Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2383

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

AstraZeneca UK Ltd

08 October 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 full submission assessed under the orphan equivalent medicine process

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

**Indication under review:** as monotherapy for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions (Ex19del) or exon 21 (L858R) substitution mutations.

**SMC restriction:** treatment with osimertinib is subject to a three-year clinical stopping rule.

In a placebo-controlled phase III study, osimertinib significantly improved disease free survival (DFS) in patients with completely resected EGFR mutation-positive NSCLC.

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

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

**Vice Chairman**
**Scottish Medicines Consortium**

## Indication

As monotherapy for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have EGFR Ex19del or L858R substitution mutations.[1, 2]

## Dosing Information

The recommended dose is 80mg osimertinib once daily (at the same time each day) taken with or without food. Patients in the adjuvant setting should receive treatment until disease recurrence or unacceptable toxicity. Treatment duration for more than 3 years was not studied.

The Summary of Product Characteristics (SPC) contains recommendations on dose reduction to manage adverse reactions.

When considering the use of osimertinib, EGFR mutation status (in tumour specimens for adjuvant treatment) should be determined using a validated test method.

Treatment with osimertinib should be initiated by a physician experienced in the use of anticancer therapies.

Refer to the SPC for further information.[1, 2]

## Product availability date

7 May 2021

Osimertinib meets SMC orphan equivalent criteria for this indication.

## Summary of evidence on comparative efficacy

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

Key evidence for this indication is from ADAURA, a multicentre, randomised, double-blind, phase III study. ADAURA recruited adult patients with completely resected primary non-squamous NSCLC who had postsurgical pathological staging IB to IIIA and an EGFR mutation (Ex19del or L858r either alone or in combination with other EGFR mutations). Patients had a World Health Organisation performance status of 0 or 1. Administration of standard postoperative adjuvant chemotherapy prior to randomisation was permitted, but was not mandatory. Patients were randomised equally to receive osimertinib 80mg orally once daily (n=339) or placebo (n=343). Randomisation occurred within 10 weeks of complete surgical resection if adjuvant chemotherapy was not administered, or within 26 weeks if adjuvant chemotherapy was administered. Treatment was to continue for planned duration of 3 years, or until disease recurrence or unacceptable toxicity. Randomisation was stratified according to staging (IB or II or IIIA), EGFR mutation type status (Ex19Del or L858R), and ethnicity (Asian or non-Asian).[3]

The primary outcome was disease-free survival (DFS) according to investigator assessment among patients with stage II to IIIA disease. DFS was defined as the time from randomisation to disease recurrence or death from any cause. Patients who were disease-free and alive at the time of analysis were censored at the date of their last assessment for disease recurrence. However, if the patient had a recurrence event or died immediately after 2 or more consecutive missed visits, the patient was censored at the time of the latest evaluable assessment for disease recurrence prior to the two missed visits. Efficacy analyses were performed in the full analysis set (FAS), which included all randomised patients. A hierarchical statistical testing strategy was applied in the following prioritised order: DFS in patients with stage II to IIIA disease, DFS in the overall study population (stage IB to IIIA disease) and overall survival, defined as the time from randomisation to the date of death (any cause), or the date the patient was last known to be alive.[3, 4]

The study was unblinded two years early, on recommendation from the independent data monitoring committee (IDMC), because of evidence of an efficacy benefit. The results to support this submission are from the unplanned interim analysis, data cut-off 17 January 2020, based on the IDMC recommendation when 156 DFS events had occurred. At the data cut off, investigator-assessed DFS was significantly longer in the osimertinib group compared with the placebo group in both the primary analysis (stage II to IIIA) and secondary analysis in the overall population (stage IB to IIIA). Overall survival data are immature.[3] The results are presented in Table 1 below.

**Table 1: Interim analysis of the primary and secondary outcome from the ADAURA study in the FAS (data cut-off 17 January 2020)[1, 3]**

| | **Osimertinib (n=233)** | **Placebo (n=237)** |
|---|---|---|
| **Investigator-assessed disease free survival (DFS) in patients in stage II to IIIA disease** | | |
| Median DFS follow-up | 22.1 months | 14.9 months |
| Number of events | 26 | 130 |
| Median DFS | Not calculable | 19.6 months |
| Hazard Ratio (99.06% CI) | 0.17 (0.11 to 0.26), p<0.001 | |
| KM estimate for DFS at 24months | 90% | 44% |
| | **Osimertinib (n=339)** | **Placebo (n=343)** |
| **Investigator-assessed disease free survival (DFS) in patients in the overall population** | | |
| Median DFS follow-up | 22.1 months | 16.6 months |
| Number of events | 37 | 159 |
| Median DFS | Not calculable | 27.5months |
| Hazard ratio (99.12% CI) | 0.20 (0.14 to 0.30), p<0.001 | |
| KM estimate for DFS at 24 months | 89% | 52% |
| **Overall survival in overall population** | | |
| Median OS follow-up | 26.1 months | 24.6 months |
| Deaths | 9 | 20 |
| Median overall survival | Not calculable | Not calculable |
| Hazard ratio (99.98% CI) | 0.40 (0.09 to 1.83) | |
| KM estimate for overall survival at 24 months | 100% | 93% |

CI=confidence interval, DFS=disease free survival, FAS=full analysis set, KM=Kaplan Meier, OS=overall survival

The time to CNS recurrence or death was assessed as an exploratory outcome. The proportion of patients with CNS disease recurrence or death events was 1.8% (6/339) and 11% (39/343) in the osimertinib and placebo groups, respectively, with CNS disease recurrence recorded for 1.2% and 10% of patients and death recorded for 0.6% and 1.7% of patients. The hazard ratio for CNS recurrence or death was 0.18 (95% confidence interval [CI]: 0.01 to 0.33), with median CNS disease-free survival not reached in the osimertinib group and 48.2 months in the placebo group.[3]

Subgroup analysis of investigator assessed DFS in the overall population were consistent with the main study results. The DFS benefit with osimertinib was observed in patients who had received adjuvant chemotherapy (n=410) (Hazard ratio [HR]=0.16, [95% CI: 0.10 to 0.26]) and in those who had not received adjuvant chemotherapy (n=272) (HR=0.23, [95% CI: 0.13 to 0.40]).[3]

Health Related Quality of Life (HRQoL) was assessed using Short Form-36 (SF-36) questionnaires, a validated instrument measuring general health status. Scores range from 0 to 100 with higher scores indicating better health.[3] This instrument was used at randomisation, weeks 12, 24 and then every 24 weeks until treatment completion or discontinuation and completion rates were ≥85% across all visits in both arms. Baseline scores were comparable. From baseline to week 96, physical component summary (PCS) and mental health component summary (MCS) scores increased by 1.13 and 1.34 points for osimertinib and 2.31 and 2.68 for placebo with no clinically meaningful differences between arms. There were also no clinically meaningful differences between osimertinib and placebo for time to deterioration of PCS or MCS.[5]

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

## Summary of evidence on comparative safety

In the ADAURA study at data cut-off 17 January 2020, the median duration of total treatment exposure in the osimertinib group was 22.5 months and in the placebo group was 18.7 months. Any treatment-emergent adverse event (AE) were reported by 98% (329/337) of patients in the osimertinib group and 89% (306/343) in the placebo group. In the osimertinib and placebo groups respectively, patients reporting a grade 3 or higher AE were 20% versus 13%, patients with a reported serious AE were 16% versus 12%, patients with a dose reduction due to treatment emergent AEs were 8.6% versus 0.9%, the proportion of AEs that led to dose interruptions were 24% versus 11% and patients discontinuing therapy due to an AE was 11% versus 2.9%.[3, 6]

The most frequently reported treatment-related AEs of any grade with an incidence >10% in either the osimertinib group or the placebo group were: diarrhoea (39% versus 14%), paronychia (23% versus 1.2%), dry skin (20% versus 4.7%), pruritus (17% versus 6.7%) and stomatitis (16% versus 2.0%). [3]

Adverse events of special interest included interstitial lung disease and cardiac events. Interstitial lung disease (including interstitial lung disease and pneumonitis) was reported by 3.0% of patients in the osimertinib group compared with 0 in the placebo group; all events were considered mild or moderate in severity. The SPC notes that osimertinib should be discontinued if interstitial lung disease is diagnosed and appropriate treatment initiated as necessary. Cardiac events (including

ejection fraction decreased, cardiac failure, pulmonary oedema and cardiomyopathy) were reported by 4.7% in the osimertinib group and 2.9% in the placebo group. Three patients in the osimertinib group and one patient in the placebo group had a grade 3 event.[1, 3]

Overall the Medicines and Healthcare Products Regulatory Agency (MHRA) considered that osimertinib was well tolerated by most patients and no major safety concerns were identified in the ADAURA study. The safety profile of osimertinib in this indication appeared consistent with the known safety profile of osimertinib in the advanced disease setting.[4]

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

## Summary of clinical effectiveness issues

Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer accounting for 80% to 89% of all cases. Epidermal growth factor receptor mutations occur in 10% to 15% of lung cancers and are more common in women and in people who have never smoked or have been light smokers. Approximately 90% of EGFR mutations are either Ex19del or L858R point mutations. Guidelines recommend surgical resection as the preferred treatment option for suitable patients with stage I, II and IIIA NSCLC due to its curative potential. Adjuvant platinum-based chemotherapy may be offered to patients with resected stage II and IIIA NSCLC, the benefit is less clear in patients with stage IB disease and as such it is only recommended for patients with high risk disease. A two-drug combination with cisplatin is preferred, with cisplatin-vinorelbine being the most studied. This can be given over three to four cycles. Osimertinib within the indication under review would be added to the current standard of care in early NSCLC, which may or may not include platinum-based adjuvant chemotherapy. EGRF-targeted therapies are used in the treatment of relapsed and advanced/metastatic NSCLC, osimertinib is the first EGFR-targeted adjuvant therapy for use in patients with early NSCLC.[7-9] Clinical experts consulted by SMC considered that osimertinib fills an unmet need in this therapeutic area as a targeted therapy. Osimertinib meets SMC orphan equivalent criteria for this indication.

In ADAURA, at the data cut-off, investigator-assessed DFS in patients with stage II to IIIA NSCLC was significantly longer in the osimertinib group compared with the placebo group. This was supported by the key secondary outcome, investigator-assessed DFS in the overall population (patients with stage IB to IIIA disease). The MHRA considered these results clinically meaningful.[3, 4]

The main limitation in the evidence presented is the immaturity of the data. The results from ADAURA have been reported from an early unplanned interim analysis on recommendation from the independent data monitoring committee because of evidence of an efficacy benefit. At the data cut-off, DFS data were immature and overall survival data were highly immature (as less than 5% of the overall study population had died). The study is ongoing and a final analysis for overall survival is planned for 2023, when approximately 94 deaths have occurred (approximately 20% maturity) in the stage II to IIIA population. This will also include an exploratory analysis for DFS. Therefore, long-term follow-up for efficacy and safety in the adjuvant setting is limited and no firm conclusions can be drawn on the proposed treatment duration as only 12% of patients in the osimertinib group completed the 3-year study treatment period. Due to data immaturity, overall

survival benefit cannot be ascertained. The extent that the delay in time to recurrence may be translated into overall survival benefit is also unknown and was noted by some clinical experts consulted by SMC. Cross over from placebo to osimertinib will likely confound the longer-term analysis. The study was not powered for overall survival and results for this outcome are descriptive only.[3, 4]

In Scotland, patients with NSCLC who are being considered for radical treatment have a staging PET-CT scan to detect occult distant metastases.[7] This was not mandatory in ADAURA and, therefore, staging may not reflect clinical practice in Scotland.

Active surveillance is a relevant comparator in Scottish practice and subgroup analysis indicated a consistent benefit with osimertinib if patients did or did not receive adjuvant chemotherapy.[3]

Clinical experts consulted by SMC generally indicated that osimertinib represented a therapeutic advancement for this indication due to the favourable DFS results demonstrated in the ADAURA study. Most considered it would be used as per the licensed indication. As an additional adjuvant treatment there would be clinical and pharmacy service implications to manage tolerability and supply, although numbers are expected to be low. Companion diagnostic testing for EGFR mutations is required: 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 orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Non-small cell lung cancer (NSCLC) with an EGFR mutation is an aggressive disease that has a considerable physical, psychological, economic and social impact on patients and their families. There is a significant risk of recurrence with symptomatic central nervous system (CNS) metastases, which can occur quickly after surgery. Patients affected by EGFR positive NSCLC are generally younger than typical lung cancer patients, non-smokers, more likely to be female, often still working and with a young family. Therefore, the diagnosis is particularly devastating and affects all aspects of life.
- There is a high unmet need for patients with this condition as, following complete resection, further treatment options are limited. Suitable patients are offered adjuvant chemotherapy; however, this treatment is often poorly tolerated and is of limited benefit. Consequently, many patients decline treatment because of the significant burden from severe side effects, frequent hospital visits and the impact this can have on personal and family life.
- Osimertinib is the first TKI licensed as an adjuvant treatment for resected EGFR positive NSCLC. Results from the ADAURA study demonstrated a significant disease free survival benefit and a reduction CNS recurrence. Patients might expect to have a good quality of

life for longer, be able to live independently, continue to work, participate family and social activities and continue a normal life.

- Osimertinib is generally well tolerated and has a manageable side effect profile. The once daily oral formulation is convenient for patients and carers.
- If accepted by SMC adjuvant osimertinib is likely to be used as per the licensed indication, in patients with resected stage IB to IIIA NSCLC with an EGFR mutation, with or without adjuvant chemotherapy. PACE clinicians noted that the number of eligible patients is likely to be very small.

**Additional Patient and Carer Involvement**

We received patient group submissions from EGFR Positive UK and the Scottish Lung Cancer Nurses Forum. EGFR Positive UK is a registered charity and the Scottish Lung Cancer Nurses Forum is an unincorporated organisation. EGFR Positive UK has not received any pharmaceutical company funding in the past two years. Scottish Lung Cancer Nurses Forum has received 100% pharmaceutical company funding in the past two years, including from the submitting company. A representative from EGFR Positive UK participated in the PACE meeting. The key points of the submissions from both 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 of osimertinib for adjuvant treatment after complete tumour resection in adult patients with NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. The economic analysis was presented against active monitoring for disease recurrence as the sole comparator.

A semi-Markov multi-state transition model was implemented, comprising five mutually-exclusive health states that represent the disease course and survival of patients over time: 'Disease-free (DF)', 'Locoregional recurrence (LRR)', '1st line treatment for distant metastatic NSCLC (DM1)', '2nd line treatment for distant metastatic NSCLC (DM2)', and 'Death' as the absorbing state. The cycle length was 30 days with patients either remaining in the starting DF state, or transitioning to the disease progression states or death at the end of each cycle. An NHS perspective and a 37-year lifetime horizon were selected in the base case of the economic model. A treatment stopping rule was included in the model consistent with the ADAURA study protocol with patients assumed to stop treatment with osimertinib by year 3.

The transition probabilities for patients moving from the DF state to the disease recurrence states (i.e. LRR and DM1) were informed by the ADAURA data.[3] Limited post-recurrence follow-up data were available from ADAURA at the data cut-off (January 2020), so the probability of transitioning from LRR to DM1 was based on real-world evidence from a large cancer patient database.[10] Limited survival data from ADAURA also meant the probability of transitioning from DM1 to DM2 and from either DM state to death, was determined using the FLAURA study data.[11] FLAURA was the key trial of osimertinib versus standard of care (erlotinib/gefitinib) in the metastatic setting.

The outcomes from the ADAURA study were DFS and overall survival, which were determinants of treatment effect in the economic model. Extrapolation of DFS and overall survival beyond the observed follow-up period using standard parametric functions was required to generate probabilities for individual transitions between health states.

**Table 2: Parametric distributions and data sources used in the base case**

| Transitions | Parametric distributions | Data source |
|---|---|---|
| TP1: DF → LRR | Lognormal | ADAURA |
| TP2: DF → DM1 | Generalised gamma | ADAURA |
| TP3: DF → Death | Background mortality | UK life tables |
| TP4: LRR → DM1 | Lognormal | CancerLinQ |
| TP5: LRR → Death | Background mortality | UK life tables |
| TP6: DM1 → DM2 | Weibull | FLAURA |
| TP7: DM1 → Death | Exponential / background mortality | FLAURA/UK life tables |
| TP8: DM2 → Death | Weibull | FLAURA |

Abbreviations: DF, disease-free; DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; LRR, locoregional recurrence.

The model and extrapolation functions also incorporated a cure assumption, to capture the expected functional cure of patients beyond the currently available follow up DFS data from ADAURA. In the base case it was assumed that patients who remained disease free at five years could be considered functionally cured and experience a mortality risk matching that of the UK general population.

State-specific utilities were applied in the model. Utility values were based on SF-36 data from the ADAURA study, which were then mapped to EQ-5D scores. Due to the immaturity of the data, only the utility value for the DF state could be calculated from ADAURA. However, the final DF health state utility value was higher than age-and sex-matched general population utility estimate of 0.799. Hence, the lower, more conservative general population estimate was applied to the DF state in the base case analysis. For the LR health state, the utility value was assumed to be the same as DF as no other data sources were available. For the DM1 and DM2 health states, health related quality of life data were obtained from the FLAURA study and generated utility values of 0.794 and 0.704 respectively. Age and adverse event related disutilities were also applied in the model.

Acquisition costs for osimertinib, EGFR TKIs and subsequent chemotherapies were included in the analysis, as were the costs associated with any radiotherapy. Unit costs for disease management, managing adverse events, and end of life care were also accounted for. The analysis also included one-off EGFR mutation testing costs applied in the first cycle to all patients on osimertinib, and as a one-off cost for patients in the active monitoring arm who received an EGFR-TKI on progression to the DM1 health state.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price for osimertinib. A PAS discount is in place for afatinib, which is a subsequent treatment in the model, and this was included in the results used for decision-making by using estimates of the comparator PAS price. The results

presented do not take account of the PAS for afatinib 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 due to commercial confidentiality and competition law issues.

The base case analysis presented by the submitting company produced an incremental cost-effectiveness ratio (ICER) of £18,636 per quality-adjusted life-year (QALY) with the osimertinib PAS against active monitoring.

**Table 3: Selected scenario analysis**

| | **Scenario** | **£/QALY vs active monitoring** |
|---|---|---|
| | ***Base Case*** | ***£18,636*** |
| 1 | Osimertinib cure timepoint: 7 years | £18,810 |
| 2 | Maximum cure percentage (both arms): 80% | £17,636 |
| 3 | Percentage treated with EGFR-TKIs in DM1 (osimertinib arm): 25%. Remaining patients receiving PDC | £18,463 |
| 4 | Second-best fit viable survival curves for transition probabilities | £24,697 |
| 5 | Alternate utility values (DF=0.72; LRR=0.62; DM1 & DM2=0.67) | £20,694 |
| 6 | Combined scenario 4 + 5 | £27,742 |
| 7 | Removal of structural cure assumption | £19,589 |
| 8 | Percentage treated with EGFR-TKIs in DM1 (osimertinib arm): 75%. Remaining patients receiving PDC | £18,809 |

Abbreviations: DF, disease-free; DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; LRR, locoregional recurrence; PDC, pemetrexed and cisplatin; QALY, quality-adjusted life-year

There were a number of limitations with the analysis which include the following:

- The economic analysis excludes platinum-based chemotherapy as a relevant comparator. Under current practice, adjuvant platinum-based chemotherapy may be offered to some patients with resected stage II and IIIA NSCLC, the benefit is less clear in patients with stage IB disease and as such it is only recommended for patients with high risk disease. A two-drug combination with cisplatin is preferred, with cisplatin-vinorelbine being the most studied. The company argues that adjuvant chemotherapy is only offered to a small minority of patients and as such should not be considered a relevant comparator. SMC clinical experts indicated that patients would be offered adjuvant chemotherapy, albeit uptake was typically low.
- The ADAURA study data are highly immature. At the time of the interim data cut-off (January 2020), DFS data maturity was only 33.2%. Overall survival data were extremely immature (only 5% of events). This was largely due to the early un-blinding of the study based on the strong DFS benefit observed. The clinical effectiveness data incorporated into the economic model rely heavily on DFS being a surrogate marker for improved overall survival. There is empirical uncertainty regarding this correlation and DFS translating into

overall survival gains is not guaranteed.

- In the absence of long-term follow-up data from ADAURA, a cure assumption was incorporated into the economic model. A proportion of patients achieving long-term DFS were assumed to be functionally cured and would revert to an age-adjusted general population mortality rate following cure. In the base case analysis, the cure rate in the osimertinib arm increased linearly, starting from 0% at year 5 and reaching a peak of 95% at year 10. In contrast, 95% of patients receiving active monitoring (placebo) were assumed to be functionally cured after 5 years. The company maintains that this is a conservative estimate based on evidence from an external study investigating adjuvant chemotherapy and feedback from clinicians. Whilst there remains some residual uncertainty about the curative potential of adjuvant osimertinib, the assumption used is plausible and largely consistent with real-world evidence. Removal of the cure assumption did not have a major upward impact on the ICER and the cure rate was not a key driver of cost effectiveness in the model.
- There is considerable uncertainty about utility values included in the analysis. The utility values applied in the base case were not sourced from ADAURA. A matched general population utility value was applied to the DF state, and values for the DM states were obtained from the FLAURA study. A utility value for the LRR state could not be sourced and it was assumed to equal the DF state. Deterministic sensitivity analysis showed that the utility value of the DF state had the second largest impact on cost-effectiveness.
- There is uncertainty regarding the impact of introducing adjuvant osimertinib on subsequent treatments as this is a change in clinical practice. In the base case analysis it was assumed that 50% of patients in the osimertinib arm who progress to DM1 would be treated with erlotinib/afatinib. For the remaining 50% of patients, it was assumed they would be treated with platinum doublet chemotherapy. There is potential for the proportion of patients receiving subsequent therapies to vary in clinical practice, which will have an impact on downstream costs and associated resource use.

The Committee 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 as osimertinib is an orphan-equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted osimertinib for restricted use in NHSScotland.

## Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published "Management of lung cancer: A national clinical guideline (SIGN 137)" in February 2014.[7] The guidance makes the following relevant recommendations:

- Patients with stage I and II NSCLC should be considered for curative surgery whenever possible.
- Patients with [stage IIIA and] proven early N2 NSCLC may be considered for surgery as part of multimodality treatment. All of these cases must be discussed at the multidisciplinary team meeting.
- Patients with good performance status (PS 0-1) who have completely resected NSCLC (stage II to IIIa) should be offered platinum based postoperative systemic anticancer therapy.
- Patients with NSCLC who have had complete tumour resection should not receive postoperative radiotherapy, except as part of a randomised trial.[7]

The National Institute for Health and Care Excellence (NICE) published "Lung cancer: diagnosis and management" in 2019[8]. This guidance makes the following relevant recommendations:

- Offer postoperative chemotherapy to people with good performance status (WHO 0 or 1) and T1a–4, N1–2, M0 NSCLC.
- Consider postoperative chemotherapy for people with good performance status (WHO 0 or 1) and T2b–4, N0, M0 NSCLC with tumours greater than 4 cm in diameter.
- Offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy.

The European Society for Medical Oncology (ESMO) published "Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in 2017[9] and the guidance was subsequently updated in 2020. The guidance makes the following relevant recommendations for stage I and II disease:

- Surgery should be offered to all patients with stage I and II NSCLC as the preferred treatment to all who are willing to accept procedure-related risks.
- Adjuvant chemotherapy should be offered to patients with resected stage II and III NSCLC and can be considered in patients with resected stage IB disease and a primary tumour >4 cm. Pre-existing comorbidity, time from surgery and postoperative recovery need to be taken into account in this decision taken in a multidisciplinary tumour board.
- For adjuvant chemotherapy, a two-drug combination with cisplatin is preferable [I, A]. In randomised studies, the attempted cumulative cisplatin dose was up to 300mg/m$^2$, delivered in three to four cycles. The most frequently studied regimen is cisplatin–vinorelbine.
- At the present time, the choice of adjuvant therapy should not be guided by molecular analyses, e.g. ERCC1 mutation testing.

- In the current state of knowledge, targeted agents should not be used in the adjuvant setting.

The guidance predates the availability of osimertinib and therefore no specific recommendations were made.

## Additional information: comparators

Active surveillance, some clinical experts also considered platinum-based chemotherapy to represent a relevant comparator.

## Additional information: list price of medicine under review

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

*Costs from BNF online [01/07/2021]. Costs do not take patient access schemes into consideration.*

## Additional information: budget impact

The submitting company estimated there would be 25 patients eligible for treatment with osimertinib in year 1 and in year 5.

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.**

**References**


1. AstraZeneca UK Limited. Osimertinib 80mg film coated tablets (Tagrisso®). Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated: 10/05/2021.

2. AstraZeneca UK Limited. Osimertinib 40mg film coated tablets (Tagrisso®). Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated: 14/05/2021.

3. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M*, et al.* Osimertinib in resected EGFR-mutated non-small-cell lung cancer. New England Journal of Medicine. 2020;383(18):1711-23.

4. Medicines & Healthcare products Regulatory Agency. Public Assessment Report. Osimertinib (Tagrisso®) 40mg and 80mg Film-coated tablets. PLGB 17901/0340-0341. Last updated July 2021. Available at: https://mhraproducts4853.blob.core.windows.net/docs/7d80e811da5b9fe6dca425f09bc6d8e1b65e7792.

5. Marie Curie Cancer C. Patient-reported outcomes from ADAURA: osimertinib as adjuvant therapy in patients with resected EGFR mutated (EGFRm) NSCLC. Abstract presented at: 2020 World Conference on Lung Cancer; January 28-31, 2021. Available at: https://library.iaslc.org/search?search_keyword=ADAURA [last accessed: 22/02/2021].

6. AstraZeneca. Clinical Study Report: A Phase III, Double-blind, Randomized, Placebo-Controlled Multi-centre, Study to Assess the Efficacy and Safety of AZD9291 versus Placebo, in Patients with Epidermal Growth Factor Receptor Mutation Positive Stage IB-IIIA Non-small Cell Lung Carcinoma, following Complete Tumour Resection With or Without Adjuvant Chemotherapy (ADAURA).

7. Scottish Intercollegiate Guidelines Network (SIGN). Management of lung cancer: A national clinical guideline (SIGN137). 2014. Available at: https://www.sign.ac.uk/our-guidelines/management-of-lung-cancer/.

8. National Institute for Health and Care Excellence (NICE). Lung cancer: diagnosis and management. 2019 [cited 2021 May 11 ]; Available from: https://www.nice.org.uk/guidance/ng122.

9. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J*, et al.* Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv1-iv21. Epub 2017/09/09.

10. CancerLinQ: how it works.

11. AstraZeneca. Clinical study report, second interim data cut: a Phase III, Double-blind, Randomised Study to Assess the Efficacy and Safety of AZD9291 versus a Standard of Care Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor as First-line Treatment in Patients with Epidermal Growth Factor Receptor Mutation-positive, Locally-advanced or Metastatic Non-small-cell Lung Cancer (FLAURA).

This assessment is based on data submitted by the applicant company up to and including 13 August 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.*