Cost-effectiveness of osimertinib (Tagrisso®) for adjuvant treatment, after complete tumour resection, in adult patients with stage IB-IIIA non-small cell lung cancer whose tumour has epidermal growth factor receptor exon 19 deletions (ex19del) or exon 21 substitution (L858R) mutations

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost effectiveness of osimertinib (Tagrisso®). Following assessment of the Applicant's submission, the NCPE recommends that osimertinib (Tagrisso®) not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an appraisal of the Applicant's (AstraZeneca Pharmaceuticals) Health Technology Assessment of osimertinib (Tagrisso®). The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health-related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **May 2023**

Summary

In August 2022, AstraZeneca Pharmaceuticals submitted a dossier, which investigated the clinical effectiveness, cost effectiveness, and potential budget impact of osimertinib for adjuvant treatment, after complete tumour resection, in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumour has epidermal growth factor receptor (EGFR) exon 19 deletions (ex19del) or exon 21 substitution (L858R) mutations. Reimbursement is sought under the High-Tech Drug Arrangement. Osimertinib is the first therapy to be licensed for the adjuvant treatment, following complete tumour resection, of patients with EGFR-mutated NSCLC.

Osimertinib is a third-generation tyrosine kinase inhibitor. It is an irreversible inhibitor of EGFRs harbouring sensitising-mutations and T790M. This leads to inhibition of cell growth, while showing significantly less activity against EGFR in wild-type cell lines. The recommended dose of osimertinib is 80mg taken orally once daily. For this indication, as per the Summary of Product Characteristics, treatment should be administered until disease progression or unacceptable toxicity. Notably, treatment duration of greater than three years has not been studied.

The Applicant anticipates that osimertinib will be used in line with its licensed indication. Of note, osimertinib is placed after adjuvant chemotherapy (where patients receive chemotherapy). This is in line with clinical opinion, the pivotal ADAURA trial, and the European Society for Medical Oncology treatment guidelines. The comparator of relevance to this setting is active monitoring.

1. Comparative Effectiveness of Osimertinib

The ADAURA trial is a phase III, double-blind, randomised, placebo-controlled, multi-centre study. This study was designed to assess the safety and efficacy of osimertinib versus placebo, in patients with stage IB-IIIA EGFR-mutated (ex19del or L858R) NSCLC who have undergone complete tumour resection, with or without post-operative adjuvant chemotherapy. Eligible patients were randomised 1:1 to osimertinib (n=339) or placebo (n=343). Treatment, in both arms, continued until disease recurrence, unacceptable toxicity, or a maximum treatment duration of three years. The primary endpoint was investigator-

assessed disease-free survival (DFS). Overall survival (OS) was a key secondary endpoint. The primary population was patients with stage II-IIIA disease. The overall population included all randomised patients (i.e. stage IB-IIIA disease); this is the population of relevance to this assessment.

The data presented are based on an early, unplanned, interim analysis, which was performed on recommendation from the Independent Data Monitoring Committee. The data cut-off date was 17th January 2020. Based on this analysis, in the overall population, osimertinib was associated with a statistically significant improvement in DFS compared to placebo (hazard ratio (HR) 0.20; 95% CI 0.15 to 0.27). The April 2022 data cut indicated that osimertinib had a median DFS of 65.8 months (95% CI 61.7 to non-calculatable) compared with 28.1 months (95% CI 22.1 to 35.0) for placebo (HR 0.27; 95% CI 0.21 to 0.34). At the January 2020 data cut, OS data were highly immature (4.3% maturity, with 29 events reported). Osimertinib was associated with a numerically favourable OS versus placebo; however, this was not statistically significant. As OS did not reach statistical significance in the primary population, the OS analysis in the overall population is exploratory (as per the statistical analysis plan). Updated data, which demonstrated an OS benefit, were presented to the Review Group; however, these are considered confidential by the Applicant. Due to the immaturity of the OS data presented here, results should be interpreted with caution.

2. Safety of Osimertinib

The safety profile observed in ADAURA was consistent with the known safety profile of osimertinib. A total of 97.6% of patients in the osimertinib arm and 89.2% in the placebo arm experienced an AE of any grade. The most common AEs experienced by patients in the osimertinib arm were diarrhoea (46.3%), paronychia (25.2%), dry skin (23.4%), and pruritis (19.3%). These were reported with an incidence of at least 10 percentage points higher in the osimertinib arm when compared to the placebo arm. Diarrhoea was also the most common AE in the placebo arm (19.8%).

Overall, the EPAR highlighted that although the safety profile of osimertinib does not suggest major concerns or new safety signals, long-term follow-up is necessary in the current context of adjuvant treatment.

3. Cost Effectiveness of Osimertinib

Methods

A de novo semi-Markov model was developed and constructed to evaluate the cost effectiveness of osimertinib for the indication under assessment. This model comprised five health states; disease-free survival, locoregional recurrence, first-line treatment distant metastasis, second-line treatment distant metastasis, and death. Direct evidence for osimertinib versus active monitoring ('placebo') was available from ADAURA. This informed transitions from the disease-free survival health state. The OS data from ADAURA were not used directly in the model (due to the immaturity of this OS data). Instead, the model assumed that benefit accrued in the model is gained through the disease-free survival health state, informed by DFS data from ADAURA. Transitions from the other health states were informed by the CancerLinQ database and the FLAURA trial. CancerLinQ is a real-world evidence database, which provided data for patients with stage IB-IIIA EGFR-mutated NSCLC, following tumour resection, who had experienced locoregional recurrence. This study informed transitions from the locoregional recurrence health state. The FLAURA trial was a phase III, double-blind randomised controlled trial, which evaluated the safety and efficacy of osimertinib versus EGFR tyrosine kinase inhibitors (gefitinib or erlotinib) in patients with EGFR-mutated, advanced or metastatic NSCLC. This study informed transitions from the distant metastasis health states (first- and second-line treatment).

Parametric survival models were used to estimate the probability of transitioning between the health states over time. The Applicant assumed that 90% of patients in the disease-free survival health state, in both the osimertinib and active monitoring arms, were 'cured' after five years. This assumption was a key driver in the cost-effectiveness model; however, it is not well supported by the available ADAURA trial data. Clinical opinion also indicated that this estimate is highly uncertain. A time horizon of 37 years (lifetime) and cycle length of 4.35 weeks was employed. Utility data were derived from the ADAURA and FLAURA trials, and also from the literature. The Review Group had concerns regarding the clinical plausibility of the high utility values employed. The cost categories considered in the model were drug acquisition, administration, EGFR-testing, AEs, healthcare resource use, central nervous system metastasis management costs, subsequent treatment, and terminal care.

Results

Analyses presented in this document are based on the list price of interventions. The NCPE implemented a number of changes to the Applicant's base case assumptions to reflect the NCPE preferred assumptions. The most notable of these included: reducing the proportion considered 'cured' in the disease-free health state to 85%, adjusting transitions to death by a standardised mortality ratio, and capping utility, in the disease-free survival and locoregional health states, so that it does not exceed that of the general population. A 'cure' proportion of 85%, for the disease-free health state, was derived from registry data sourced from the literature. As these data were sourced from a non-European setting, it is unclear how reflective this estimate is of the true 'cure' proportion in Irish clinical practice. The results of the NCPE-adjusted and Applicant base case analyses are presented in Table 1 and Table 2, respectively.

Table 1 Results of NCPE-adjusted base case analysis[a]

Treatment Strategy	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Active Monitoring	165,033	6.17			
Osimertinib[bc]	267,256	7.62	102,223	1.45	70,595

ICER: Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year.
[a]Total costs and QALYs presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.
[b]Price of osimertinib was updated by the Review Group to align with the March 2023 Price Realignment.
[c]There is a commercial-in-confidence patient access scheme (CIC PAS) in place for osimertinib; not shown in this table.

Table 2 Results of Applicant base case analysis[a]

Treatment Strategy	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Active Monitoring	164,685	6.48			
Osimertinib[bc]	261,720	8.15	97,035	1.68	57,892

ICER: Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year.
[a]Total costs and QALYs presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.
[b]Price of osimertinib was updated by the Review Group to align with the March 2023 Price Realignment.
[c]There is a commercial-in-confidence patient access scheme (CIC PAS) in place for osimertinib; not shown in this table.

The Review Group highlight that both the NCPE-adjusted and Applicant base case analyses are highly uncertain. Osimertinib, in the adjuvant setting, represents a step change in the treatment pathway of NSCLC. There is uncertainty regarding the impact of introducing adjuvant osimertinib on subsequent treatments, most notably the use of osimertinib in the

metastatic setting. The base case analyses arbitrarily assumed that 50% of patients in the osimertinib arm receive retreatment in the metastatic setting. It is unclear whether this reflects what will occur in clinical practice. Of note, increasing the proportion who received retreatment in the metastatic setting to 100% increased the NCPE-adjusted base case ICER to €76,116 per QALY. This relatively small impact on the ICER is influenced by the assumption that 85% of patients in the disease-free health state at five years were considered 'cured'. Thus, reducing the proportion of patients transitioning to the metastatic setting and receiving retreatment. This assumption is highly uncertain. Of key importance also, DFS, used to inform treatment benefit in the model, is not a validated surrogate for OS for this therapy in this line of treatment.

Sensitivity analysis

In the NCPE-adjusted base case, the mean probabilistic ICER was closely aligned with the deterministic ICER. Osimertinib had a 9.1% probability of cost effectiveness, versus active monitoring, at the €45,000 per QALY threshold (0% at the €20,000 per QALY threshold). In the one-way sensitivity analysis, the main driver of cost effectiveness was the discount rate on outcomes. This emphasises that a large proportion of the outcome gain in the model occurs after year one in the model, in the extrapolated phase. The disease-free survival health state utility value, for osimertinib and active monitoring, was also a key driver. Scenario analyses indicated that the model was highly sensitive to changes in several parameters, most notably assumptions regarding 'cure'. When the proportion 'cured' in the disease-free survival health state was reduced to 50%, the NCPE-adjusted base case ICER increased to €103,353 per QALY. Assuming a 'cure' time point of eight years increased the NCPE-adjusted base case ICER to €151,921 per QALY.

4. Budget Impact of Osimertinib

The price-to-wholesaler of a 30-tablet pack of osimertinib 80mg is €5,868.97. Assuming a treatment duration of 36 months (36.525 cycles), the total cost per treatment course is €216,061. Note, this estimate does not account for treatment discontinuation. A VAT rate of 0% applies, as osimertinib is an oral product.

The Applicant used estimates from several sources to inform the eligible population estimates. These included the National Cancer Registry Ireland, clinical opinion, and the literature. Based on these data, the Applicant assumed that 21 patients will be eligible for treatment in year one, increasing to 30 patients by year five. This assumes an EGFR testing rate of 60% in year one, 70% in year two, and 80% from year three onwards. Assuming a market share of 80% (year one) to 90% (year five), the total population treated with osimertinib over five years was estimated to be 216. The Review Group considered the population estimates to be subject to considerable uncertainty.

Based on the Applicant assumptions, the cumulative five-year gross drug budget impact was estimated to be €16.44 million. Assuming an EGFR testing rate of 100% in years one to five increased the cumulative five-year gross drug budget impact to €22.54 million. As the comparator is active monitoring, which was assumed to accrue no drug-related costs, the cumulative net drug budget impact of osimertinib was equal to that of the cumulative gross drug budget impact. When EGFR testing costs (Applicant base case assumptions) and the cost offsets from subsequent treatments were accounted for, the cumulative five-year net health budget impact of osimertinib was €14.10 million.

5. Patient Organisation Submission

No Patient Organisation Submissions were received during the course of this assessment.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that osimertinib not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*. This recommendation considers the high uncertainty in both the Applicant and NCPE-adjusted base case analyses. The ICER is considerably higher when alternative assumptions regarding 'cure' are employed. The probability of cost effectiveness, in the NCPE-adjusted base case, was low. There is also uncertainty in the five-year gross drug budget impact, which will be higher should the EGFR testing rate in clinical practice reach 100%.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.