Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2382

osimertinib 40mg and 80mg film-coated tablet (Tagrisso®)

AstraZeneca

10 December 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the end of life and orphan equivalent medicine process

osimertinib (Tagrisso®) is accepted for use within NHSScotland.

Indication under review: As monotherapy for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.

Osimertinib, compared with two other EGFR tyrosine kinase inhibitors, improved progression-free survival in adults with locally advanced or metastatic NSCLC with activating EGFR mutations.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations[1, 2]

Dosing Information

Osimertinib 80mg orally once daily (at the same time each day) until disease progression or unacceptable toxicity.

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose should be reduced to 40mg once daily. Further details are noted in the summary of product characteristics (SPC).[1, 2]

Treatment with osimertinib should be initiated by a physician experienced in the use of anticancer therapies. When considering the use of osimertinib, EGFR mutation status in tumour or plasma specimens should be determined using a validated test method.[1, 2]

Product availability date

8 June 2018

Osimertinib meets SMC end of life and orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Osimertinib is a tyrosine kinase inhibitor (TKI) that irreversibly inhibits EGFR with activating mutations and the TKI-resistance mutation T790M, leading to apoptosis (death) of cancer cells.[1, 2]

The key evidence supporting the efficacy and safety of osimertinib comes from a double-blind phase III study, FLAURA, which recruited adults who were treatment-naïve for locally advanced or metastatic NSCLC with an EGFR mutation (Ex19del or L858R) and had World Health Organisation (WHO) performance status of 0 or 1. Randomisation was stratified by mutation (Ex19del or L858R) and ethnicity (Asian or non-Asian).[3, 4]

Patients were equally assigned to oral osimertinib 80mg once daily or EGFR TKI based on site preference of either gefitinib 250mg once daily or erlotinib 150mg once daily. Treatment continued until unacceptable toxicity or disease progression (although treatment after progression was permitted at the investigator's discretion if there was continued clinical benefit). Patients in the control EGFR TKI group could cross over after disease progression to receive osimertinib if they had the T790M mutation.[3, 4]

The primary outcome was progression-free survival (PFS) assessed by investigator using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. A hierarchical procedure was used to adjust for multiplicity in testing the key endpoints in the following order: PFS, overall survival, and central nervous system (CNS) PFS.[3, 4]

At data cut-off for PFS primary analysis (12 June 2017), PFS was significantly increased with osimertinib, compared with control EGFR TKI. Sensitivity analysis results using PFS assessed by a blinded independent central review (BICR) were consistent with the primary analysis.[4] Overall survival data were not mature and did not achieve the pre-specified significance value at this data cut-off; however, at the final data cut-off for overall survival (25 June 2019), median overall survival was significantly longer with osimertinib, compared with control EGFR TKI. Across patients with CNS metastases at baseline (n=128), CNS PFS (assessed using BICR data) was significantly improved with osimertinib compared to control EGFR TKI. Since a hierarchical procedure was used to adjust for multiplicity in testing the key endpoints of PFS, overall survival, and CNS PFS, the statistical significance achieved on the final analysis of overall survival meant that the difference observed in CNS PFS between groups could be considered statistically significant.[4, 5] The objective response rate (ORR), where response was defined as complete or partial response on RECIST version 1.1, was similar across the treatment groups. However, median duration of response was longer in the osimertinib group. Lastly, exploratory analyses of time from randomisation to second progression after start of subsequent treatment (PFS2) suggest that the PFS benefit in the osimertinib group was maintained to the next disease progression after the start of subsequent therapy.[3-5] Results of the primary outcome and relevant secondary and exploratory outcomes are detailed in Table 1.

Table 1. Results of the primary and relevant secondary and exploratory outcomes in the FLAURA study.[3-7]

	Osimertinib (n=279)	**Control EGFR-TKI (n=277)**
PFS based on investigator assessment (data cut-off June 2017)		
Median duration of follow-up for PFS, months	15.0	9.7
Patients with PFS events	136	206
Median PFS, months	18.9	10.2
HR (95% confidence interval); p-value	0.46 (0.37 to 0.57); <0.05	
Overall survival (data cut-off June 2019)		
Median duration of follow-up for overall survival, months	35.8	27
Median overall survival, months	38.6	31.8
HR (95% confidence interval); 2-sided p-value	0.80 (0.64 to 1.00); <0.05	
Survival at 12 months, %	89%	83%
Survival at 24 months, %	74%	59%
Survival at 36 months, %	54%	44%
CNS PFS (data cut-off June 2017)[a]		
Patients with CNS metastases at baseline	n=61	n=67
Patients with CNS PFS events, n	18	30
Median CNS PFS, months	NE	13.9

HR (95% confidence interval); p-value	0.48 (0.26 to 0.86); <0.05	
ORR and DOR based on investigator assessment (data cut-off June 2017)		
Patients with response, n (%)	223 (80%)	210 (76%)
Odds ratio (95% confidence interval)	1.27 (0.85 to 1.90)	
Complete response, n (%)	7 (2.5%)	4 (1.4%)
Partial response, n (%)	216 (77%)	206 (74%)
Median duration of response, months	17.2	8.5
PFS2 (data cut-off June 2017)		
Patients with second progression, n	73	106
Median PFS2, months	NE	20
HR (95% confidence interval)	0.58 (0.44 to 0.78)	

a) Analysis conducted using BICR data on CNS full analysis set**.**
BICR= blinded independent central review; CNS= central nervous system; DOR= duration of response; EGFR-TKI= epidermal growth factor receptor tyrosine kinase inhibitor; HR= Hazard ratio; NE= not estimable; ORR= objective response rate; PFS= progression-free survival; PFS2= second progression after start of subsequent treatment.

Although the results favoured osimertinib for progression-free survival in both Asian and non-Asian participants, the magnitude of benefit associated with osimertinib over the comparator was greater in the non-Asian subgroup. There was a benefit associated with osimertinib treatment in the non-Asian subgroup measured by overall survival but there did not seem to be a difference in overall survival results in the Asian subgroup.[5, 6]

There were no significant differences between the treatment groups in change from baseline in European Organisation for Research and Treatment of Cancer (EORTC) quality of life core 30 items (QLQ-C30) and lung cancer 13 items (QLQ-LC13).[3]

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

The EMA review noted that no new safety signals have been detected from the FLAURA study. The safety profile of osimertinib was in line with adverse events previously described.[3]

At the cut-off for the final analysis of overall survival (25 June 2019), the median exposure was 20.7 months and 11.5 months, for osimertinib and control EGFR TKI. The rate of adverse events across osimertinib and control EGFR TKI treatment groups was 98% and these were treatment-related in 91% and 92% of patients. Serious adverse events were reported by 27% of patients in each group and were treatment-related in 8.2% and 9.4%, respectively. Severe adverse events of at least grade 3 were reported by 42% and 47% of patients and were treatment-related in 18% and 29%, respectively. Adverse events leading to discontinuation of study treatment occurred in 15% and 18% of patients.[3]

The most common adverse event in both the osimertinib and control EGFR TKI groups was diarrhoea (60% and 58%) and rash or acne (59% and 79%).[5]

At data cut-off for primary analysis of PFS (12 June 2017), for adverse effects of special interest within the osimertinib group, compared with control EGFR TKI group, there were lower rates of hepatic adverse events, (14% versus 36%,mainly due to differences in raised liver enzymes: AST, 9.3% versus 24%, and ALT, 6.5% versus 27%) and of skin effects, (74% versus 85%, mainly due to rashes/acne, 58% versus 78%), but higher rates of gastrointestinal events (41% versus 32%, mainly due to oral inflammation, 34% versus 23%), and cardiac events related to QT interval (10.4% versus 4.7%).[3]

There were decreases from baseline in platelets, neutrophils, and leukocytes early in treatment with osimertinib, although values appeared to stabilise after the initial drop. In the osimertinib group, compared with control EGFR TKI group, there was a worsening in platelets for (52% versus 12%); leucocytes (73% versus 32%); neutrophils (41% versus 9.9%); and lymphocytes (65% versus 36%). There were higher rates of adverse events related to reduced platelets (thrombocytopenia and platelet count decreased) (15% versus 1.8%); leucopenia or white blood cell count decreased (16% versus 2.9%); neutropenia or neutrophil count decreased (11% versus 1.1%); lymphocyte count decreased (3.2% versus 0.4%); and lymphopenia (2.2% versus 1.1%), respectively.[3]

Summary of clinical effectiveness issues

Locally advanced or metastatic NSCLC is an incurable and life-threatening condition.[3] Current standard first-line treatment for patients with EGFR activating mutations is an EGFR TKI, such as erlotinib, gefitinib, afatinib or dacomitinib.[8-10] These have all been accepted by SMC for use in this setting within NHSScotland. Osimertinib is a third generation EGFR TKI licensed for first-line treatment of locally advanced or metastatic NSCLC.[1, 2, 8, 10] Osimertinib in this indication meets SMC end-of-life and orphan equivalent criteria.

In the key study, FLAURA, osimertinib compared with control EGFR TKI (erlotinib or gefitinib) increased PFS by 8.7 months and overall survival by 6.8 months. Osimertinib produced a similar ORR compared with the control EGFR TKI, but increased median duration of response by around 8 months. There was also improved CNS PFS with osimertinib.[3-5]

In first-line setting, the vast majority of patients given EGFR TKI develop TKI resistance and in approximately 50% to 65% resistance is due to development of a second-site EGFR-TKI resistance-conferring 'gatekeeper' point mutation, T790M.[2] Osimertinib is currently used within NHSScotland for patients who have received an EGFR TKI and have the T790M mutation. The EMA considered PFS2 data useful in assessing any impact of early introduction of osimertinib on subsequent lines of therapy. PFS2 was longer in the osimertinib group, compared with the control EGFR TKI group, with a hazard ratio (HR) of 0.58, although the EMA noted that there were low event numbers and data were immature.[2]

Subgroup analysis of PFS by race, sex, age, smoking history, CNS metastases, WHO performance status and EGFR mutation were consistent with the primary analysis.[11, 12] There were numerical differences in PFS and also in overall survival HR, with the smaller subgroup of non-Asian patients

having experienced better relative treatment effects with osimertinib than Asian patients.[4, 5] The company suggested these results may be due to differences in treatment management rather than ethnicity, but treatment pathway was not a pre-specified subgroup for analysis.

In addition, approximately 85% to 90% of patients with EGFR sensitising mutations have Ex19del or L858R mutations. Only patients with these mutations were included in the FLAURA study and it does not provide data on the efficacy of osimertinib in patients with rarer EGFR sensitising mutations. However, the licence was not restricted to these mutations based on other available evidence, including early preclinical data.[3]

Patients with WHO performance status of 2 or greater or unresolved toxicity from previous therapy were excluded from the FLAURA study. This may limit the application of results to less fit patients.

The FLAURA study provided a comparison with two of the medicines considered current standard of care, that is, investigator's choice of either erlotinib or gefitinib. The study was not powered or designed to compare PFS between osimertinib versus gefitinib and osimertinib versus erlotinib, separately; and these analyses were not performed. Patients in the control EGFR TKI group received gefitinib or erlotinib based on standard treatment at their centre. Study centres declared their choice of comparator prior to site initiation. In some regions there was only one drug of choice. Allocation to these medicines was not stratified by ethnicity and type of EGFR mutation. It is likely that separate analyses for gefitinib and erlotinib may be confounded. The submitting company assumed that erlotinib and gefitinib may have equivalent efficacy based on results from several published network meta-analyses (NMAs) and studies including the Chinese Thoracic Oncology Group (CTONG) 0901 study[13]

There are no direct comparative data versus other standard first-line treatments such as afatinib. The submitting company also made the assumption of equivalent efficacy between afatinib and gefitinib and erlotinib. A network for an indirect comparison of osimertinib versus afatinib was constructed using two studies: FLAURA, which compared osimertinib versus gefitinib/erlotinib, and LUX-LUNG-7, which compared gefitinib versus afatinib.[3, 4, 14] However, a formal indirect comparison was not performed. The phase IIb study, LUX-LUNG-7, found that afatinib, compared with gefitinib, prolonged PFS, with a HR of 0.73 (95% CI: 0.57 to 0.95; p=0.017), with much of the difference occurring after 12 months. Median PFS were similar across the groups at 11.0 and 10.9 months, respectively.[14] The submitting company also presented published NMAs and retrospective cohort studies to support that the three TKIs (afatinib and gefitinib and erlotinib) have equal efficacy. However, considering the evidence (PFS in LUX-LUNG-7) that suggests that there may be PFS improvements with afatinib when compared with gefitinib, it remains uncertain if afatinib, gefitinib and erlotinib can be considered equivalent in terms of efficacy.

Based on Scottish prescribing uptake data, dacomitinib and gefitinib were not considered relevant comparators by the submitting company.

A companion diagnostic is required, testing for EGFR mutations. Contact local laboratory for information.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of osimertinib, as an end of life and orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- EGFR-positive locally advanced or metastatic NSCLC is an incurable, life-limiting and debilitating condition with a substantial burden of symptoms, including shortness of breath, pain and fatigue. These patients have a higher incidence of brain metastases which can have a large impact on the patient's ability to self-care and live independently.
- Osimertinib delays disease progression for a longer time (about 9 months on average) compared with other EGFR inhibitors, may be associated with a lower incidence of side effects (rash and diarrhoea) and has a more convenient administration schedule, which all optimise the potential to get the most out of this increased period of time when the patient is generally well and can actively participate in family life (for example to make memories or go on holiday).
- Osimertinib, compared with other EGFR inhibitors, is more effective in prevention and treatment of CNS metastases, which can have a huge impact on the patient's quality of life and ability to live independently and can be associated with a substantial strain on their family / carers.
- Osimertinib increased overall survival in the clinical study by over six months on average, compared to other treatments. This additional time is highly valued by patients and their families.
- Patients are often well informed about all available treatments for the condition. The perception that the patient is receiving optimum treatment and the improvement in the patient's health with the use of osimertinib first-line may alleviate some of the emotional and psychological impact associated with an incurable life-limiting diagnosis. Carers have reported that patients have a more positive outlook while taking osimertinib and this can reduce the strain on the family.
- Using osimertinib as a first-line treatment would avoid the need to perform repeat biopsies (which can be associated with anxiety and discomfort) or additional tests at the time of progression to provide evidence of T790M mutation, which are currently required to access osimertinib as second-line treatment.
- There is experience within NHSScotland in the use of osimertinib as a second-line treatment and no changes are needed to clinic infrastructure to use it as a first-line treatment. By avoiding the need for repeat biopsies at the time of disease progression, use of osimertinib as a first-line treatment may reduce the workload of radiology and pathology.

Additional Patient and Carer Involvement

We received patient group submissions from the Roy Castle Lung Cancer Foundation, Scottish Lung Cancer Nurses Forum and EGFR Positive UK. Roy Castle Lung Cancer Foundation and EGFR Positive UK are registered charities and the Scottish Lung Cancer Nurses Forum is an unincorporated organisation. Roy Castle Lung Cancer Foundation has received 12.5% pharmaceutical company funding in the past two years, including from the submitting company. Scottish Lung Cancer Nurses Forum has received 100% pharmaceutical company funding in the past two years, including from the submitting company. EGFR Positive UK has not received any pharmaceutical company funding in the past two years. Representatives from the Roy Castle Lung Cancer Foundation and the Scottish Lung Cancer Nurses Forum participated in the PACE meeting. The key points of the submissions from all three organisations have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis for the comparison of osimertinib with afatinib and erlotinib as first-line treatments of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations. The analysis adopted a life-time horizon of 20 years.

The economic analysis incorporated a partitioned-survival model with three health states: progression-free, progressed and dead. The cycle length was 30 days and a half-cycle correction was included.

In the analysis, patients received osimertinib, afatinib or erlotinib at the licensed dose until discontinuation mainly due to progression or adverse events but some patients were treated after progression as observed in the main clinical trial. Relative dose adjustments were also included.

Clinical efficacy data used in the economic model were obtained from the non-Asian subgroup of the FLAURA study. Equivalent efficacy was assumed between erlotinib and gefitinib in the clinical study and between erlotinib and afatinib in the economic model. Data on overall survival, progression-free survival and time to treatment discontinuation were modelled beyond the median trial follow-up period using parametric models informed by statistical fit and clinical expert opinion. Modelled subsequent treatment in second line included osimertinib for 51% and platinum doublet chemotherapy (PDC) for 29% of patients in the comparator arm. In the osimertinib arm 80% were assumed to receive PDC. In third line, patients received either PDC or docetaxel + nintedanib in the comparator arm and only docetaxel plus nintedanib in the osimertinib arm. A much higher proportion of patients in the osimertinib arm were assumed to receive no third line treatment (60% versus 24% in the comparator arms).

Health state utility data in the economic model came from the relevant sub-group of the FLAURA study. EORTC QLQ-C30 data, collected in the study, were mapped to EQ-5D-3L using a published mapping algorithm.[15] One-off treatment-specific utility decrements associated with adverse events were also applied in the model.

Aside from medicine acquisition and administration costs, other costs included in the analysis were drug monitoring costs, T790M testing for patients treated with osimertinib in second line, costs associated with resource use in the progression-free and progressed states (outpatient appointments [nurse, specialist nurse, general practitioners, therapist], computerised tomography scans, electrocardiograms, etc.), costs associated with progression due to CNS metastasis, subsequent treatments and end of life costs.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price for osimertinib. A PAS is also in place for afatinib and erlotinib.

The base case results and selected scenario analyses are presented in table 2 below. The most substantial ICER increases were associated with the population used to derive treatment effects. Subsequent treatment costs are expected to be a major driver of cost-effectiveness, however, requested scenario analyses were not provided. Incorporating a treatment waning effect does not have an impact on the ICER but the analysis still assumes a relatively long-lasting treatment effect for osimertinib (10 years). Assumptions regarding long-term overall survival extrapolations also increase the ICER.

Table 2: Selected scenario analyses (list price for all medicines)

	Scenario	Base case	ICER (versus afatinib)	ICER (versus erlotinib)
0	Base case	-	£59,903	£64,846
1	ITT population from FLAURA (covariate adjusted)	Non-Asian population from FLAURA	£141,008	£162,883
2	Treatment waning effect after 10 years	No treatment waning effect	£60,877	£65,915
3	Overall survival: Weibull (independent models)	Overall survival: Log-normal (independent models)	£83,608	£90,879
4	Second line osimertinib in comparator arm: 29.8%	Second line osimertinib (51%)	£75,174	£80,115
5	Second line osimertinib in comparator arm: 41.3%	Second line osimertinib (51%)	£66,858	£71,800

The results presented do not take account of the PAS for osimertinib, afatinib or erlotinib but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company, which used an estimate of the PAS price for afatinib and erlotinib due to commercial confidentiality and competition law issues.

Key limitations with the analysis were:

- Uncertainties remain around the assumption of equivalent efficacy for afatinib and erlotinib/gefitinib. Data from the phase IIb randomised controlled study LUX-LUNG 7 suggests improved PFS for afatinib versus gefitinib, and this was noted by SMC clinical experts when they were asked to comment on the reasonableness of the assumed equivalence. The company has not presented a formal indirect comparison. Instead, the assumption was made based on a summary of the results of six published network meta-analyses and two retrospective cohort studies.

- There are uncertainties around the treatment effect for osimertinib. The company have used the clinical efficacy observed in a small subset of the FLAURA study, the non-Asian population (38% of FAS), stating that the results are more relevant to the Scottish population. No biologically plausible reason for differing outcomes by ethnicity was presented. Instead, it was assumed that ethnicity was a surrogate for region of treatment, which in turn was a surrogate for differing treatment pathways. Direct analysis of those differences would have been more appropriate than using ethnicity. Using the clinical efficacy observed in the ITT population substantially increases the ICER (table 2, scenario 1). It should be noted that in this analysis, the ITT data have been adjusted for covariates to reflect expected results if FLAURA was conducted in Europe. While the covariate- adjusted results were helpful to see, the SMC statistical advisor raised some concerns that the analysis used a relatively simple covariate adjustment and may have some limitations.

- Upon request for clarification, the company stated that a higher proportion of non-Asian patients in the osimertinib arm received cytotoxic chemotherapy in subsequent lines compared with Asian patients, which may more closely resemble clinical practice in Scotland. However, it should be noted that these differences are very small (77% in the Asian population versus 82% in the non-Asian population). The company also pointed out the results for the Japanese patients (22% of FAS) were key drivers of the treatment effect differences between Asian and non-Asian population. The company indicated that analysis had not been conducted to exclude only Japanese patients from the clinical data sets and thus it was not possible to run the economic analysis on this basis.

- There are uncertainties around the distribution of subsequent treatments, especially in the comparator arm where 51% of patients were assumed to be treated with second-line osimertinib. The subsequent treatment costs in the comparator arm are substantially higher than those in the osimertinib arm, and therefore may be a major driver of cost-effectiveness. The requested scenario analyses (table 2, scenarios 4 and 5) show the impact of assuming lower rates of osimertimib use as a second line treatment in the comparator arm. While the company stated that the rate of 51% reflects increasing confidence to use this treatment since the time of the previous submission to SMC (when a rate of 33% was used), SMC clinical experts suggested usage was lower than the rate assumed in the current submission. As such, this is an important source of uncertainty in the economic evaluation.

- Arguably, the utility weight in the comparator arm should also be adjusted to reflect the more safe and efficacious second line treatment, compared with cytotoxic chemotherapies in the osimertinib arm. However, a common utility value for progressed disease was assumed.
- Treatment effect for osimertinib is assumed to continue for the full duration of the model. On request, the company provided a scenario assuming a treatment waning effect at 10 years, which shows no impact in the ICER (table 2, scenario 3). Given that patients in the comparator arm are treated with a more efficacious treatment (osimertinib) in second line, compared with patients in the osimertinib arm, a treatment effect waning may begin at an earlier time point.

The Committee also considered the benefits of osimertinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy was satisfied. In addition, as osimertinib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted osimertinib for use in NHSScotland.

Additional information: guidelines and protocols

In February 2014, the Scottish Intercollegiate Guidelines Network (SIGN) issued publication number 137, Management of Lung Cancer. For first-line treatment of stage IIIB or IV NSCLC it recommends that first line single agent TKIs should be offered to patients with advanced NSCLC who have a sensitising EGFR mutation. Adding combination systemic anticancer therapy to a TKI confers no benefit and should not be used.[16]

In March 2019, the National Institute for Health and Care Excellence (NICE) issued clinical guideline number 122, Lung Cancer: Diagnosis and Management. For guidance on initial treatment for stage IIIB and IV non-squamous NSCLC in people EGFR-TK mutation this references the NICE technology appraisal guidance on afatinib, erlotinib and gefitinib. The respective technology appraisals, numbers 310, 258 and 192, recommend these EGFR TKI as first-line treatment options.[17]

European Society for Medical Oncology (ESMO**)** published in September 2020 the clinical practice guidelines: 'Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up'. For patients within the indication under review, these guidelines recommend first-line treatment with osimertinib as the preferred option; however, patients with a tumour with a sensitising EGFR mutation could also receive first-line EGFR TKIs including erlotinib, gefitinib or afatinib, or dacomitinib. In addition, erlotinib/bevacizumab are also considered front-line treatment option in patients with EGFR-mutated tumours. Likewise, addition of carboplatin and pemetrexed to gefitinib represents another first-line option for these patients.[18]

Additional information: comparators

Afatinib and erlotinib.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Osimertinib	**80mg orally once daily**	**70,009**

Costs from BNF online on 6 August 2021. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 192 patients eligible for treatment with osimertinib in each year, to which confidential uptake rates were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 17 September 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.