] OR lung neoplasm*[tiab]) AND (large cell[tiab] OR squamous cell[tiab])	11130
#8	Search Pulmonary[tiab] AND (adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab])	6084
#7	Search (pulmonary cancer*[tiab] OR pulmonary carcinoma*[tiab] OR pulmonary neoplasm*[tiab]) AND (nonsmall cell[tiab] OR non-small cell[tiab])	142
#6	Search Bronchial[tiab] AND (adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab])	1468
#5	Search (bronchial cancer*[tiab] OR bronchial carcinoma*[tiab] OR bronchial neoplasm*[tiab]) AND (nonsmall cell[tiab] OR non-small cell[tiab])	400
#4	Search lung[tiab] AND (adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab])	29416
#3	Search (lung cancer*[tiab] OR lung carcinoma*[tiab] OR lung neoplasm*[tiab]) AND (nonsmall cell[tiab] OR non-small cell[tiab])	52566
#2	Search NSCLC[tiab] OR NSCLCs[tiab]	33892
#1	Search osimertinib*[tiab] OR Tagrisso*[tiab] OR mereletinib*[tiab] OR AZD9291[tiab] OR AZD-9291[tiab]	404

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: Tagrisso/osimertinib, non-small cell lung cancer

Select international agencies including:

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

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

Search: Tagrisso/osimertinib, non-small cell lung cancer

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

Search: Tagrisso/osimertinib, non-small cell lung cancer – last 5 years

Detailed Methododolgy

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

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 (April 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 concepts were Tagrisso (osimertinib) and non-small cell lung cancer.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. The search was limited to English-language documents, but not limited by publication year.

The search is considered up to date as of October 4, 2018.

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.

Table A3: Critical appraisal of the FLAURA trial using SIGN-50 Methodology Checklist 2: Controlled Trials.

SIGN	**Methodology Checklist 2: Controlled Trials**		
Study identification (*Include author, title, year of publication, journal title, pages*) Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113-25. DOI: 10.1056/NEJMoa1713137.			
Guideline topic:		Key Question No:	Reviewer:
Before completing this checklist, consider: 1. Is the paper a **randomised controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+ 2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.			
Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):			
6.4.1.1.1 Section 1: Internal validity			
In a well conducted RCT study…		**6.4.1.2 Does this study do it?**	
1.1	The study addresses an appropriate and clearly focused question.	Yes ☑ Can't say ☐	No ☐
1.2	The assignment of subjects to treatment groups is randomised.	Yes ☑ Can't say ☐	No ☐
1.3	*An adequate concealment method is used.*	Yes ☑ Can't say ☐	No ☐

<table>
<tr><td>1.4</td><td>The design keeps subjects and investigators ‘blind’ about treatment allocation.</td><td>Yes ☑
Can’t say ☐
No ☑</td></tr>
<tr><td>1.5</td><td>The treatment and control groups are similar at the start of the trial.</td><td>Yes ☑
Can’t say ☐
No ☐</td></tr>
<tr><td>1.6</td><td>The only difference between groups is the treatment under investigation.</td><td>Yes ☑
Can’t say ☐
No ☐</td></tr>
<tr><td>1.7</td><td>All relevant outcomes are measured in a standard, valid and reliable way.</td><td>Yes ☑
Can’t say ☐
No ☐</td></tr>
<tr><td>1.8</td><td>What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?</td><td><table><tr><th></th><th>Osimertinib</th><th>Std EGFR-TKI</th></tr><tr><td>Disease progression</td><td>31.1% (87/279)</td><td>54.5% (151/277)</td></tr><tr><td>Adverse events</td><td>12.9% (36/279)</td><td>18.1% (50/277)</td></tr><tr><td>Patient decision</td><td>4.3% (12/141)</td><td>2.9% (8/277)</td></tr></table></td></tr>
<tr><td>1.9</td><td>All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).</td><td>Yes ☑
Can’t say ☐
No ☐
Does not apply ☐</td></tr>
<tr><td>1.10</td><td>Where the study is carried out at more than one site, results are comparable for all sites.</td><td>Yes ☐
Can’t say ☑
No ☐
Does not apply ☐</td></tr>
<tr><td colspan="3">SECTION 2: OVERALL ASSESSMENT OF THE STUDY</td></tr>
<tr><td>2.1</td><td>How well was the study done to minimise bias?
Code as follows:</td><td>High quality (++) ☑
Acceptable (+) ☐
Low quality (-) ☐
Unacceptable – reject 0 ☐</td></tr>
<tr><td>2.2</td><td>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?</td><td>Refer to 1.2.4 Interpretation and 1.3 Conclusions.</td></tr>
</table>

2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Refer to 1.2.3 Factors Related to Generalizability of the Evidence for details. Of note, the FLAURA trial is a global trial that involved 132 sites in 29 countries, including Canada. The FLAURA trial compares osimertinib to gefitinib and erlotinib; there is no comparative data for osimertinib versus alectinib, an important comparator in the Canadian setting.
2.4	**Notes.** Summarise the authors' conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	
	Notes 1.1 - Yes, the phase 3 FLAURA trial assessed the efficacy and safety of osimertinib in patients with previously untreated EGFR mutation–positive advanced NSCLC as compared with the standard EGFR-TKIs, gefitinib or erlotinib. **Notes 1.2** - According to the trial protocol, eligible patients were to be centrally randomized using Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). **Notes 1.3** - According to the trial protocol, eligible patients were to be centrally randomized using Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). The study drug was to be labelled using a unique material pack code that is linked to the randomization code and the IVRS/IWRS was to assign the bottles of study material to be dispensed to each patient. **Notes 1.4** - The following methods were used to ensure blinding: the study drug was to be labelled using a unique material pack code that is linked to the randomization code and the IVRS/IWRS was to assign the bottles of study material to be dispensed to each patient. The trial was a double-dummy study where each patient received either active-osimertinib and comparator-matched placebo or active comparator and osimertinib-placebo. Both active and placebo tablets were to be identical and presented in the same packaging. Of note, following independent central confirmation of progression, the patient may then be unblinded to establish randomized treatment; this unblinding of patients at this stage did not impact the primary outcome. If randomized to standard EGFR-TKI treatment arm, the patient may be a candidate to receive open-label osimertinib. Patients who have been unblinded prior to central confirmation of progression were not able to receive open-label osimertinib. **Notes 1.5** - Refer to Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. N Engl J Med 2018;378:113-25. DOI: 10.1056/NEJMoa1713137. Page 4 Treatment and control groups look reasonably similar, except in age range. The ages of patients in the osimertinib group were between 26 and 85, whereas the ages of patients in the standard EGFR-TKI group were between 35 and 93. The median age, however, was the same in both groups (64 years old). **Notes 1.6** - Of note, patients in standard EGFR-TKI arm were allowed to cross over to open-label osimertinib if they had confirmed progression and by blinded independent central review and post-progression documentation of T790M-positive mutation status. This does not however affect the primary endpoint (PFS) results. **Notes 1.7** - Yes, there are clearly described outcome measures. **Notes 1.9** - Yes, according to the Trial Protocol, the full analysis set included all globally randomized patients, including patients who were randomized but did not subsequently receive treatment. **Notes 1.10** - Can't say, no site specific data is given. **Notes 2.1** – For the primary analysis (PFS), ascertainment bias, evaluation-time bias, and attrition bias were addressed in sensitivity analyses (i.e. blinded independent central review) and were consistent with the primary PFS analysis. **Other notes:** • According to the Trial Protocol, approximately 359 events of progression or death from 530 randomized patients were required to achieve 90% power to detect a hazard ratio of 0.71 at a two-sided alpha-level of 5%. However, at the time of the data cut-off, 342 events of progression or death occurred; this is 17 fewer events required to achieve 90% power to detect a hazard ratio of 0.71 at a two-sided alpha-level of 5%. • Given that the interim OS analysis results were immature at the time of the data cut-off and did not reach formal statistical significance for the interim analysis, OS data should be interpreted with caution.	

	• As well, because of the hierarchical statistical testing strategy, CNS PFS could not be formally tested for statistical significance and therefore, reported results related to CNS PFS should be interpreted with caution. • The assessment of patient-reported QoL is limited, and therefore as currently presented, may not fully capture the QoL experience of all patients in the trial. The QoL results were only available in poster form, and therefore have not been fully peer-reviewed. As a result, QoL data should be interpreted with caution. • There were two notable amendments to the trial protocol: - Amendment 1 (April 13, 2015), patients randomized to receive standard EGFR-TKI were permitted to cross over to receive open label osimertinib, if they had confirmed progression and by blinded independent central review and post progression documentation of T790M-positive mutation status; - Amendment 2 (September 24, 2015), the defined sample size for randomization was reduced from 650 to 530 patients. • Also, there were notable changes to the planned analyses (final SAP version 3.0 Feb 2017) which are not reflected in the final protocol (Edition 3, Sep 2015): - Change in the alpha spending for overall survival, which was requested by the FDA; and - T790M progression-free survival removed from testing hierarchy and replace with CNS progression-free survival. According to AstraZeneca, CNS progression-free survival was considered to be more clinically relevant than T790M progression-free survival subgroup analysis, which was based on new emerging data since the final protocol. The Statistical Analysis Plan was updated to reflect the above Amendments (1 and 2) and changes to the planned analyses and can be found in the final SAP version 3.0 Feb 2017. • Protocol Deviations: see above section for text related to the most common and second most common protocol deviations. As an example, a total of 3 patients (2 in the osimertinib group and 1 in the standard EGFR-TKI group) were enrolled (at the same US trial site) were not treatment-naïve for locally-advanced or metastatic NSCLC at trial entry. This protocol deviation is important to highlight as it compromises the integrity of the screening and enrolment process. However, given the small number of patients that were incorrectly enrolled and randomized, this protocol deviation is not likely to impact the study results. • Missing Data: According to the Study Protocol, in general, other than for partial dates (concomitant medication and adverse events start dates; and concomitant medication and adverse events end dates), missing data will not be imputed and will be treated as missing with the exceptions specified for certain efficacy variables (e.g. Imputation rules for lab values outside of quantification range) There was missing RECIST assessment for efficacy for 67 patients (12.1%; none were missing at baseline; rather the majority were single missing assessments 41 patients (14.7%) were from the osimertinib group and 26 patients (9.4%) in the standard EGFR-TKI group). • A hierarchical statistical testing strategy was used to adjust for multiplicity in testing PFS, OS, and CNS PFS.

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 10.

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