# Single Technology Appraisal

# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

**Contents:**

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from AstraZeneca:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Roy Castle Lung Cancer Foundation

4. **External Assessment Report** prepared by Bristol Technology Assessment Group

5. **External Assessment Report – factual accuracy check**

6. **Statements from experts:**
   a. Dr. Shobhit Baijal, Consultant Medical Oncologist – clinical expert, nominated by British Thoracic Oncology Group
   b. Patient expert, nominated by NICE

*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

## Document B

## Company evidence submission

**May 2024**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **ID6328 Osimertinib FLAURA 2 Doc B 150524 redacted** | **1.0** | **Yes** | **15th May 2024** |

# Contents



# Tables and figures





# Abbreviations

| | |
|---|---|
| ABCP | Atezolizumab + bevacizumab + carboplatin + paclitaxel |
| AE | Adverse event |
| AIC | Akaike information criterion |
| ALK | Anaplastic lymphoma kinase |
| BIC | Bayesian information criterion |
| BICR | Blinded independent central review |
| BMI | Body mass index |
| BNF | British National Formulary |
| BRAF | Serine/threonine-protein kinase B-Raf |
| BSA | Body surface area |
| CADTH | Canadian Agency for Drugs and Technologies in Health |
| CEA | Cost-effectiveness analysis |
| CEAC | Cost-effectiveness acceptability curve |
| cFAS | Central nervous system full analysis set |
| CI | Confidence interval |
| CNS | Central nervous system |
| CR | Complete response |
| CRD | Centre for Reviews and Dissemination |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | Circulating tumour DNA |
| CUA | Cost-utility analysis |
| DCO | Data cut off |
| DCR | Disease control rate |
| DoR | Duration of response |
| DSA | Deterministic sensitivity analysis |
| DSU | Decision Support Unit |
| EGFR | Epidermal growth factor receptor |
| EGFRm | Epidermal growth factor receptor mutation |
| EMA | European Medicines Agency |
| eMIT | Electronic market information tool |
| EORTC-QLQ-C30 | European Organisation for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire |
| EORTC-QLQ-L13 | European Organisation for Research and Treatment of Cancer 13-item lung cancer module |
| EQ-5D-5L | EuroQoL-5 Dimensions-5 levels |
| ESMO | European Society for Medical Oncology |
| FAS | Full analysis set |

| | |
|---|---|
| FDA | Food and Drug Administration |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| HTA | Health technology assessment |
| ICER | Incremental cost-effectiveness ratio |
| IxRS | Interactive voice/web response system |
| KM | Kaplan–Meier |
| MMRM | Mixed models for repeated measures |
| NCCN | National Comprehensive Cancer Network |
| NHB | Net health benefit |
| NSCLC | Non-small cell lung cancer |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progressed disease |
| PDC | Platinum drug chemotherapy |
| PFS | Progression-free survival |
| PFS2 | Time to second progression |
| PHA | Proportional hazards assumption |
| PR | Partial response |
| PRO | Patient reported outcomes |
| PS | Performance status |
| PSA | Probabilistic sensitivity analysis |
| PSM | Partitioned survival model |
| PSS | Personal Social Services |
| PSSRU | Personal Social Services Research Unit |
| QALY | Quality-adjusted life year |
| QD | Once daily |
| QoL | Quality of life |
| RCT | Randomised controlled trial |
| RDI | Relative dose intensity |
| RTK | Receptor tyrosine kinase |
| SAE | Serious adverse event |
| SAS | Safety analysis set |
| SD | Standard deviation |
| SE | Standard error |
| SLR | Systematic literature review |
| SMC | Scottish Medicines Consortium |
| SmPC | Summary of product characteristics |
| SoC | Standard of care |

| | |
|---|---|
| StD | Stable disease |
| TA | Technology appraisal |
| TKI | Tyrosine kinase inhibitor |
| TFST | Time to first subsequent treatment |
| TSST | Time to second subsequent treatment |
| TTD | Time to treatment discontinuation |
| VAS | Visual Analogue Scale |
| WBRT | Whole brain radiation therapy |
| WHO | World Health Organization |
| WTP | Willingness-to-pay |

## B.1 Decision problem, description of the technology and clinical care pathway

### *B.1.1 Decision problem*

The submission covers the technology's full anticipated marketing authorisation for this indication:

[redacted] (see Appendix C).

**Table 1: The decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Intervention** | Osimertinib with pemetrexed and platinum-based chemotherapy | As per NICE scope | |
| **Population** | Adults with untreated advanced EGFR mutation-positive NSCLC | [redacted] | This is in line with the population of the pivotal FLAURA2 trial, and consistent with the anticipated licensed indication for osimertinib with pemetrexed and platinum-based chemotherapy |
| **Comparator(s)** | Established clinical management without osimertinib with pemetrexed and platinum-based chemotherapy including:<br>• Osimertinib<br>• Dacomitinib<br>• Afatinib<br>• Erlotinib<br>• Gefitinib | Osimertinib | Osimertinib monotherapy represents the current SoC for patients in England who are receiving first-line treatment for locally advanced/metastatic NSCLC and is used in 86% of EGFRm patients.[1] The alternative treatments (dacomitinib, afatinib, erlotinib and gefitinib) are rarely used and osimertinib with pemetrexed and platinum-based chemotherapy is expected to displace osimertinib monotherapy only. This positioning was validated by UK clinical insight, with 9 UK-based clinical experts consulted as part of an advisory board unanimously stating that osimertinib monotherapy was their current first-line treatment of choice for metastatic EGFRm NSCLC.[2] This is further supported by current clinical guidelines such as ESMO, where osimertinib is recommended as the preferable first-line treatment option for patients with a classical activating EGFR mutation (exon 19 deletion or exon 21 L858R), especially for patients with CNS metastases.[3] |



| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Outcomes** | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• response rates<br>• duration of response<br>• time to treatment discontinuation<br>• adverse effects of treatment<br>• health-related quality of life | As per NICE scope | |

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; SoC, standard of care.



## *B.1.2 Description of the technology being evaluated*

Details of the technology being appraised in the submission are provided in Table 2. The draft summary of product characteristics (SmPC) for osimertinib is provided in Appendix C.[4]

**Table 2: Technology being evaluated**

| | |
|---|---|
| **UK approved name and brand name** | Osimertinib (TAGRISSO®) with pemetrexed and platinum-based chemotherapy |
| **Mechanism of action** | Osimertinib provides highly selective and irreversible inhibition of activating sensitising EGFR mutation (EGFRm+) and activating resistance mutation T790M, without affecting the activity of wild-type EGFR. Inhibition of phosphorylation of EGFR and downstream signalling leads to tumour growth inhibition and also induces cell cycle arrest.<br>Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.[5]<br>Carboplatin and cisplatin interfere with DNA synthesis by producing intra-strand and inter-strand crosslinks, leading to cytotoxicity.[6, 7] |
| **Marketing authorisation/CE mark status** | A marketing authorisation application is expected to be submitted to the MHRA in [redacted], with marketing authorisation expected in [redacted] |
| **Indications and any restriction(s) as described in the summary of product characteristics (SmPC)** | ***Indication covered in this submission:***<br>Osimertinib is expected to be indicated [redacted]<br>***Existing relevant indications for osimertinib:***<br>Osimertinib as monotherapy is indicated for:<br>• the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations<br>• the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations<br>• the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC |
| **Method of administration and dosage** | Osimertinib is available as 40 mg or 80 mg oral tablets. The recommended dose is 80 mg once a day when taken with pemetrexed and platinum-based chemotherapy until disease progression or unacceptable toxicity.<br>The recommended dose of pemetrexed is 500 mg/m$^2$ of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.[5]<br>The recommended dose of carboplatin is 5–7 mg/ml/min[6]<br>The recommended dose of cisplatin is 75 mg/m2 BSA infused over two hours approximately 30 minutes after completion of pemetrexed infusion.[5] |

| | |
|---|---|
| | Both carboplatin and cisplatin are given after completion of the pemetrexed infusion on the first day of each 21-day cycle.[5, 8] |
| **Additional tests or investigations** | EGFR mutation status should be determined by a validated test method, using either tumour DNA derived from a tissue sample or ctDNA obtained from a plasma sample. NICE recommends testing for EGFRm in people with previously untreated, locally advanced/metastatic NSCLC.[9] |
| **List price and average cost of a course of treatment** | Osimertinib is available at a list price of £5,770 per 30 tablets (40 mg or 80 mg).[10] The average cost of a course of treatment is £104,705.51.†<br>Carboplatin/cisplatin are available at a list price of £29.27/£71.44 per vial.[11] The average cost of a course of treatment is £218.52.†<br>Pemetrexed is available at a list price of £24.52/vial.[11] The average cost of a course of treatment is £4,635.38.† |
| **Patient access scheme (if applicable)** | [redacted] |

† The average cost of a course of treatment was based on the median extent of exposure (months) for each individual treatment in FLAURA2.[8]
Abbreviations: ctDNA, circulating tumour DNA; EGFR, epidermal growth factor receptor; MHRA, Medicines and Healthcare products Regulatory Agency; NSCLC, non-small cell lung cancer.

### *B.1.3 Health condition and position of the technology in the treatment pathway*

*Disease overview*

- **Lung cancer is the third most common cancer and the most common cause of cancer deaths in the UK[12]**
- **NSCLC accounts for 86% of all lung cancer cases[13]**
- **Approximately 10% of NSCLC cases harbour EGFR mutations (EGFRm),[14] of which exon 19 deletions and L858R point mutations account for around 90% of cases[15, 16]**
- **Compared with tumours without EGFRm, the presence of EGFRm is associated with more aggressive disease progression and a higher rate of central nervous system (CNS) metastases[17, 18]**
- **More than 65% of patients with lung cancer in England are diagnosed with unresectable advanced (stage III) or metastatic (stage IV) disease,[19] for which there is no cure; fewer than 5% of patients diagnosed with metastatic disease remain alive after 5 years[20]**
- **The health-related quality of life (HRQoL) of patients with locally advanced/metastatic NSCLC is negatively affected by the symptom burden associated with disease, which worsens with progression, and can also be affected by treatment-related adverse events (AEs) and toxicity[21, 22]**

*Clinical management*

- **The current standard of care (SoC) in the UK for locally advanced/metastatic NSCLC with EGFR exon 19 deletions and L858R point mutations is the third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib[2]**
- **Osimertinib monotherapy provided a step-change extension in progression-free survival (PFS) and overall survival (OS) compared with the first-generation EGFR TKIs erlotinib and gefitinib with significant improvement in median PFS (18.9 vs 10.2 months; p<0.001)[23] and significantly longer median OS (38.6 versus 31.8 months; p=0.0446)[24] in the FLAURA trial**
- **Osimertinib crosses the blood-brain barrier[25, 26] and has been shown to significantly delay CNS disease progression compared with erlotinib and gefitinib[27]**

*Unmet need*

- **Despite the clinical benefits observed with osimertinib in locally advanced/metastatic EGFRm NSCLC, patients eventually experience disease progression due to development of treatment resistance[16]**

- **Therefore, additional regimens are required to maximise clinical outcomes for patients in the first-line locally advanced/metastatic EGFRm NSCLC treatment setting, delaying progression for as long as possible**

### B.1.3.1 Lung cancer overview

Lung cancer is the third most common cancer in the UK, with 48,500 cases diagnosed each year.[12] NSCLC accounts for 86% of all lung cancer cases.[13] NSCLC is further classified as squamous or non-squamous (including adenocarcinoma or large-cell carcinoma),[28] with non-squamous carcinomas accounting for 74% of NSCLC cases.[13]

#### *B.1.3.1.1 Pathophysiology and risk factors*

The pathophysiology of lung cancer is complex and, although the exact cause of lung cancer is not fully understood, it has been hypothesised that exposure to carcinogens causes genetic mutations and modifications in protein synthesis, resulting in the abnormal growth of cells in the lung. Common mutations thought to result in the development of lung cancer occur in the *EGFR*, anaplastic lymphoma kinase (*ALK*), serine/threonine-protein kinase B-Raf (*BRAF*) and Kirsten rat sarcoma virus (*KRAS*) genes.[29] Risk factors include lifestyle (e.g. smoking), environmental and occupational exposure to carcinogens, with risk increasing with age.[30]

#### *B.1.3.1.2 Clinical presentation*

Early-stage NSCLC is often asymptomatic, and patients may not receive a diagnosis until their disease has reached an advanced stage.[31] Symptoms, which typically develop once the cancer becomes more advanced, include a persistent cough, coughing up blood, persistent breathlessness, unexplained tiredness and weight loss, repeated chest infections, and pain on breathing or coughing.[32] More than 65% of patients with lung cancer in England are diagnosed with unresectable advanced (stage III; where the cancer is found in the lung and nearby lymph nodes)[33] or metastatic disease (stage IV; where the cancer had spread to both lungs, the fluid around the lungs and/or to other parts of the body such as the brain or liver).[19, 33] The CNS is a common metastatic site for NSCLC, with around 20–40% of patients developing metastases during the course of the disease.[34] The most common

symptoms of CNS metastasis include headaches, cognitive deficits, ataxia, seizures, and visual and speech problems, which can greatly impact patients' HRQoL in addition to the symptoms from the primary tumour.[35]

#### *B.1.3.1.3 NSCLC with EGFR mutations*

EGFR is a receptor tyrosine kinase (RTK) which activates signalling pathways leading to cell growth and survival and plays a central role in the pathogenesis and progression of many carcinomas.[16, 36] EGFR mutations can cause the receptor to be in a continually active state i.e. constitutive activation, leading to upregulation of pro-survival pathways and confer oncogenic properties to cells which become dependent on EGFR for their survival. Several known EGFR mutations (EGFRm) have been mapped to the tyrosine kinase domain of EGFR. Exon 19 deletions and L858R point mutations account for around 90% of all NSCLC EGFRm, with other mutations infrequently reported.[15, 16]

The presence of EGFRm is associated with more aggressive disease progression than patients whose tumours do not harbour EGFRm.[17] In particular, patients with EGFRm have a higher rate of brain metastases than patients with wild-type EGFR (70% vs 38%).[18]

##### B.1.3.1.3.1 Molecular profiling

The identification of clinically relevant mutations in genes such as *EGFR*, *ALK* and *BRAF* can help to predict the course of disease and guide targeted treatment decisions. Tumour tissue biopsy is the preferred sample type for genetic mutation testing in advanced NSCLC. Cytology samples may be used if a biopsy is not available, but sample quality and tumour cell content may be lower than with a biopsy sample. Alternatively, circulating tumour DNA (ctDNA) samples can be used if biopsy or cytology samples are not available, but these may have a high false-negative rate.[37, 38] NICE recommends testing for EGFRm in people with previously untreated, locally advanced/metastatic NSCLC.[9]

#### *B.1.3.1.4 Epidemiology*

In the UK, the frequency of EGFRm in patients with stage III/ IV non squamous NSCLC is approximately 10%.[14] EGFRm are more common in women than in men

(44% versus 24%), in adenocarcinoma than non-adenocarcinoma (38% vs 12%) and in never-smokers than in past or current smokers (49% vs 22%).[39]

#### *B.1.3.1.5 Prognosis*

Lung cancer is the most common cause of cancer death in the UK.[12] Five-year survival decreases dramatically with disease stage (Table 3); in a mixed population of patients with NSCLC (mutation type not specified) from 2016–2020, fewer than 5% of patients diagnosed with metastatic (stage IV) disease remain alive after 5 years.[20]

**Table 3: Lung cancer survival by known stage at diagnosis (cases diagnosed from 2016–2020), England[20]**

| Stage | 5-year survival, % |
|---|---|
| I | 62.7 |
| II | 40.9 |
| III | 16.0 |
| IV | 4.3 |

CNS metastases are associated with poor median survival and significant worsening of HRQoL; median OS is 4–9 months with chemotherapy and 7 months for patients receiving whole brain radiation therapy (WBRT).[40, 41] Untreated patients with CNS metastases have a median survival of just 2 months.[40, 42]

#### *B.1.3.1.6 Disease burden*

The HRQoL of patients with locally advanced/metastatic NSCLC is negatively affected by the symptom burden associated with disease, which worsens with progression, and can also be affected by treatment-related AEs and toxicity.[21, 22] Typical symptoms of locally advanced/metastatic NSCLC that impact HRQoL include a persistent cough, chest pain, dyspnoea, fatigue, loss of appetite and weight loss.[43, 44] Following disease progression, patients experience a decline in their HRQoL, likely due to an associated increase in symptom burden.[43, 44] In a prospective, multi-country, cross-sectional analysis of patients with Stage IIIB or IV NSCLC, a decline in HRQoL (as measured by EuroQoL-5 Dimensions [EQ-5D] index values) was observed for patients with progressive disease vs those who remained progression free (0.58 vs 0.70, respectively).[43] Brain metastases in patients with EGFRm NSCLC

are associated with a higher frequency of seizures, speech problems, focal neurological deficits, vision disorder, fatigue, nausea, headaches, problems with memory, altered mental status, and mobility issues.[45] This high symptom burden translates into a clinically meaningful deterioration in HRQoL for patients with brain metastases compared with patients without brain metastases ($p<0.0001$).[46]

### B.1.3.2 Current clinical care pathway

#### *B.1.3.2.1 Aim of treatment*

There is no cure for locally advanced/metastatic EGFRm NSCLC; therefore, treatment goals are focused on delaying disease progression, prolonging survival, improving quality of life, and alleviating symptoms. Potential benefits of treatment should be balanced with the risk of additional toxicities.[47]

#### *B.1.3.2.2 Evolution of targeted therapies*

An overview of NICE-recommended TKI therapies for the first-line treatment of EGFRm NSCLC is presented in Table 4.

Gefitinib and erlotinib were the first generation of TKIs that were shown to be effective in the treatment of advanced/metastatic EGFRm NSCLC. These therapies are reversible small molecule adenosine triphosphate analogues originally designed to inhibit the tyrosine kinase activity of wild-type EGFR.[16] Although these treatments demonstrated improved PFS compared with platinum-based chemotherapy,[48, 49] most patients who respond to therapy ultimately develop disease progression after about 9–10 months of treatment, based on clinical trial findings,[48, 49] due to the development of drug-resistant mutations in EGFR (such as T790M) or through activation of bypass signalling pathways (e.g. c-Met amplification).[50]

Second-generation TKIs (including afatinib and dacomitinib) were developed to more potently inhibit wild-type and mutant forms of EGFR, including T790M. These are irreversible inhibitors with a greater binding affinity for the EGFR kinase domain and can also block signalling from other members of the ERbB2 family.[16] However, anti-T790M activity proved disappointing in patients who had developed resistance to gefitinib and erlotinib. For first line-treatment of EGFRm NSCLC, disease

progression was reported within approximately 11 months in the afatinib LUX-Lung 3 and 6 pivotal trials[51, 52] and 14.7 months in the dacomitinib ARCHER 1050 trial.[53]

Osimertinib is a third-generation TKI which is structurally distinct from other EGFR TKIs, resulting in a unique activity profile. It irreversibly targets EGFR TKI-sensitising- and T790M resistance-mutant forms of EGFR, while sparing wild-type EGFR.[54] Osimertinib monotherapy provided a step-change extension in PFS and OS compared with first-generation EGFR TKIs for patients with locally advanced/metastatic EGFRm NSCLC; in the FLAURA trial, osimertinib monotherapy was associated with a significant improvement in median PFS of 18.9 months compared with 10.2 months with erlotinib and gefitinib (HR: 0.46 [95% CI: 0.37, 0.57]; p<0.001)[23] and significantly longer median OS (38.6 months versus 31.8 months; HR: 0.80 [95.05% CI: 0.64, 1.00]; p=0.0446.[24] As a result of the superior outcomes demonstrated, osimertinib has become the SoC for the treatment of first-line locally advanced/metastatic EGFRm NSCLC in the UK.[2]

**Table 4: Overview of NICE-recommended TKI therapies for first-line treatment of EGFRm NSCLC**

| Therapy | Type of inhibition | EGFR target | Pivotal clinical trials | mPFS | mOS |
|---|---|---|---|---|---|
| Osimertinib | Covalent, irreversible | Ex19del, L858R, T790M | FLAURA[23, 24] | Osimertinib vs gefitinib or erlotinib: 18.9 months vs 10.2 months (p<0.001) | Osimertinib vs gefitinib or erlotinib: 38.6 months vs 31.8 months (p=0.046) |
| Dacomitinib | Covalent, irreversible | Ex19del, L858R | ARCHER 1050[53, 55] | Dacomitinib vs gefitinib: 14.7 months vs 9.2 months (p<0.0001) | Dacomitinib vs gefitinib: 34.1 months vs 27.0 months (p=0.0155) |
| Afatinib | Covalent, irreversible | Ex19del, L858R | LUX-Lung3[51, 56] | Afatinib vs cisplatin + pemetrexed: 11.1 months vs 6.9 months; p=0.001 | Afatinib vs cisplatin + pemetrexed: 28.2 months vs 28.2 months (p=NS) |
| | | | LUX-Lung6[52, 56] | Afatinib vs cisplatin + gemcitabine: 11.0 months vs 5.6 months (p<0.001) | Afatinib vs cisplatin + gemcitabine: 23.1 months vs 23.5 months (p=NS) |
| Erlotinib | Reversible | Ex19del, L858R | EURTAC[48] | Erlotinib vs platinum chemo: 9.7 months vs 5.2 months (p<0.0001) | Erlotinib vs platinum chemo: 19.3 months vs 19.5 months (p=0.87). |
| Gefitinib | Reversible | Ex19del, L858R | IPASS[49, 57] | Gefitinib vs carboplatin + paclitaxel: 9.5 months vs 6.3 months (p<0.0001) | Gefitinib vs carboplatin + paclitaxel: 21.6 months vs 21.9 months (p=NS) |

Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; mOS, median overall survival; mPFS, median progression-free survival; NS, not significant; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.



**Efficacy of TKIs in targeting CNS metastases**

CNS metastases are associated with a particularly poor prognosis; median OS is 4–9 months with chemotherapy and 7 months for patients receiving WBRT,[40, 41] while untreated patients with CNS metastases have a median survival of just 2 months.[40, 42] Due to limited CNS penetration with earlier generation TKIs, patients with active CNS metastases were largely excluded from the initial pivotal trials of first-generation EGFR-TKIs, and clinical trial data indicate that approximately one-third of patients develop CNS metastases after an initial response to first- and second-generation EGFR-TKIs.[26, 58]

Compared with first- and second-generation EGFR TKIs, pre-clinical data have indicated that osimertinib is able to cross the blood-brain barrier, and therefore target CNS metastases.[25, 26] These observations are further supported by results from the FLAURA trial in which the PFS benefit observed with osimertinib treatment in patients with CNS metastases at trial entry was consistent with the benefit seen in the overall trial population.[23] In a subset of patients who had measurable and/or non-measurable CNS metastases documented at baseline in FLAURA, patients in the osimertinib treatment group had a 52% reduction in the risk of CNS disease progression compared with the erlotinib or gefitinib group (hazard ratio [HR] 0.48; [95% CI, 0.26 to 0.86]; p=0.014).[27]

#### *B.1.3.2.3 Treatment guidelines and current clinical practice*

NICE currently recommends a range of treatment options for the first-line management of locally advanced/metastatic EGFRm NSCLC, including platinum-based chemotherapy as well as first-, second- and third-generation TKIs (Figure 1). In 2020, osimertinib monotherapy was recommended by NICE for untreated locally advanced/metastatic EGFRm NSCLC in adults.[59] Osimertinib monotherapy is also recommended as an option for the treatment of EGFR T790M mutation-positive locally advanced/metastatic NSCLC after progression with an alternative first-line EGFR TKI.[60]

Whilst multiple treatment options are recommended by NICE in the first-line setting, the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines recommend osimertinib monotherapy as the

first-line treatment of choice for the patient for locally advanced/metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R mutations.[3, 61]

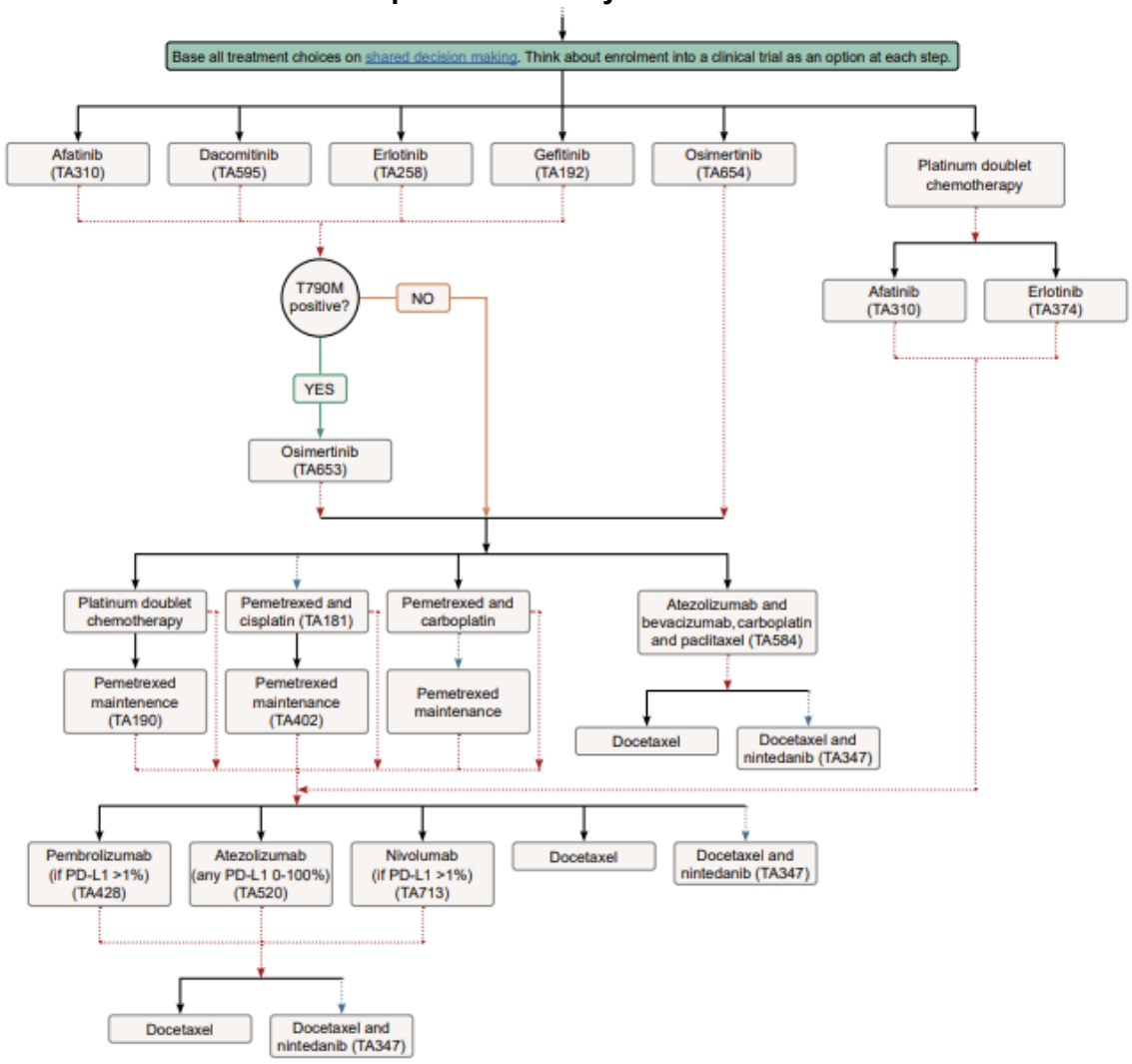
Specific ESMO guideline recommendations for stage IV NSCLC with EGFRm are as follows:[3]

- All patients with a sensitising EGFR mutation should receive first-line EGFR TKIs irrespective of clinical parameters including PS, gender, tobacco exposure and histology.
- Osimertinib is the preferable first-line treatment option for patients with a classical activating EGFR mutation (exon 19 deletion or exon 21 L858R), especially for patients with CNS metastases.

Current UK clinical practice is aligned to relevant clinical guidelines and osimertinib monotherapy is SoC.[2] The efficacy of osimertinib monotherapy has led to a frontline EGFRm NSCLC market share of 86%.[1] This positioning was validated by UK clinical insight with 9 UK-based clinical experts consulted as part of an advisory board (see Section B.2.3.5) unanimously stating that osimertinib monotherapy was their current treatment of choice for first-line metastatic EGFRm NSCLC.[2]

**Figure 1: NICE-recommended options for the systemic treatment of EGFRm NSCLC[47]**




### *B.1.3.2.4 Unmet needs in the management of first-line locally advanced/metastatic EGFRm NSCLC*

Despite the availability of a range of first-line NICE-recommended treatment options, the most efficacious treatment option,[48, 49, 51] osimertinib monotherapy, has a median PFS of 18.9 months.[23]

In the management of locally advanced/metastatic NSCLC, it is important that patients receive the most effective treatment possible as their first-line therapy. Clinical experts consulted as part of an advisory board have commented that it is important to give patients the most effective treatment upfront.[2] Approximately 28% of patients with locally advanced/metastatic EGFRm NSCLC die before receiving second-line therapy,[62, 63] whilst around 25–30% of patients who remain alive receive

no systemic treatment due to fitness or personal choice.[64] This may be particularly true within populations with a greater burden of disease and who have a poorer prognosis, such as in patients with CNS metastases, challenging tumour mutations such as EGFR L858R mutations and/or those with high tumour burden.[65]

An additional regimen is required to maximise clinical outcomes for patients in the first-line locally advanced/metastatic EGFRm NSCLC treatment setting, delaying progression for as long as possible and ensuring that patients receive the strongest option first to provide the highest chance of improved survival outcomes.

#### *B.1.3.2.5 Osimertinib with pemetrexed and platinum-based chemotherapy*

##### B.1.3.2.5.1 Rationale for adding chemotherapy to osimertinib

Despite the significant improvement in efficacy observed with osimertinib monotherapy compared with previous generations of TKIs, patients eventually develop treatment resistance and experience disease progression.[16] Resistance mechanisms to osimertinib are more diverse than to first- and second-generation TKIs[3] and develop through multiple EGFR-dependent and independent mechanisms.[66] It was therefore considered that a combination regimen may offer improved efficacy against heterogeneous tumours, thus delaying treatment resistance.

Previous evidence has shown that the addition of concurrent chemotherapy to first-generation TKIs can offer improved efficacy coupled with a manageable safety profile when compared with TKI monotherapy alone.[67] In a randomised, open-label Phase 3 study, gefitinib in combination with carboplatin and pemetrexed demonstrated significantly improved median PFS compared with gefitinib monotherapy (20.9 months vs 11.2 months [HR: 0.49; 95% CI: 0.39, 0.62; p<0.01]) among patients with newly-diagnosed metastatic EGFRm NSCLC.[68] An additional retrospective study showed that addition of chemotherapy to erlotinib resulted in improved PFS (18.9 months; 95% CI: 14.4, 25.9) compared with previously reported data with sequential use of erlotinib and chemotherapy (median PFS range: 8.4–13.1 months).[69]

It was therefore hypothesised that the addition of platinum-based chemotherapy to osimertinib monotherapy may induce a synergistic effect and facilitate the

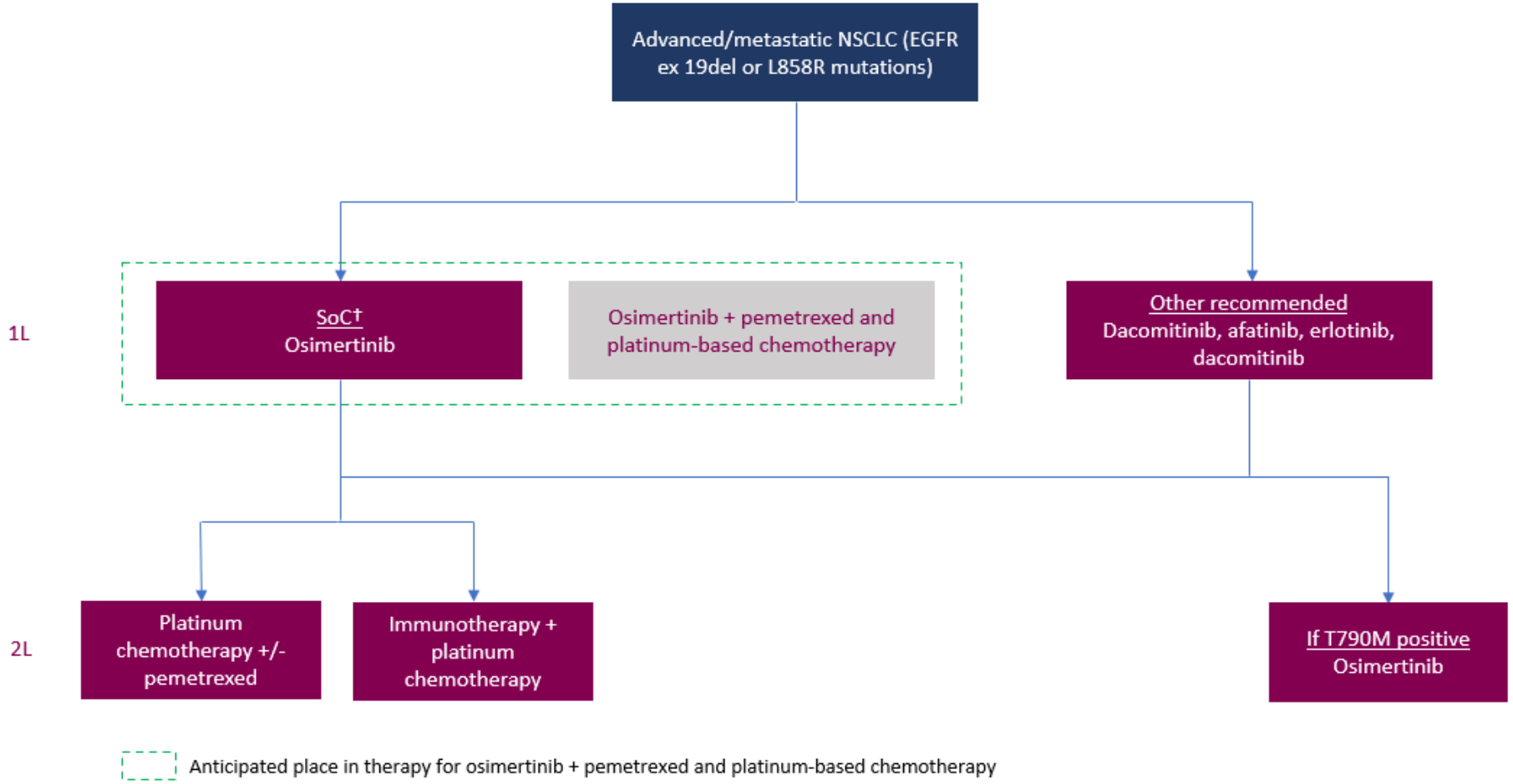
destruction of different cancer cell populations, thereby controlling several routes of resistance and restricting the development of drug tolerance.[70, 71] This hypothesis was tested in the pivotal Phase 3 FLAURA2 study (described in Section B.2.3).

#### B.1.3.2.5.2 Place in therapy

The anticipated licensed indication for osimertinib with pemetrexed and platinum-based chemotherapy is [redacted]. As described in Section B.1.3.2.3, based on guidelines and clinical expert feedback, the current SoC for this patient population in England is osimertinib monotherapy.[3, 70] Osimertinib with pemetrexed and platinum-based chemotherapy should be an option for patients who might benefit from more intense combination treatment (Figure 2). As pemetrexed is indicated for patients with locally advanced/metastatic NSCLC who do not have a predominantly squamous histology,[5] osimertinib with pemetrexed and platinum-based chemotherapy is expected to be used in patients with non-squamous histology only.

**Figure 2: Current treatment pathway for locally advanced/metastatic EGFRm NSCLC based on current guidelines and clinical input**




†Based on clinical expert opinion[2] and UK market share data.[1]
Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; SoC, standard of care.
Source: Hendriks et al (2023);[3] AstraZeneca data on file (2023);[2] AstraZeneca data on file (2024).[64]

### *B.1.4 Equality considerations*

Use of osimertinib with pemetrexed and platinum-based chemotherapy is not expected to raise any equality issues.

## B.2 Clinical effectiveness

***Overview***

- **FLAURA2 is an ongoing, global, Phase 3, open-label, randomised study to assess the efficacy and safety of osimertinib with or without pemetrexed and platinum-based chemotherapy in patients with untreated locally advanced/metastatic EGFRm NSCLC**
- **A statistically significant and clinically meaningful 38% reduction in the risk of investigator assessed disease progression or death was observed in the osimertinib + chemotherapy arm compared with the osimertinib monotherapy arm (HR: 0.62 [95% CI: 0.49, 0.79]; p<0.0001), at the primary endpoint data cut off (DCO 03 April 2023)**
  - **Median PFS was approximately 8.8 months longer in the osimertinib + chemotherapy arm compared with the osimertinib monotherapy arm, with sustained separation of Kaplan-Meier (KM) curves seen from 3 months post-randomisation to the end of follow-up (24 months)**
  - **The PFS benefit observed for osimertinib + chemotherapy compared with osimertinib monotherapy included patients in pre-defined subgroups with poor prognostic factors such as CNS metastasis status at study entry and L858R EGFR mutation type**
  - **A clinically meaningful reduction in the risk of CNS disease progression or death was observed with osimertinib + chemotherapy versus osimertinib monotherapy (HR: 0.58 [95% CI: 0.33, 1.01]) for patients with CNS metastases at baseline**
- **At the second interim OS analysis (08 January 2024), with 41% data maturity, a favourable OS benefit in favour of osimertinib + chemotherapy was observed (HR: 0.75 [95% CI 0.57, 0.97])**
- **High response rates were observed in both treatment arms, with a numerically higher objective response rate (ORR) and a clinically meaningful improvement in median DoR in the osimertinib + chemotherapy arm**
- **Osimertinib in combination with pemetrexed and platinum-based chemotherapy demonstrated a manageable safety and tolerability profile, consistent with the known profile of the individual treatment components, with no detriment in QoL**

***Clinical effectiveness conclusions***

- **Osimertinib + chemotherapy significantly improves PFS with a trend towards improved OS and no detrimental impact on HRQoL compared**

**with the current SoC, osimertinib monotherapy, in patients with untreated advanced or metastatic EGFRm NSCLC**

- **Clinical benefits were also observed in hard-to-treat populations such as patients with CNS metastases and L858R mutations**
- **Osimertinib + chemotherapy therefore provides an opportunity to build on the efficacy of the current SoC, with a more intensified treatment regimen that can maximise long-term outcomes for suitable patients**

### *B.2.1 Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify randomised controlled trial (RCT) evidence on the efficacy and safety of first-line treatments for the treatment of adult patients with unresectable locally advanced/metastatic EGFRm NSCLC, including osimertinib plus chemotherapy.

The SLR study question was specified using the Population, Intervention, Comparator, Outcome and Study type (PICOS) framework. Full details of the methodology, including search strategy, PRISMA flow diagram, list of included studies and list of excluded studies at full text review is provided in Appendix D.

### *B.2.2 List of relevant clinical effectiveness evidence*

The SLR identified one relevant RCT reporting on the clinical effectiveness of osimertinib plus chemotherapy, FLAURA2 (Table 5).

**Table 5: Clinical effectiveness evidence**

| | |
|---|---|
| **Study** | FLAURA2 |
| **Study design** | Phase 3, international, open-label, randomised study |
| **Population** | Patients with EGFRm (exon 19 deletion or L858R mutation) advanced NSCLC who had not previously received treatment for advanced disease |
| **Intervention(s)** | Osimertinib + pemetrexed and cisplatin/carboplatin |
| **Comparator(s)** | Osimertinib |
| **Indicate if study supports application for marketing authorisation** | Yes |
| **Indicate if study used in the economic model** | Yes |
| **Rationale if study not used in model** | NA |

| Study | FLAURA2 |
|---|---|
| **Reported outcomes specified in the decision problem** | • **Overall survival**<br>• **Progression-free survival**<br>• Response rate<br>• Duration of response<br>• **Time to treatment discontinuation†**<br>• **Adverse effects of treatment**<br>• **Health-related quality of life** |

†TTD was not included in the pre-specified trial outcomes however have been calculated for the purpose of the economic model.
Abbreviations: EGFR, epidermal growth factor receptor; NA, not applicable; NSCLC, non-small cell lung cancer.

## *B.2.3 Summary of methodology of the relevant clinical effectiveness evidence*

### B.2.3.1 Summary of trial methodology - FLAURA2 (Study D5169C00001)

FLAURA2 is an ongoing, global, Phase 3, open-label, randomised study to assess the efficacy and safety of osimertinib with or without pemetrexed and platinum-based chemotherapy in patients with epidermal growth factor receptor mutation positive (EGFRm; Ex19del and/or L858R) locally advanced/metastatic NSCLC, who have not received any prior treatment for advanced disease.

The methodology for and data from FLAURA2 is drawn from multiple sources. These include the clinical study protocol,[70], clinical study report (CSR),[8] interim data on file report of the second interim analysis,[72] conference presentations,[73-75] and publications.[76, 77]

#### *B.2.3.1.1 Data cut-off*

Analyses presented in this report were based on the primary analysis of the randomised period, conducted at a DCO date of 03 April 2023 and a second interim analysis conducted at a DCO of 08 January 2024 (an ad-hoc analysis of the OS outcome provided as part of US Food and Drug Administration [FDA]-specific regulatory procedures). A final OS analysis will be conducted when the data are approximately 60% mature.[70]

### B.2.3.2 Study objectives

The primary objective of the study was to demonstrate a statistically significant improvement in investigator-assessed PFS with osimertinib plus chemotherapy compared with osimertinib monotherapy treatment.

#### *B.2.3.2.1 Study locations*

The study included 151 sites in 21 countries across Europe (including 5 in the UK, enrolling 23 patients), Asia-Pacific, North America, South America, and Africa.

### B.2.3.3 Trial design

The FLAURA2 study was conducted in two parts: the safety run-in period, and the open-label, Phase 3, randomised period. Following a positive recommendation by the Safety Review Committee based on the evaluation of data from the safety run-in period, the randomised period was initiated. The following sections describe the methods and results of the randomised period only.

Patients who fulfilled the study eligibility criteria (see Table 6) were randomised in a 1:1 ratio to receive osimertinib plus chemotherapy or osimertinib monotherapy.

**Osimertinib plus chemotherapy arm:** Patients received osimertinib 80 mg once daily (QD), in combination with pemetrexed (500 mg/m$^2$) plus either cisplatin (75 mg/m$^2$) or carboplatin (AUC5) (administered on Day 1 of 21-day cycles for 4 cycles), followed by osimertinib, 80 mg QD, plus pemetrexed (500 mg/m$^2$) maintenance (every 3 weeks).

**Osimertinib monotherapy arm:** Patients received osimertinib 80 mg QD.

Patients in both treatment arms received randomised treatment until Response Evaluation Criteria in Solid Tumors (RECIST) 1.1-defined disease progression, unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met. Patients could continue to receive study treatment with osimertinib beyond RECIST 1.1-defined progression if, in the judgement of the investigator, they were receiving clinical benefit and did not meet any discontinuation criteria.

The study did not permit crossover between treatment arms. Prior to randomisation, the investigator decided which chemotherapy regimen a patient would receive if they were randomised to osimertinib plus chemotherapy arm. At the investigator's discretion, patients who discontinued cisplatin alone or carboplatin alone could be switched to the alternative platinum-based agent in combination with pemetrexed and osimertinib for the remainder of the platinum doublet therapy cycles, up to a maximum of 4 cycles.

An overview of the trial design is presented in Figure 3.

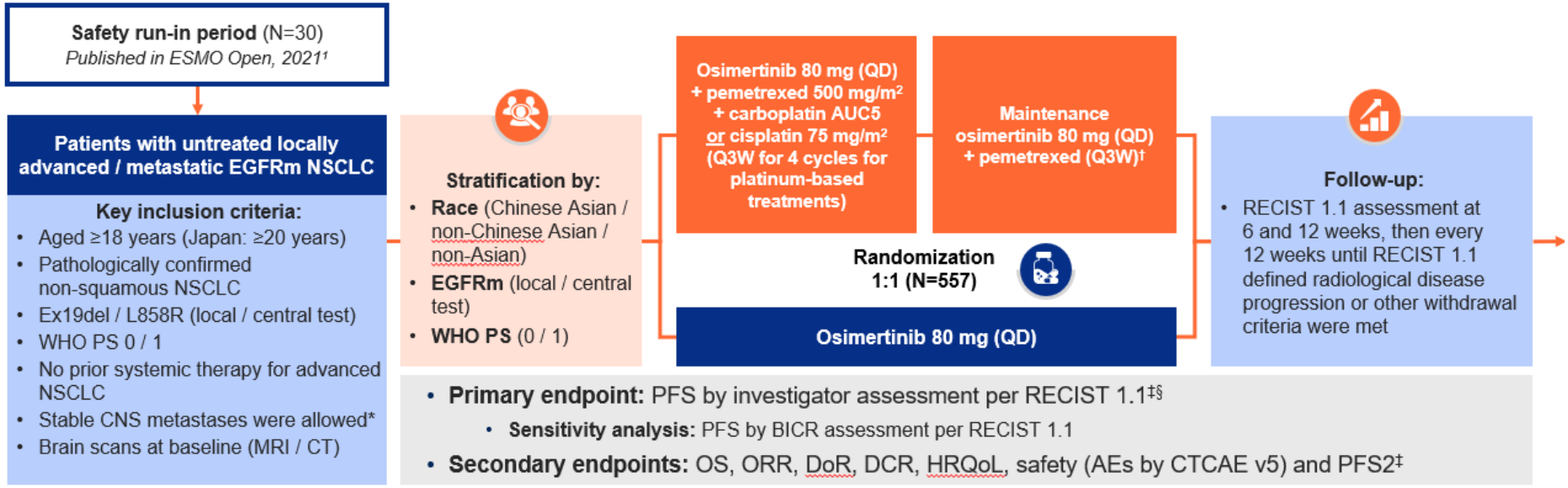
#### *B.2.3.3.1 Method of randomisation and blinding*

Eligible patients were centrally randomised to each study treatment arm using the interactive voice/web response system (IxRS). Randomisation was stratified by race (Chinese/Asian vs non-Chinese/Asian vs non-Asian), World Health Organisation (WHO) performance status (PS) (0 vs 1), and method for tissue testing (central vs local). It was anticipated that approximately 60% Asian patients and 40% non-Asian patients would be recruited. If a patient withdrew from the study, then their patient number was not reused, and withdrawn patients were not replaced.

FLAURA2 is an open-label, sponsor-blind study. Investigators and patients were not blinded during the study to avoid placing an unnecessary burden on patients. However, the sponsor was blinded to treatment assignment and did not have access to any aggregate summaries by treatment arm during the study.

**Figure 3: FLAURA2 study design**




*Not requiring steroids for at least two weeks; †Pemetrexed maintenance continued until a discontinuation criterion was met; ‡Efficacy analyses in the full analysis set, defined as all patients randomized to study treatment regardless of the treatment actually received, and safety analyses in the safety analysis set, defined as all randomized patients who received ≥1 dose of study treatment – one patient who was randomized to osimertinib plus platinum-pemetrexed received only osimertinib and was therefore included in the osimertinib monotherapy safety analysis set; §The study provided 90% power to demonstrate a statistically significant difference in PFS assuming HR=0.68 at 5% two-sided significance level.
Abbreviations: AE, adverse event; AUC, area under the concentration-time curve during any dosing interval; BICR, blinded independent central review; CNS, central nervous system; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ctDNA, circulating tumour DNA; DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; ESMO, European Society for Medical Oncology; Ex19del, exon 19 deletion, an in-frame deletion occurring within exon 19, which encodes part of the kinase domain; L858R, sensitising mutation in the EGFR gene with substitution of a leucine with an arginine at position 858 in exon 21; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PS, performance status; PFS, progression-free survival; PFS2, time to second progression; QD, every day; Q3W; every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy; WHO, World Health Organisation.
Source: Janne et al. (2023);[75] CSR.[8]

#### *B.2.3.3.2 Eligibility criteria*

Details of key inclusion and exclusion criteria for FLAURA2 are presented in Table 6.

A full list of inclusion and exclusion criteria is presented in Appendix M.

**Table 6: Eligibility criteria – FLAURA2**

| Inclusion | Exclusion |
|---|---|
| • Males and females aged ≥18 years of age (≥20 years in Japan)<br>• Pathologically confirmed non-squamous NSCLC; NSCLC of mixed histology was allowed<br>• Newly diagnosed locally advanced (clinical Stage IIIB, IIIC), metastatic NSCLC (clinical Stage IVA or IVB) or recurrent NSCLC not amenable to curative surgery or radiotherapy†<br>• The tumour harboured one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del or L858R), either alone or in combination with other EGFR mutations, which may have included T790M‡<br>• Provision of a baseline plasma sample and an unstained, archival tumour tissue sample in a quantity sufficient to allow for central confirmation of EGFR mutation status<br>• WHO PS of 0 to 1 at screening with no clinically significant deterioration in the previous 2 weeks<br>• Life expectancy >12 weeks at Day 1<br>• ≥1 lesion, not previously irradiated that could be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have had a short axis of ≥15 mm) with CT or MRI, and that was suitable for accurate repeated measurements | • Patients with spinal cord compression; symptomatic and unstable brain metastases, except for those who had completed definitive therapy, were not on steroids, and had a stable neurological status for ≥2 weeks after completion of the definitive therapy and steroids<br>• Past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD<br>• Evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, or active infection including hepatitis B, hepatitis C, and human immunodeficiency virus<br>• Mean resting QTc >470 msec, obtained from 3 ECGs, using the screening clinic ECG machine-derived QTcF value<br>• Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG<br>• Any factors that increased the risk of QTc prolongation or risk of arrhythmic events<br>• Inadequate bone marrow reserve or organ function (see Appendix M further details)<br>• Any concurrent and/or other active malignancy that required treatment within 2 years of first dose of IP<br>• Any unresolved toxicities from prior systemic therapy greater than CTCAE Grade 1 at the time of starting study treatment<br>• Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of osimertinib<br>• Prior treatment with any systemic anti-cancer therapy for advanced NSCLC not amenable to curative surgery or radiation<br>• Prior treatment with an EGFR-TKI<br>• Major surgery within 4 weeks of the first dose of IP<br>• 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 IP<br>• Use of medications or herbal supplements known to be strong inducers of CYP3A4 (at least 3 weeks prior)<br>• Participation in another clinical study with an investigational product during the 4 weeks prior to Day 1 |

† Prior adjuvant and neo-adjuvant therapies (chemotherapy, radiotherapy, immunotherapy, biologic therapy, investigational agents), or definitive adiation/chemoradiation with or without regimens including immunotherapy, biologic therapy, investigational agents, were permitted as long as treatment was completed at least 12 months prior to the development of recurrent disease.
Abbreviations: CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion, an in-frame deletion occurring within exon 19, which encodes part of the kinase domain; ILD, interstitial lung disease; IP, investigational product; L858R, sensitising mutation in the EGFR gene with substitution of a leucine with an arginine at position 858 in exon 21; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PS, performance status; QTc, corrected QT interval; QTcF, corrected QT interval by Fridericia; TKI, tyrosine kinase inhibitor; WHO, World Health Organization.
Source: CSR.[8]

#### *B.2.3.3.3 Trial drugs*

A summary of the study treatments administered in the randomised period is provided in Table 7.

**Table 7: Study treatments and dose modifications – FLAURA2**

| | Osimertinib | Chemotherapy | | |
|---|---|---|---|---|
| Study treatment name | Osimertinib (AZD9291) | Carboplatin | Cisplatin | Pemetrexed |
| Dosage formulation | 80 mg oral tablet<br>*Dose reduction*:<br>40 mg oral tablet<br>*Dose reduction 2:*<br>*Discontinue* | 5 mg/mL/min (AUC 5)<br>*Dose reduction 1:* AUC 3.75<br>*Dose reduction 2:* AUC 2.5<br>*Dose reduction 3: Discontinue* | 75 mg/m$^2$<br>*Dose reduction 1:* 56 mg/m$^2$<br>*Dose reduction 2:* 38 mg/m$^2$<br>*Dose reduction 3: Discontinue* | 500 mg/m$^2$<br>*Dose reduction 1:* 375 mg/m$^2$<br>*Dose reduction 2:* 250 mg/m$^2$<br>*Dose reduction 3: Discontinue* |
| Route of administration | Oral | IV infusion | IV infusion | IV infusion |
| Dosing instructions | One tablet, once daily, commencing on Cycle 1 Day 1 until RECIST 1.1-defined disease progression. | Administration in accordance with local practice and labels over 15 to 60 minutes, after pemetrexed infusion, Q3W for 4 cycles. | Administration in accordance with local practice and labels, approximately 30 minutes after pemetrexed infusion, Q3W for 4 cycles.<br>Hydration was to be given and immediately preceding and following infusion. | Administration over 10 minutes in accordance with local practice on Day 1 Q3W for 4 cycles, followed by maintenance therapy Q3W until RECIST 1.1-defined disease progression.<br>To reduce the severity of toxicity, patients must also receive vitamin supplementation and corticosteroid pre-treatment |

Abbreviations: AUC, area under the concentration-time curve during any dosing interval; IV, intravenous; Q3W every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours;
Source: CSR.[8]

#### B.2.3.3.3.1 Dose modifications

Osimertinib is the SoC for patients with locally advanced/metastatic treatment-naïve EGFRm NSCLC. To circumvent potential overlapping toxicities, it was recommended, if clinically appropriate (and where osimertinib interruption was not mandated), that dose delay/dose reduction of chemotherapy be prioritised above osimertinib dose modifications. This enabled management of toxicities whist simultaneously maintaining the dose intensity of the SoC.

Only one dose reduction was permitted for osimertinib treatment, and osimertinib was discontinued following a second dose reduction caused by toxicity. A maximum of two dose reductions were permitted for each chemotherapy component (i.e., cisplatin, carboplatin, pemetrexed). A third dose reduction of any chemotherapy treatment due to toxicity in a patient resulted in the discontinuation of that agent. The dose of any agent that was reduced due to toxicity may not have been re-escalated. Dose modifications for study treatments are presented in Table 7.

#### *B.2.3.3.4 Permitted and disallowed concomitant medications*

Patients were permitted to receive pre-treatment and concomitant treatments, as recommended by the approved label for pemetrexed, carboplatin or cisplatin as clinically indicated by the investigator. However, guidance on restricted and prohibited medications were considered prior to treatment permission. Pre-treatment for chemotherapy was required to be completed prior to initiation of the osimertinib plus chemotherapy treatment arm.

Concomitant medications that were permitted or disallowed during FLAURA2 were as follows:

- ***Permitted medications:*** Pre-medication for the management of diarrhoea, nausea and vomiting were permitted in patients receiving osimertinib plus chemotherapy treatment. The use of calcium folinate/folinic acid in the management of pemetrexed overdose could be considered. Leukocyte-depleted blood transfusions were permitted, as well as concomitant corticosteroid/bisphosphonates/RANK-ligand inhibitors for management of bone metastases. Palliative local therapy, including radiotherapy and surgical resection were permitted in patients in survival follow-up or with no evidence of clinical progression. Vaccines were administered in accordance with local labels.
- ***Disallowed medications:*** Other anti-cancer therapies, investigational agents (other than those under investigation in FLAURA2) and non-palliative radiotherapy were prohibited.
- ***Restricted medications:*** Any concomitant use of medications, herbal supplements or foods that are known to be strong inducers of CYP3A4 must

have been discontinued for an appropriate period before patient screening and for a period of 3 months after the last dose of osimertinib. Use of medications whose disposition is dependent on breast cancer resistance protein and/or P-glycoprotein with a narrow therapeutic index, including rosuvastatin were closely monitored in patients for signs of changed tolerability while receiving osimertinib. Patients taking rosuvastatin had creatine phosphokinase levels monitored, with rosuvastatin use stopped upon patient experiences of AEs suggestive of muscle toxicity. Due to the possibility of an interaction between anti-cancer chemotherapy, warfarin or other anticoagulants, patients receiving pemetrexed were monitored regularly for changes in prothrombin time or International Normalized Ratio. Granulocyte colony stimulating factors were not permitted to be used prophylactically during cycle 1 of chemotherapy. Following the first cycle, growth factors were permitted to be used in accordance with local standards of care. Antiemetic drugs that prolong the QT interval and are clearly associated with a known risk of Torsades de Pointes (TdP) were not permitted; however, antiemetic drugs that were categorised as having a possible risk of TdP were allowed with careful monitoring of electrocardiograms and electrolytes.

Additional concomitant medications to support safety and wellbeing may have been given according to local standards of care and at the discretion of the investigator.

#### *B.2.3.3.5 Primary outcome*

The primary outcome of the study was PFS, defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the patient withdrew from study treatment or received another anti-cancer therapy prior to progression. PFS was based on investigator assessment (according to RECIST 1.1). An additional PFS sensitivity analysis for ascertainment bias (using blinded independent central review [BICR]) was also performed. The analysis of PFS uses a stratified log-rank test for generation of the p-value.

#### *B.2.3.3.6 Other outcomes used in the economic model and/or specified in the scope*

##### B.2.3.3.6.1 Key secondary efficacy outcome

OS was defined as the time from the date of randomisation until death due to any cause regardless of whether the patient withdraws from study treatment or received another anticancer therapy (i.e., date of death or censoring – date of randomisation + 1). OS data were analysed using the same methodology and model as for the PFS analysis.

##### B.2.3.3.6.2 Other secondary efficacy assessments

All additional secondary efficacy endpoints were investigator assessed according to RECIST 1.1. Definitions were as follows:

- **Objective response rate (ORR):** The percentage of patients with at least one investigator-assessed visit response of complete response (CR) or partial response (PR) and was based on all randomised patients. Data obtained up until progression, or last evaluable assessment in the absence of progression, were included in the assessment of ORR. The denominator was defined as the subset of all randomised patients. ORR was also assessed by BICR. ORR by BICR was analysed using logistic regression models by stratification factors.
- **Duration of response (DoR):** The time from the date of first documented response until date of documented progression or death in the absence of disease progression (i.e., date of PFS event or censoring – date of first response + 1). DoR was analysed descriptively for responding patients.
- **Depth of response:** The relative change in the sum of the longest diameters of RECIST target lesions at the nadir in the absence of new lesions or progression of non-target lesions compared with baseline by investigator assessment. The effect of osimertinib plus chemotherapy treatment on best percentage change in target lesion tumour size was estimated from an analysis of covariance model, with covariates for stratification factors, baseline tumour size, and time from baseline scan to randomisation.
- **Disease control rate (DCR):** the percentage of patients who have a best objective response of CR or PR or stable disease (StD) by RECIST 1.1, as

assessed by the investigator. For patients with a best objective response of StD, a RECIST assessment of StD must have been observed at least 6 weeks minus 1 week to allow for an early assessment within the assessment window (study day 35) following randomisation to be included in the numerator of the calculation for DCR. DCR was analysed using the same methodology as ORR.

- Post-progression outcomes:
  - **Time to second progression (PFS2):** the time from the date of randomisation to the earliest of the progression event subsequent to first subsequent therapy or death. The second progression event must have occurred after discontinuation of the study treatment administered after the initial PFS event.
  - **Time to first subsequent therapy (TFST):** defined as the time from the date of randomisation to the earlier of the date of anti-cancer therapy start date following study treatment discontinuation or death.
  - **Time to second subsequent therapy (TSST):** the time from the date of randomisation to the earlier of the date of second subsequent anti-cancer therapy start date following study treatment discontinuation or death.

#### B.2.3.3.6.3 Health-related quality of life outcomes

Patient-reported outcomes (PROs) included as secondary endpoints were assessed using the European Organisation for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire (EORTC-QLQ-C30) and the European Organisation for Research and Treatment of Cancer 13-item lung cancer module (EORTC QLQ-LC13). A description of these measures is provided in Appendix M.

Data were summarised based on the following pre-specified items: global health status/QoL (2 items scale in EORTC QLQ-C30), physical function (5 items scale in EORTC QLQ-C30), fatigue (3 items scale in EORTC QLQ-C30), appetite loss (1 item scale in EORTC QLQ-C30), dyspnoea (3 items scale in EORTC QLQ-LC13), cough (1 item in EORTC QLQ-LC13), chest pain (1 item in EORTC QLQ-LC13).

Key outcomes assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 were as follows:

- **Time to deterioration:** Defined as the time from randomisation until the date of the first clinically meaningful worsening (a change in the score from baseline of ≥10).
- **Time to definitive deterioration**: Defined as time from the date of patient's best PRO score to the date of first deterioration that is reported at all subsequent non-missing visits, or to the date of a single deterioration followed by death or a single deterioration followed by monotone missing data afterwards (missed one or more PRO assessments after the single deterioration).
- **Change from baseline:** Primary PRO scores for cough, dyspnoea, chest pain, fatigue, appetite loss, physical function, and global health status/QoL were analysed separately for each treatment comparison using a mixed models for repeated measures (MMRM) analysis with use of all data from baseline up to PD or 19 months. The analysis compares the average treatment effect from the point of randomisation until PD or 19 months (whichever is earlier), excluding visits with excessive missing data (defined as more than 75% missing data).

Data from the EuroQoL-5 Dimensions- 5 Levels (EQ-5D-5L) questionnaire were collected as exploratory endpoints and presented using summaries and descriptive statistics.

#### B.2.3.3.6.4 Adverse events

Any AEs occurring after the first dose and within 28 days of discontinuation of the investigational product (i.e., the last dose of study treatment) but prior to or on the start date of a subsequent anti-cancer treatment were included in the AE summary tables. AE data are evaluated according to the following categories: All AEs (including those causality related to study treatment), AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher, AEs leading to dose modification, AEs with an outcome of death, serious adverse events (SAEs), and AEs leading to discontinuation.

### *B.2.3.3.7 Pre-planned subgroups*

Subgroup analyses were conducted by comparing PFS between treatments in a number of pre-specified subgroups based on demography and disease baseline

characteristics. Predefined subgroups included ethnicity, age, sex, smoking history, CNS metastases status at study entry, and EGFR mutation type (Ex19del or L858R). These pre-planned subgroup analyses assessed the consistency of treatment effect across expected prognostic and/or predictive factors. For each subgroup, the HR and 95% CI were calculated from a single Cox proportional hazards model that contained a term for treatment, the subgroup covariate of interest, and the treatment by subgroup interaction term.

#### B.2.3.4 Baseline characteristics and demographics

Demographic characteristics were well balanced between treatment arms (Table 8) and were representative of the English target patient population in line with clinical expert opinion.[2] The median age was 61 years (range: 26 to 85 years). The majority of patients were Asian (63.7%), female (61.4%) and never-smokers (66.2%).

Disease characteristics were also generally balanced between the two treatment groups (Table 9). Almost all randomised patients had primary lung cancer of predominantly adenocarcinoma histology (550 patients [98.7%]), with the majority of patients having metastatic disease at baseline (536 patients [96.2%]). Median time from initial diagnosis to the first dose of study treatment (1.1 months) and median baseline target lesion tumour size (57.0 mm) were identical between treatment arms.

**Table 8: Demographic characteristics of participants in FLAURA2 across treatment groups (randomised period – FAS)**

| FLAURA2<br>Baseline characteristics | Osi + chemo<br>(N=279) | Osimertinib<br>(N=278) | Total<br>(N=557) |
|---|---|---|---|
| Age (years) | | | |
| Median (min, max) | 61.0 (26, 83) | 61.5 (30, 85) | 61.0 (26, 85) |
| Sex, n (%) | | | |
| Female | 173 (62.0) | 169 (60.8) | 342 (61.4) |
| Race, n (%) | | | |
| Asian | 179 (64.2) | 176 (63.3) | 355 (63.7) |
| White | 74 (26.5) | 83 (29.9) | 157 (28.2) |
| American Indian or Alaskan Native | 11 (3.9) | 6 (2.2) | 17 (3.1) |
| Black or African | 2 (0.7) | 3 (1.1) | 5 (0.9) |
| Other | 13 (4.7) | 10 (3.6) | 23 (4.1) |
| BMI ($kg/m^2$)† | | | |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Smoking status, n (%) | | | |
| Never | 188 (67.4) | 181 (65.1) | 369 (66.2) |
| Smoker | 91 (32.6) | 97 (34.9) | 188 (33.8) |

† Body mass index = [weight (kg) / [height (m)]$^2$
Abbreviations: BMI, body mass index; FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy.
Source: Planchard et al. (2023);[77] Janne et al. (2023);[75] CSR.[8]

**Table 9: Disease characteristics at baseline (randomised period – FAS)**

| FLAURA2<br>Baseline characteristics | Osi + chemo<br>(N=279) | Osimertinib<br>(N=278) | Total<br>(N=557) |
|---|---|---|---|
| WHO PS, n (%) | | | |
| 0 (Normal activity) | 104 (37.3) | 102 (36.7) | 206 (37.0) |
| 1 (Restricted activity) | 174 (62.4) | 176 (63.3) | 350 (62.8) |
| 2 (In bed less than or equal to 50% of the time) | 1 (0.4) | 0 | 1 (0.2) |
| AJCC stage (8th edition) at initial diagnosis, n (%) | | | |
| Stage IIIB | [redacted] | [redacted] | [redacted] |
| Stage IIIC | [redacted] | [redacted] | [redacted] |
| Stage IVA | [redacted] | [redacted] | [redacted] |
| Stage IVB | [redacted] | [redacted] | [redacted] |
| Overall extent of disease at study entry, n (%) | | | |
| Metastatic† | 265 (95.0) | 271 (97.5) | 536 (96.2) |
| Locally advanced‡ | 14 (5.0) | 7 (2.5) | 21 (3.8) |
| Histology type, n (%)§ | | | |

| FLAURA2<br>Baseline characteristics | Osi + chemo (N=279) | Osimertinib (N=278) | Total (N=557) |
|---|---|---|---|
| Adenocarcinoma§ | 275 (98.6) | 275 (98.9) | 550 (98.7) |
| Adenosquamous carcinoma | 2 (0.7) | 0 | 2 (0.4) |
| Other | 2 (0.7) | 3 (1.1) | 5 (0.9) |
| Number of patients with metastases (by location), n (%)¶ | | | |
| CNS | 116 (41.6) | 110 (39.6) | 226 (40.6) |
| Liver | 43 (15.4) | 66 (23.7) | 109 (19.6) |
| Lung/Pleura | [redacted] | [redacted] | [redacted] |
| Lymph nodes | [redacted] | [redacted] | [redacted] |
| Bone + locomotive | 132 (47.3) | 142 (51.1) | 274 (49.2) |
| Extra-thoracic | 147 (52.7) | 149 (53.6) | 296 (53.1) |
| Other | [redacted] | [redacted] | [redacted] |
| Time from initial diagnosis to the first dose, months | | | |
| n | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Median (min, max) | [redacted] | [redacted] | [redacted] |
| Baseline target lesion tumour size, mm†† | | | |
| n | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Median (min, max) | 57.0 (10, 284) | 57.0 (11, 221) | 57.0 (10, 284) |

† Metastatic disease – patient has any metastatic site of disease; ‡ Locally advanced – patient has only locally advanced sites of disease; § Represents a combination of the following adenocarcinoma categories: NOS, acinar, papillary, bronchiolo-alveolar, and solid with mucous formation; ¶ This is a programmatically derived composite endpoint with a list of contributing data sources; †† Sum of longest diameters of target lesions at baseline.
Abbreviations: AJCC, American Joint Committee on Cancer; FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy; PS, Performance status; SD, standard deviation; WHO, World Health Organization.
Source: Planchard et al. (2023);[77] CSR.[8]

#### *B.2.3.4.1 Determination of EGFRm status*

The prevalence of confirmed EGFRm status was broadly balanced between treatment arms, as confirmed by either a prospective central or pre-existing local EGFRm test. Overall, 337 patients (60.5%) had tumours which harboured the Ex19del mutation, 213 patients (38.2%) had tumours which had the L858R mutation, and 4 patients (0.7%) had tumours which harboured both Ex19del and L858R mutations, each with balanced proportions between treatment arms.[77] One patient in the osimertinib plus chemotherapy and two patients in the osimertinib monotherapy

had unknown EGFR mutation status at baseline. Further details of EGRFm status for all randomised patients are provided in Table 10.

**Table 10: EGFRm testing method and mutation type at randomisation (randomised period - FAS)**

| EGFR Testing Method<br>Mutation Type | Number (%) of patents | | |
|---|---|---|---|
| | Osi + chemo (N=279) | Osimertinib (N=278) | Total (N=557) |
| Central test | [redacted] | [redacted] | [redacted] |
| Exon 19 deletion | [redacted] | [redacted] | [redacted] |
| Exon 21 L858R | [redacted] | [redacted] | [redacted] |
| EGFRm unknown / not detected† | [redacted] | [redacted] | [redacted] |
| Local test | [redacted] | [redacted] | [redacted] |
| Exon 19 deletion | [redacted] | [redacted] | [redacted] |
| Exon 21 L858R | [redacted] | [redacted] | [redacted] |
| Both Exon 19 deletion and Exon 21 L858R | [redacted] | [redacted] | [redacted] |
| EGFRm not detected‡ | [redacted] | [redacted] | [redacted] |

† One patient was randomised based on an invalid central tissue result (and was therefore categorised as EGFRm status of unknown); a retrospective baseline ctDNA result was Ex19del positive. Patient E1343032 was randomised based on a negative central tissue result (and was therefore categorised as EGFRm status of not detected); a retrospective baseline ctDNA result was L858R positive; ‡One patient was randomised based on local result of L858R positive, which was subsequently updated to L861Q positive and confirmed by central test result.
Abbreviations: ctDNA, circulating tumour DNA; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; Ex19del, exon 19 deletion, an in-frame deletion occurring within exon 19, which encodes part of the kinase domain; L858R, sensitising mutation in the EGFR gene with substitution of a leucine with an arginine at position 858 in exon 21; FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy.
DCO: 03 April 2023
Source: CSR.[8]

The majority of patients received at least one permitted concomitant medication during the study (osimertinib plus chemotherapy arm: [redacted]; osimertinib monotherapy arm: [redacted]). The most commonly used concomitant medications (reported for ≥20% of patients in either treatment arm) are summarised in Table 11.

**Table 11: Concomitant medications (≥20% of patients in either treatment arm) (randomised period - FAS)**

| ATC Classification Generic term | Number (%) of patents | | |
|---|---|---|---|
| | Osi + chemo (N=279) | Osimertinib (N=278) | Total (N=557) |
| Number of patients with a concomitant medication | [redacted] | [redacted] | [redacted] |
| Proton pump inhibitors | [redacted] | [redacted] | [redacted] |
| Anilides | [redacted] | [redacted] | [redacted] |
| Paracetamol | [redacted] | [redacted] | [redacted] |
| Glucocorticoids | [redacted] | [redacted] | [redacted] |
| Dexamethasone | [redacted] | [redacted] | [redacted] |
| Other viral vaccines | [redacted] | [redacted] | [redacted] |
| Tozinameran | [redacted] | [redacted] | [redacted] |
| Serotonin (5HT3) antagonists | [redacted] | [redacted] | [redacted] |
| Antipropulsives | [redacted] | [redacted] | [redacted] |
| Corticosteroids, potent (group III) | [redacted] | [redacted] | [redacted] |
| Other antiemetics | [redacted] | [redacted] | [redacted] |
| Benzodiazepine derivatives | [redacted] | [redacted] | [redacted] |
| Other antihistamines for systemic use | [redacted] | [redacted] | [redacted] |
| Antiemetics and antinauseants | [redacted] | [redacted] | [redacted] |
| Osmotically acting laxatives | [redacted] | [redacted] | [redacted] |
| Colony stimulating factors | [redacted] | [redacted] | [redacted] |
| Electrolyte solutions | [redacted] | [redacted] | [redacted] |

A patient can have one or more generic terms reported under a given ATC text. Includes medications which are ongoing or with a stop date on or after the first dose date of study treatment (and which started prior to or during study treatment).
Abbreviations: ATC, Anatomical Therapeutic Chemical; FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy.
DCO: 03 April 2023
Source: CSR.[8]

At the 03 April 2023 DCO, 154 patients (55.2%) in the osimertinib plus chemotherapy arm and 123 patients (44.2%) in the osimertinib monotherapy arm continued to receive at least one randomised study treatment (Table 12). A lower proportion of patients who had discontinued treatment received a post-treatment anticancer therapy in the osimertinib plus chemotherapy arm (57/123 patients [46.3%]) compared with the osimertinib monotherapy arm (91/151 patients [60.3%]). The most common post-treatment anti-cancer therapy in both treatment arms was cytotoxic chemotherapy (33.3% of patients in the osimertinib plus chemotherapy arm and 53.6% of patients in the osimertinib monotherapy arm).

**Table 12: Post study treatment anticancer therapy (randomised period – FAS)**

| | Number (%) patients† | |
|---|---|---|
| | Osi + chemo (N=279) | Osimertinib (N=278) |
| Discontinued randomised study treatment | 123 (44.1) | 151 (54.3) |
| Any post-treatment anti-cancer therapy | 57 (20.4) | 91 (32.7) |
| No post-treatment anti-cancer therapy | 66 (23.7) | 60 (21.6) |
| Ongoing randomised study treatment | 154 (55.2) | 123 (44.2) |
| Did not receive study treatment | 2 (0.7) | 4 (1.4) |
| **Types of post-treatment anticancer therapy received** | | |
| Cytotoxic chemotherapy | 41 (14.7) [33.3]] | 81 (29.1) [53.6 |
| Platinum compounds | 19 (6.8) [15.4] | 78 (28.1) [51.7] |
| Folic acid analogues (pemetrexed) | 8 (2.9) [6.5] | 55 (19.8) [36.4] |
| Taxanes | 26 (9.3) [21.1] | 39 (14.0) [25.8] |
| EGFR-TKI | 18 (6.5) [14.6] | 39 (14.0) [25.8] |
| First or second-generation EGFR-TKI | 12 (4.3) [9.8] | 22 (7.9) [14.6] |
| Third generation EGFR-TKI | 6 (2.2) [4.9] | 22 (7.9) [14.6] |
| Osimertinib | 6 (2.2) [4.9] | 19 (6.8) [12.6] |
| Aumolertinib | 0 | 3 (1.1) [2.0] |
| VEGF Inhibitor – Monoclonal antibody | 14 (5.0) [11.4] | 38 (13.7) [25.2] |
| PD-1/PD-L1 inhibitor – Immunotherapy | 10 (3.6) [8.1] | 22 (7.9) [14.6] |
| Other | 11 (3.9) [8.9] | 19 (6.8) [12.6] |

† The number of patients is shown with percentages (%) calculated as the proportion of patients in the FAS and secondly [%] as the proportion of patients who discontinued randomised study treatment.
A patient may be counted in multiple rows if they receive more than one post treatment anticancer therapy.
Includes anticancer therapies with a start date after the last dose date of study treatment.
Note: Treatment beyond progression is not counted as a subsequent anticancer therapy, this is considered a continuation of first-line therapy.
Abbreviations: EGFR, epidermal growth factor receptor; FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand-1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] CSR.[8]

### B.2.3.5 Expert elicitation/opinion

An advisory board was conducted in November 2023 with 9 oncologists based in the UK. The objective of the advisory board was:

- To understand clinician views on the data from the FLAURA2 study to help inform the submission strategy.
- To align on the patient/disease characteristics that drive treatment decision making in the UK clinical setting.

- To discuss current EGFRm NSCLC clinical pathways and the potential impact, as well as associated considerations, of the results of the FLAURA2 study.

Insights from the advisory board are provided throughout the dossier. The report, which is qualitative in nature is provided as a confidential 'Data on File' reference.[2]

A further five one to one interviews were conducted with clinical experts based in the UK (four medical oncologists and one clinical oncologist) to support clinical assumptions and statements used for this submission. The report is provided as a confidential 'Data on File' reference.[64]

## *B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

### B.2.4.1 Populations analysed

Details of the population analysis sets defined in FLAURA2 along with their use in the study are presented in Table 13.

**Table 13: Population analysis sets – FLAURA2**

| Analysis set (based on the global cohort) | Definition | Purpose |
|---|---|---|
| FAS | All randomised patients (as randomised, regardless of actual treatment). The FAS was used for all efficacy analyses, and treatment arms were compared on the basis of randomised study treatment. | Demography and baseline characteristics, efficacy analyses |
| cFAS | All patients who undertook a brain scan in the screening/baseline period, had their scan sent for CNS BICR, and were identified by that review as having non-measurable and/or measurable brain disease at baseline (i.e., at least one non-measurable and/or one measurable brain lesion noted at baseline). | Exploratory CNS efficacy analyses |
| cEFR | A subset of the cFAS analysis set. All patients who had a CNS scan during the screening/baseline period, had their scan sent for independent neuro-radiologist review, and were identified by that review as having at least one measurable CNS lesion at baseline. | Further exploratory CNS endpoints analyses |
| Safety Analysis Set | All randomised patients who received at least one dose of study treatment. Safety data were not formally analysed but are summarised descriptively according to treatment actually received (e.g., a patient who was randomised to osimertinib plus chemotherapy but who received only osimertinib is summarised under the osimertinib monotherapy arm). | Exposure and safety analyses |

Abbreviations: BICR, blinded independent central review; CNS, central nervous system; FAS, full analysis set; cEFR, central nervous system evaluable for response
Source: CSR.[8]

### B.2.4.2 Hypothesis objective

The objective of FLAURA2 was to demonstrate that the combination of osimertinib plus chemotherapy (i.e., pemetrexed plus platinum-based chemotherapy), followed by osimertinib and pemetrexed maintenance therapy in the first-line setting could improve long-term treatment outcomes for patients with advanced EGFRm NSCLC compared with standard of care osimertinib monotherapy. The hypothesis of improved PFS could be tested when approximately 278 PFS events (approximately 50% maturity) had occurred.

### B.2.4.3 Statistical analysis

To ensure strong control of the type I error rate, α=0.05 (2-sided), the primary endpoint PFS and the key secondary endpoint OS were tested in sequential order. The hierarchical testing procedure determined that if PFS was statistically significant at the time of the primary PFS analysis, then subsequent hypothesis testing for OS

would be performed at overall α=0.05 significance level (2-sided) using O'Brien-Fleming spending function. If the primary PFS analysis was not statistically significant, the hypothesis testing of OS was not to be performed.

Statistical analyses were conducted for each endpoint as follows:

- **PFS:** analysed using a log-rank test stratified by race, WHO PS, and method used for EGFR tissue testing for randomisation.
- **OS:** two analyses of OS were planned as part of the hierarchical testing procedure, the first was conducted at the time of the primary analysis of PFS, and a final analysis was planned to be performed at approximately 60% data maturity, when approximately 334 death events (across both arms) have occurred. OS data were analysed using the same methodology and model as for PFS analysis.
- **ORR:** analysed using a logistic regression stratified by race, WHO PS, and method used for tissue testing. The results of the analysis were presented in terms of an odds ratio together with its associated 95% profile likelihood CI and 2-sided p-value.
- Remaining secondary endpoints were summarised descriptively.

#### B.2.4.4 Sample size and power calculation

Approximately 556 patients were randomised, in a 1:1 ratio (osimertinib plus chemotherapy vs osimertinib monotherapy) in the randomised period of the study. The study was not powered for individual subgroup comparisons, and no multiplicity adjustments were made.

The primary endpoint, investigator-assessed PFS, was analysed when approximately 278 PFS events and at least 16 months of follow-up after the last subject in had occurred in the 556 randomised patients (approximately 50% maturity). If the true PFS hazard ratio (HR) for the comparison of the two treatment arms was 0.68, 278 progression events would provide 90% power to demonstrate a statistically significant difference in PFS at a 5% two-sided significance level. This translates to an improvement in median PFS from 19 months to 28 months, assuming exponential distribution and proportional hazards. The minimum critical HR

is 0.79, which translates to an approximate median PFS improvement from 19 months to 24 months.

#### B.2.4.5 Data management and patient withdrawals

Patients were free to discontinue study treatment at any time without prejudice to further treatment. Patients were asked about the reason(s) for discontinuation of treatment and the presence of any AEs. A patient continuing at least one study treatment was not considered to be discontinued from study treatment and was to continue assessments per the schedule of assessments. A patient was still considered to be ongoing in the study if they did not withdraw their consent for the study and study visits continued according to the study plan. Patients may have been discontinued from all study treatments for the following reasons: RECIST 1.1-defined progression (if the patient was no longer receiving clinical benefit), patient decision, investigator decision, AEs, severe non-compliance, incorrect initiation of study treatment, or pregnancy. Upon discontinuation of all study treatments, patients were to be treated in accordance with the local standard of care.

A patient could withdraw from the study at any time at their own request, without prejudice to further treatment. The investigator informed patients who had decided to withdraw about modified follow-up option such as, telephone contact, a contact with a relative or treating physician, or information from medical records. If the patient withdrew consent for disclosure of future information, the sponsor could retain and continue to use any data collected before withdrawal of consent.

#### B.2.4.6 Participant flow in the relevant randomised controlled trials

From May 2020 to November 2021, 887 patients were enrolled in the study and underwent screening. Following confirmation of eligibility, a total of 557 patients at 136 study centres across 21 countries worldwide were randomly assigned to treatment. Of these, 551 (98.9%) received at least one dose of study treatment. In the randomisation period, 279 patients were assigned to the osimertinib plus chemotherapy arm and 276 patients received treatment. The remaining 278 patients were assigned to the osimertinib monotherapy arm and 275 patients received treatment. At the DCO date, 197 patients (70.6%) in the osimertinib plus

chemotherapy arm and 191 patients (68.7%) in the osimertinib monotherapy arm were receiving ongoing treatment. See Appendix D for full details of participant flow.

### *B.2.5 Critical appraisal of the relevant clinical effectiveness evidence*

A summary of the quality assessment for FLAURA2 is provided in Table 14.

A complete quality assessment is provided in Appendix D.

**Table 14: Quality assessment results for FLAURA2**

| Trial number (acronym) | FLAURA2 |
|---|---|
| Was randomisation carried out appropriately? | Yes |
| Was the concealment of treatment allocation adequate? | Yes |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Yes |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | No |
| Were there any unexpected imbalances in drop-outs between groups? | No |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | No |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Yes |

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

### *B.2.6 Clinical effectiveness results of the relevant studies*

#### B.2.6.1 FLAURA2

At the DCO for the primary PFS analysis (03 April 2023), a statistically significant and clinically meaningful improvement in PFS in the osimertinib plus chemotherapy treatment arm compared with the osimertinib monotherapy arm was observed. OS data were therefore tested per the hierarchical testing procedure at the DCO of the primary PFS analysis. OS data at the DCO date were immature (26.8% maturity), with no detriment in OS for patients randomised to receive osimertinib plus chemotherapy compared with osimertinib monotherapy.

High response rates (>75%) were observed in both treatment arms, and a clinically meaningful 8.7-month improvement in median DoR was also observed in the osimertinib plus chemotherapy arm compared with the osimertinib monotherapy arm.

Overall, PRO data demonstrated a clinically meaningful improvement for coughing in both treatment arms, and a trend towards improvement in HRQoL with osimertinib plus chemotherapy treatment after completion of platinum chemotherapy.

A second interim analysis was conducted at a DCO of 08 January 2024. This was an ad-hoc analysis provided as part of US FDA-specific regulatory procedures solely consisting of the OS outcome. The overall maturity of OS was 41%. There was a favourable trend towards improved OS with osimertinib plus chemotherapy versus osimertinib monotherapy.[78]

The FLAURA2 study is ongoing, allowing for further follow-up analyses. A final analysis of OS will be conducted when the data are approximately 60% mature.[70]

#### *B.2.6.1.1 Primary efficacy outcome*

##### B.2.6.1.1.1 Progression-free survival (03 April 2023 DCO)

At the DCO of the primary data analysis (03 April 2023), there were 120 PFS events (43.0%) reported in the osimertinib plus chemotherapy arm and 166 PFS events (59.7%) reported in the osimertinib monotherapy arm, with an overall data maturity of 51.3% (Table 15). A statistically significant and clinically meaningful 38% reduction in the risk of disease progression or death was observed in the osimertinib plus chemotherapy arm compared with the osimertinib monotherapy arm, based on investigator assessment per RECIST 1.1 (HR: 0.62 [95% CI: 0.49, 0.79]; p<0.0001).

The KM estimate of median PFS was approximately 8.8 months longer in the osimertinib plus chemotherapy arm (25.5 months) compared with the osimertinib monotherapy arm (16.7 months) (Table 15). A sustained separation in the KM curves in favour of the osimertinib plus chemotherapy arm was observed from the second RECIST 1.1 scan at 3 months post-randomisation, extending up to the end of follow-up (24 months) (Figure 4).

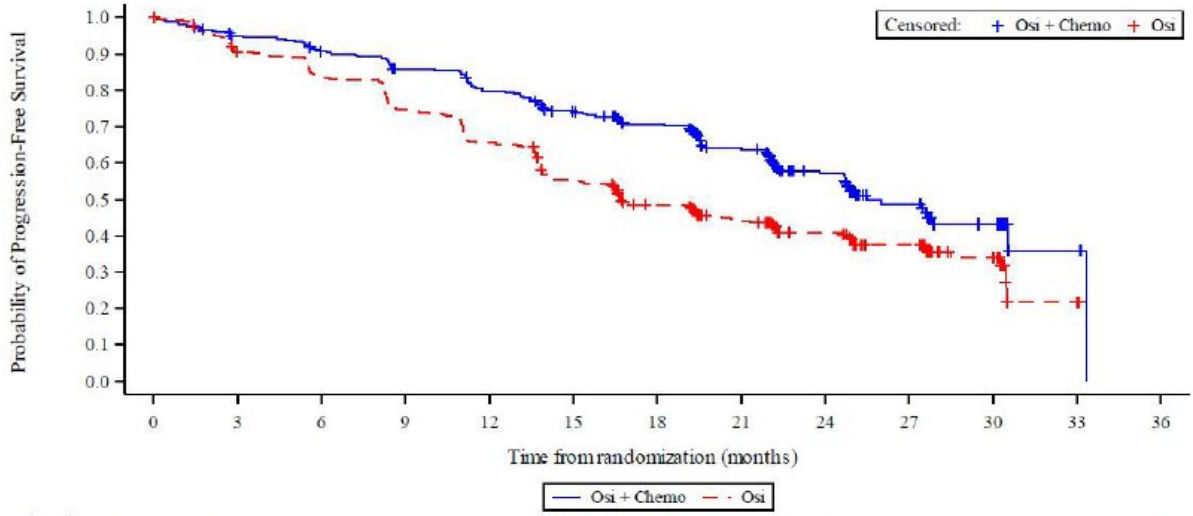
**Table 15: Progression-free survival by investigator assessment (randomised period – FAS)**

| | Osi + chemo (N=279) | Osimertinib (N=278) |
|---|---|---|
| **Progression status, n (%)** | | |
| **Progression - total** | **120 (43.0)** | **166 (59.7)** |
| RECIST progression† | 95 (34.1) | 158 (56.8) |
| Target lesions‡ | 51 (18.3) | 75 (27.0) |
| Non-target lesions‡ | 31 (11.1) | 68 (24.5) |
| New lesions‡ | 46 (16.5) | 73 (26.3) |
| Death§ | 25 (9.0) | 8 (2.9) |
| **No progression - total** | **159 (57.0)** | **112 (40.3)** |
| Censored RECIST progression due to missing visits¶ | 1 (0.4) | 0 |
| Censored death due to missing visits¶ | 6 (2.2) | 2 (0.7) |
| Progression free at time of analysis†† | 143 (51.3) | 106 (38.1) |
| Lost to follow-up‡‡ | 0 | 0 |
| Withdrawn consent‡‡ | 8 (2.9) | 3 (1.1) |
| Discontinued study for other reasons‡‡ | 1 (0.4) | 1 (0.4) |
| **Comparison between groups** | | |
| Hazard ratio (95% CI) | 0.62 (0.49, 0.79) | |
| 2-sided p-value | <0.0001 | |
| **Median PFS** | | |
| Median PFS (months) (95% CI)§§ | 25.5 (24.7, NC) | 16.7 (14.1, 21.3) |
| PFS rate at 6 months (%) (95% CI)§§ | 90.7 (86.6, 93.6) | 83.5 (78.6, 87.4) |
| PFS rate at 12 months (%) (95% CI)§§ | 79.7 (74.3, 84.1) | 65.5 (59.5, 70.8) |
| PFS rate at 18 months (%) (95% CI)§§ | 70.6 (64.7, 75.7) | 48.5 (42.4, 54.3) |
| PFS rate at 24 months (%) (95% CI)§§ | 57.2 (50.4, 63.3) | 40.8 (34.7, 46.9) |
| Median (range) follow-up for PFS in all patients (months)¶¶ | 19.5 (0, 33.3) | 16.5 (0, 33.1) |
| Median (range) follow-up for PFS in censored patients (months)††† | 22.2 (0, 33.1) | 23.7 (0, 33.1) |

†Only includes progression events that occur within 2 consecutive scheduled visits (plus visit window) of the last evaluable assessment (or randomisation); ‡Target lesions, non-target lesions, and new lesions are not necessarily mutually exclusive categories; §Death in the absence of RECIST progression, within 2 visits of baseline or last RECIST assessment (Not Evaluable is not considered as missing visit); ¶RECIST progression or death occurred more than 2 consecutive scheduled visits (plus visit window) after last previous evaluable RECIST assessment or baseline if no valid post-baseline assessment. Patients are censored at last previous evaluable RECIST assessment or randomisation date; †† Includes patients, known to be alive, with no evaluable baseline RECIST assessment (censored at Day 1) or censored at last evaluable RECIST assessment; ‡‡ Patients censored at last evaluable RECIST assessment or randomisation; §§ Calculated using the KM method; ¶¶ Calculated as the median, minimum, and maximum time from randomisation to date of progression or date of censoring in all patients; ††† Calculated as the median, minimum, and maximum time from randomisation to date of censoring (date last known to have not progressed) in censored (not progressed) patients only.
Abbreviations: CI, confidence interval; FAS, full analysis set; NC, not calculable; Osi + chemo, osimertinib plus chemotherapy; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] CSR.[8]

**Figure 4: KM plot of progression-free survival (months) by investigator assessment (randomised period – FAS)**




Abbreviations: FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] CSR.[8]

#### B.2.6.1.1.2 Sensitivity analysis (03 April 2023 DCO)

Ascertainment bias was assessed by analysis of PFS by BICR in the FAS and was consistent with the investigator-based analysis (Table 16). At the 03 April 2023 DCO date, 240 PFS events by BICR assessment were reported, comprising of 102 PFS events (36.6%) in the osimertinib plus chemotherapy arm and 138 PFS events (49.6%) in the osimertinib monotherapy arm, with an overall data maturity of 43.1% (Table 16).

Consistent with the investigator-based analysis, the HR was 0.62 (95% CI: 0.48, 0.80; nominal p=0.0002). An approximate 9.5-month reduction in the risk of disease progression or death was observed in the osimertinib plus chemotherapy arm compared with the osimertinib monotherapy arm.

The KM curve of PFS by BICR also demonstrated early separation between treatment arms in favour of osimertinib plus chemotherapy from the second RECIST 1.1 scan at 3 months post-randomisation and throughout the remaining duration of follow-up (Figure 5).

**Table 16: Progression-free survival by BICR assessment (randomised period – FAS)**

| | Osi + chemo (N=279) | Osimertinib (N=278) |
|---|---|---|
| **Progression status, n (%)** | | |
| **Progression – total** | **102 (36.6)** | **138 (49.6)** |
| RECIST progression[†] | 75 (26.9) | 124 (44.6) |
| Target lesions[‡] | 48 (17.2) | 79 (28.4) |
| Non-target lesions[‡] | 21 (7.5) | 34 (12.2) |
| New lesions[‡] | 23 (8.2) | 47 (16.9) |
| Death[§] | 27 (9.7) | 14 (5.0) |
| **No progression – total** | **177 (63.4)** | **140 (50.4)** |
| Censored RECIST progression due to missing visits[¶] | 1 (0.4) | 0 |
| Censored death due to missing visits[¶] | 11 (3.9) | 16 (5.8) |
| Progression free at time of analysis[††] | 154 (55.2) | 119 (42.8) |
| Lost to follow-up[‡‡] | 0 | 0 |
| Withdrawn consent[‡‡] | 10 (3.6) | 4 (1.4) |
| Discontinued study for other reasons[‡‡] | 1 (0.4) | 1 (0.4) |
| **Comparison between groups** | | |
| Hazard ratio (95% CI) | 0.62 (0.48, 0.80) | |
| 2-sided p-value | 0.0002 | |

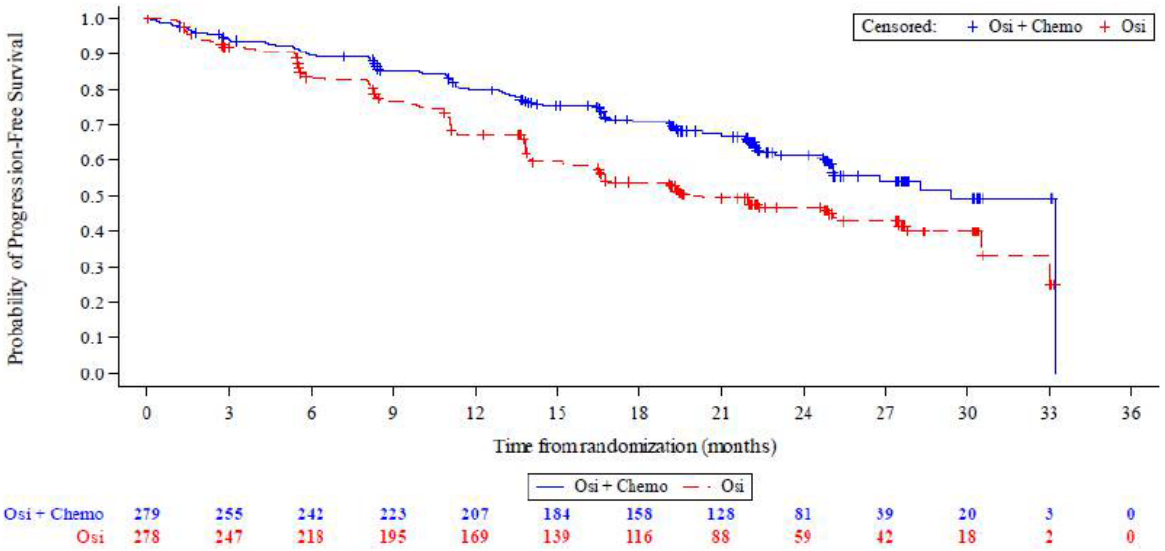

 

| | Osi + chemo (N=279) | Osimertinib (N=278) |
|---|---|---|
| **Median PFS** | | |
| Median PFS (months) (95% CI)§ | 29.4 (25.1, NC) | 19.9 (16.6, 25.3) |
| PFS rate at 6 months (%) (95% CI) §§ | 89.7 (85.5, 92.8) | 83.3 (78.3, 87.3) |
| PFS rate at 12 months (%) (95% CI) §§ | 79.8 (74.5, 84.2) | 67.3 (61.2, 72.6) |
| PFS rate at 18 months (%) (95% CI) §§ | 71.2 (65.2, 76.3) | 54.0 (47.6, 60.0) |
| PFS rate at 24 months (%) (95% CI) §§ | 61.6 (54.8, 67.7) | 46.8 (40.2, 53.2) |
| Median (range) follow-up for PFS in all patients (months) ¶¶ | 19.4 (0, 33.2) | 14.6 (0, 33.2) |
| Median (range) follow-up for PFS in censored patients (months) ††† | 22.1 (0, 33.1) | 22.0 (0, 33.2) |

† Only includes progression events that occur within 2 consecutive scheduled visits (plus visit window) of the last evaluable assessment (or randomisation); ‡ Target lesions, non-target lesions, and new lesions are not necessarily mutually exclusive categories; § Death in the absence of RECIST progression, within 2 visits of baseline or last RECIST assessment (Not Evaluable is not considered as missing visit); ¶ RECIST progression or death occurred more than 2 consecutive scheduled visits (plus visit window) after last previous evaluable RECIST assessment or baseline if no valid post-baseline assessment. Patients are censored at last previous evaluable RECIST assessment or randomisation date; †† Includes patients, known to be alive, with no evaluable baseline RECIST assessment (censored at Day 1) or censored at last evaluable RECIST assessment; ‡‡ Patients censored at last evaluable RECIST assessment or randomisation; §§ Calculated using the KM method. ¶¶ Calculated as the median, minimum, and maximum time from randomisation to date of progression or date of censoring in all patients; ††† Calculated as the median, minimum, and maximum time from randomisation to date of censoring (date last known to have not progressed) in censored (not progressed) patients only.
Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; NC, not calculable; Osi + chemo, osimertinib plus chemotherapy; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] CSR.[8]

**Figure 5: KM plot of progression-free survival (months) by BICR assessment (randomised period – FAS)**




Abbreviations: BICR, blinded independent central review; FAS, full analysis set; Osi + Chemo, osimertinib plus chemotherapy.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] CSR.[8]

### B.2.6.1.1.3 Concordance between investigator and BICR assessments of PFS

Analysis of discrepancy rates between investigator and BICR assessment of PFS demonstrated strong concordance between the assessment methods, with an 82.1% agreement on progressions and non-progressions in the osimertinib plus chemotherapy arm, and a 75.6% agreement on progressions and non-progressions in the osimertinib monotherapy arm (Table 17).

**Table 17: Disagreements between investigator and BICR Assessment of RECIST progression (randomised period – FAS)**

| | Osi + chemo (N=279) | Osimertinib (N=278) | Difference (osi + chemo) – osi |
|---|---|---|---|
| **Discrepancy rate, %** | | | |
| Early discrepancy rate† | [redacted] | [redacted] | [redacted] |
| Late discrepancy rate‡ | [redacted] | [redacted] | [redacted] |
| **RECIST progression§ declared by: (n [%])** | | | |
| Investigator but not central review | [redacted] | [redacted] | [redacted] |
| Central review but not investigator | [redacted] | [redacted] | [redacted] |
| Investigator and central review | [redacted] | [redacted] | [redacted] |

| | Osi + chemo (N=279) | Osimertinib (N=278) | Difference (osi + chemo) – osi |
|---|---|---|---|
| Progression data agreement (within 2 weeks) | [redacted] | [redacted] | [redacted] |
| Progression date ≥2 weeks earlier by central review than by investigator | [redacted] | [redacted] | [redacted] |
| Progression date ≥2 weeks earlier by investigator than by central review | [redacted] | [redacted] | [redacted] |

† Progression events that occur after two or more missed visits, were censored at the latest evaluable RECIST assessment, or Day 1 if there are no evaluable visits. Patients who do not have a baseline assessment were censored at Day 1; ‡ Early discrepancy rate is the frequency of investigator declared progressions before central review as a proportion of all investigator progressions; § Late discrepancy rate is the frequency of investigator declared progressions after central review as a proportion of all discrepancies.
Abbreviations: BICR, blinded independent central review; FAS, full analysis set; NA, not applicable; Osi + chemo, osimertinib plus chemotherapy; RECIST, Response Evaluation Criteria in Solid Tumours.
DCO: 03 April 2023
Source: CSR.[8]

### *B.2.6.1.2 Secondary efficacy outcomes*

#### B.2.6.1.2.1 Overall survival

***Second interim analysis: 08 January 2024 DCO***

At the second interim OS analysis (08 January 2024), the overall maturity of OS was 41%.[78] There was a favourable trend towards improved OS with osimertinib plus chemotherapy versus osimertinib monotherapy (HR: 0.75 [95% CI 0.57, 0.97]) (Table 18). The OS KM curves (Figure 6) demonstrated continuing separation in favour of the osimertinib plus chemotherapy arm from 18 months and throughout the remaining duration of follow-up.

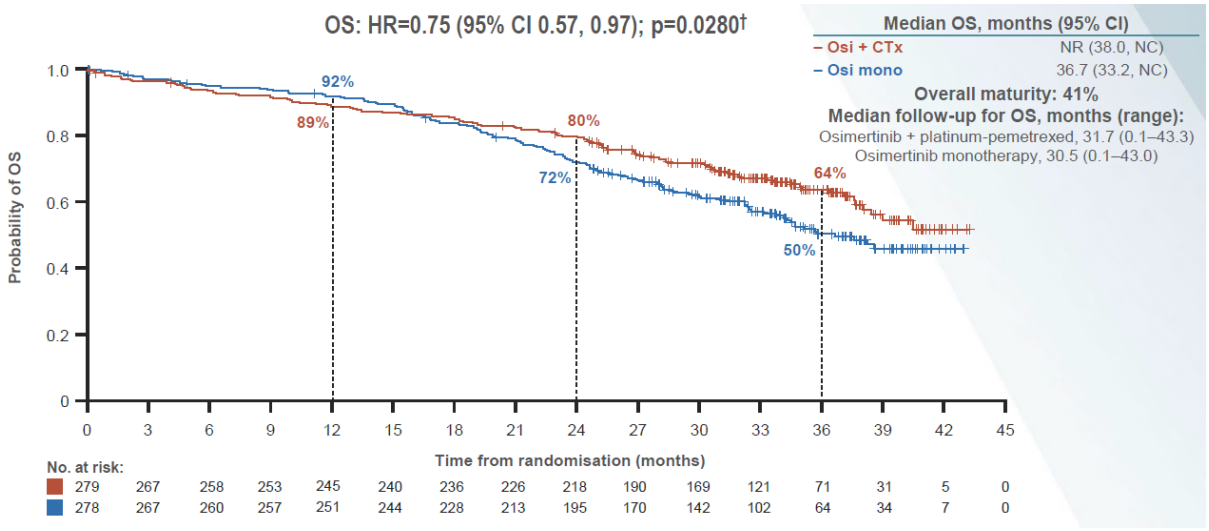
**Table 18: Overall survival (08 January 2024 DCO)**

| | Osi + chemo (N=279) | Osimertinib (N=278) |
|---|---|---|
| Events, n | 100 | 126 |
| Maturity (%) | 35.8 | 45.3 |
| RMST, months (95% CI) | 33.8 (32.3, 35.4) | 32.2 (30.7, 33.7) |
| Median, months (95% CI) | NR (38.0, NR) | 36.7 (33.2, NR) |
| Hazard ratio (95% CI) | 0.75 (0.57, 0.97) | |

Abbreviations: CI, confidence interval; DCO, data cut-off; NR, not recorded; Osi + chemo, osimertinib plus chemotherapy; RMST, restricted mean survival time.
DCO: 08 January 2024.
Source: AstraZeneca 2024[78]; AstraZeneca data on file 2024.[72]

**Figure 6: Kaplan-Meier plot of OS (months) (DCO 08 January 2024)**




Abbreviations: CI, confidence interval; Ctx, chemotherapy; DCO, data cut-off; HR, hazard ratio; NC, not calculable; NR, not reported; OS, overall survival.
DCO: 08 January 2024.
Source: Valdiviezo et al. (2024).[73]

### *First interim analysis: 03 April 2023 DCO*

In accordance with the hierarchical testing procedure, OS was initially analysed at the DCO of the primary PFS analysis. At the initial, interim OS analysis, the OS data were immature, with 71 deaths (25.4%) in the osimertinib plus chemotherapy arm, and 78 deaths (28.1%) in the osimertinib monotherapy arm (26.8% maturity of data).

The HR at the time of the interim OS analysis was 0.90 (adjusted 99.84% CI: 0.54, 1.51; p=0.5238) (Table 19), which was not statistically significant per the O'Brien-Fleming spending function. Median OS was not reached in either treatment arm (Table 19 and Figure 7). Overall, these data indicate there was no detriment in OS for patients randomised to receive osimertinib plus chemotherapy compared with osimertinib monotherapy.

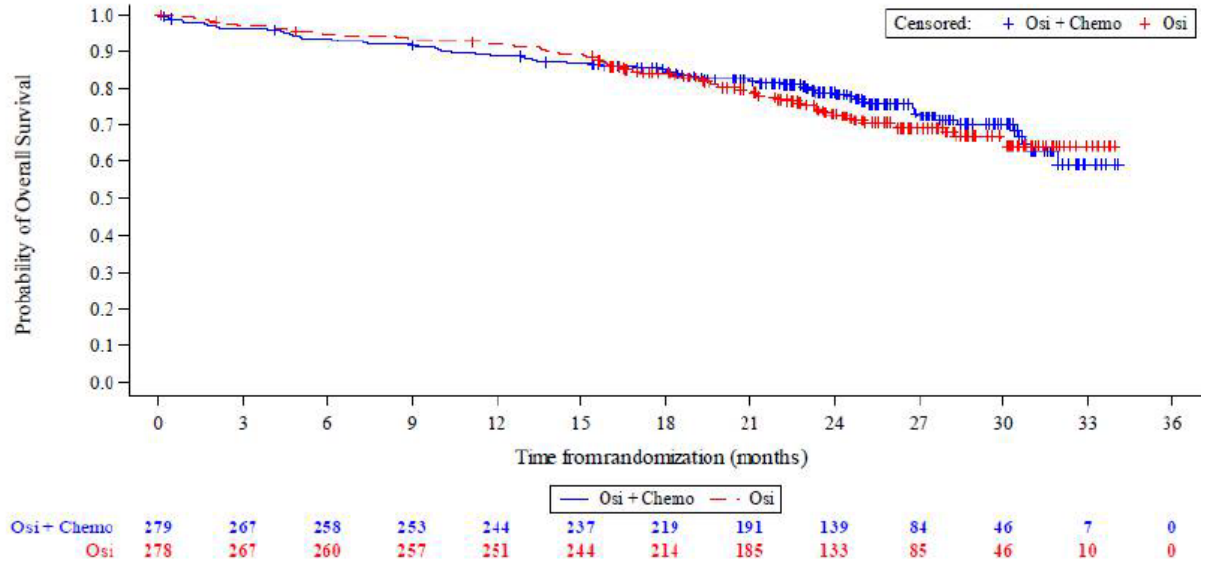
**Table 19: Overall survival (randomised period – FAS)**

| | Osi + chemo (N=279) | Osimertinib (N=278) |
|---|---|---|
| **Survival status, n (%)** | | |
| Death | 71 (25.4) | 78 (28.1) |
| Still in survival follow-up† | 197 (70.6) | 191 (68.7) |
| Terminated Prior to death‡ | 11 (3.9) | 9 (3.2) |
| Completed | 0 | 0 |
| Withdrawal by subject | 10 (3.6) | 8 (2.9) |
| Lost to follow-up | 0 | 0 |
| Other | 1 (0.4) | 1 (0.4) |
| **Comparison between groups** | | |
| Hazard ratio (95% CI) | 0.90 (0.65, 1.24) | |
| Adjusted 99.84% CI | 0.54, 1.51 | |
| 2-sided p-value | 0.5238 | |
| **Median overall survival** | | |
| Median OS (months) (95% CI)§ | NC (31.9, NC) | NC (NC, NC) |
| OS at 6 months (%) (95% CI) § | 93.5 (89.9, 95.9) | 94.9 (91.6, 97.0) |
| OS at 12 months (%) (95% CI) § | 88.8 (84.4, 92.0) | 92.0 (88.1, 94.7) |
| OS at 18 months (%) (95% CI) § | 85.4 (80.7, 89.1) | 84.2 (79.3, 88.0) |
| OS at 24 months (%) (95% CI) § | 78.9 (73.4, 83.4) | 73.0 (66.9, 78.1) |
| Median (range) follow-up for OS in all patients (months)¶ | 23.9 (0.1, 34.1) | 23.7 (0.1, 33.9) |
| Median (range) follow-up for OS in censored patients (months) †† ‡ | 25.0 (0.2, 34.1) | 25.1 (0.1, 33.9) |

† Includes patients known to be alive at DCO; ‡ Includes patients with unknown survival status or patients who were lost to follow-up; § Calculated using the KM method; ¶ Time from randomisation to date of death or to date of censoring for censored patients; †† Time from randomisation to date of censoring (date last known to be alive) for patients who have not died at the time of analysis.
Abbreviations: CI, confidence interval; DCO, data cut-off; FAS, full analysis set; KM, Kaplan-Meier; NC, not calculable; Osi + chemo, osimertinib plus chemotherapy; OS, overall survival.
DCO: 03 April 2023
Source: CSR.[8]

**Figure 7: Kaplan-Meier plot of OS (months) (randomised period – FAS)**




Abbreviations: FAS, full analysis set; NC, non-calculable; Osi + chemo, osimertinib plus chemotherapy; OS, overall survival.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] CSR.[8]

Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the log cumulative hazards plot, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the log odds diagnostic plot, parallel lines indicate proportional odds and in the log-normal diagnostic plot, parallel lines indicate constant acceleration (data not shown).

#### B.2.6.1.2.2 Objective response rate (03 April 2023 DCO)

High response rates (>75%) were observed in both treatment arms, with a higher ORR in the osimertinib plus chemotherapy arm (83.2%) compared with the osimertinib monotherapy arm (75.5%), based on investigator assessment (Table 20). The adjusted ORR was higher with osimertinib plus chemotherapy combination treatment than osimertinib monotherapy (OR: 1.61 [95% CI: 1.06, 2.44]; nominal p=0.0261). In total, 82.8% of patients treated with osimertinib plus chemotherapy and 74.8% of patients treated with osimertinib monotherapy had a PR to treatment.

**Table 20: Objective response by investigator assessment (randomised period –FAS)**

| | Osi + chemo (N=279) | Osimertinib (N=278) |
|---|---|---|
| **Best objective response, n (%)** | | |
| Response† | 232 (83.2) | 210 (75.5) |
| Complete response | 1 (0.4) | 2 (0.7) |
| Partial response | 231 (82.8) | 208 (74.8) |
| Non-response | 47 (16.8) | 68 (24.5) |
| StD ≥35 days‡ | 34 (12.2) | 51 (18.3) |
| Progression | 7 (2.5) | 12 (4.3) |
| RECIST progression | 1 (0.4) | 9 (3.2) |
| Death | 6 (2.2) | 3 (1.1) |
| Not evaluable | 6 (2.2) | 5 (1.8) |
| StD ≤35 days | 0 | 0 |
| Death (>13 weeks) with no evaluable RECIST assessment | 0 | 1 (0.4) |
| Other not evaluable | 6 (2.2) | 4 (1.4) |
| **Comparison between groups** | | |
| Unadjusted response rate (95% CI)§ | 83.15 (78.24, 87.35) | 75.54 (70.05, 80.48) |
| Odds ratio (95% CI)¶ | 1.60 (1.05, 2.42) | |
| 2-sided p-value†† | 0.0261 | |
| Adjusted response rate (95% CI)‡‡ | 84.40 (79.51, 88.30) | 77.10 (71.52, 81.85) |
| Odds ratio (95% CI)‡‡ | 1.61 (1.06, 2.44) | |
| 2-sided p-value‡‡ | 0.0261 | |

† Response did not require confirmation; ‡ Stable disease must have been observed at least 6 weeks minus one week to allow for an early assessment within the assessment window (study day 35) following randomisation; § The CI is calculated using the Clopper-Pearson exact method for binomial proportions; ¶ This analysis was performed using logistic regression with a factor for treatment; †† The p-value was calculated based on the likelihood ratio test which compared 2 models (one model with the intercept only and a second model including the treatment factor); ‡‡ The analysis was performed using a logistic regression stratified by race (Chinese/Asian vs Non-Chinese/Asian vs Non-Asian), WHO performance status (0 vs 1), and method used for tissue testing (central vs local).
An odds ratio >1 favours osimertinib plus chemotherapy.
Abbreviations: CI, confidence interval; FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy; RECIST, Response Evaluation Criteria in Solid Tumors.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] CSR.[8]

Assessment of ORR by BICR was consistent with investigator-assessed ORR. The adjusted ORR was 92.3% in the osimertinib plus chemotherapy arm and 83.7% in the osimertinib arm, (OR: 2.33 [95% CI: 1.37, 3.96]; nominal p=0.0017 in favour of the osimertinib plus chemotherapy treatment arm) (Table 21).

**Table 21: Objective response by BICR assessment (randomised period – FAS)**

| | Osi + chemo (N=279) | Osimertinib (N=278) |
|---|---|---|
| **Best objective response, n (%)** | | |
| Response† | 256 (91.8) | 230 (82.7) |
| Complete response | 2 (0.7) | 1 (0.4) |
| Partial response | 254 (91.0) | 229 (82.4) |
| Non-response | 23 (8.2) | 48 (17.3) |
| StD ≥35 days‡ | 10 (3.6) | 29 (10.4) |
| Progression | 9 (3.2) | 15 (5.4) |
| RECIST progression | 3 (1.1) | 12 (4.3) |
| Death | 6 (2.2) | 3 (1.1) |
| No evidence of disease | 0 | 0 |
| Not evaluable | 4 (1.4) | 4 (1.4) |
| Death (>13 weeks) with no evaluable RECIST assessment | 1 (0.4) | 0 |
| Other not evaluable | 3 (1.1) | 4 (1.4) |
| **Comparison between groups** | | |
| Unadjusted response rate (95% CI)§ | 91.76 (87.89, 94.70) | 82.73 (77.77, 86.99) |
| Odds ratio (95% CI)¶ | 2.32 (1.37, 3.94) | |
| 2-sided p-value†† | 0.0013 | |
| Adjusted response rate (95% CI)‡‡ | 92.33 (88.51, 94.96) | 83.77 (78.68, 87.84) |
| Odds ratio (95% CI)‡‡ | 2.33 (1.37, 3.96) | |
| 2-sided p-value‡‡ | 0.0017 | |

† Response did not require confirmation; ‡ Stable disease must have been observed at least 6 weeks minus one week to allow for an early assessment within the assessment window (study day 35) following randomisation. §The CI is calculated using the Clopper-Pearson exact method for binomial proportions; ¶ This analysis was performed using logistic regression with a factor for treatment; †† The p-value was calculated based on the likelihood ratio test which compared 2 models (one model with the intercept only and a second model including the treatment factor); ‡‡ The analysis was performed using a logistic regression stratified by race (Chinese/Asian vs Non-Chinese/Asian vs Non-Asian), WHO performance status (0 vs 1), and method used for tissue testing (central vs local).
An odds ratio >1 favours osimertinib plus chemotherapy.
Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy; RECIST, Response Evaluation Criteria in Solid Tumors; StD, stable disease.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] CSR.[8]

### B.2.6.1.2.3 Duration of response (03 April 2023 DCO)

A clinically meaningful 8.7-month improvement in median DoR was observed with osimertinib plus chemotherapy treatment (median DoR of 24.0 months) compared with patients who received osimertinib monotherapy (median DOR of 15.3 months)

(Table 22). A clear separation of the 95% CIs between the two treatment arms was observed for the estimated median DoR (Figure 8).

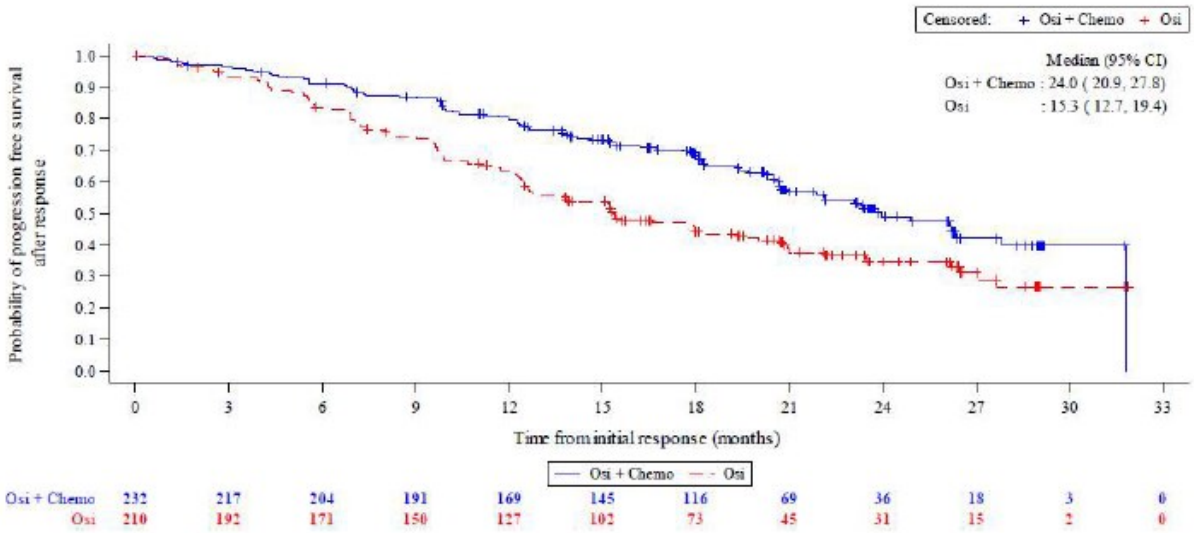
**Table 22: Duration of response in patients in objective response by investigator assessment (randomised period – FAS)**

| | Osi + chemo (N=279) | Osimertinib (N=278) |
|---|---|---|
| Number (%) of patients with objective response | 232 (83.2) | 210 (75.5) |
| Number (%) of responders who subsequently progressed or died† | 99 (42.7) | 127 (60.5) |
| **Duration of response** | | |
| Median DoR (months) (95% CI)‡ | 24.0 (20.9, 27.8) | 15.3 (12.7, 19.4) |
| **KM estimated percentages remaining in response** | | |
| 6 months (95% CI)§ | 91.1 (86.6, 94.2) | 83.5 (77.7, 87.9) |
| 12 months (95% CI)§ | 79.7 (73.7, 84.4) | 63.8 (56.8, 70.0) |
| 18 months (95% CI)§ | 69.1 (62.4, 74.9) | 44.2 (37.1, 51.0) |
| 24 months (95% CI)§ | 48.9 (40.5, 56.7) | 34.6 (27.4, 42.0) |
| **Time to onset of response, weeks** | | |
| Mean (std) | 10.33 (9.940) | 11.28 (13.496) |
| Median | 6.36 | 6.29 |
| Min, Max | 4.9, 61.0 | 4.6, 99.0 |

† Percentage is based on the number of patients with response; ‡ Calculated using the KM method; § KM estimated percentages remaining in response.
Abbreviations: CI, confidence interval; DoR; duration of response; FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] CSR.[8]

**Figure 8: Kaplan-Meier plot of DoR (months) in patients with an objective response by investigator assessment (randomised period – FAS)**




Abbreviations: CI, confidence interval; DoR; duration of response; FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy.
DCO: 03 April 2023
Source: CSR.[8]

Assessment of DoR by BICR was consistent with DoR by investigator assessment (Table 23). A clinically meaningful 7.3-month improvement in median DoR was observed for patients randomised to receive osimertinib plus chemotherapy compared with those randomised to receive osimertinib monotherapy (Table 23).

**Table 23: Duration of response in patients in objective response by BICR assessment (randomised period – FAS)**

| | Osi + chemo (N=279) | Osimertinib (N=278) |
|---|---|---|
| Number (%) of patients with objective response | 256 (91.8) | 230 (82.7) |
| Number (%) of responders who subsequently progressed or died† | 87 (34.0) | 103 (44.8) |
| **Duration of response** | | |
| Median DoR (months) (95% CI)‡ | 28.3 (23.7, NC) | 21.0 (17.8, NC) |
| **KM estimated percentages remaining in response** | | |
| 6 months (95% CI)§ | 93.2 (89.3, 95.7) | 90.6 (85.9, 93.7) |
| 12 months (95% CI)§ | 81.4 (75.9, 85.8) | 72.7 (66.2, 78.2) |
| 18 months (95% CI)§ | 69.6 (63.1, 75.3) | 56.1 (48.8, 62.8) |
| 24 months (95% CI)§ | 56.3 (47.8, 63.9) | 44.5 (36.2, 52.4) |

† Percentage is based on the number of patients with response; ‡ Calculated using the KM method; § KM estimated percentages remaining in response.
Abbreviations: BICR, blinded independent central review; CI, confidence interval; DoR; duration of response; FAS, full analysis set; NC, not calculable; Osi + chemo, osimertinib plus chemotherapy.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] CSR.[8]

#### B.2.6.1.2.4 Depth of response

Overall, the median best percentage change in target lesion size from baseline per investigator assessment was similar between treatment arms (-52.63% in the osimertinib plus chemotherapy arm, and -50.00% in the osimertinib monotherapy arm), with a least square mean difference between arms of -3.36% (Table 24).

A clinically meaningful ≥50% reduction in target lesion size was reported for 54.5% of patients in the osimertinib plus chemotherapy arm, and 50.0% of patients in the osimertinib monotherapy arm). A ≥70% reduction in target lesion size was reported for 16.5% of patients in the osimertinib plus chemotherapy arm and 15.1% of patients in the osimertinib arm (Table 24). Depth of response by BICR assessment was reported to be consistent with the investigator assessment (data not reported).

**Table 24: Depth of response in patients by investigator assessment (randomised period – FAS)**

| | Osi + chemo (N=279) | Osimertinib (N=278) |
|---|---|---|
| Number of patients with a baseline and on-treatment tumour measurements | 275 | 276 |
| **Best percentage change from baseline for sum of longest diameters** | | |
| Mean (std) | [redacted] | [redacted] |
| Median | -52.63 | -50.00 |
| Min, Max | [redacted] | [redacted] |
| **Number (%) of patients with best % change from baseline** | | |
| ≥30% reduction | [redacted] | [redacted] |
| ≥50% reduction | [redacted] | [redacted] |
| ≥70% reduction | [redacted] | [redacted] |
| **Comparison between groups†** | | |
| Treatment effect least square mean (95% CI) | [redacted] | [redacted] |
| Least square mean differences (95% CI) | [redacted] | |
| 2-sided p-value | [redacted] | |

† The analysis was performed using analysis of covariance with baseline tumour size and time from baseline scan to randomisation as covariates and with factors race (Chinese/Asian vs Non-Chinese/Asian vs Non-Asian), WHO performance status (0 vs 1), and method used for tissue testing (central vs local). A difference in least square means <0 favours osimertinib plus chemo.
Abbreviations: CI, confidence interval; FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy; std, standard deviation.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] CSR.[8]

### B.2.6.1.2.5 Disease control rate

A high DCR (>90%) was observed in both treatment arms (95.3% in the osimertinib plus chemotherapy arm, and 93.9% in the osimertinib monotherapy arm) (Table 25). When accounting for stratification factors using logistic regression, the adjusted DCR was [redacted]% in the osimertinib plus chemotherapy arm, and [redacted]% in the osimertinib monotherapy arm, with an odds ratio of [redacted] which favoured the osimertinib plus chemotherapy treatment arm (Table 25).

**Table 25: Disease control rate by investigator assessment (randomised period – FAS)**

| | Osi + chemo (N=279) | Osimertinib (N=278) |
|---|---|---|
| Number (%) of patients with disease control | [redacted] | [redacted] |
| **Comparison between groups** | | |
| Unadjusted response rate (95% CI)† | 95.34 (92.16, 97.50) | 93.88 (90.39, 96.40) |
| Odds ratio (95% CI)‡ | [redacted] | |
| 2-sided p-value§ | [redacted] | |
| Adjusted response rate (95% CI)¶ | [redacted] | [redacted] |
| Odds ratio (95% CI)¶ | [redacted] | |
| 2-sided p-value¶ | [redacted] | |

† The CIs are calculated using the Clopper-Pearson exact method for binomial proportions; ‡ This analysis was performed using logistic regression with a factor for treatment; § The p-value was calculated based on the likelihood ratio test which compared 2 models (one model with the intercept only and a second model including the treatment factor); ¶ The analysis was performed using a logistic regression stratified by race (Chinese/Asian vs Non-Chinese/Asian vs Non-Asian), WHO performance status (0 vs 1), and method used for tissue testing (central vs local).
An odds ratio >1 favours osimertinib plus chemotherapy.
Abbreviations: CI, confidence interval; FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy; WHO, World Health Organization.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] CSR.[8]

#### *B.2.6.1.3 Patient reported outcomes/quality of life*

PROs were assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires. PRO functioning and symptom subscales including global health status/HRQoL, appetite, dyspnoea, cough, chest pain, physical functioning or fatigue were assessed whereby, a clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 points.

##### B.2.6.1.3.1 Compliance

The overall compliance rate for both the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires were high (>91%) at the baseline for both treatment arms and remained high (≥80%) to Week 82 (Month 19).

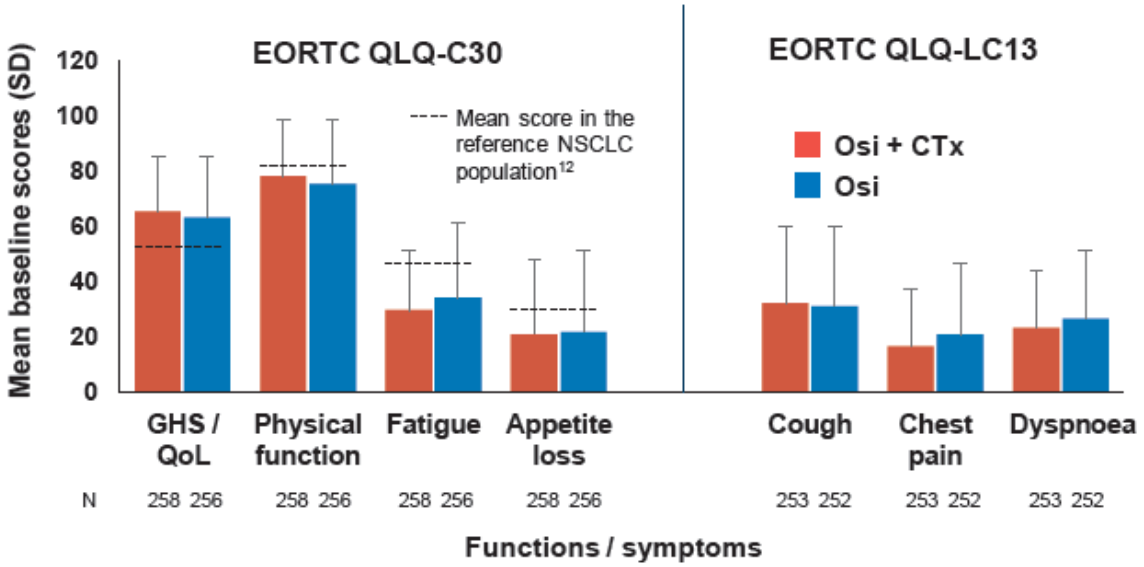
##### B.2.6.1.3.2 Baseline scores

Baseline scores were balanced between treatment arms in both EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires (Figure 9). In both treatment arms, patients had intermediate-to-high degrees of overall functioning and global health status/QoL (scores ≥63) based on the QLQ-C30 questionnaire, with no or mild symptomatology

(scores ≤34), based on data from both questionnaires. Overall, the study population was generally mildly symptomatic, reflecting the good overall WHO PS at baseline.

**Figure 9: Mean PRO scores at baseline†**




† Pre-specified key functions / symptoms are shown.
Abbreviations: CTx, chemotherapy; EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; NSCLC, non-small cell lung cancer; Osi, osimertinib; PRO, patient-reported outcomes; QoL, quality of life; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-LC13, Quality of Life Questionnaire Lung Cancer 13; SD, standard deviation.
Source: Lee et al. (2024)[74]

#### B.2.6.1.3.3 Change from baseline

Overall, average change from baseline analyses, based on MMRM modelling, demonstrated a non-clinically meaningful improvement in global health status/QoL and physical functioning in both treatment arms. Clinically meaningful improvements in cough and non-clinically meaningful improvements in dyspnoea and chest pain were observed in both treatment arms. No clinically meaningful changes in fatigue were reported in either treatment arm. A non-clinically meaningful worsening in appetite loss was observed in the osimertinib plus chemotherapy arm throughout the study. In the osimertinib monotherapy arm, a non-clinically meaningful improvement was observed (Table 26 and Figure 10).

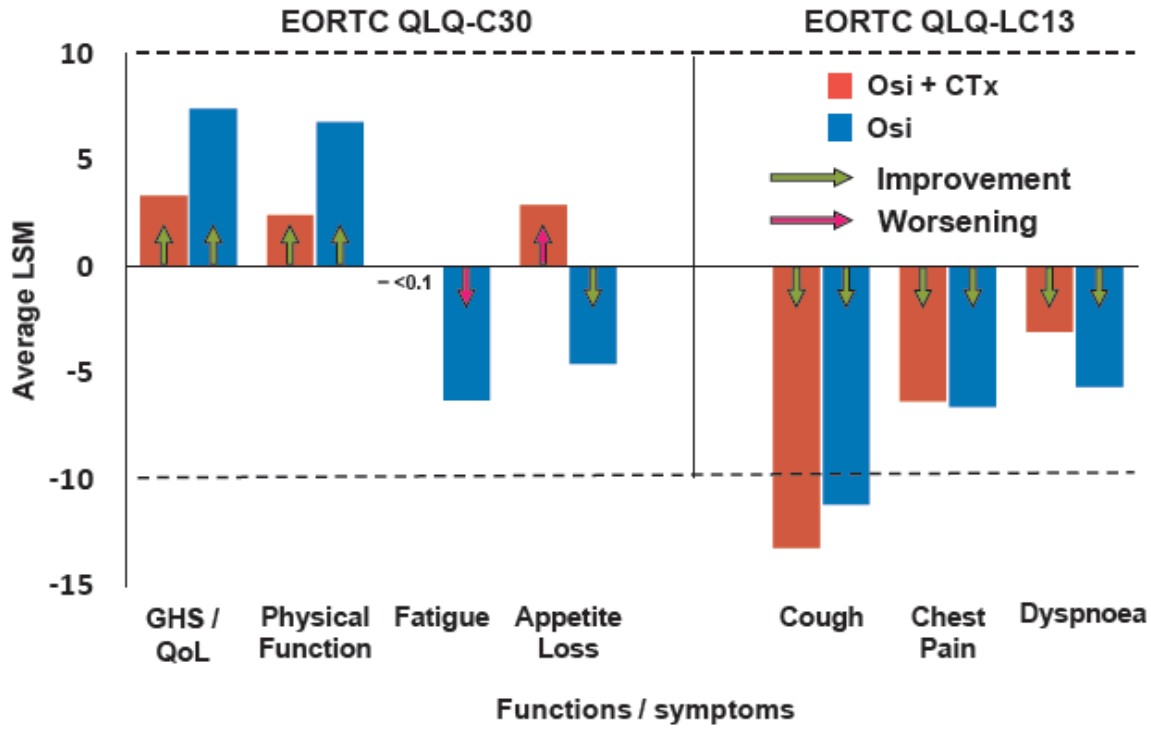
**Table 26: Summary of change from baseline in primary PRO domains and symptoms, MMRM (randomised period – FAS)**

| Primary PRO Scales | Treatment arm | N | Average LS mean† (95% CI) | Average difference in change from baseline in LS means† (Osi +chemo – Osi) (95% CI) |
|---|---|---|---|---|
| **Scale (EORTC QLQ-C30 questionnaire)** | | | | |
| Global health status / QoL | Osi + chemo | 253 | 3.32 (1.67, 4.98) | -4.06 (-6.42, -1.69) |
| | Osimertinib | 253 | 7.38 (5.70, 9.07) | |
| Physical Function | Osi + chemo | 253 | 2.37 (0.70, 4.04) | -4.37 (-6.75, -1.99) |
| | Osimertinib | 253 | 6.74 (5.04, 8.43) | |
| Fatigue | Osi + chemo | 253 | -0.03 (-1.91, 1.84) | 6.28 (3.60, 8.96) |
| | Osimertinib | 253 | -6.31 (-8.22, -4.40) | |
| Appetite loss | Osi + chemo | 253 | 2.87 (0.82, 4.92) | 7.45 (4.52, 10.38) |
| | Osimertinib | 253 | -4.58 (-6.67, -2.48) | |
| **Symptoms (EORTC QLQ-LC13 questionnaire)** | | | | |
| Dyspnoea | Osi + chemo | 253 | -3.09 (-4.70, -1.49) | 2.57 (0.28, 4.86) |
| | Osimertinib | 251 | -5.67 (-7.30, -4.04) | |
| Coughing | Osi + chemo | 253 | -13.23 (-14.85, -11.62) | -2.04 (4.35, 0.26) |
| | Osimertinib | 251 | -11.19 (-12.83, -9.55) | |
| Pain in chest | Osi + chemo | 253 | -6.33 (-7.66, -4.99) | 0.29 (-1.62, 2.20) |
| | Osimertinib | 251 | -6.61 (-7.98, -5.25) | |

† Average includes all patients contributing to the MMRM model over all visits (ie, over 19 months or until progression disease). The score values are calculated by averaging across patients overall mean across all visits. The analysis was performed using a MMRM analysis on the change from baseline in PRO symptom score or functional at each visit up to 19 months (579 days), including subject (as a random effect), treatment, visit (as fixed effect and repeated measure) and treatment by visit interaction as explanatory variables, with the baseline PRO score as a covariate along with the baseline PRO score by assessment interaction. Approach to select the covariance structure is specified in the SAP.
Abbreviations: CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; FAS; full analysis set; LS; least squares; N, number; NC, not calculable; Osi + chemo, osimertinib plus chemotherapy; PRO, patient-reported outcome; QLQ-C30, 30-Item Core Quality-of-Life Questionnaire; QLQ-LC13, 13-item lung cancer module; TTD, time to deterioration.
DCO: 03 April 2023
Source: CSR.[8]

**Figure 10: Change from baseline in PRO scales and items over all visits (MMRM)**




Note: dotted line indicates a clinically meaningful change.
Abbreviations: CTx, chemotherapy; EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; LSM, least-squares mean; MMRM, mixed model for repeated measures; Osi, Osimertinib; PRO, patient-reported outcomes; QoL, quality of life; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-LC13, Quality of Life Questionnaire Lung Cancer 13.
DCO: 03 April 2023.
Source: Lee et al. (2024).[74]

Non-clinically meaningful improvements in GHS/QoL and dyspnoea were seen throughout treatment in both arms. A clinically meaningful improvement in coughing was observed from Week 5 onwards in the osimertinib plus chemotherapy arm, and from Week 6 onwards in the osimertinib arm (Figure 11).

#### B.2.6.1.3.4 Time to deterioration

In the prespecified PRO scales of physical functioning, fatigue, appetite loss, and dyspnoea, a clinically meaningful delayed time to confirmed deterioration was observed in favour of the osimertinib monotherapy arm (estimated HRs ≥1.0) (Table 27 and Figure 11). Time to confirmed deterioration also favoured the osimertinib monotherapy arm for overall global health status/QoL and physical function (estimated HRs ≥1.0) and the osimertinib plus chemotherapy arm for coughing (HR of 0.77) (Table 27 and Figure 11).

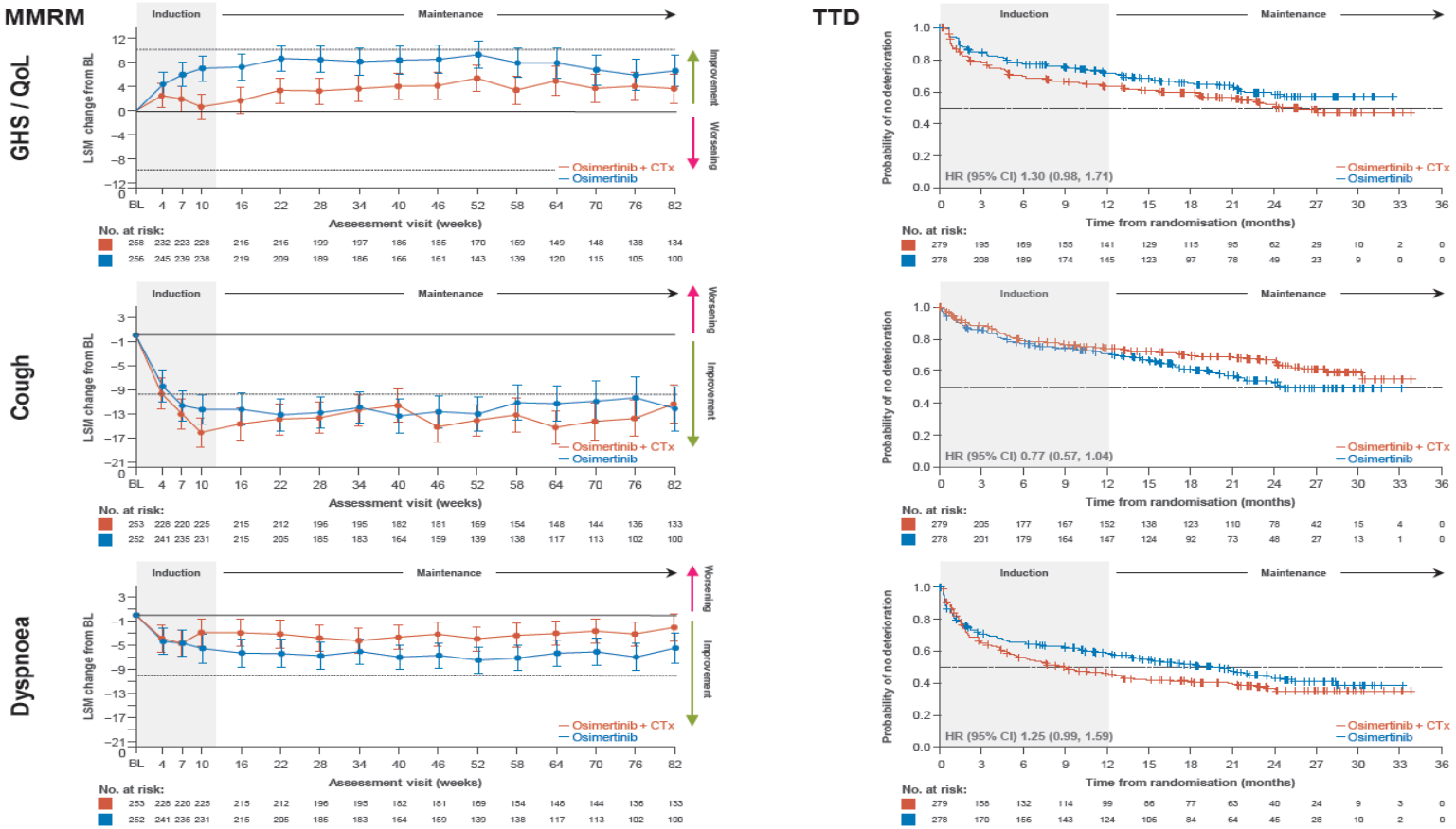
**Table 27: Analysis of time to confirmed deterioration in primary PRO domains and symptoms (randomised period – FAS)**

| Primary PRO Scales | Treatment arm | N | Number (%) of patients with events† | Median TTD (months) (95% CI)‡ | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| **Scale (EORTC QLQ-C30 questionnaire)** | | | | | |
| Global health status / QoL | Osi + chemo | 279 | [redacted] | [redacted] | [redacted] |
| | Osimertinib | 278 | | | |
| Physical Function | Osi + chemo | 279 | [redacted] | [redacted] | [redacted] |
| | Osimertinib | 278 | | | |
| Fatigue | Osi + chemo | 279 | [redacted] | [redacted] | [redacted] |
| | Osimertinib | 278 | | | |
| Appetite loss | Osi + chemo | 279 | [redacted] | [redacted] | [redacted] |
| | Osimertinib | 278 | | | |
| **Symptoms (EORTC QLQ-LC13 questionnaire)** | | | | | |
| Dyspnoea | Osi + chemo | 279 | [redacted] | [redacted] | [redacted] |
| | Osimertinib | 278 | | | |
| Coughing | Osi + chemo | 279 | [redacted] | [redacted] | [redacted] |
| | Osimertinib | 278 | | | |
| Pain in chest | Osi + chemo | 279 | [redacted] | [redacted] | [redacted] |
| | Osimertinib | 278 | | | |

† Percentages are based on number of patients included in the analysis n. Events comprise confirmed deterioration, or death in the absence of confirmed deterioration; ‡ Calculated using the KM method
Patients with baseline scores of <10 for global health status/QoL and functioning, baseline scales of >90 for symptom scales were censored at day 1. The analysis was performed using a log rank test stratified by race (Chinese/Asian vs Non-Chinese/Asian vs Non-Asian), WHO performance status (0 vs 1), and method used for tissue testing (central vs local).
A hazard ratio <1 favours osimertinib plus chemotherapy.
Abbreviations: CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; FAS; full analysis set;; N, number; NC, not calculable; Osi + chemo, osimertinib plus chemotherapy; PRO, patient-reported outcome; QLQ-C30, 30-Item Core Quality-of-Life Questionnaire; QLQ-LC13, 13-item lung cancer module; TTD, time to deterioration.
DCO: 03 April 2023
Source: CSR.[8]

**Figure 11: Changes in GHS/QoL, cough and dyspnoea over time; MMRM and time to deterioration**




Note: Dotted lines indicate clinically meaningful change. Induction represents the first four treatment cycles where patients in the osimertinib + chemotherapy treatment arm received osimertinib + pemetrexed and platinum-based chemotherapy. Maintenance represents subsequent treatment cycles where patients in the osimertinib + chemotherapy arm received osimertinib + pemetrexed. and maintenance periods refer to the osimertinib and chemotherapy arm.
Abbreviations: BL, baseline; CTx, chemotherapy; GHS, global health status; LSM, least-squares mean; MMRM, mixed model for repeated measures; PRO, patient-reported outcomes; QoL, quality of life; TTD, time to symptom deterioration (time from randomisation until the date of the first clinically meaningful worsening [a change in the score from baseline of ≥10 points] which was confirmed at a subsequent assessment or death by any cause).
Source: Lee et al. (2024).[74]

#### B.2.6.1.3.5 Exploratory endpoint – EQ-5D-5L

Mean absolute EQ-Visual Analogue Scale (VAS) scores at the baseline were well balanced between treatment arms (71.7 in the osimertinib plus chemotherapy arm and 70.6 in the osimertinib monotherapy arm). Post-baseline, mean EQ-5D-5L VAS scores progressively increased (i.e., improved) in both treatment arms, with no notable differences between arms.

Baseline scores for the EQ-5D-5L domains were similar between treatment arms, with a slightly higher number of patients in the osimertinib plus chemotherapy arm reporting no problems in the domains of mobility, self-care, usual activities, and pain/discomfort than in the osimertinib monotherapy arm. Post-baseline, all EQ-5D-5L domains remained mostly stable or improved at several assessments throughout the study. Details of EQ-5D-5L summary statistics are presented in Table 28.

**Table 28: EQ-5D-5L summary statistics (randomised period – FAS)**

| Treatment | Scenario | Patients | Observations | Mean (SD) | Median (IQR) | Min | Max |
|---|---|---|---|---|---|---|---|
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |

Abbreviations: EQ-5D, EuroQoL-5 Dimensions; FAS, full analysis set; IQR, interquartile range; Osi + chemo, osimertinib plus chemotherapy; SD, standard deviation.
Source: AstraZeneca (2024).[79]

#### *B.2.6.1.4 Efficacy conclusions*

FLAURA2 study met its primary objective, demonstrating that treatment with osimertinib in combination with pemetrexed and platinum-based chemotherapy resulted in a statistically significant and clinically meaningful 38% reduction in the risk of disease progression or death compared with osimertinib monotherapy (HR: 0.62 [95% CI: 0.49, 0.79]; p<0.0001). Osimertinib plus chemotherapy treatment resulted in an 8.8-month improvement in median PFS compared with osimertinib monotherapy with separation of curves at 3 months post-randomisation in favour of the osimertinib plus chemotherapy arm for the entire duration of the follow-up. At the second interim OS analysis, data remained immature (41%), but with a favourable trend towards improved OS with osimertinib plus chemotherapy versus osimertinib

monotherapy (HR: 0.75 [95% CI 0.57, 0.97]). Furthermore, high response rates (>75%) were observed in both treatment arms, with a numerically higher ORR and a clinically meaningful 8.7-month improvement in median DoR in the osimertinib plus chemotherapy arm compared with the osimertinib monotherapy arm. PRO data showed a non-clinically meaningful improvement in global health status/QoL and physical functioning in both treatment arms.

The results of FLAURA2 demonstrate that treatment with osimertinib and chemotherapy in combination provides a significant and clinically meaningful benefit to patients with advanced EGFRm (Ex19del and/or L858R) NSCLC. These data support the hypothesis that the addition of chemotherapy to osimertinib treatment in the first-line metastatic setting may improve treatment outcomes in this patient population.

### *B.2.7 Subgroup analysis*

Pre-planned subgroup analyses included ethnicity, age, sex, smoking history, CNS metastases status at study entry, and EGFR mutation type (Ex19del or L858R) to assess the consistency of treatment effect across expected prognostic and/or predictive factors. For each subgroup, the HR and 95% CI was calculated from a single Cox proportional hazards model that contains a term for treatment, the subgroup covariate of interest, and the treatment by subgroup interaction term.

Results for each were presented on a forest plot including the HR and 95% profile likelihood CI, along with the results of the overall primary analysis. At the 03 April 2023 DCO, a PFS benefit for osimertinib plus chemotherapy compared with osimertinib monotherapy was observed consistently across all predefined subgroups analysed, including high-risk groups such as patients with CNS metastases and the L858R mutation (Figure 12). As expected in a subgroup analysis, a degree of variability was observed across all subgroups, particularly in the subgroups with a smaller number of patients and fewer PFS events observed. An additional analysis was performed to assess the consistency of treatment benefit across the predefined subgroups by means of an overall global interaction test. The results of the analysis indicated that there was no evidence of a quantitative interaction (p=0.1608), which therefore confirms the consistency of the treatment benefit. At the second interim 08

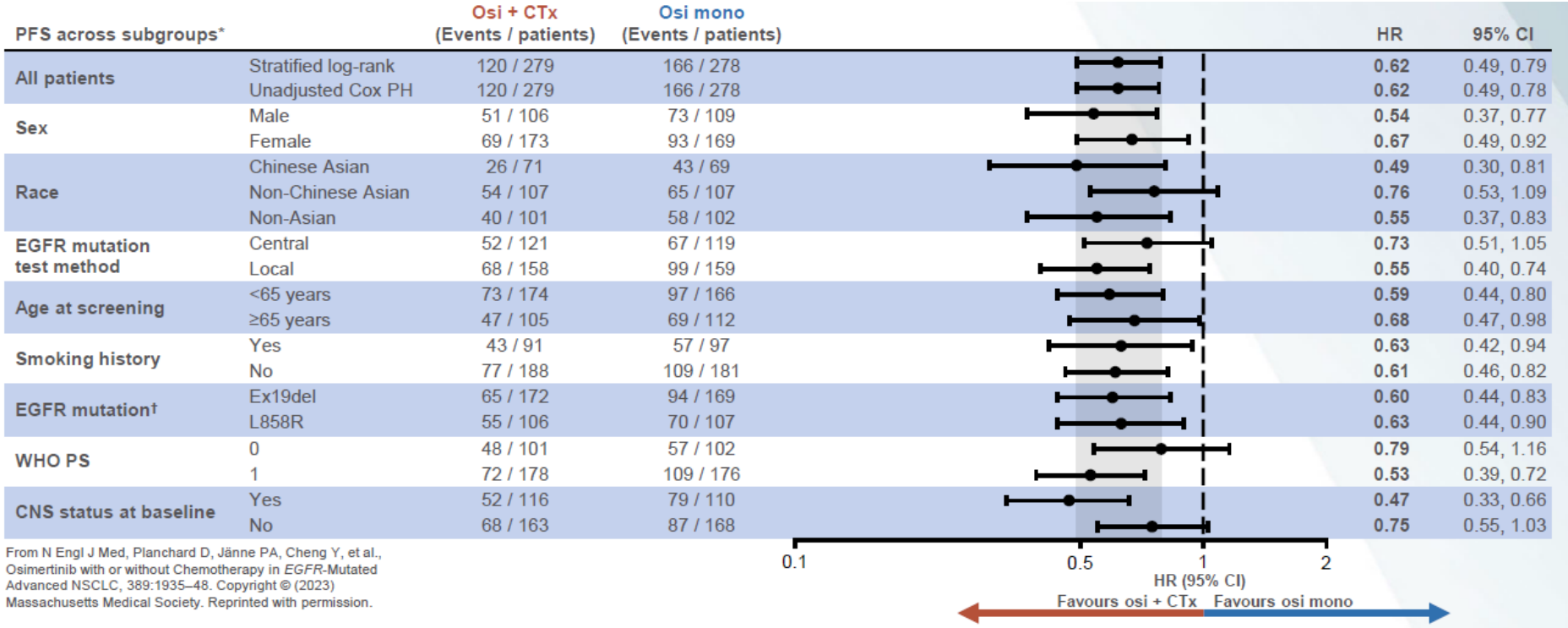

 

January 2024 DCO, an OS benefit was observed in favour of osimertinib plus chemotherapy across the majority of subgroups (Figure 13).

However, the study was not powered for individual subgroup comparisons, and no multiplicity adjustments were made. The lower number of patients and events across the individual subgroups may lead to greater uncertainty in their point estimates and wider CIs. Full results are presented in Appendix E.

**Figure 12: Subgroup analysis of progression-free survival (months) by investigator assessment (randomised period – FAS)**



| PFS across subgroups* | | Osi + CTx (Events / patients) | Osi mono (Events / patients) | HR | 95% CI |
|---|---|---|---|---|---|
| All patients | Stratified log-rank | 120 / 279 | 166 / 278 | 0.62 | 0.49, 0.79 |
| | Unadjusted Cox PH | 120 / 279 | 166 / 278 | 0.62 | 0.49, 0.78 |
| Sex | Male | 51 / 106 | 73 / 109 | 0.54 | 0.37, 0.77 |
| | Female | 69 / 173 | 93 / 169 | 0.67 | 0.49, 0.92 |
| Race | Chinese Asian | 26 / 71 | 43 / 69 | 0.49 | 0.30, 0.81 |
| | Non-Chinese Asian | 54 / 107 | 65 / 107 | 0.76 | 0.53, 1.09 |
| | Non-Asian | 40 / 101 | 58 / 102 | 0.55 | 0.37, 0.83 |
| EGFR mutation test method | Central | 52 / 121 | 67 / 119 | 0.73 | 0.51, 1.05 |
| | Local | 68 / 158 | 99 / 159 | 0.55 | 0.40, 0.74 |
| Age at screening | <65 years | 73 / 174 | 97 / 166 | 0.59 | 0.44, 0.80 |
| | ≥65 years | 47 / 105 | 69 / 112 | 0.68 | 0.47, 0.98 |
| Smoking history | Yes | 43 / 91 | 57 / 97 | 0.63 | 0.42, 0.94 |
| | No | 77 / 188 | 109 / 181 | 0.61 | 0.46, 0.82 |
| EGFR mutation† | Ex19del | 65 / 172 | 94 / 169 | 0.60 | 0.44, 0.83 |
| | L858R | 55 / 106 | 70 / 107 | 0.63 | 0.44, 0.90 |
| WHO PS | 0 | 48 / 101 | 57 / 102 | 0.79 | 0.54, 1.16 |
| | 1 | 72 / 178 | 109 / 176 | 0.53 | 0.39, 0.72 |
| CNS status at baseline | Yes | 52 / 116 | 79 / 110 | 0.47 | 0.33, 0.66 |
| | No | 68 / 163 | 87 / 168 | 0.75 | 0.55, 1.03 |

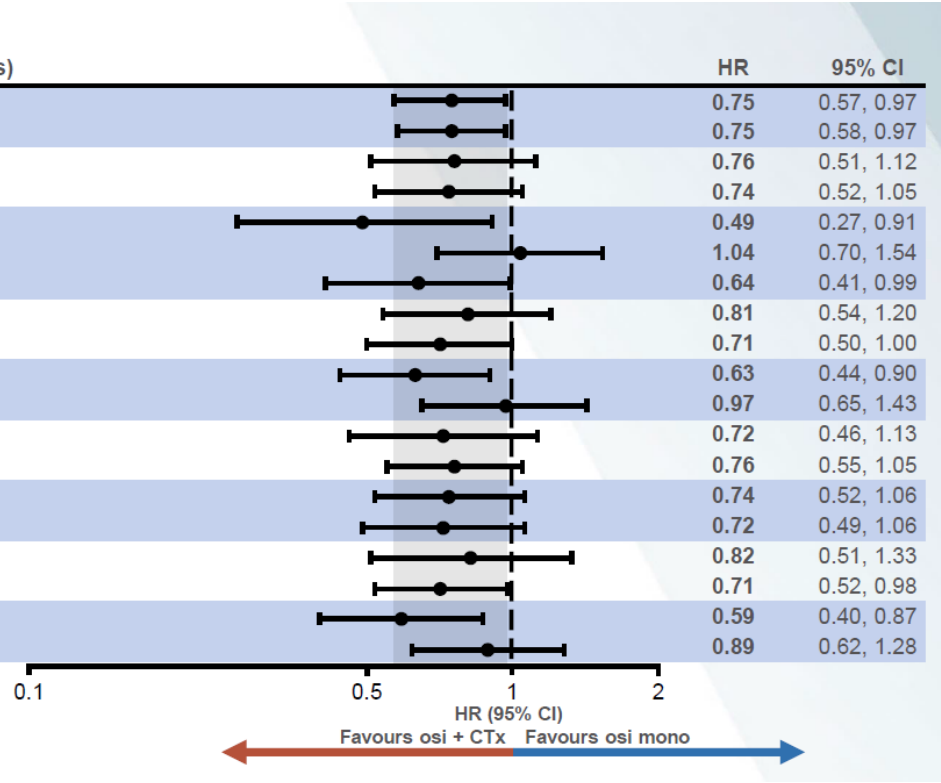




Abbreviations: CI, confidence interval; CNS; central nervous system EGFR; epidermal growth factor receptor; FAS, full analysis set; HR, hazard ratio; Osi + chemo, osimertinib plus chemotherapy; WHO, World Health Organization.
DCO: 03 April 2023
Source: Planchard et al. (2023);[77] Valdiviezo et al. (2024).[73]; CSR.[8]

**Figure 13: Subgroup analysis of overall survival (months)**

| OS across subgroups | | Osi + CTx (Events / patients) | Osi mono (Events / patients) | HR | 95% CI |
|---|---|---|---|---|---|
| All patients | Stratified log-rank | 100 / 279 | 126 / 278 | 0.75 | 0.57, 0.97 |
| | Unadjusted Cox PH | 100 / 279 | 126 / 278 | 0.75 | 0.58, 0.97 |
| Sex | Male | 45 / 106 | 55 / 109 | 0.76 | 0.51, 1.12 |
| | Female | 55 / 173 | 71 / 169 | 0.74 | 0.52, 1.05 |
| Race | Chinese Asian | 16 / 71 | 29 / 69 | 0.49 | 0.27, 0.91 |
| | Non-Chinese Asian | 50 / 107 | 48 / 107 | 1.04 | 0.70, 1.54 |
| | Non-Asian | 34 / 101 | 49 / 102 | 0.64 | 0.41, 0.99 |
| EGFR mutation test method | Central | 44 / 121 | 53 / 119 | 0.81 | 0.54, 1.20 |
| | Local | 56 / 158 | 73 / 159 | 0.71 | 0.50, 1.00 |
| Age at screening | <65 years | 52 / 174 | 73 / 166 | 0.63 | 0.44, 0.90 |
| | ≥65 years | 48 / 105 | 53 / 112 | 0.97 | 0.65, 1.43 |
| Smoking history | Yes | 33 / 91 | 43 / 97 | 0.72 | 0.46, 1.13 |
| | No | 67 / 188 | 83 / 181 | 0.76 | 0.55, 1.05 |
| EGFR mutation† | Ex19del | 52 / 172 | 69 / 169 | 0.74 | 0.52, 1.06 |
| | L858R | 48 / 106 | 57 / 107 | 0.72 | 0.49, 1.06 |
| WHO PS | 0 | 30 / 101 | 36 / 102 | 0.82 | 0.51, 1.33 |
| | 1 | 70 / 178 | 90 / 176 | 0.71 | 0.52, 0.98 |
| CNS status at baseline | Yes | 44 / 116 | 62 / 110 | 0.59 | 0.40, 0.87 |
| | No | 56 / 163 | 64 / 168 | 0.89 | 0.62, 1.28 |




†Patients with both Ex19del and L858R were included in the Ex19del group.
Abbreviations: CI, confidence interval; CNS, central nervous system; CTx, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; mono, monotherapy; osi, osimertinib; PH, proportional hazards; PS, performance status; WHO World Health Organization.
DCO: 08 January 2024.
Source: Valdiviezo et al. (2024).[73]

## *B.2.8 Meta-analysis*

FLAURA2 is the only Phase 3 RCT reporting on the efficacy and safety of osimertinib plus chemotherapy in patients with advanced EGFRm NSCLC, therefore a meta-analysis was not feasible.

## *B.2.9 Indirect and mixed treatment comparisons*

Head-to-head clinical trial data are available for osimertinib plus chemotherapy versus the main comparator used in English clinical practice (osimertinib monotherapy) based on guidelines[3] and clinical expert opinion.[2] No further studies were identified in the SLR that were deemed relevant to the decision problem being addressed in this submission, therefore an indirect or mixed-treatment comparison was not deemed necessary.

## *B.2.10 Adverse reactions*

### B.2.10.1 FLAURA2

The FLAURA2 AE analyses presented in this section were conducted based on the safety analysis set (SAS), which consisted of 276 patients who received at least one dose of study treatment in the osimertinib plus chemotherapy arm, and 275 patients who received at least one dose of osimertinib in the osimertinib arm. The analyses of AEs presented comprise those events with an onset date on or after the date of the first dose of study treatment, up to and including the 28-day follow-up period, or until the 03 April 2023 DCO date.

#### *B.2.10.1.1 Exposure*

The overall duration of exposure to any study treatment in the SAS ranged from 0.1 to 33.8 months, with a median total exposure of 21.09 months (Table 29). Total median exposure was higher in the osimertinib plus chemotherapy arm (22.31 months) compared with the osimertinib monotherapy arm (19.32 months). Overall, the number of patients exposed, and the totality of exposure to each study treatment were considered adequate to characterise the safety and efficacy profile of both study treatment arms in the target patient population.



**Table 29: Extent of exposure (randomised period – safety analysis set)**

| | Osi + chemo (N=276) | | | | Osimertinib (n=275) |
|---|---|---|---|---|---|
| | Osimertinib (n=276) | Carboplatin/Cisplatin (n=276) | Pemetrexed (n=276) | Overall (n=276)† | |
| **All study treatment: total exposure (months)‡, §** | | | | | |
| Mean (std) | 19.67 (9.053) | 2.58 (0.742) | 12.06 (9.836) | 19.80 (9.016) | 18.12 (8.908) |
| Median | 22.26 | 2.76 | 8.28 | 22.31 | 19.32 |
| Min, max | 0.1, 33.8 | 0.7, 4.1 | 0.7, 33.8 | 0.7, 33.8 | 0.1, 33.8 |
| Total treatment years | 452.3 | 59.3 | 277.3 | 455.3 | 415.3 |
| **All study treatment: Cumulative total exposure over time¶** | | | | | |
| ≥1 day | 276 (100.0) | 276 (100.0) | 276 (100.0) | 276 (100.0) | 275 (100.0) |
| ≥1 month | 267 (96.7) | 253 (91.7) | 254 (92.0) | 268 (97.1) | 274 (99.6) |
| ≥3 months | 256 (92.8) | 45 (16.3) | 216 (78.3) | 256 (92.8) | 256 (93.1) |
| ≥12 months | 214 (77.5) | 0 | 118 (42.8) | 214 (77.5) | 200 (72.7) |
| ≥24 months | 109 (39.5) | 0 | 53 (19.2) | 113 (40.9) | 77 (28.0) |
| **Osimertinib: actual exposure (months)¶** | | | | | |
| Mean (std) | 19.32 (9.032) | NA | NA | 19.36 (9.004) | 17.95 (8.904) |
| Median | 21.83 | NA | NA | 21.83 | 19.02 |
| Min, max | 0.1, 33.4 | NA | NA | 0.1, 33.4 | 0.1, 33.8 |
| Total treatment years | 444.5 | NA | NA | 445.3 | 411.3 |
| **Osimertinib: cumulative actual exposure over time** | | | | | |
| ≥1 day | 276 (100.0) | NA | NA | 276 (100.0) | 275 (100.0) |
| ≥1 month | 266 (96.4) | NA | NA | 266 (96.4) | 274 (99.6) |
| ≥3 months | 255 (92.4) | NA | NA | 256 (92.8) | 256 (93.1) |
| ≥6 months | 238 (86.2) | NA | NA | 239 (86.6) | 235 (85.5) |
| ≥12 months | 213 (77.2) | NA | NA | 213 (77.2) | 198 (72.0) |
| ≥24 months | 99 (35.9) | NA | NA | 99 (35.9) | 76 (27.6) |

† Patient received any of the study drugs (osimertinib, cisplatin, carboplatin, or pemetrexed); ‡ For osimertinib, Total exposure = [min(last dose date where dose >0 mg, date of death, date of DCO) – first dose date + 1] / 30.4375; § For pemetrexed, cisplatin, and carboplatin, Total exposure = [min(last dose date where dose >0 mg, date of death, date of DCO) – first dose date + 21] / 30.4375; ¶ Actual exposure = [total exposure – total duration of dose interruptions (i.e., number of days with dose = 0 mg)] / 30.4375. Total treatment-years is the sum of treatment durations of all patients by treatment group.
Abbreviations: NA, not applicable; Osi + chemo, osimertinib plus chemotherapy.
DCO: 03 April 2023
Source: CSR.[8]



### *B.2.10.1.2 AE overview*

Nearly all patients in both treatment arms experienced an AE (100% of patients in the osimertinib plus chemotherapy arm and 97.5% of patients in the osimertinib monotherapy arm) (Table 30). The proportion of patients that experienced an AE reported as causally related to treatment was higher in the osimertinib plus chemotherapy arm (97.5%) compared with the osimertinib monotherapy arm (87.6%). Other types of AEs which were higher in the osimertinib plus chemotherapy arm compared with the osimertinib monotherapy arm included Grade ≥3 AEs (63.8 vs 27.3%), AEs leading to dose modifications (71.7 vs 20.4%), SAEs (37.7 vs 19.3%), and AEs leading to discontinuation of any study drug (47.8 vs 6.2%) and were mainly driven by expected chemotherapy-related toxicities. The addition of chemotherapy to osimertinib had a minimal impact on the rate of osimertinib discontinuation due to AEs (10.9% of patients in the osimertinib plus chemotherapy arm versus 6.2% of the osimertinib monotherapy arm). The proportions of patients who had an AE with outcome of death were low in both treatment arms (6.5% in the osimertinib plus chemotherapy arm and 2.9% in the osimertinib monotherapy arm).

**Table 30: Overview of adverse events (randomised period - safety analysis set)**

| AE category | Number (%) of patients[†] | |
|---|---|---|
| | Osi + chemo (N=276) | Osimertinib (N=275) |
| **Any AE** | **276 (100.0)** | **268 (97.5)** |
| Causally related to treatment[‡] | 269 (97.5) | 241 (87.6) |
| Causally related to osimertinib | 241 (87.3) | 241 (87.6) |
| Causally related to chemotherapy | 264 (95.7) | 6 (2.2)[¶] |
| Causally related to carboplatin/cisplatin | 104 (37.7) | NA |
| Causally related to pemetrexed | 130 (47.1) | NA |
| **Any AE of CTCAE Grade ≥3** | **176 (63.8)** | **75 (27.3)** |
| Causally related to treatment[‡] | 146 (52.9) | 29 (10.5) |
| Causally related to osimertinib | 81 (29.3) | 29 (10.5) |
| Causally related to chemotherapy | 138 (50.0) | NA |
| Causally related to carboplatin/cisplatin | 104 (37.7) | NA |
| Causally related to pemetrexed | 130 (47.1) | NA |



| AE category | Number (%) of patients[†] | |
|---|---|---|
| | Osi + chemo (N=276) | Osimertinib (N=275) |
| **Any AE with outcome of death** | **18 (6.5)** | **8 (2.9)** |
| Causally related to treatment[‡] | 5 (1.8) | 1 (0.4) |
| Causally related to osimertinib | 3 (1.1) | 1 (0.4) |
| Causally related to chemotherapy | 4 (1.4) | NA |
| Causally related to carboplatin/cisplatin | 2 (0.7) | NA |
| Causally related to pemetrexed | 3 (1.1) | NA |
| **Any SAE (including events with outcome of death)** | **104 (37.7)** | **53 (19.3)** |
| Causally related to treatment[‡] | 52 (18.8) | 15 (5.5) |
| Causally related to osimertinib | 36 (13.0) | 15 (5.5) |
| Causally related to chemotherapy | 48 (17.4) | NA |
| Causally related to carboplatin/cisplatin | 36 (13.0) | NA |
| Causally related to pemetrexed | 46 (16.7) | NA |
| **Any AE leading to discontinuation of any study drug** | **132 (47.8)** | **17 (6.2)** |
| Leading to osimertinib discontinuation | 30 (10.9) | 17 (6.2) |
| Leading to chemotherapy discontinuation | 125 (45.3) | NA |
| Causally related to carboplatin/cisplatin | 46 (16.7) | NA |
| Causally related to pemetrexed | 119 (43.1) | NA |
| **Any AE leading to dose modification of any study drug[§]** | **198 (71.7)** | **56 (20.4)** |
| Leading to osimertinib discontinuation | 131 (47.5) | 56 (20.4) |
| Leading to chemotherapy discontinuation | 157 (56.9) | NA |
| Causally related to carboplatin/cisplatin | 94 (34.1) | NA |
| Causally related to pemetrexed | 151 (54.7) | NA |
| **Any AE leading to dose reduction of any study drug** | **91 (33.0)** | **8 (2.9)** |
| Leading to osimertinib dose reduction | 27 (9.8) | 8 (2.9) |
| Leading to chemotherapy discontinuation | 75 (27.2) | NA |
| Causally related to carboplatin/cisplatin | 49 (17.8) | NA |
| Causally related to pemetrexed | 64 (23.2) | NA |



| AE category | Number (%) of patients† | |
|---|---|---|
| | Osi + chemo (N=276) | Osimertinib (N=275) |
| **Any AE leading to dose interruption of any study drug¶** | **175 (63.4)** | **52 (18.9)** |
| Leading to osimertinib dose interruption | 120 (43.5) | 52 (18.9) |
| Leading to chemotherapy dose interruption | 121 (43.8) | NA |
| Causally related to carboplatin/cisplatin | 50 (18.1) | NA |
| Causally related to pemetrexed | 117 (42.4) | NA |

† Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories; ‡ As assessed by the investigator. Causally related to any study drug; § Dose interruptions also include chemotherapy delays; ¶ It is noted that data for these patients were entered into the clinical database error; these patients did not receive any chemotherapy (carboplatin/cisplatin or pemetrexed) treatment, and therefore relatedness to these drugs is not applicable. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of treatment but prior to the start of a new anti-cancer therapy.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Osi + chemo, osimertinib plus chemotherapy; NA, not applicable.
MedDRA version 25.1
DCO: 03 April 2023
Source: CSR.[8]

### *B.2.10.1.3 Most common AEs by preferred term*

The most common AEs occurring in the osimertinib plus chemotherapy arm were anaemia (46.4% of patients), diarrhoea (43.5% of patients), and nausea (43.1% of patients) (Table 31). The most common AEs in the osimertinib monotherapy arm were diarrhoea (40.7% of patients), paronychia (26.5% of patients), and dry skin (24.0% of patients) (Table 31). Overall, AEs reported with a higher incidence (>10% difference) in the osimertinib plus chemotherapy arm compared with the osimertinib monotherapy arm were primarily well-characterised chemotherapy related adverse drug reactions including anaemia, nausea, neutropenia, decreased appetite, vomiting, constipation, fatigue, neutrophil count decreased, thrombocytopenia, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, platelet count decreased, and oedema peripheral.

**Table 31: Adverse events by preferred term (reported in >10% of patients in either treatment arm) (randomised period - safety analysis set)**

| MedDRA preferred term | Number (%) of patients | |
|---|---|---|
| | Osi + chemo (N=276) | Osimertinib (N=275) |
| Patients with any AE | 276 (100) | 268 (97.5) |
| Anaemia | 128 (46.4) | 22 (8.0) |
| Diarrhoea | 120 (43.5) | 112 (40.7) |
| Nausea | 119 (43.1) | 28 (10.2) |
| Decreased appetite | 85 (30.8) | 26 (9.5) |
| Constipation | 81 (29.3) | 28 (10.2) |
| Rash | 77 (27.9) | 57 (20.7) |
| Fatigue | 76 (27.5) | 26 (9.5) |
| Vomiting | 73 (26.4) | 17 (6.2) |
| Neutropenia | 68 (24.6) | 9 (3.3) |
| Stomatitis | 68 (24.6) | 50 (18.2) |
| Paronychia | 65 (23.6) | 73 (26.5) |
| Neutrophil count decreased | 62 (22.5) | 16 (5.8) |
| COVID-19 | 57 (20.7) | 39 (14.2) |
| Alanine aminotransferase increased | 56 (20.3) | 21 (7.6) |
| Platelet count decreased | 51 (18.5) | 19 (6.9) |
| Thrombocytopenia | 51 (18.5) | 12 (4.4) |
| Dry skin | 50 (18.1) | 66 (24.0) |
| Aspartate aminotransferase increased | 48 (17.4) | 13 (4.7) |
| Blood creatinine increased | 46 (16.7) | 12 (4.4) |
| White blood cell count decreased | 44 (15.9) | 18 (6.5) |
| Oedema peripheral | 42 (15.2) | 12 (4.4) |
| Dermatitis acneiform | 37 (13.4) | 36 (13.1) |
| Urinary tract infection | 36 (13.0) | 28 (10.2) |
| Leukopenia | 35 (12.7) | 11 (4.0) |
| Insomnia | 34 (12.3) | 18 (6.5) |
| Dizziness | 32 (11.6) | 16 (5.8) |
| Weight decreased | 32 (11.6) | 22 (8.0) |
| Cough | 31 (11.2) | 29 (10.5) |
| Pyrexia | 31 (11.2) | 15 (5.5) |
| Arthralgia | 28 (10.1) | 32 (11.6) |
| Pruritus | 22 (8.0) | 31 (11.3) |

Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of treatment but prior to the start of a new anti-cancer therapy.
MedDRA version 25.1
Abbreviations: AE, adverse event; Osi + chemo, osimertinib plus chemotherapy.
Source: Planchard et al. (2023);[77] CSR.[8]



#### *B.2.10.1.4 Adverse events by causality*

Investigator-assessed causally-related AEs were reported in a higher proportion of patients in the osimertinib plus chemotherapy arm (97.5%) than the osimertinib arm (87.6%). This was mainly due to AEs reported as causally related to pemetrexed (92.8%), with fewer patients reported as having AEs causally related to osimertinib (87.3%) or cisplatin/carboplatin (88.8%) in the osimertinib plus chemotherapy arm (Table 30).

***Osimertinib***

The most frequently reported investigator-assessed AEs that were causally related to osimertinib were diarrhoea (30.8%), paronychia (22.5%), rash (22.5%), stomatitis (20.3%), and dry skin (15.6%) in the osimertinib plus chemotherapy arm and diarrhoea (34.2%), paronychia (25.8%), dry skin (21.5%), rash (17.8%), and stomatitis (17.5%) in the osimertinib monotherapy arm. These AEs have been previously identified as osimertinib adverse drug reactions.

***Carboplatin/cisplatin***

The most frequently reported investigator-assessed, AEs that were causally related to carboplatin/cisplatin were nausea (34.1%), anaemia (31.9%), neutropenia (19.6%), fatigue and decreased appetite (both 18.1%), vomiting (16.7%), platelet count decreased (16.3%), neutrophil count decreased (15.9%), and diarrhoea (15.2%).

***Pemetrexed***

The most frequently reported investigator-assessed AEs that were causally related to pemetrexed were anaemia (38.8%), nausea (31.2%), fatigue (22.1%), neutropenia (21.7%), neutrophil count decreased (21.4%), decreased appetite (19.9%), diarrhoea (19.2%), vomiting (18.5%), platelet count decreased (17.0%), ALT increased and thrombocytopenia (both 16.3%), and white blood cell count decreased (15.6%).

#### *B.2.10.1.5 Adverse events by severity*

Approximately half of patients (49.3%) reported AEs that were maximum CTCAE Grade 3 (severe) in the osimertinib plus chemotherapy arm (Table 32). In the



osimertinib monotherapy arm, most patients reported AEs which were maximum CTCAE Grade 1 and 2 (17.5% and 52.7% of patients, respectively) (Table 32). Few patients reported life-threatening AEs with a maximum severity of CTCAE Grade 4 in both treatment arms (8.0% of patients in the osimertinib plus chemotherapy arm and 1.1% of patients in the osimertinib arm).

**Table 32: Summary of AEs by maximum reported CTCAE grade (randomised period - safety analysis set)**

| Maximum reported CTCAE grade | Number (%) of patients | |
|---|---|---|
| | Osi + chemo (N=276) | Osimertinib (N=275) |
| Total | 276 (100) | 268 (97.5) |
| 1 | 7 (2.5) | 48 (17.5) |
| 2 | 93 (33.7) | 145 (52.7) |
| 3 | 136 (49.3) | 63 (22.9) |
| 4 | 22 (8.0) | 3 (1.1) |
| 5 | 18 (6.5) | 9 (3.3)† |

† One patient died one day after the DCO date of the current analysis; a maximum CTCAE Grade 5 event (AE of organising pneumonia) was reported for this patient, however, at the time of the DCO the outcome was recorded as 'not recovered/not resolved' in the clinical database. This patient is therefore not included in the summary of AEs leading to death.
Includes AE with onset date on or after the date of first dose and up to and including 28 days following discontinuation of treatment but prior to the start of a new anti-cancer therapy.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off; Osi + chemo, osimertinib plus chemotherapy.
MedDRA version 25.1
Source: CSR.[8]

Overall, CTCAE Grade ≥3 AEs were reported by 176 patients (63.8%) in the osimertinib plus chemotherapy arm and 75 patients (27.3%) in the osimertinib monotherapy arm. The most common CTCAE Grade ≥3 AEs reported in the osimertinib plus chemotherapy arm were anaemia (19.9% of patients), neutropenia (13.4% of patients), and neutrophil count decreased (11.2% of patients). These are adverse drug reactions which are to be expected with chemotherapy treatment and reflect the known haematological toxicity profile of the individual chemotherapy components. In the osimertinib monotherapy arm, no individual CTCAE Grade ≥3 AEs were reported by ≥2% of patients (Table 33).

AE onset, frequency and severity were highest during the induction period, and gradually reduced over time. In the osimertinib plus chemotherapy arm, the onset of Grade ≥3 AEs reduced by approximately 50% between 0–3 months (n=135; 49%) and 3–9 months (n=62; 24%).[80]

**Table 33: Summary of CTCAE Grade ≥3 AEs by system organ class and preferred term occurring in ≥2% of patients in either treatment arm (randomised period – safety analysis set)**

| System organ class/MedDRA preferred term | Number (%) of patients | | |
|---|---|---|---|
| | Osi + chemo (N=276) | Osimertinib (N=275) | Total (N=551) |
| Patients with any AE | 176 (63.8) | 75 (27.3) | 251 (45.6) |
| Anaemia | 55 (19.9) | 1 (0.4) | 56 (10.2) |
| Neutropenia | 37 (13.4) | 2 (0.7) | 39 (7.1) |
| Thrombocytopenia | 19 (6.9) | 3 (1.1) | 22 (4.0) |
| Febrile neutropenia | 11 (4.0) | 0 (0.0) | 11 (2.0) |
| Leukopenia | 8 (2.9) | 0 (0.0) | 8 (1.5) |
| Neutrophil count decreased | 31 (11.2) | 2 (0.7) | 33 (6.0) |
| Platelet count decreased | 21 (7.6) | 0 (0.0) | 21 (3.8) |
| White blood cell count decreased | 9 (3.3) | 1 (0.4) | 10 (1.8) |
| Ejection fraction decreased | 8 (2.9) | 3 (1.1) | 11 (2.0) |
| Pneumonia | 6 (2.2) | 5 (1.8) | 11 (2.0) |
| Diarrhoea | 8 (2.9) | 1 (0.4) | 9 (1.6) |
| Pulmonary embolism | 6 (2.2) | 3 (1.1) | 9 (1.6) |
| Decreased appetite | 8 (2.9) | 2 (0.7) | 10 (1.8) |
| Fatigue | 8 (2.9) | 1 (0.4) | 9 (1.6) |

Includes adverse events with onset date on or after the date of first dose and up to and including 28 days following discontinuation of treatment but prior to the start of a new anti-cancer therapy.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Osi + chemo, osimertinib plus chemotherapy.
MedDRA version 25.1
Source: CSR.[8]

### B.2.10.2 Additional studies

An additional Phase 2 study which assessed the efficacy and safety of osimertinib and pemetrexed with either cisplatin or carboplatin provides additional supporting data on AE associated with osimertinib plus chemotherapy. Details of this study are

provided in Appendix F. This study was not identified in the clinical SLR as it was not a randomised study.

#### B.2.10.3 Safety overview

Osimertinib in combination with pemetrexed and platinum-based chemotherapy demonstrated a manageable safety and tolerability profile in the target patient population. The frequencies, severity and types of AEs reported were reflective of the known toxicities and established safety profiles of osimertinib, cisplatin/carboplatin and pemetrexed. The higher frequency of AEs reported in the osimertinib plus chemotherapy arm were due to expected chemotherapy-associated adverse drug reactions, with no evidence of synergistic toxicity when osimertinib is given in combination with chemotherapy. Rates of osimertinib discontinuation were low in both treatment arm (10.9% in the osimertinib plus chemotherapy arm versus 6.2% in the osimertinib monotherapy arm) demonstrating that osimertinib treatment was well tolerated when given concurrently with chemotherapy.

### *B.2.11 Ongoing studies*

FLAURA2 is currently ongoing. The final OS analysis will be conducted when the data are approximately 60% mature (currently anticipated to be [redacted]).

### *B.2.12 Interpretation of clinical effectiveness and safety evidence*

#### B.2.12.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

**Summary of clinical trial evidence**

The efficacy and safety of osimertinib plus chemotherapy has been demonstrated by FLAURA2, an ongoing, global, Phase 3, open-label, randomised study to assess the efficacy and safety of osimertinib with or without pemetrexed and platinum-based chemotherapy as first-line treatment in patients with EGFRm (Ex19del and/or L858R) locally advanced/metastatic NSCLC, who have not received any prior treatment for advanced disease.

FLAURA2 met its primary objective, demonstrating a statistically significant and clinically meaningful 38% reduction in the risk of disease progression or death with osimertinib plus chemotherapy compared with osimertinib monotherapy (HR: 0.62 [95% CI: 0.49, 0.79]; p<0.0001). Analysis of PFS by BICR was consistent with the investigator-based analysis, with a 9.5-month improvement in median PFS observed in the osimertinib plus chemotherapy arm compared with the osimertinib arm (median PFS: 29.4 months vs 19.9 months, respectively). The PFS benefit of osimertinib plus chemotherapy compared with osimertinib monotherapy was consistently observed across all prespecified subgroup analyses, including ethnicity, CNS metastases status at study entry, and EGFR mutation type. Particularly, for patients with CNS metastases at baseline, osimertinib plus chemotherapy increased median PFS compared with osimertinib monotherapy (24.9 months vs 13.8 months, respectively; HR: 0.47). CNS PFS was also increased in patients with non-measurable CNS lesions at baseline (27.6 months versus 21.0 months, respectively). In an analysis of a subset of patients who had baseline detected plasma EGFRm, osimertinib plus chemotherapy (n=147 patients) also increased median PFS compared with osimertinib monotherapy (n=161 patients; 24.8 months [95% CI: 19.6, 27.9] versus 13.9 months [95% CI: 13.6, 16.6]; HR: 0.60 [95% CI 0.45, 0.80].[81] For details of the CNS PFS results, please see Appendix M.

Secondary outcomes including OS, ORR and DoR also favoured osimertinib plus chemotherapy. A second interim analysis was conducted at a DCO of 08 January 2024. This analysis was an ad-hoc analysis provided as part of US FDA-specific regulatory procedures solely consisting of the OS outcome. At the second interim OS analysis the data were immature (41%), however there was a trend towards improved OS with osimertinib plus chemotherapy compared with osimertinib monotherapy (HR: 0.75 [95% CI 0.57, 0.97]). High response rates (>75%) were observed in both treatment arms, and a clinically meaningful 8.7-month improvement in median DoR was also observed in the osimertinib plus chemotherapy arm compared with the osimertinib arm.

PRO data showed a non-clinically meaningful improvement in global health status/QoL and physical functioning in both treatment arms.

The safety profile of osimertinib in combination with pemetrexed and platinum-based chemotherapy was reflective of the known toxicities and established safety profiles of osimertinib, cisplatin/carboplatin and pemetrexed. The higher frequency of AEs reported in the osimertinib plus chemotherapy arm was due to expected chemotherapy-associated adverse drug reactions, with no evidence of synergistic toxicity when osimertinib is given in combination with chemotherapy. Rates of osimertinib discontinuation were low in both treatment arms (10.9% vs 6.2% in the osimertinib plus chemotherapy and osimertinib monotherapy arms, respectively) demonstrating that osimertinib treatment was well tolerated when given concurrently with chemotherapy.

**Discussion on clinical evidence**

Approximately 15% of NSCLCs harbour EGFRm[15] which are associated with more aggressive disease progression and a higher rate of brain metastases than tumours with wild type EGFR.[17, 18] Osimertinib monotherapy provided a step-change extension in PFS and OS compared with the first-generation EGFR TKIs erlotinib and gefitinib with significant improvement in median PFS (18.9 vs 10.2 months; $p<0.001$)[23] and significantly longer median OS (38.6 versus 31.8 months; $p=0.0446$) demonstrated in the FLAURA trial.[24] Despite the clinical benefits observed with osimertinib monotherapy, however, patients eventually experience disease progression due to development of treatment resistance.[16] Additional regimens are required to maximise clinical outcomes for patients in the first-line locally advanced/metastatic EGFRm NSCLC treatment setting, delaying progression for as long as possible and ensuring that patients receive the best first-line treatment option.

Combinations of EGFR TKIs with chemotherapy are hypothesised to have complementary mechanisms of action to delay resistance by enhancing destruction of different cell populations within NSCLC tumours, resulting in a potentially stronger antitumour effect than the separate monotherapies alone.[82] Osimertinib plus chemotherapy treatment has demonstrated a statistically significant and clinically meaningful 38% reduction in the risk of disease progression or death compared with

osimertinib monotherapy, with a consistent benefit reported across all pre-specified subgroups, including among patients with higher unmet need such as those with CNS metastases and those with EGFR L858R mutations.[8, 77] The clinically significant efficacy benefit observed with osimertinib plus chemotherapy compared with osimertinib monotherapy was achieved without a clinically meaningful deterioration in HRQoL. Furthermore, at the second interim OS analysis, there was a positive trend towards improved OS for patients in the osimertinib plus chemotherapy arm compared with those in the osimertinib monotherapy arm. When interpreting the comparable OS benefit observed for osimertinib plus chemotherapy vs osimertinib monotherapy, consideration should be given to the OS benefit provided by osimertinib monotherapy, which provides a high baseline for comparison.[8, 24, 77]

The clinically meaningful benefit of osimertinib plus chemotherapy observed in the analysis of PFS was also supported by data from the secondary RECIST-based efficacy endpoints of ORR, DoR, DCR, and depth of response. Furthermore, although data were immature at the time of this analysis, the post-progression endpoints of TFST, PFS2 and TSST suggest a positive trend for the long-term treatment benefit of osimertinib plus chemotherapy beyond first progression (see Appendix M for these results).[77] These data emphasise the clinically meaningful efficacy gain achieved with FLAURA2 against the current SoC osimertinib monotherapy.

Patients with EGFRm have a higher rate of brain metastases than patients with wild-type EGFR (70% vs 38%).[18] CNS metastases can have a substantial impact on symptom burden and QoL[35] and are associated with poor median survival.[40] Osimertinib is able to cross the blood-brain barrier, and therefore target CNS metastases.[25, 26] In the pre-defined central nervous system full analysis set (cFAS), a clinically meaningful reduction (42%) in the risk of CNS disease progression or death was observed in the osimertinib plus chemotherapy arm compared with the osimertinib monotherapy arm (HR: 0.58; 95% CI: 0.33, 1.01) for patients with CNS metastases at baseline (see Appendix M). These data indicate that combining osimertinib and chemotherapy in the first-line treatment setting provides a highly clinically meaningful enhancement in CNS benefit vs osimertinib alone in patients

with CNS metastases. It has been suggested that the presence of CNS metastases may disrupt the blood-brain barrier, thus facilitating the penetration of chemotherapy and contributing to the synergistic effect observed with osimertinib plus pemetrexed and platinum-based chemotherapy on CNS progression.[76]

Although worsening in some PRO functioning and symptom subscales were noted during the period in which platinum-based chemotherapy was administered, the addition of chemotherapy to osimertinib was shown to have a tolerable and manageable safety profile. The frequency and severity of AEs reported were in line with those expected based on the established safety profiles of osimertinib, cisplatin/carboplatin and pemetrexed, with no evidence of synergistic toxicity between osimertinib and chemotherapy agents. The study allowed for dose modifications or discontinuation measures to manage anticipated chemotherapy-induced toxicities. The actual median exposure to osimertinib was similar to the total median exposure in both treatment arms, indicating that any dose modifications had a minimal impact on osimertinib exposure.

Osimertinib plus chemotherapy significantly improves PFS with a trend towards improved OS and no detrimental impact on HRQoL compared with the current standard of care, osimertinib monotherapy, in patients with untreated locally advanced/metastatic EGFRm NSCLC. Clinical benefits were also observed in high-risk populations such as patients with CNS metastases and L858R mutations. Osimertinib plus chemotherapy therefore provides an opportunity to build on the efficacy of the current SoC, with a more intensified treatment regimen that can maximise long-term outcomes for suitable patients.

#### B.2.12.2 Strengths and limitations of the clinical evidence base for the technology

***Internal validity***

FLAURA2 is a large, multinational, well controlled and well conducted study. FLAURA2 employed an open-label, sponsor-blind, randomised design to minimise risk of bias. To avoid placing an undue burden on patients, investigators and patients

were not blinded to study treatment. As pemetrexed administration was administered by IV infusion, an open-label trial was deemed appropriate to avoid the need for an IV chemotherapy placebo, which would not be feasible due to the potential impact on QoL measures. The sponsor was blinded to treatment assignment and did not have access to any aggregate summaries by treatment arm during the study.

Study population and disease characteristics were well balanced across treatment arms. As expected, based on the target patient population, 96.2% of patients were randomised with metastatic disease at baseline, which was predominately balanced by location between treatment arms.

To minimise any risk of delay in starting treatment, and to reflect the current global clinical practice, study inclusion criteria allowed for enrolment, randomisation, and stratification based on EGFR mutation type identified by either local accredited laboratory or central testing. The use of the companion diagnostic test showed a high concordance (93.1%) between local and confirmatory central test results, indicating that this population is readily identifiable in clinical practice.

As the FLAURA2 study was open label in design, there was the potential for investigator assessment bias based on awareness of treatment regimen assignment and the progress of treatment. To address this potential bias, a sensitivity analysis for ascertainment bias was conducted by BICR assessment. Analysis of discrepancy rates between investigator and BICR assessment demonstrated a high level of concordance between the assessment methods (see Section B.2.6.1.1.2). Sensitivity analyses of PFS for evaluation-time bias, attrition bias, randomisation bias (using stratification factors) and the impact of COVID-19 indicated no evidence of bias; a consistent improvement in PFS was observed in the osimertinib plus chemotherapy arm compared with the osimertinib arm in all sensitivity analyses (data not shown). These data were consistent with the primary PFS analysis and demonstrate the robustness of the evaluation.

***External validity***



FLAURA2 reflects the proposed indication and anticipated use of osimertinib plus chemotherapy in clinical practice in England. The trial dosing for osimertinib in FLAURA2 matches the licensed indication (see Section B.1.1) and its use in UK clinical practice.

Osimertinib monotherapy is the first-line treatment of choice for patients with locally advanced/metastatic NSCLC whose tumours have EGFR Ex19del or L858R substitution mutations based on ESMO clinical guidelines and feedback from UK clinical experts[2, 3] and is therefore the relevant comparator for this submission.

The baseline characteristics of patients in FLAURA2 were consistent with the expected characteristics of patients with locally advanced/metastatic EGFRm NSCLC in England according to feedback received by 9 UK clinicians in an advisory board meeting.[2]

PFS was considered the most appropriate endpoint for FLAURA2, as a well-established clinical outcome, relevant to the oncology setting. Progression was defined according to RECIST 1.1, which is the well-recognised international standard for measurement of tumour burden.[83] In conjunction with OS, which typically requires a long follow-up period in order to collect mature data, PFS can measure outcomes in studies with shorter follow-ups and is not affected by crossover or confounding later lines of therapy; it therefore represents a direct effect of osimertinib plus chemotherapy. In addition, PFS is a patient-relevant endpoint and can act as a surrogate for OS in cases where access to treatments is urgent, such as the metastatic setting where patients have limited prognosis and are thus in need of rapid access to more effective treatments. Regulatory agencies allow PFS to be used as a primary endpoint to evaluate drug efficacy in metastatic cancers; the European Medicines Agency (EMA) allows PFS to be selected as the primary endpoint for cancers, normally requiring OS to be reported as a secondary endpoint.[83] However, in situations where there is a substantial treatment effect on PFS, or where there is an expected long period of survival after progression, precise estimate of OS may not be required for EMA approval.[83] For example, the FLAURA trial supported the regulatory approval and subsequent reimbursement of osimertinib

monotherapy in NSCLC and the establishment of this treatment regimen as SoC across many markets with PFS as a primary endpoint, supported by OS as a secondary endpoint. At the second interim OS analysis in FLAURA2, data remained immature (41%); although there was a favourable trend towards improved OS with osimertinib plus chemotherapy versus osimertinib monotherapy, the full survival benefit of osimertinib plus chemotherapy is yet to be established. The post-progression endpoints of TFST, PFS2 and TSST suggest a positive trend for the long-term treatment benefit of osimertinib plus chemotherapy beyond first progression[77] (see Appendix M).



## B.3 Cost effectiveness

***Overview***

- **A 3-state partitioned survival model (PSM) was developed to assess the cost effectiveness of osimertinib plus chemotherapy in the first-line treatment of patients with locally advanced (stage IIIB–IIIC) or metastatic (stage IV) EGFRm NSCLC**
- **Health states included progression-free, progressed disease and death**
- **The analysis was consistent with the NICE reference case and took an NHS and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% and evaluated over a 20-year time horizon**
- **Baseline characteristics and clinical efficacy (OS and PFS) were sourced from the FLAURA2 Phase 3 clinical trial for both the osimertinib plus chemotherapy, and osimertinib monotherapy arms**
- **EQ-5D-5L data were collected in FLAURA2 and were mapped to the EQ-5D-3L scale. These data were used in the model base case for the osimertinib plus chemotherapy, and osimertinib monotherapy arms for the progression-free health state. Sourced from the literature, the utility value from Labbe et al 2017 was used as the base case value for the progressed health state**
- **In the deterministic base case economic analysis, treatment with osimertinib plus chemotherapy compared with osimertinib monotherapy was associated with an increase in life years ([redacted] years), increased quality-adjusted life years (QALYs; [redacted] per patient), and an incremental cost of [redacted] per patient**
- **As a result, osimertinib plus chemotherapy was considered cost effective against osimertinib monotherapy at a threshold of £30,000 per QALY, with incremental cost-effectiveness ratios (ICERs) of £27,280.04 per QALY gained**



- **In probabilistic sensitivity analysis (PSA), it was shown that at a willingness-to-pay threshold (WTP) of £30,000 per QALY, osimertinib plus chemotherapy is associated with a 52% probability of being cost effective**
- **Key drivers of the model identified by the deterministic sensitivity analysis (DSA) were the parameters related to the progression-free health state utility, the proportion of patients that receive ABCP as a second-line therapy in both arms, and the administration cost associated with pemetrexed. In all deterministic sensitivity analyses, the ICER remained below a WTP threshold of £30,000 per QALY**
- **The scenario analyses also demonstrated that osimertinib plus chemotherapy was cost-effective in the majority of scenarios at a WTP threshold of £30,000 per QALY**
- **In summary, the cost-effectiveness analysis (CEA) indicates that osimertinib plus chemotherapy is cost-effective versus osimertinib monotherapy at the NICE WTP threshold of £30,000 per QALY**

### *B.3.1 Published cost-effectiveness studies*

A global SLR was conducted in May 2023 and updated in May 2024 to identify available economic evaluations, appraise cost-effectiveness evaluations, and examine cost and resource use in patients with unresectable locally advanced/metastatic EGFRm NSCLC. The SLR was conducted as per guidance from the Cochrane Handbook for Systematic Reviews of Interventions,[84] Centre for Reviews and Dissemination (CRD)'s Guidance for Undertaking Reviews in Healthcare,[85] and Methods for the Development of NICE Public Health Guidance. Full details of the SLR search strategy, study selection process, and results are presented in Appendix G.

A total of 44 relevant publications were identified for inclusion in the economic evaluation SLR (42 identified in the original SLR and 2 in the update). None of the studies identified were purely from a UK perspective. In addition to the peer-



reviewed literature, a further 13 HTA submission were identified, three of which reported CEAs conducted from a UK healthcare system perspective and were therefore considered to be relevant to clinical practice in England (Table 34).

### *B.3.2 Economic analysis*

None of the CEAs identified in the economic SLR included osimertinib plus chemotherapy (i.e., pemetrexed plus cisplatin/carboplatin) as a comparator. It was therefore necessary to develop a *de novo* economic model for this submission. Previous NICE TAs of treatments for patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations (TA654, TA595 and TA411),[59, 86, 87] along with published CEAs identified in the economic SLR, were used to inform the model structure, assumptions, and data sources.

The objective of the economic evaluation was to assess the cost effectiveness of osimertinib plus chemotherapy for the treatment of patients with EGFR mutation-positive locally advanced (stage IIIB–IIIC) or metastatic (stage IV) NSCLC versus osimertinib monotherapy.

The CEA was conducted considering an NHS and PSS perspective over a 20-year time horizon, by which point <1% of modelled patients were alive. The CEA is based on data from the FLAURA2 Phase 3 clinical trial (see Section B.2.3), and information obtained from previous NICE technology appraisals and published literature. The model is described in greater detail in the following sections.



**Table 34: Summary list of published cost-effectiveness studies**

| Study, country, design | Population | Interventions | Model summary | Model inputs | Base case results | Conclusions and reported study limitations |
|---|---|---|---|---|---|---|
| NICE, 2020[88]<br><br>TA654<br><br>UK<br><br>CUA | Untreated locally advanced or metastatic EGFRm NSCLC in adults | Osimertinib | • Model type: PSM<br>• Time horizon: 20 years<br>• Perspective: payer<br>• Cycle length: NR<br>• Discount costs: 3.5%<br>• Discount effects: 3.5%<br>• Health states: PF, PD, death | • Utility values<br>– PFS: 0.794<br>– PD: 0.678<br>• Utility source: FLAURA<br>• Cost source: BNF, CMU, NHS reference costs, unit costs of Health and Social Care | • Mean total costs: NR<br>• Mean total QALY: NR<br>• ICER:NR | • Osimertinib is recommended for untreated locally advanced or metastatic EGFR mutation-positive NSCLC in adults<br>• Limitations:<br>– Modelling the duration of treatment effect with a PSM |
| NICE, 2019[86]<br><br>TA595<br><br>UK<br><br>CUA | Untreated locally advanced or metastatic EGFRm NSCLC in adults | Dacomitinib | • Model type: PSM<br>• Time horizon: 15 years<br>• Perspective: payer<br>• Cycle length: 28 days<br>• Discount costs: 3.5%<br>• Discount effects: 3.5%<br>• Health states: pre-progressed, post-progression, death | • Costs<br>Dacomitinib list price: £2,703<br>• Utility values:<br>– PD: 0.64 (ERG utility: 0.678)<br>• AE disutilies: not included in model<br>• ERG AE disutilies<br>– Diarrhoea: -0.15<br>– Fatigue: -0.18<br>– ALT increased: 0 | • Mean total costs: NR<br>• Mean total QALY: NR<br>• ICER: <£30,000/QALY | • Dacomitinib is recommended as an option for untreated locally advanced or metastatic EGFR mutation-positive NSCLC in adults.<br>• Limitations:<br>– The ERG thought it was more appropriate to use utility values from ARCHER 1050 for PD, due to data limitations from Labbe. Following discussions, a utility value of 0.678 was used |

| Study, country, design | Population | Interventions | Model summary | Model inputs | Base case results | Conclusions and reported study limitations |
|---|---|---|---|---|---|---|
| | | | | – Paronychia: -0.20<br>– Rash: -0.20<br>• Utility source: Labbe et al. (2017)[89] TA653[60] | | as there were also limitations to ARCHER 1050. |
| NICE, 2016[87]<br><br>TA411<br><br>UK<br><br>CUA | Locally advanced or metastatic EGFR-expressing squamous NSCLC in adults who have not had chemotherapy | Necitumumab | • Model type: State-transition model<br>• Time horizon: Lifetime<br>• Perspective: payer<br>• Cycle length: 3-weeks<br>• Discount costs: 3.5%<br>• Discount effects: 3.5%<br>• Health states: pre-progressed, post-progression, death | • Utility values: NR<br>• Utility source: SQUIRE<br>• Cost inputs:<br>– EGFR-expression test: £42 per test<br>– Cost source: NR | • Mean total costs: NR<br>• Mean total QALY: NR<br>• Company ICER: £57,725/QALY<br>• ERG ICER: £169,612/QALY<br>• Most plausible ICER: £110,000-170,000/QALY | • Necitumumab was not recommended<br>• Limitations:<br>– The populations were relatively small post-hoc subgroups with high risk of bias.<br>– There is limited clinical justification for why the effectiveness of necitumumab bay differ between regions |

Abbreviations: AE, adverse event; BNF, British National Formulary; CMU, Commercial Medicines Unit; CUA, cost utility analysis; EGFR, epidermal growth factor receptor; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; NR, not reported; NSCLC, non-small cell lung cancer; PD, progressed disease; PF, progression free; PFS, progression free survival; PSM, partitioned survival model; QALYs, quality-adjusted life years.

### B.3.2.1 Patient population

The economic model considers patients with previously untreated locally advanced/metastatic EGFRm (Ex19del or L858R mutations) NSCLC. This is consistent with the population in the anticipated licensed indication (see Appendix C), the population outlined in the decision problem (see Table 1) and the FAS of the FLAURA2 trial.[8, 77] The baseline characteristics of the FLAURA2 population are summarised in Section B.2.3.4, Table 8. Median patient age was 61 years, 61% of patients were female and mean BMI was 24.38 kg/m$^2$. Overall, baseline characteristics were well balanced between the treatment groups.

### B.3.2.2 Model structure

A *de novo* PSM was developed in Microsoft® Excel, using Visual Basic for Applications (VBA) functionality to compare the cost effectiveness of osimertinib plus chemotherapy with osimertinib monotherapy. This model structure was deemed the most appropriate based on the clinical data available and the widely accepted suitability of the approach used in oncology (NICE DSU TSD19).[90]

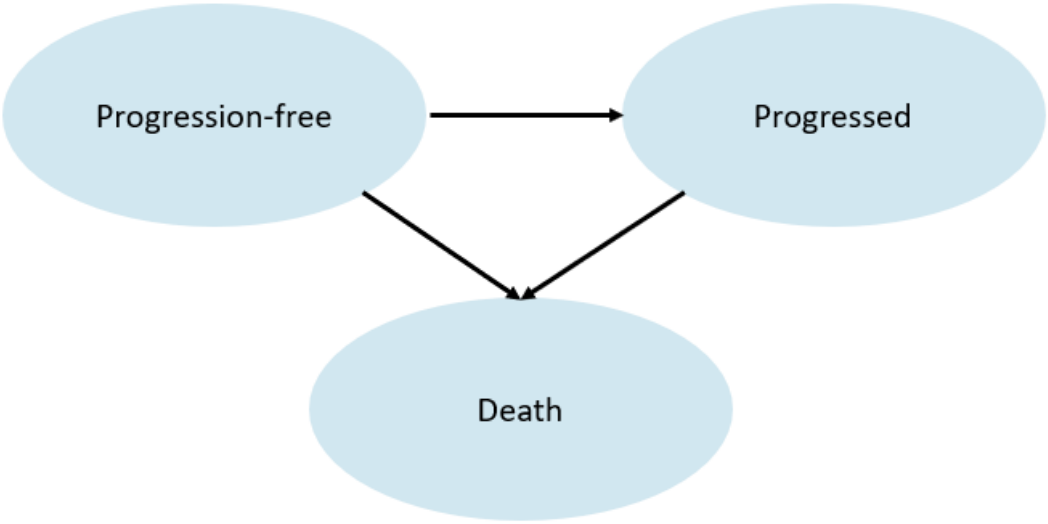
The structure of the model is similar to that used in numerous prior economic evaluations of treatments for metastatic NSCLC, including TA595[86] and TA654.[59]

The model consists of the following mutually exclusive health states (Figure 14): progression-free, progressed disease, and death.



**Figure 14: Three-state model schematic**

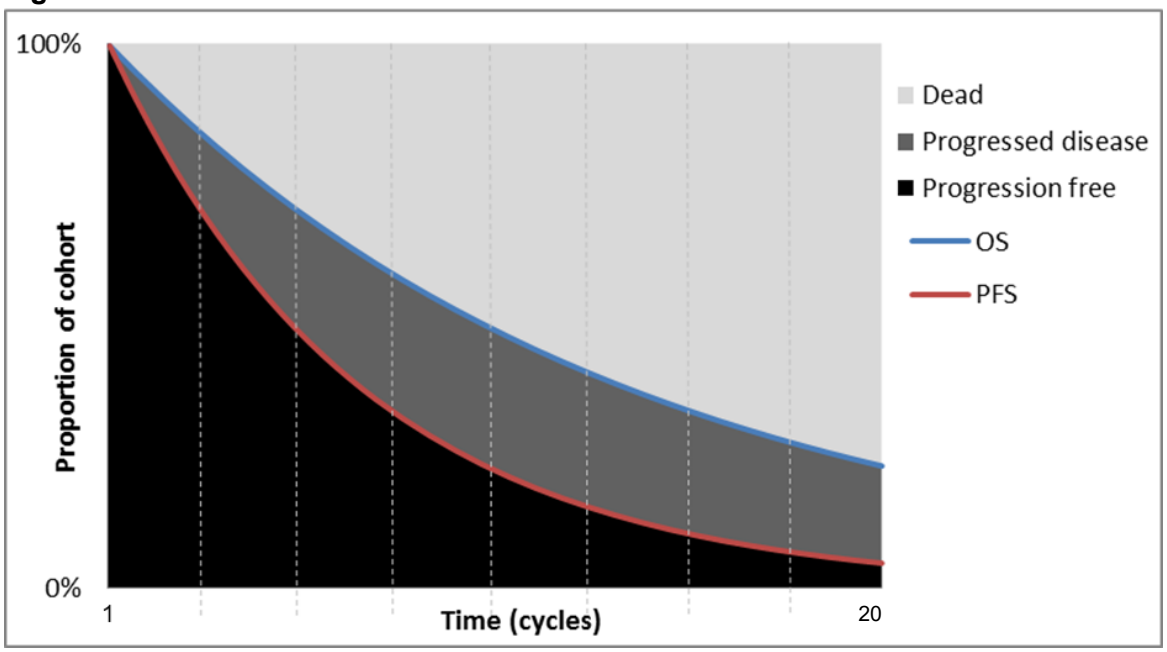



State membership is determined from a set of non-mutually exclusive survival curves. The cohort enters the model in the progression-free health state and any transitions to progressed disease and death are defined by the PFS and OS curves. The proportion of the cohort remaining in the progression-free health state over time is derived directly from the PFS curve. State membership for the death state is calculated as 1 minus the OS curve, and state membership for the progressed-disease health state is derived from the difference between the OS and the PFS curve (the proportion of patients who are alive and have progressed). This is illustrated in Figure 15.



**Figure 15: Model schematic**




This schematic is for illustrative purposes only and does not represent the FLAURA2 data.
Abbreviations: OS, overall survival; PFS, progression-free survival.

The partitioned survival approach allows for direct modelling of PFS and OS (primary and secondary endpoints in FLAURA2, respectively) based on trial-observed events, generally providing accurate predictions for the within-trial period. However, a limitation of this model structure is that survival functions for OS and PFS are modelled independently, and therefore the dependency between the endpoints beyond the trial period is ignored.

Life years are estimated by summing the proportion of patients in non-death health states in each model cycle. Utility weights are applied to each health state, with quality-adjusted life years (QALYs) estimated by multiplying the proportion of patients in the state by the corresponding utility value. Costs are assigned to each health state and multiplied by the proportion of patients occupying the state to estimate the total health state costs. The costs and health benefits (life years and QALYs) are summed across the 20-year time horizon to estimate the total costs and health benefits per treatment arm.

### B.3.2.3 Features of the economic analysis

An overview of the features of the economic analysis and a comparison with previous NICE evaluations in NSCLC is presented in Table 35, which outlines model parameters and sources that were considered when performing the analysis for osimertinib plus chemotherapy.

Patients transition in the model using model cycle lengths of 30 days, which was considered sufficiently granular to capture any meaningful changes in cost and health outcomes and also reflect the osimertinib treatment cycle length. The model time horizon was 20 years, which was considered a 'lifetime' (extrapolation of the OS data indicates that <1% of patients will be alive by year 20) and is consistent with previous appraisals (Table 35). An alternative time horizon 10 years was explored in scenario analyses. Half-cycle correction was also applied to account for mid-cycle progressions (Table 35).

In line with the NICE reference case, benefits and costs were accrued in each cycle and were discounted annually at a rate of 3.5% for both benefits and costs. A scenario analyses utilising a 1.5% discount rate was explored in a scenario analysis.



**Table 35: Features of the economic analysis**

| | Previous evaluations | | | Current evaluation | |
|---|---|---|---|---|---|
| **Factor** | **TA654[59]** | **TA595[86]** | **TA411[87]** | **Chosen values for current appraisal** | **Justification** |
| Time horizon | 20-years | 15-years | Lifetime | 20 years | Less than 1% of patients are alive at the 20-year time point. This denotes that health benefits and cost accrual not captured by the time horizon will be minimal. |
| Cycle length | NR | 28-days | 3-week | 30 days | The cycle length should be sufficiently short enough to capture clinical changes, but long enough to maintain computational efficiency. A 30-day cycle length was determined to achieve this. A 30-day cycle length also reflects the osimertinib pack size. |
| Model structure | PSM | PSM | State-transition model | PSM | This model structure aligns with existing submissions in NSCLC and is commonly used in oncology modelling. |
| Source of utilities | Pivotal efficacy trial (FLAURA) for PFS and 1L PD, Labbé et al. (2017)[89] for subsequent PD or BSC | Pivotal efficacy trial (ARCHER 1050) and Labbé et al. (2017)[89] | Pivotal efficacy trial (SQUIRE) for PFS, Khan et al. (2015) for PD[41] | FLAURA2 and Labbe et al. (2017)[89] | The utility values from FLAURA2 are used to inform the PFS health state. These values were chosen as they are from the clinical trial which contains robust data specifically for EGFR mutation-positive NSCLC patients on treatment. The estimated PD health utility from FLAURA2 was higher than expected, this may have been due to the limited number of measurements for post-progression health utilities, most of which occurred immediately after progression. Labbe et al. (2017)[89], a longitudinal cohort study conducted in Canada, provided utility values for PD based on assessments conducted over multiple occasions, capturing patients' long-term deterioration of HRQoL. Although the study was not conducted in a UK setting, results based on UK conversions were reported and PD value was considered more appropriate than the one reported in FLAURA2. Furthermore, this study was used to inform the PD health state utility in TA654[59] and the PD utility value reported by Labbe et al. was very similar to those used and |

| | Previous evaluations | | | Current evaluation | |
|---|---|---|---|---|---|
| **Factor** | **TA654[59]** | **TA595[86]** | **TA411[87]** | **Chosen values for current appraisal** | **Justification** |
| | | | | | accepted by ERGs in two previous NSCLC NICE submissions; TA402[91] and TA347.[92] |
| Source of costs | BNF, CMU, NHS reference costs, PSSRU | BNF, eMIT, NHS reference costs, PSSRU | NHS reference costs, PSSRU, BNF, eMIT | NHS reference costs, PSSRU, BNF, eMIT | As per NICE reference case. |

Abbreviations: BNF, British National Formulary; CMU, Commercial Medicines Unit; eMIT, drugs and pharmaceutical electronic market information tool; HRQoL, health-related quality of life; NR, not reported; PD, progressed disease; PFS, progression-free survival; PSM, partitioned survival model; PSSRU, Personal Social Services Research Unit.

#### B.3.2.4 Intervention technology and comparators

The economic model allows the costs and efficacy of osimertinib plus chemotherapy (pemetrexed plus carboplatin/cisplatin) to be compared with osimertinib monotherapy.

During an advisory board, UK clinicians unanimously stated they consider osimertinib monotherapy to be the current standard of care for the treatment of patients in the first-line setting;[2] it is estimated that approximately 86% of all eligible patients are currently prescribed osimertinib in the UK.[1] In clinical practice, osimertinib plus chemotherapy is expected to displace osimertinib monotherapy only. Osimertinib plus chemotherapy should be an option for patients who might benefit from more intense combination treatment. Therefore, economic analyses are presented against osimertinib monotherapy.

In the osimertinib plus chemotherapy arm, treatment is structured into two phases: initial treatment and maintenance. During the initial treatment phase, patients receive orally administered osimertinib (80 mg QD) in combination with intravenous (IV) pemetrexed (500 mg/$m^2$) (with vitamin supplementation) plus either cisplatin (75 mg/$m^2$) or carboplatin (AUC5), with cisplatin/carboplatin administered intravenously once every 3 weeks for a maximum duration of 12 weeks. In the maintenance phase, patients continue to receive 80 mg osimertinib QD plus pemetrexed (500 mg/$m^2$) Q3W (see further details in Section B.3.6.1.1).

In the osimertinib monotherapy arm, patients were modelled to receive orally administered osimertinib (80mg OD) only.

The model assumes that patients in both arms were treated until death or another discontinuation criterion was met, in line with the FLAURA2 trial.

### *B.3.3 Clinical trial parameters and variables*

Efficacy data for osimertinib plus chemotherapy, and osimertinib monotherapy were collected from the FLAURA2 Phase 3 clinical trial. The primary data source was from



the FLAURA2 FAS, which comprised a total of 557 patients (osimertinib plus chemotherapy arm: 279 patients; osimertinib arm: 278 patients).[8, 77]

#### B.3.3.1 Methodology of curve selection

To model efficacy, survival analysis was performed on time-to-event outcomes using parametric modelling. Patient level data for OS and PFS were available for the clinical trial duration (median follow-up for PFS was 19.5 months in the osimertinib–chemotherapy group and 16.5 months in the osimertinib group).[77] Extrapolating the data beyond the clinical trial period allowed time-to-event outcomes to be modelled over the 20-year time horizon.

Initially, seven standard parametric models (exponential, gamma, generalised gamma, Gompertz, loglogistic, lognormal, Weibull) were fitted for each treatment group. To identify the best model fit, the following were considered:

- **Assessment of whether the proportional hazards assumption** (PHA) can be considered valid through consideration of the Schoenfeld residuals and log cumulative hazard plots. The PHA was assessed based on the Schoenfeld residuals and can be considered a reasonable assumption if the plot of the Schoenfeld residuals against time does not show a pattern of changing residuals and the p-value for Schoenfeld residuals test is non-significant. The PHA was also assessed through consideration of the log cumulative hazard plots, where the logarithm of time is plotted against the estimated log cumulative hazard. If the curves for the two treatment groups are approximately parallel, the PHA can be deemed reasonable.
- **Consideration of complexity of trial hazards**
- **Akaike information criterion (AIC) and Bayesian information criterion (BIC):** model fits were evaluated using the AIC and BIC statistical criteria. Lower AIC and BIC values demonstrate a better statistical fit of the survival curve.
- **Visual inspection of modelled curves vs KM curves:** Visual inspection was performed by plotting the KM survival curves and comparing them to the

extrapolated parametric modelled curves. The curves that appear to best match the KM curves achieve the best-fit criteria.

- **Clinical validity:** the plausibility of the extrapolated parametric models was assessed using expert opinion.

All survival analyses were conducted in R using the flexsurv package,[93] and models were fitted using the standard parameterisation of flexsurv.

#### B.3.3.2 Overall survival

OS was collected as a secondary endpoint in the FLAURA2 trial. OS was defined in the trial as the time from the date of randomisation until death due to any cause. OS was analysed during the primary analysis of the randomised period, conducted at a DCO date of 03 April 2023 and a second interim analysis conducted at a DCO of 08 January 2024 (an ad-hoc analysis provided as part of US FDA-specific regulatory procedures solely consisting of the OS outcome). A final OS analysis will be conducted when the data are approximately 60% mature.[70]

The OS KM data for osimertinib monotherapy and osimertinib plus chemotherapy is presented in Figure 6. The first step in selecting the choice of parametric survival model for OS was to assess whether the PHA was upheld for the FLAURA2 data. Figure 16 show that the plot of the Schoenfeld residuals against time did not show a pattern of changing residuals and the p-value for Schoenfeld residuals test is non-significant (p=0.405), indicating that the PHA could be considered reasonable. However, the log cumulative hazard curves (Figure 17) were not parallel over time, indicating that the treatment effect varied over the trial period. On this basis it was considered that there was a violation of the PHA.



**Figure 16 Plot of Schoenfeld residuals (OS)**

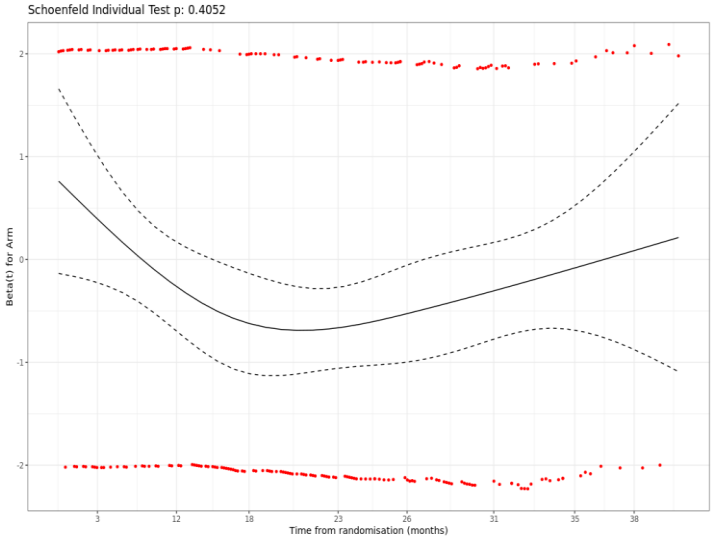
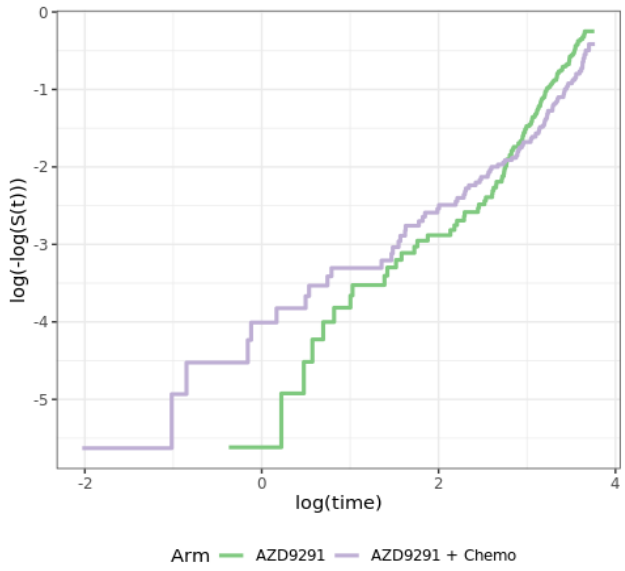



**Figure 17 Log cumulative hazard curves (OS)**




As the PHA was not considered to be a reasonable assumption, parametric models were fitted separately to both arms. In accordance with NICE DSU TSD 14[94] seven standard parametric distributions (exponential, gamma, generalised gamma, log-normal, log-logistic, Weibull, Gompertz) were fitted to the observed OS data from the FLAURA2 clinical trial. Furthermore, as specified in NICE DSU TSD 21,[95] flexible models (such as spline-based models) should also be considered where complex hazard functions exist and cannot be represented well by standard parametric models.



The raw hazard plot showed that the hazards change over the course of the trial, across both arms. A general trend of increasing hazards was observed across both arms; such a trend is consistent with expectations in the advanced NSCLC setting. However, for osimertinib monotherapy, a constant risk for 12 months was observed, followed by a sharp increase in hazards. For the osimertinib plus chemotherapy arm, a potential reduction in hazards was observed over the first 12 months, and the subsequent increase in hazards occurred at a slower rate than the osimertinib monotherapy arm. There was a potential drop in the hazards in both arms after 36 months, although this was likely driven by low patient numbers.

**Figure 18: OS hazard plot (raw): osimertinib monotherapy and osimertinib plus chemotherapy**

Abbreviations: ITT, intent-to-treat; OS, overall survival.

#### *B.3.3.2.1 Standard parametric modelling*

Statistical goodness of fit

The AIC and BIC statistics indicating the within-trial goodness-of-fit of each standard parametric survival model for osimertinib plus chemotherapy and osimertinib monotherapy are provided in 36 and Table 37, respectively. For the osimertinib plus



chemotherapy arm, the Gompertz, the Weibull and the generalised gamma distributions provided the best fits based on the AIC and BIC statistics. However, considering the relatively narrow range of AIC/BIC values, there were multiple models that provided reasonable fits based on the AIC statistic. Most distributions provided a reasonable statistical fit to the trial data, with the exception of loglogistic and lognormal.

For the osimertinib monotherapy arm, the Gompertz, the Weibull and the gamma distribution provided the best fits based on AIC and BIC statistics. However, similarly to the osimertinib plus chemotherapy arm, the majority of models provided reasonable fits according to these statistics, with the exception of generalised gamma, lognormal and exponential.

**Table 36: AIC and BIC for OS standard parametric models for osimertinib plus chemotherapy**

| Spline model | AIC | Statistical rank | BIC | Statistical rank |
|---|---|---|---|---|
| Exponential | 1078.10 | 4 | 1081.80 | 2 |
| Gamma | 1078.40 | 5 | 1085.60 | 5 |
| Generalised gamma | 1074.40 | 2 | 1085.30 | 4 |
| Gompertz | 1069.70 | 1 | 1077.00 | 1 |
| Loglogistic | 1082.80 | 6 | 1090.10 | 6 |
| Lognormal | 1097.30 | 7 | 1104.60 | 7 |
| Weibull | 1077.30 | 3 | 1084.60 | 3 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; OS, overall survival.



**Table 37: AIC and BIC for OS standard parametric model for osimertinib monotherapy**

| Parametric model | AIC | Statistical rank | BIC | Statistical rank |
|---|---|---|---|---|
| Exponential | 1290.80 | 6 | 1294.40 | 6 |
| Gamma | 1267.20 | 3 | 1274.50 | 3 |
| Generalised gamma | 1285.60 | 5 | 1292.90 | 5 |
| Gompertz | 1262.10 | 1 | 1269.40 | 1 |
| Loglogistic | 1268.50 | 4 | 1275.80 | 4 |
| Lognormal | 1285.60 | 5 | 1292.90 | 5 |
| Weibull | 1264.00 | 2 | 1271.20 | 2 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; OS, overall survival.

*Visual inspection of extrapolations vs. observed data*

Figure 19 displays the standard parametric models extrapolated over a 10-year period with the KM overlaid.

For osimertinib plus chemotherapy, only the Weibull, Gompertz and generalised gamma appeared to provide a reasonable visual fit to the KM curve, although all underestimate survival between months 9-16 (Figure 19). Similarly, only Gompertz and generalised gamma captured the observed initial drop in the hazard followed by an increase, but the increase continued sharply beyond the trial period. This resulted in these models providing the most pessimistic survival estimates in the long-term.

For the osimertinib monotherapy arm, the Weibull, Gompertz, and generalised gamma curves appeared to provide a reasonable visual fit to the KM curve (Figure 19). As with the combination arm however, there appeared to be an underestimation of survival at the earlier timepoints in the trial. The loglogistic, log-normal and gamma were able to capture the initial increase followed by the reduction in hazards, although the visual fit of the KM curves to the extrapolations was poor. All other distributions failed to capture the plateauing of hazards in the longer term.



**Figure 19: Kaplan Meier OS curves and extrapolations (standard parametric models): osimertinib monotherapy and osimertinib plus chemotherapy**

Abbreviations: OS, overall survival, osi, osimertinib.

#### *B.3.3.2.2 External validation*

Clinical validation was sought for OS extrapolations. The OS KM data for both arms from FLAURA2 and standard parametric models over a 20-year time period was provided to clinicians and they were asked to comment on the proportion of patients they would expect to be alive at different time points.

In the osimertinib plus chemotherapy arm, clinicians stated that 0% alive at 10 years would be unrealistic. They also stated that 5-10% at 20 years would be plausible. Despite the lack of consensus on curve selection between the standard distributions, two clinicians commented that gamma may be the best option presented, with another commenting Weibull to be the most clinically plausible. Two clinicians viewed the Gompertz as most plausible at early timepoints but that the tail did not align with survival expectations in a UK patient population.



For osimertinib monotherapy, at 5-years, clinicians said they would expect up to 40% of patients to be alive. At 10-years, clinicians commented that 0% alive is too pessimistic, and that this is expected to be around 10%. Despite the lack of consensus on curve selection between the standard distributions presented, one clinician commented that Weibull may be the best option, whilst two clinicians commented that gamma might be the best option.

Clinicians stated that standard distributions did not predict survival in line with their expectations, particularly at later timepoints (i.e., at 5-years, 10-years). There was no consistent view of the best-fitting distribution; however, many distributions were identified as either too optimistic or pessimistic versus survival expectations for the UK.

Flexible parametric models were therefore considered in addition to the standard parametric models to reflect the more complex observed hazard functions (NICE DSU TSD 21).[95] A frequently utilised flexible parametric method in NICE appraisals, and recommended in DSU TSD 21, is the Royston-Parmer spline-based approach, which was investigated further utilising the FLAURA2 data. Royston-Parmer spline models were fit to the data with up to 3 knots. Spline knot locations were chosen as equally spaced quantiles of the uncensored survival times, for example, at the median with one knot or at the 33.3% and 66.7% quantiles for two knots. Boundary knots were chosen as the minimum and maximum event times.

#### *B.3.3.2.3 Spline-based models*

Statistical goodness of fit

The AIC and BIC statistics indicating the within-trial goodness-of-fit of each spline-based model for osimertinib plus chemotherapy and osimertinib monotherapy are provided in Table 38 and Table 39, respectively. For the osimertinib plus chemotherapy arm, the 2-knot spline (normal scale) provided the best fit based on the AIC and BIC statistics. Most distributions provided a reasonable statistical fit to the trial data, with the exception of the 3-knot splines models.

For the osimertinib monotherapy arm, the 1-knot spline (odds scale) provided the best fit based on AIC and BIC statistics. Consistent with the osimertinib plus chemotherapy arm, the 3-knot spline models provided poor fits to the trial data according to AIC and BIC statistics.

**Table 38: AIC and BIC for OS spline-based models for osimertinib plus chemotherapy**

| Spline model | AIC | Statistical rank | BIC | Statistical rank |
|---|---|---|---|---|
| Spline 1 knot: scale = hazard | 1072.80 | 7 | 1083.70 | 3 |
| Spline 2 knots: scale = hazard | 1068.50 | 2 | 1083.10 | 2 |
| Spline 3 knots: scale = hazard | 1070.40 | 4 | 1088.60 | 5 |
| Spline 1 knot: scale = odds | 1075.50 | 8 | 1086.40 | 4 |
| Spline 2 knots: scale = odds | 1068.60 | 3 | 1083.10 | 2 |
| Spline 3 knots: scale = odds | 1070.70 | 6 | 1088.80 | 6 |
| Spline 2 knots: scale = normal | 1068.30 | 1 | 1082.80 | 1 |
| Spline 3 knots: scale = normal | 1070.60 | 5 | 1088.80 | 6 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; OS, overall survival.
Please note, a 1 knot spline normal model was not available as the model did not converge.



**Table 39: AIC and BIC for OS spline-based models for osimertinib monotherapy**

| Parametric model | AIC | Statistical rank | BIC | Statistical rank |
|---|---|---|---|---|
| Spline 1 knot: scale = hazard | 1262.20 | 2 | 1273.10 | 2 |
| Spline 2 knots: scale = hazard | 1263.50 | 3 | 1278.00 | 3 |
| Spline 3 knots: scale = hazard | 1264.90 | 5 | 1283.00 | 6 |
| Spline 1 knot: scale = odds | 1262.00 | 1 | 1272.90 | 1 |
| Spline 2 knots: scale = odds | 1264.0 | 4 | 1278.50 | 4 |
| Spline 3 knots: scale = odds | 1265.20 | 6 | 1283.30 | 7 |
| Spline 2 knots: scale = normal | 1265.60 | 7 | 1280.10 | 5 |
| Spline 3 knots: scale = normal | 1265.80 | 8 | 1283.90 | 8 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; OS, overall survival.
Please note, a 1 knot spline normal model was not available as the model did not converge.

Visual inspection of extrapolations vs. observed data

Figure 20, Figure 21 and Figure 22 show the spline-based models extrapolated over a 10-year period with the KM overlaid (on the hazard, normal and odds scale, respectively).

For osimertinib plus chemotherapy, all 1-knot models failed to capture the increase in the trial hazard from around month 15 as well as the 2- and 3-knot models. Whilst the 2-knot model on the normal scale provided the best statistical fit from the spline-based models (36), the visual fit to the KM curve is similar across both 2- and 3-knots, regardless of scale used. The 3-knot models provided more optimistic survival estimates in the long-term, highlighting the importance of clinical validation.

For osimertinib monotherapy, the 1-knot model on the hazard scale did not capture the decrease and plateau in hazards observed in the trial and predicted that hazards would increase at the highest rate over the course of the model period (10 years). The 1-knot model on the normal scale could not be fit to the data. The 1-knot model

on the odds scale was approximately equivalent to the 2-knot model on the odds scale. Similar to the combination arm, the 2-knot and 3-knot models both provided good visual fits to the data, with the 3-knot models predicting more optimistic survival estimates in the long-term, again highlighting the importance of clinical validation.

**Figure 20 Kaplan Meier OS curves and extrapolations (spline-based models on hazard scale): osimertinib plus chemotherapy and osimertinib monotherapy**

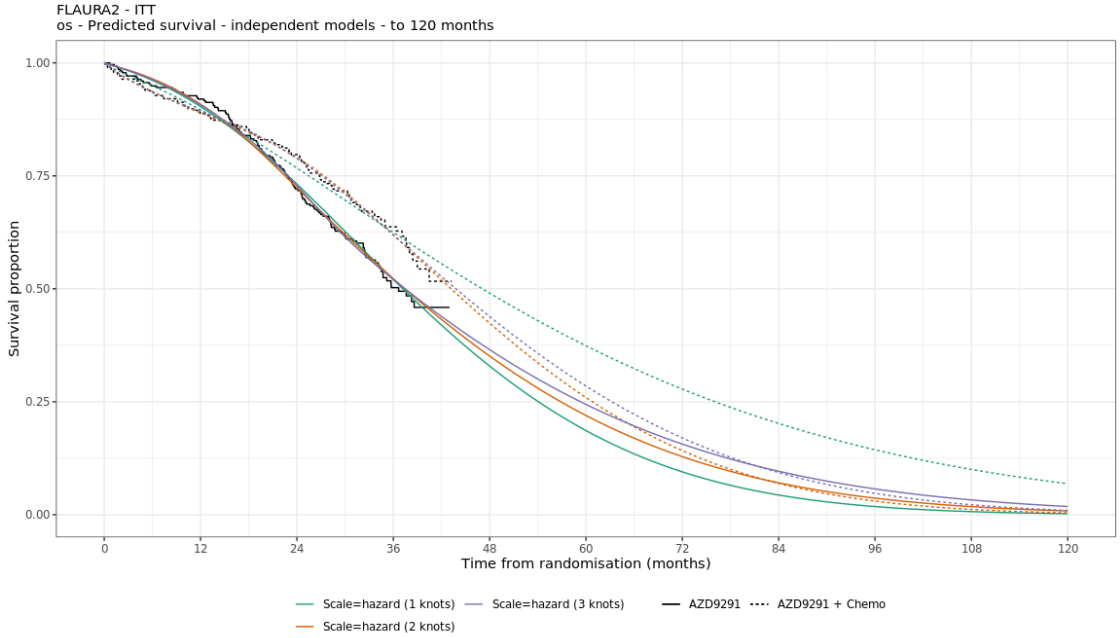




**Figure 21 Kaplan Meier OS curves and extrapolations (spline-based models on normal scale): osimertinib plus chemotherapy and osimertinib monotherapy**

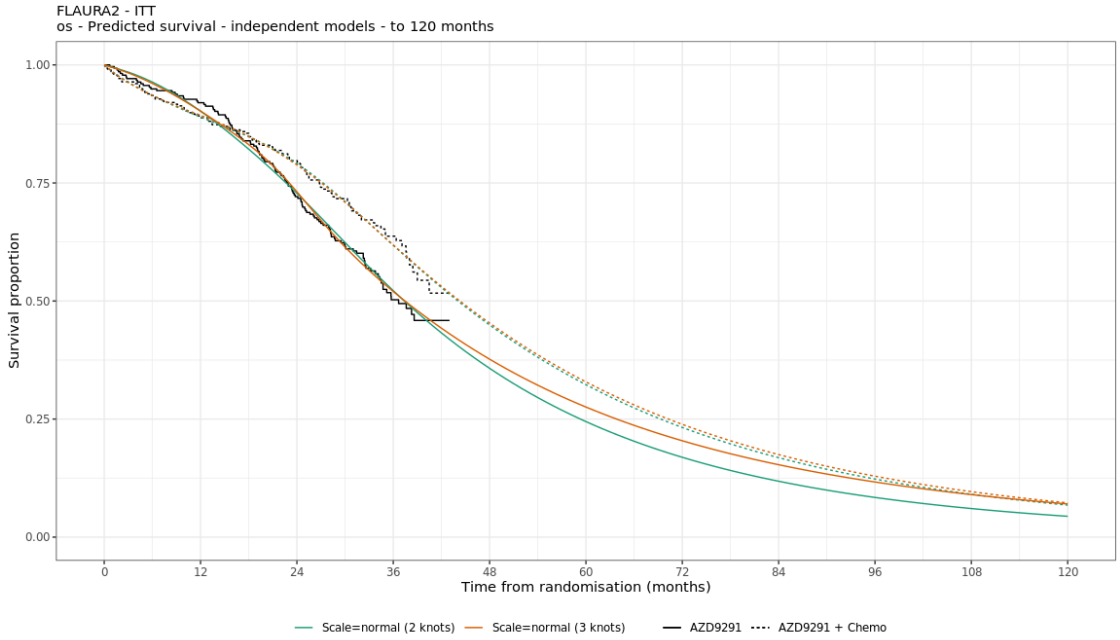
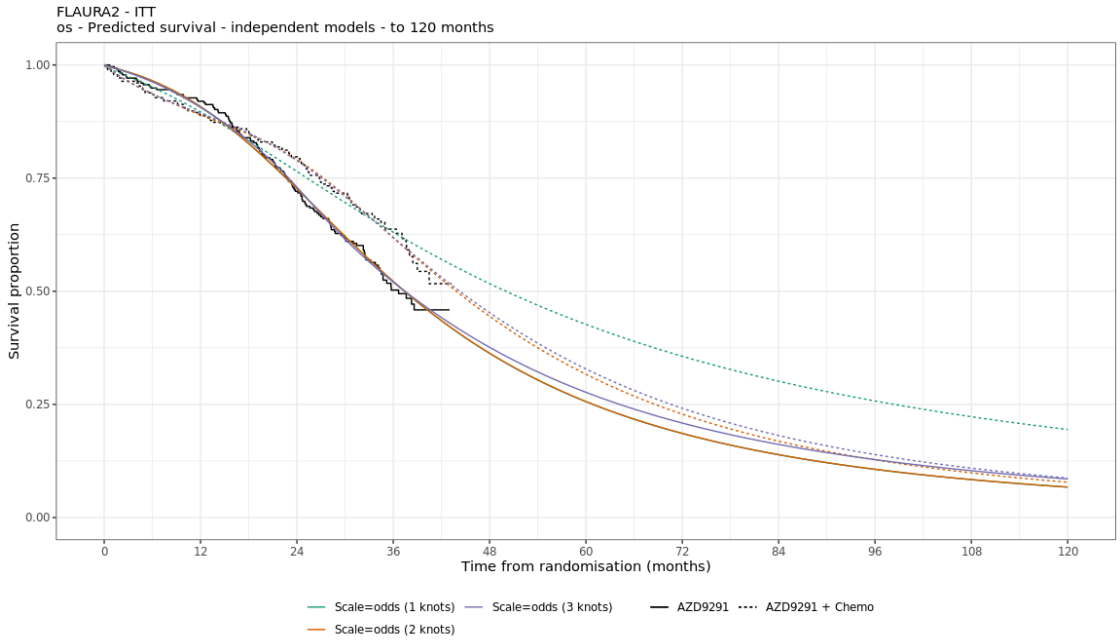



**Figure 22 Kaplan Meier OS curves and extrapolations (spline-based models on odds scale): osimertinib plus chemotherapy and osimertinib monotherapy**





#### *B.3.3.2.4 Base case curve selection*

In the base case, independently fit 2 knot models on the normal scale were selected for both the osimertinib plus chemotherapy arm and the osimertinib monotherapy arm.

As described above in section B.3.3.2.2, clinicians consistently noted the absence of a standard parametric model that represented their survival extrapolations across all timepoints. This insight, and the complex hazards, led to the investigation of more flexible model approaches. Independent fit models were justified for OS as there was evidence that the PHA could not be deemed reasonable. Spline models were justified due to the complex trial hazards, and the better visual fit to the within trial KM curves and observed hazards. The 2-knot normal model provides the best within-trial fit (according to AIC/BIC statistics) for the osimertinib plus chemotherapy arm and provides a potentially conservative estimate of survival in the long-term based on the feedback from clinicians. For osimertinib monotherapy, the 2-knot normal model provides a reasonable within-trial fit and aligns closest in the long-term with the survival estimates of clinicians interviewed.

In the scenario analyses, the 2-knot model on the odds scale was explored as this is a clinically plausible alternative with a reasonable statistical fit to the trial data. Two additional scenarios were also explored, one using the Weibull distribution for the osimertinib plus chemotherapy arm and a second using the gamma distribution on the osimertinib monotherapy arm, as the most clinically plausible standard parametric fittings with reasonable statistical fit.

### B.3.3.3 Progression-free survival

Investigator-assessed PFS (according to RECIST 1.1) was the primary outcome investigated in the FLAURA2 trial. PFS was defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the patient withdrew from study treatment or received another anti-cancer therapy prior to progression.

Investigator-assessed PFS KM data for osimertinib monotherapy and osimertinib plus chemotherapy is presented in Figure 4. The first step in selecting the choice of parametric survival model for PFS was to assess whether the PHA was upheld for the FLAURA2 data. Figure 23 shows that the plot of the Schoenfeld residuals against time does not show a pattern of changing residuals but the p-value for Schoenfeld residuals test is bordering significance (p=0.0487). However, the log cumulative hazard curves (Figure 24) were not parallel over time, indicating that the treatment effect varied over the trial period. On this basis it was considered that there was a violation of the PHA.

**Figure 23 Plot of Schoenfeld residuals (PFS)**

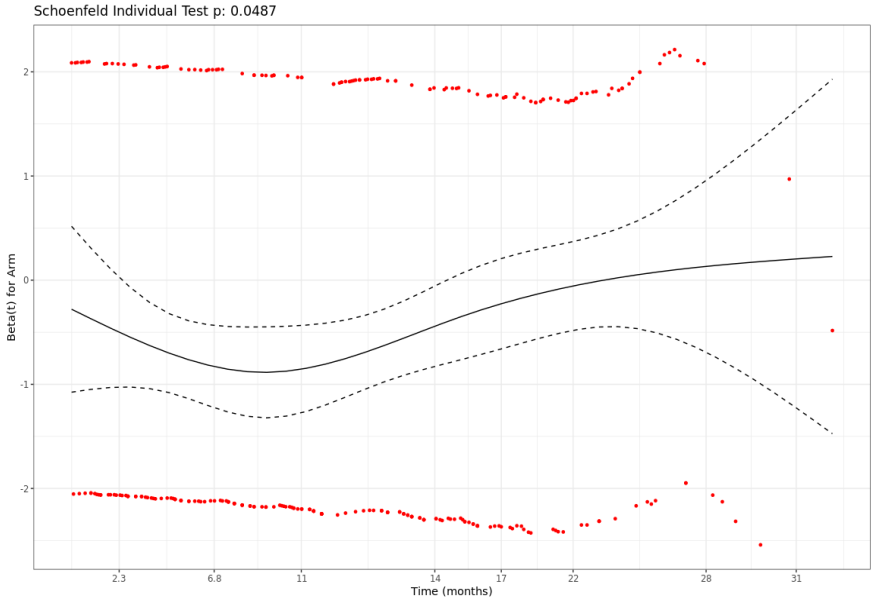
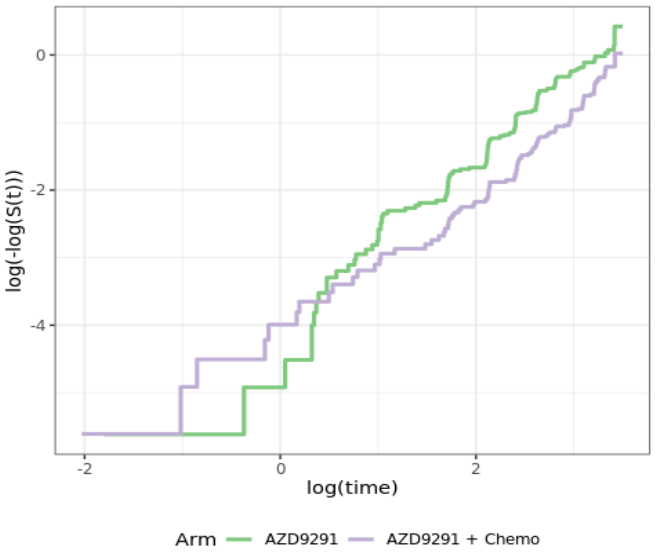




**Figure 24 Log cumulative hazard curves (PFS)**

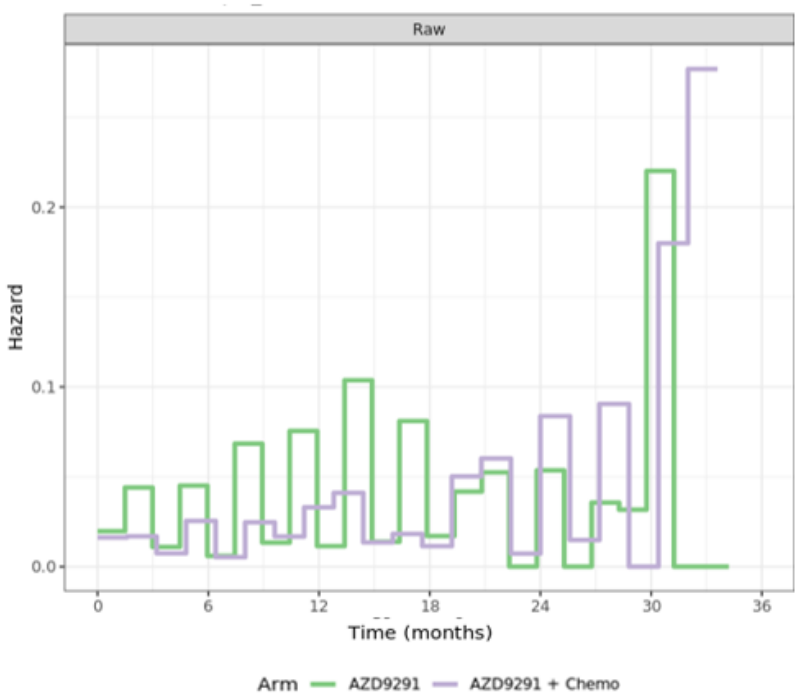



As the PHA was not considered to be a reasonable assumption, parametric models were fitted separately to both arms. As with OS, and in accordance with NICE DSU TSD 14[94] seven standard parametric distributions (exponential, gamma, generalised gamma, log-normal, log-logistic, Weibull, Gompertz) were fitted to the observed PFS data from the FLAURA2 clinical trial. To explore whether spline-based models were considered necessary, plots of the raw hazards were considered. The raw hazard plot shows that the hazards are generally increasing over the duration of the trial (Figure 25), such a trend is consistent with expectations in the advanced NSCLC setting. There is a potential change in the hazard in both arms towards the end of the trial, although this is likely driven by low patient numbers.



**Figure 25: Raw hazard plot**




For this reason, flexible parametric models were not considered necessary for PFS.

#### *B.3.3.3.1 Statistical goodness of fit*

The AIC and BIC statistics indicating the within-trial goodness-of-fit of each model for osimertinib plus chemotherapy and osimertinib monotherapy are provided in Table 40 and Table 41, respectively.

For osimertinib plus chemotherapy, the AIC and BIC scores showed that most standard parametric distributions fit the observed data well, with the exception of lognormal. Of the distributions, the AIC and BIC rankings indicated that the Gompertz, generalised gamma and Weibull distributions were the best fitting.



**Table 40 AIC and BIC for PFS parametric model for osimertinib plus chemotherapy**

| Parametric model | AIC | Statistical rank | BIC | Statistical rank |
|---|---|---|---|---|
| Exponential | 1139.50 | 6 | 1143.10 | 5 |
| Gamma | 1132.70 | 4 | 1140.00 | 4 |
| Generalised gamma | 1126.70 | 2 | 1137.60 | 2 (=) |
| Gompertz | 1123.40 | 1 | 1130.70 | 1 |
| Loglogistic | 1137.60 | 5 | 1144.90 | 6 |
| Lognormal | 1154.90 | 7 | 1162.20 | 7 |
| Weibull | 1130.30 | 3 | 1137.60 | 2 (=) |

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; PFS, progression-free survival.

For osimertinib monotherapy, the AIC and BIC scores showed that all standard parametric distributions fit the observed data well. Of the distributions, the AIC and BIC rankings indicated that the loglogistic, gamma and Weibull distributions were the best fitting.

**Table 41 AIC and BIC for PFS parametric model for osimertinib monotherapy**

| Parametric model | AIC | Statistical rank | BIC | Statistical rank |
|---|---|---|---|---|
| Exponential | 1427.10 | 7 | 1430.70 | 4 |
| Gamma | 1420.10 | 2 | 1427.40 | 2 |
| Generalised gamma | 1421.40 | 4 | 1432.30 | 5 |
| Gompertz | 1425.80 | 6 | 1433.10 | 7 |
| Loglogistic | 1419.30 | 1 | 1426.50 | 1 |
| Lognormal | 1425.30 | 5 | 1432.60 | 6 |
| Weibull | 1421.10 | 3 | 1428.30 | 3 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; PFS, progression-free survival.

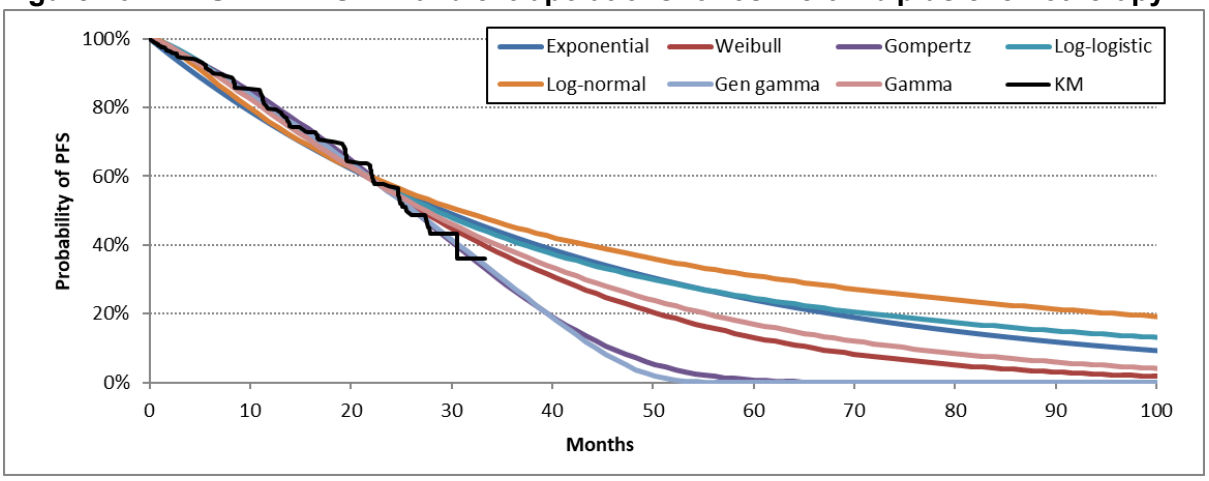
#### *B.3.3.3.2 Visual inspection of extrapolations vs. observed data*

For osimertinib plus chemotherapy, the generalised gamma, Gompertz and Weibull extrapolations provided reasonably good visual fits compared to the KM curve (Figure 26). Both the generalised gamma and Gompertz models have increasing hazards, which continued to increase sharply beyond the trial period. The Weibull distribution also has an increasing hazard function, but the increase is not as severe.



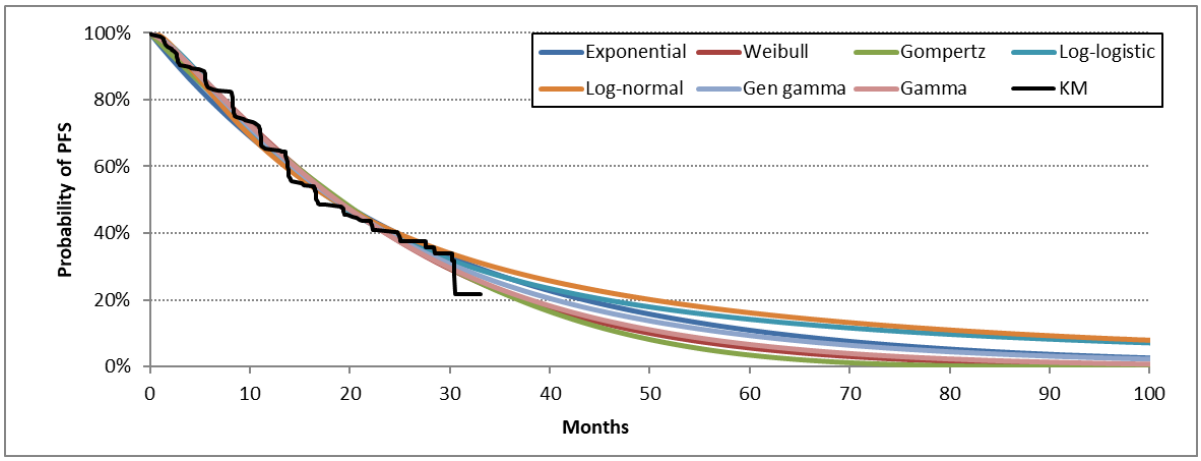
**Figure 26: FLAURA2 PFS KM and extrapolations for osimertinib plus chemotherapy**




Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

For osimertinib monotherapy, all of the curves provided a reasonable visual fit to the KM curve (Figure 27). From the three best-fitting according to AIC/BIC, loglogistic models showed decreasing hazards, and gamma and Weibull models showed gradually increasing hazards, with the gamma curves plateauing more in the long-term . A general trend of increasing hazards is consistent with expectations in the advanced NSCLC setting; the gamma and Weibull distributions provided a good visual fit.

**Figure 27: FLAURA2 PFS KM and extrapolations for osimertinib monotherapy**




Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.



To ensure that the PFS and OS curves did not cross, the model includes functionality to bound the PFS by the OS curve, thereby avoiding this illogical inconsistency.

#### *B.3.3.3.3 External validation*

Clinical opinion was sought on progression-free survival expectations in these patients. The clinicians were provided with the observed PFS for osimertinib monotherapy and osimertinib plus chemotherapy from the FLAURA2 clinical trial, and PFS estimates for each parametric distribution over a 10-year time period.

For osimertinib plus chemotherapy, one clinician estimated that 3-year PFS would be between 30-40%, and one clinician estimated 5-year PFS would be around 20%. Whilst clinicians were shown all standard distributions, the three best fitting models identified so far have been provided in Table 42 alongside the clinician estimates. Two clinicians viewed the Gompertz and generalised gamma extrapolations as too pessimistic, particularly in the longer-term. Two clinicians considered the Weibull distribution more reflective of their expectations and the most plausible distribution.

**Table 42: External validation for osimertinib plus chemotherapy (PFS)**

| | Generalised gamma | Gompertz | Weibull | Clinical expectations |
|---|---|---|---|---|
| 3-years | 29.1% | 28.4% | 36.7% | 30-40% (N=1) |
| 5-years | 0.0% | 0.8% | 13.7% | 20% (N=1)<br>17% (N=1)† |

†Based on comment that the Gamma distribution 5-year survival was most plausible.
Abbreviations: PFS, progression-free survival.

For osimertinib monotherapy, five clinicians said that the loglogistic distribution is considered too optimistic, and that a range of 5-9% is clinically plausible at 5-years. Three clinicians considered the 5-year survival predicted by the Gompertz distribution was too pessimistic. One clinician considered those patients who have not progressed after 3-years to not progress for some time, and therefore, expect a plateau in the survival curve. Whilst clinicians were shown all standard distributions, the three best fitting models identified so far have been provided in Table 43 alongside the clinician estimates.



**Table 43: External validation for osimertinib monotherapy (PFS)**

| | Loglogistic | Gamma | Weibull | Clinical expectations |
|---|---|---|---|---|
| 3-years | 26.8% | 22.8% | 22.2% | No specific commentary |
| 5-years | 14.4% | 7.1% | 6.0% | 14%-16% too optimistic (N=5)<br>5-9% is clinically plausible (N=3) |

Abbreviations: PFS, progression-free survival.

#### *B.3.3.3.4 Base case curve selection*

In the base case, independently fit Weibull models were selected for both the osimertinib plus chemotherapy and osimertinib monotherapy arms. To ensure that the PFS and OS curves did not cross, the model includes functionality to bound the PFS by the OS curve, thereby avoiding this illogical inconsistency.

Independent fit models were justified for PFS as there was evidence that the PHA could not be deemed reasonable. Spline models were not considered necessary for further exploration. The AIC/BIC statistics indicated that most distributions provided reasonable within-trial fits. The Weibull distribution was selected as it has a good within-trial fit and aligned closest with clinicians' expectations of PFS in the long-term.

In the scenario analyses, the Gompertz model was explored for osimertinib plus chemotherapy as a conservative extrapolation with a good statistical fit to the trial data. The gamma model was explored for osimertinib monotherapy as it was considered a clinically plausible alternative with a reasonable statistical fit to the trial data.

### B.3.3.4 Treatment duration

Treatment duration for both treatment arms was estimated based on time to treatment discontinuation (TTD) data from the FLAURA2 clinical trial. In FLAURA2, the most frequently reported reason for discontinuation of osimertinib treatment (in both trial arms) was disease progression (24.6% in the osimertinib plus chemotherapy arm, 42.9% in the osimertinib monotherapy arm). Alternatively, AEs

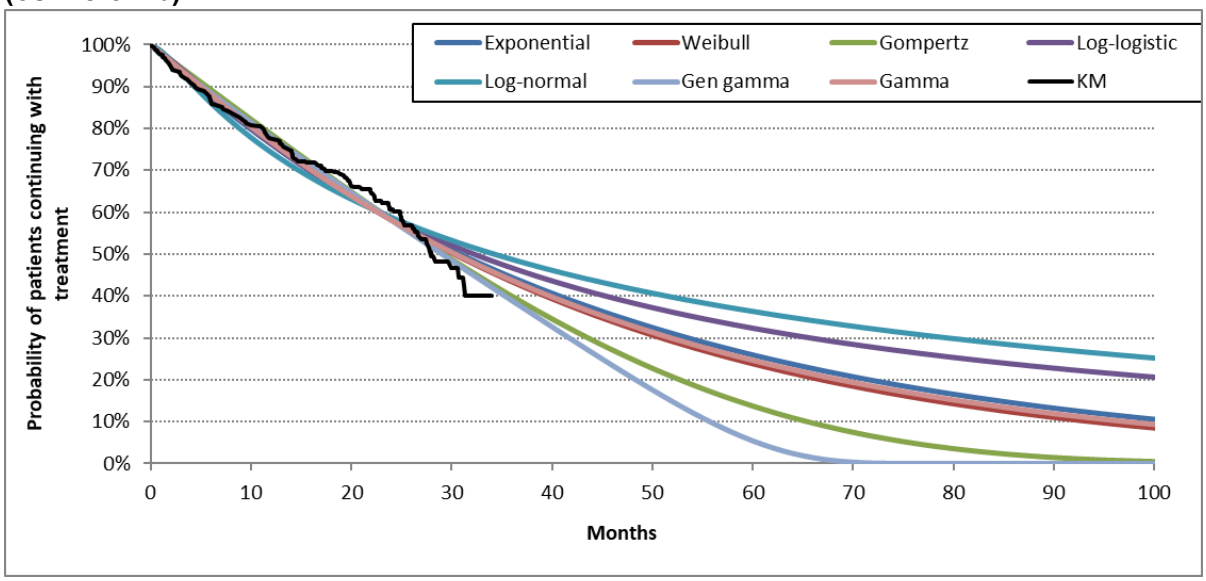


were the most frequent reason for the carboplatin/cisplatin and pemetrexed treatment elements in the combination arm (17.0% and 43.1%, respectively) therefore, the TTD and PFS curves from the FLAURA2 clinical trial differ due to some patients discontinuing before progression. Given the differences in treatment duration across the elements of the osimertinib plus chemotherapy arm, TTD was modelled separately for each treatment. Carboplatin/cisplatin was not modelled based on TTD data given the fixed number of cycles received. Detail on treatment duration for carboplatin/cisplatin is provided in Section B.3.6.1.2.2.

Figure 28 presents the parametric models fitted to the FLAURA2 TTD data for osimertinib in the osimertinib plus chemotherapy arm, Table 44 shows the corresponding AIC and BIC ranks.

**Figure 28: FLAURA2 TTD KM and extrapolations for osimertinib plus chemotherapy (osimertinib)**




Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.



**Table 44: AIC and BIC for TTD parametric modes for osimertinib plus chemotherapy (osimertinib)**

| Parametric model | AIC | Statistical rank | BIC | Statistical rank |
|---|---|---|---|---|
| Exponential | 1181.30 | 3 | 1184.90 | 1 |
| Gamma | 1183.00 | 5 | 1190.30 | 4 |
| Generalised gamma | 1181.00 | 2 | 1191.90 | 5 |
| Gompertz | 1180.50 | 1 | 1187.80 | 2 |
| Loglogistic | 1187.70 | 6 | 1194.90 | 6 |
| Lognormal | 1194.50 | 7 | 1201.80 | 7 |
| Weibull | 1182.80 | 4 | 1190.10 | 3 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; TTD, time to treatment discontinuation.

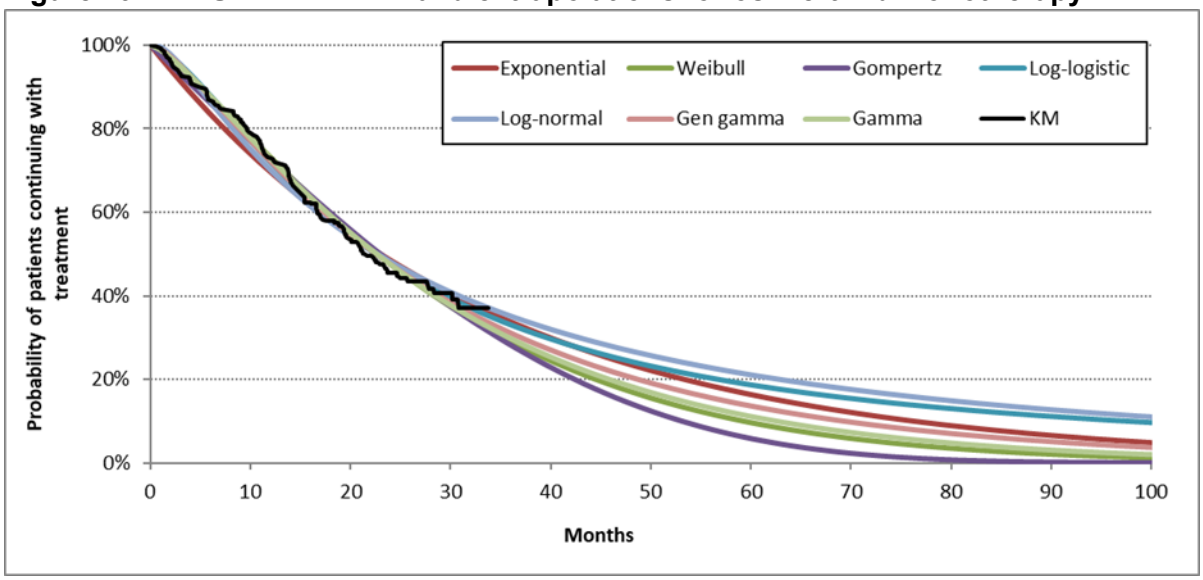
The AIC and BIC scores show that all the parametric distributions fit the data similarly. Based on a visual comparison of the KM curve to the extrapolations only the Gompertz and generalised gamma distributions captured the tail of the curve and were considered clinically plausible estimates in the long term. As the AIC and BIC rankings suggest that the Gompertz distribution was the best statistically fitting extrapolation this was considered the most appropriate extrapolation in the base case. In a scenario analysis the generalised gamma model was tested as considered a plausible alternative.

Figure 29 and Table 45 show the parametric models fitted to osimertinib monotherapy FLAURA2 TTD data and their corresponding AIC and BIC ranks.



**Figure 29: FLAURA2 TTD KM and extrapolations for osimertinib monotherapy**




Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

**Table 45: AIC and BIC for TTD parametric modes for osimertinib monotherapy**

| Parametric model | AIC | Statistical rank | BIC | Statistical rank |
|---|---|---|---|---|
| Exponential | 1361.50 | 7 | 1365.20 | 5 |
| Gamma | 1354.40 | 2 | 1361.60 | 2 |
| Generalised gamma | 1356.00 | 4 | 1366.90 | 7 |
| Gompertz | 1359.20 | 6 | 1366.50 | 6 |
| Loglogistic | 1354.30 | 1 | 1361.50 | 1 |
| Lognormal | 1357.90 | 5 | 1365.10 | 4 |
| Weibull | 1355.00 | 3 | 1362.30 | 3 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; TTD, time to treatment discontinuation.

The AIC and BIC scores show that all parametric distributions provide a reasonable fit to the observed data. Based on the AIC and BIC rankings, a loglogistic extrapolation was the most suitable distribution for TTD extrapolation in the osimertinib monotherapy arm. However, the loglogistic extrapolation predicts a decreasing hazard ratio, and it was therefore considered that it may overpredict treatment duration. The gamma distribution was the second best-fitting with a close AIC/BIC score to the loglogistic distribution and was not considered to overpredict treatment duration compared with the loglogistic distribution. Therefore, the gamma distribution was selected for the base case. The Weibull distribution was the next

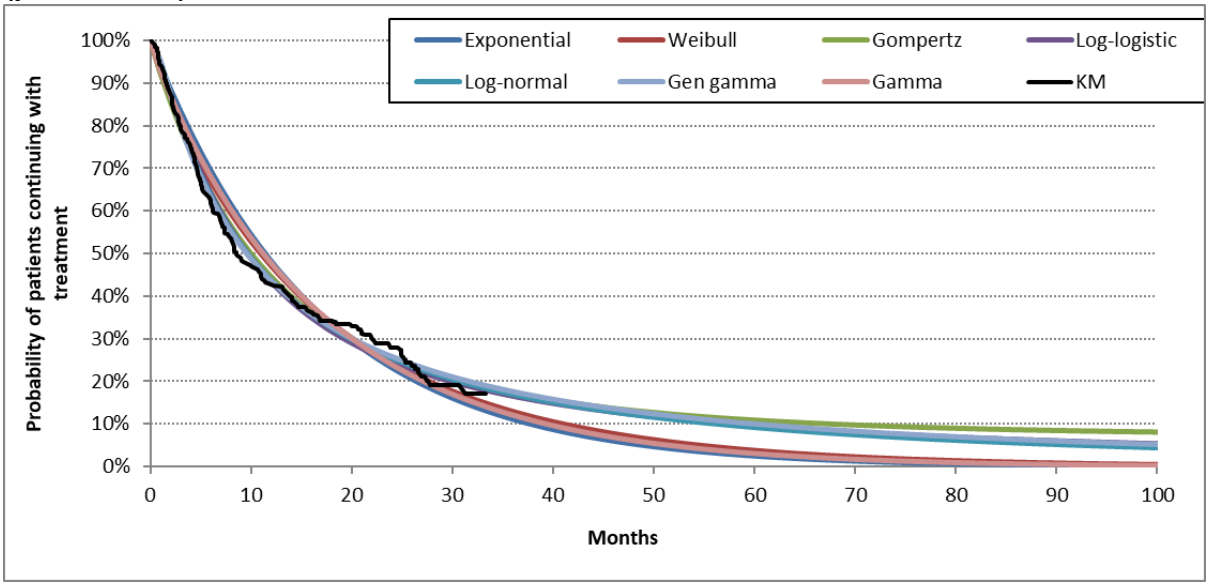


best-fitting after gamma and also considered plausible, so this was tested in the scenario analyses.

Figure 30 presents the parametric models fitted to the FLAURA2 TTD data for pemetrexed in the osimertinib plus chemotherapy arm. Table 46 show the corresponding AIC and BIC ranks.

**Figure 30: FLAURA2 TTD KM and extrapolations for osimertinib plus chemotherapy (pemetrexed)**




Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

**Table 46: AIC and BIC for TTD parametric modes for osimertinib plus chemotherapy (pemetrexed)**

| Parametric model | AIC | Statistical rank | BIC | Statistical rank |
|---|---|---|---|---|
| Exponential | 1590.70 | 6 | 1594.30 | 5 |
| Gamma | 1591.60 | 7 | 1598.80 | 7 |
| Generalised gamma | 1573.10 | 2 | 1584.00 | 3 |
| Gompertz | 1582.50 | 4 | 1589.70 | 4 |
| Loglogistic | 1575.90 | 3 | 1583.20 | 2 |
| Lognormal | 1571.30 | 1 | 1578.50 | 1 |
| Weibull | 1589.80 | 5 | 1597.10 | 6 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; TTD, time to treatment discontinuation.



Given the narrow range of the AIC and BIC scores, all the parametric distributions were considered to provide similar fits to the observed data. Of the distributions, the AIC and BIC rankings suggest that the lognormal, loglogistic and generalised gamma distributions were the best statistically fitting extrapolations for the pemetrexed TTD data. Both the lognormal and the loglogistic predict a decreasing hazard ratio which is not consistent with chemotherapy treatment, it was therefore considered that they may both overpredict treatment duration.

Furthermore, it was considered implausible to expect patients to be receiving treatment beyond 5 years; of the standard distributions, the exponential distribution predicted the lowest proportion on therapy at 5 years. Considering all standard distributions had similar fits to the observed data, and the exponential survival distribution predicted the lowest proportion on therapy at 5 years, this extrapolation was considered the most appropriate to model pemetrexed TTD data.

In the base case, all TTD curves were not bound by PFS due to the expectation that some patients experiencing disease progression might continue their treatment for a slightly longer duration in clinical practice until they switch to an alternative treatment. A scenario analysis that does bound TTD to PFS was explored in a scenario analysis, although both TTD and PFS remained bound by OS in this scenario.

## *B.3.4 Measurement and valuation of health effects*

### B.3.4.1 Health-related quality-of-life data from clinical trials

In the FLAURA2 clinical trial, EQ-5D-5L utility data were collected every 4 weeks from baseline. A total of 6,812 pre-progression observations were made across 535 subjects, and 612 post-progression observations were made across 194 subjects, with most observations occurring immediately after progression in the post-progression group.

In the FLAURA2 trial, both treatment arms were well balanced in terms of mean EQ-5D-5L VAS score at baseline (71.7 in the osimertinib plus chemotherapy arm and

70.6 in the osimertinib arm). Post-baseline, mean EQ-5D-5L VAS scores progressively increased (i.e. improved) in both treatment arms, with no notable differences between arms.[8]

Baseline scores for the EQ-5D-5L domains were broadly similar between treatment arms, with slightly more patients in the osimertinib plus chemotherapy arm reporting no problems in the domains of mobility, self-care, usual activities, and pain/discomfort than in the osimertinib arm. Post-baseline, all EQ-5D-5L domains remained mostly stable or improved at several assessments throughout the study.[8]

#### B.3.4.2 Mapping

The NICE reference case recommends the use of the EQ-5D-3L and that, if only the EQ-5D-5L was used to collect QoL values, these values should be mapped onto the 3L value set for use in CEA.

The mapping algorithm used by Hernández Alava et al. (2023)[96] was used to map the EQ-5D data onto the EQ-5D-3L scale. The statistical relationship between EQ-5D health state utility and treatment, and health status was assessed using regression analysis. This was performed before the values were mapped from 5L to 3L. To account for the repeated measurements in the study, a mixed model for repeated measures (MMRM) method was used to model EQ-5D-3L health state utilities. The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression. Due to censoring, the EQ-5D-5L observations obtained during this period have an unknown/missing health status and therefore, were omitted from the analysis. Only patients with a complete EQ5D questionnaire (with all 5 questions responded to) were included.

For each modelled regression analysis, parameter estimates, and marginal (‘least square’) means were estimated, including 95% confidence intervals.

The marginal (‘least square’) mean provides a model-based estimate of the mean utility score by status (treatment and/or Progression status) that is averaged over observations and with adjustment for repeated measures. The estimated marginal mean and its associated standard error or confidence interval were used as the

health-related quality of life (HRQoL) inputs to populate the cost-effectiveness model.

### B.3.4.3 Health-related quality-of-life studies

A SLR was conducted in 20 June 2023 and updated in May 2024 to identify studies reporting on HRQoL of treatment-naïve adult patients with unresectable stage III or IV EGFR-mutated NSCLC. In total, 18 unique publications and 8 HTA submissions were identified. Full details of the SLR are presented in Appendix H.

### B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

In accordance with the NICE process and methods,[97] the model base case implements EQ-5D data which were collected in the FLAURA2 trial to inform the progression-free health state utility values. However, the estimated PD health utility from FLAURA2 was higher than expected and may be due to the limited number of measurements for post-progression health utilities, most of which occurred immediately after progression. As a result, the base case analysis used a PD HSUV sourced from a real-world study of health state utilities in Canadian patients with lung cancer. Labbé et al. (2017) evaluated utility scores using a longitudinal cohort of Canadian outpatients diagnosed with metastatic lung cancer across various disease health states (EGFR, ALK, NSCLC). Using the EQ-5D-3L, health state utility scores were compared by mutational status, therapy, response to treatment and severity of symptoms. The PD utility value based on UK conversations generated by Labbé et al. for the EGFR NSCLC was 0.64. This value was obtained by assessment on multiple occasions over time, therefore capturing patients' long-term deterioration of HRQoL.[89] TA653[60] (EAG recommendation) used the value from Labbé et al. (2017)[89] for the PD health state. Furthermore, the UK converted PD utility value reported by Labbe et al. was very similar to those used and accepted by ERGs in two previous NSCLC NICE submissions: TA309/TA402[91] and TA347.[92]

**Table 47: Summary of utility values for cost-effectiveness analysis**

| State | Utility value: mean (standard error) | 95% confidence interval | Reference in submission | Justification |
|---|---|---|---|---|
| Progression free | [redacted] | [redacted] | B.3.4.1 | FLAURA2 |
| Progressed disease | 0.640 (0.07) | LCI, 0.503; UPCI, 0.777 | | Labbé et al. (2017)[89] |

Abbreviation: LCI, lower confidence interval, UPI, upper confidence interval

A scenario analysis utilising progressed-disease utility values reported by FLAURA2 was explored to determine the impact on model outcomes.

### B.3.4.5 Adverse reactions

Safety outcomes were assessed in patients who received at least one dose of study treatment in the FLAURA2 trial. To reflect AEs with the highest impact on HRQoL and costs to public healthcare providers, only events grade 3 or above according to the CTCAE v5.[98] that were observed in at least 2% of patients in at least one trial arm were included in the model.

Costs (Table 65) and disutilities (Table 49) associated with AEs were applied in the first model cycle. This approach assumes that patients only experience the consequences of AEs once, regardless of the length of time they are on treatment.

**Table 48: Grade ≥3 treatment-related AEs occurring in ≥2% of patients**

| AE | Osimertinib + chemotherapy (N=276) n (%) | Osimertinib monotherapy (N=275) n (%) |
|---|---|---|
| **Patients with Grade ≥3 AE** | **176 (63.8)** | **75 (27.3)** |
| Diarrhoea | 8 (2.9%) | 1 (0.36%) |
| Fatigue | 8 (2.9%) | 1 (0.36%) |
| Anaemia | 55 (19.93%) | 1 (0.36%) |
| Decreased appetite | 8 (2.9%) | 2 (0.73%) |
| Pneumonia | 6 (2.17%) | 5 (1.82%) |
| Neutropenia | 37 (13.41%) | 2 (0.73%) |
| Neutrophil count decreased | 31 (11.23%) | 2 (0.73%) |
| Platelet count decreased | 21 (7.61%) | 0 (0.00%) |



| AE | Osimertinib + chemotherapy (N=276) n (%) | Osimertinib monotherapy (N=275) n (%) |
|---|---|---|
| Thrombocytopenia | 19 (6.88%) | 3 (1.09%) |
| Febrile neutropenia | 11 (3.99%) | 0 (0.00%) |
| White blood cell count decreased | 9 (3.26%) | 1 (0.36%) |
| Ejection fraction decreased | 8 (2.9%) | 3 (1.09%) |
| Leukopenia | 8 (2.9%) | 0 (0.00%) |
| Pulmonary embolism | 6 (2.17%) | 3 (1.09%) |

Abbreviations: AE, adverse event.
MedDRA version 25.1
Source: CSR.[8]

### B.3.4.6 Adverse event utility decrements

The impact of AEs on patient utility was accounted for by applying a disutility for the duration over which the AE was assumed to last. The resulting total utility decrement was applied to the percentage of patients experiencing the AE in the FLAURA2 trial (Table 48) in the first model cycle. Disutility values and adverse event durations were obtained from the TA654 NICE submission.[59] Any missing values were supplemented with targeted literature searches. The disutilities and durations of each AE included in the model are presented in Table 49.

**Table 49: Disutilities associated with the AEs in the economic model**

| AE | Disutility (per event) | Duration (days) | Source (disutility value) | Source (duration) |
|---|---|---|---|---|
| Diarrhoea | -0.05 | 5.53 | Nafees et al 2008[99] | Study CA046, TA306 (Taken from TA654)[59] |
| Fatigue | -0.07 | 23.78 | Nafees et al 2008[99] | PIX301 trial, TA476 (Taken from TA654)[59] |
| Anaemia | -0.07 | 23.78 | Westwood et al 2014[100] | Assumed equal to fatigue |
| Decreased appetite | -0.07 | 14.66 | Assumed equal to fatigue | TA654. NICE (2018)[59] |
| Pneumonia | -0.01 | 14.66 | Goeree et al 2016[101] | TA654. NICE (2018)[59] |
| Neutropenia | -0.09 | 14.66 | Nafees et al 2008[99] | TA654. NICE (2018)[59] |
| Neutrophil count decreased | -0.09 | 14.66 | Assumed equal to neutropenia | TA654. NICE (2018)[59] |

| AE | Disutility (per event) | Duration (days) | Source (disutility value) | Source (duration) |
|---|---|---|---|---|
| Platelet count decreased | -0.09 | 14.66 | Assumed equal to neutropenia | TA654. NICE (2018)[59] |
| Thrombocytopenia | -0.09 | 14.66 | Assumed equal to neutropenia | TA654. NICE (2018)[59] |
| Febrile neutropenia | -0.09 | 14.66 | Nafees et al 2008[99] | TA654. NICE (2018)[59] |
| White blood cell count decreased | -0.09 | 14.66 | Assumed equal to neutropenia | TA654. NICE (2018)[59] |
| Ejection fraction decreased | -0.06 | 14.66 | Assumed equal to average of other disutilities | TA654. NICE (2018)[59] |
| Leukopenia | -0.09 | 14.66 | Assumed equal to neutropenia | TA654. NICE (2018)[59] |
| Pulmonary embolism | -0.06 | 14.66 | Assumed equal to average of other disutilities | TA654. NICE (2018)[59] |

Abbreviations: AE, adverse event.

### *B.3.5 Cost and healthcare resource use identification, measurement and valuation*

Details of the SLR conducted to identify cost and healthcare resource utilisation data for patients with locally advanced or metastatic EGFRm NSCLC are presented in Appendix I. In total, 19 observational studies were identified. None of the included studies were conducted in the UK and therefore were not considered to be relevant to clinical practice in England.

### *B.3.6 Cost and healthcare resource use identification, measurement and valuation*

Details of the SLR conducted to identify cost and healthcare resource utilisation data for patients with locally advanced or metastatic EGFRm NSCLC are presented in Appendix I. In total, 13 observational studies were identified. None of the included studies were conducted in the UK and therefore were not considered to be relevant to clinical practice in England.



### B.3.6.1 Intervention and comparators' costs and resource use

#### *B.3.6.1.1 Treatment acquisition costs*

Drug acquisition costs were calculated based on available formulations, pack sizes, unit costs, and price per mg for each treatment included in the model. The dosing information was sourced from the MHRA label for each treatment and the drug acquisition costs were sourced from the eMIT[11] or, when not available on eMIT, the BNF[102] (see Section Table 51 and Table 52).

A discount of [redacted] was applied to osimertinib in the osimertinib plus chemotherapy arm and a [redacted] discount was applied in the osimertinib monotherapy arm.

The dosage of chemotherapy as well as subsequent treatment regimens (see Section B.3.6.1.4) were determined by body surface area (BSA). The mean height and weight from FLAURA2 were applied in the formula by Mosteller et al. (1987)[103] to estimate BSA.

**Table 50: Patient characteristics used in the model**

| Parameter | Input | Reference |
|---|---|---|
| Weight (kg) | 64.80 | FLAURA2[8] |
| Height (cm) | 162.60 | FLAURA2[8] |
| Body surface area ($m^2$) | 1.71 | Calculated based on average height and weight using the Mosteller formula:[103] $BSA = \sqrt{\frac{height\ (cm) \times weight(kg)}{3600}}$ |

**Abbreviations**: BSA, body surface area

#### *B.3.6.1.2 Time on treatment*

##### B.3.6.1.2.1 Osimertinib

Patients in both the intervention and comparator arm of the model receive osimertinib via a once daily oral administration. Treatment duration is based on the extrapolation of TTD data from FLAURA2 (see Section B.3.3.4). The relative dose intensities (RDI) for osimertinib in both the osimertinib plus chemotherapy and osimertinib monotherapy arm were derived from the FLAURA2 trial ([redacted] and [redacted] respectively).



#### B.3.6.1.2.2 Chemotherapy (osimertinib plus chemotherapy arm)

In the osimertinib plus chemotherapy arm, chemotherapy treatment consists of an initial treatment phase during which patients receive an oral dose of osimertinib alongside either cisplatin or carboplatin in combination with pemetrexed, with both treatments administered via IV infusion once every three weeks (for treatment cycles 1–4). The base case assumes 50% of patients receive cisplatin and 50% receive carboplatin. In the base case analysis, a maximum of four treatment cycles (each cycle equating to 21 days) of either cisplatin or carboplatin are modelled in the initial treatment phase. Since the RDI for cisplatin and carboplatin was not reported in the FLAURA2 trial, the model's base case conservatively assumed an RDI of 100%. The extrapolated TTD data for pemetrexed (shown in Figure 30) was utilised for patients receiving cisplatin and carboplatin. This approach is appropriate because patients receiving pemetrexed in the FLAURA2 trial would have also been concurrently administered cisplatin and carboplatin at the start of the trial, as per the trial protocol.

After the initial three cycles of osimertinib plus pemetrexed plus cisplatin/carboplatin, a maintenance phase follows whereby patients receive treatment with pemetrexed alongside daily osimertinib.

The protocol outlines that patients randomised to the osimertinib plus chemotherapy arm would receive pemetrexed until RECIST 1.1-defined progression by the Investigator, or until another discontinuation criteria was met (patient decision, investigator decision, AEs, non-compliance, incorrect initiation or pregnancy). In FLAURA2, median actual exposure to pemetrexed was 8.28 months (range: 0.7 to 33.8 months), and more than half of all patients who received pemetrexed (180 patients [65.2%]) had a dose modification during the course of the study. Whilst the proportion of patients with a pemetrexed dose modifications was notable, the mean RDI of pemetrexed remained high (90.0%), indicating that these treatment modifications had a minimal overall impact on the actual pemetrexed dose delivered relative to the intended dose through to treatment discontinuation. The treatment acquisition costs associated with osimertinib plus chemotherapy and osimertinib monotherapy as presented in Table 51 and Table 52.

**Table 51: Osimertinib plus chemotherapy treatment acquisition costs included in the economic model**

| Treatment | | Admin method | Dose per admin | Admins per cycle | Treatment cycle length | RDI | Strength per vial/cap | Vials/ caps per pack | Stopping rule | Cost per pack (incl. discount) | Cost per tx cycle | Cost per 30 days[†] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Initial phase** | | | | | | | | | | | | |
| Chemotherapy | Cisplatin | IV | 75 mg/m$^2$ | 1 | 21 days | 100.0% | 100 mg | 1 | 84 days | £29.27 | £37.56 | £75.73[‡] |
| | Carboplatin | IV | 575 mg | 1 | 21 days | 100.0% | 600 mg | 1 | 84 days | £71.44 | £68.47 | |
| **Maintenance phase** | | | | | | | | | | | | |
| Chemotherapy | Pemetrexed | IV | 500 mg/m$^2$ | 1 | 21 days | [redacted] | 100 mg | 1 | N/A | £24.52 | £188.77 | £269.67 |
| Osimertinib | | Oral | 80 mg | 30 | 30 days | [redacted] | 80 mg | 30 | N/A | [redacted] | [redacted] | [redacted] |

Abbreviations: IV, intravenous; tx treatment

[†] Cost per 30-day cycle calculated as the cost per cycle multiplied by 30 (the model cycle length) divided by the treatment cycle length

[‡] Calculated as the weighted average of the cost per 30 days for cisplatin and carboplatin.

**Table 52: Osimertinib monotherapy treatment acquisition costs included in the economic model**

| Treatment | Admin method | Dose per admin | Admins per cycle | Treatment cycle length | RDI | Strength per vial/cap | Vials/caps per pack | Stopping rule | Cost per pack (incl. discount) | Cost per tx cycle | Cost per 30 days[†] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | Oral | 80 mg | 30 | 30 days | [redacted] | 80 mg | 30 | N/A | [redacted] | [redacted] | [redacted] |

Abbreviations: IV, intravenous; tx, treatment

[†] Cost per 30-day cycle calculated as the cost per cycle multiplied by 30 (the model cycle length) divided by the treatment cycle length



### *B.3.6.1.3 Administration costs*

Table 53 presents the administration costs associated with the first-line treatments. Administration costs were applied on a per cycle basis to patients on treatment. As patients receive cisplatin or carboplatin at the same time as pemetrexed, no administration costs were applied to cisplatin or carboplatin to avoid double counting.

**Table 53: Administration costs associated with first-line treatments**

| Treatment | | Cost per treatment cycle | Cost per 30 days | Reference |
|---|---|---|---|---|
| Chemotherapy | Cisplatin | £0.00 | £0.00 | Set to £0.00 to avoid double counting |
| | Carboplatin | £0.00 | £0.00 | |
| | Pemetrexed | £345.00 | £492.86 | NHS Payment Scheme2023/25:[104] average, SB13Z & SB15Z, Deliver more Complex Parenteral Chemotherapy at First Attendance & Deliver Subsequent Elements of a Chemotherapy Cycle |
| Osimertinib | | £10.40† | £10.40 | PSSRU 2023:[105] £52 per hour of Band 6 pharmacist assuming a dispensing time of 12 minutes |

Abbreviations: NHS, National Health Service.

† Cost per treatment cycle calculated as £52/60 x 12 = £10.40

### *B.3.6.1.4 Subsequent treatment costs*

Following discontinuation of first-line treatment, patients may switch to an alternative second-line and third-line treatment. Information was available from FLAURA2 on which subsequent treatments patients received (see Table 12). however, to reflect NHS clinical practice, the distributions across second-line treatments were reweighted by clinical expert input. Clinical experts also advised that 10–20% of patients receiving 2L treatment could receive atezolizumab + bevacizumab + carboplatin + paclitaxel as a subsequent treatment (ABCP), a treatment option not captured in the FLAURA2 trial.[64] Therefore, it was assumed that, of patients requiring 2L treatment, 15% in the osimertinib plus chemotherapy arm [redacted] and 15% in the osimertinib monotherapy arm [redacted] would receive ABCP. The



clinicians also advised that pemetrexed would not be permitted as a subsequent treatment for patients treated with osimertinib plus chemotherapy. The removal of pemetrexed was accounted for in the ABCP distribution by subtracting the difference between the rates from the proportion of patients clinical experts expected to be treated with ABCP as a 2L treatment [redacted]. To account for ABCP in the osimertinib monotherapy arm, the proportion of patients clinical experts expected to be treated with 2L pemetrexed and docetaxel were reweighted equally by subtracting half of the proportion of patients treated with ABCP [redacted]). This approach was adopted because the clinicians stated the docetaxel and pemetrexed percentages were too high in the osimertinib monotherapy arm.

The modelling of subsequent treatment benefit is implicitly accounted for in the extrapolated OS data from FLAURA2. While the ABCP regimen was not included as a subsequent treatment in FLAURA2, treatment classes that the components of the ABCP regimen would fall into (taxanes, VEGF Inhibitor, PD-1/PD-L1 inhibitor, and platinum compounds) were included as treatment options. It is assumed that these components serve as an adequate proxy for ABCP, therefore it was also assumed that ABCP benefits are captured within OS. Similarly, while the FLAURA2 subsequent treatment data doesn't explicitly capture PDC, it does report platinum compounds and folic acid analogues (pemetrexed), which are components of PDC. Therefore, it is assumed that the benefits of PDC are captured within OS from FLAURA2.

Due to the nature of partitioned survival modelling, it is not possible to accurately account for patients who discontinue and die in the same cycle. This can result in a minor overestimation of subsequent treatment costs as it does not account for patients who die prior to progression. However, this is not expected to have a significant impact on the ICER.

The cost of subsequent treatments was estimated based on the following parameters:

- Distribution of patients across second-line and third-line treatments
- Treatment costs
- Mean duration of treatment

Table 54 and Table 55 show the distribution of patients across 2L and 3L treatments, respectively.

**Table 54: Distribution of patients across 2L treatments**

| From ↓To → | PDC | Pemetrexed | Docetaxel | ABCP | Reference in submission |
|---|---|---|---|---|---|
| Osimertinib + chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] | AstraZeneca (2023) FLAURA2 Clinical Study Report[8] Clinical expert input |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; PDC, platinum doublet chemotherapy.

**Table 55: Distribution of patients across 3L treatments**

| From ↓To → | PDC | Pemetrexed | Docetaxel | ABCP | Reference in submission |
|---|---|---|---|---|---|
| Osimertinib + chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] | AstraZeneca (2023) FLAURA2 Clinical Study report |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] | |

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; PDC PDC, platinum doublet chemotherapy.

The treatment duration for platinum doublet chemotherapy (PDC) was based on the median duration of chemotherapy in the ABCP group and the BCP group reported in the IMPower150 trial.[106] The treatment duration for pemetrexed was based on the mean duration of treatment of the platinum–pemetrexed arm from the AURA3 trial.[107] This source was considered most appropriate, given the data are more mature TTD data than that reported in the FLAURA2 trial. Docetaxel had a treatment duration of 3 months which was obtained from the INTEREST study (converted to 30 days).[108] The treatment duration for ABCP was based on the median duration of atezolizumab in ABCP arm reported by Socinski et al. (2018).[106] The model assumes all treatments have the same duration in both the second- and third-line settings. The treatment duration of subsequent treatments is presented in Table 56.



**Table 56: Treatment duration of subsequent treatment**

| Treatment | Duration (months) | Duration converted to 30 days | Reference |
|---|---|---|---|
| PDC | 2.2 | 2.23 | Socinski et al. (2018)[106] IMPower150 median TTD of platinum-pemetrexed |
| Pemetrexed | 4.2 | 4.26 | Mok et al. (2017)[107] AURA3 median TTD of platinum-pemetrexed |
| Docetaxel | 3 | 3.04 | Kim E et al. (2008)[108] Docetaxel mean duration |
| ABCP | 8.2 | 8.32 | Socinski et al. (2018).[106] Median duration of atezolizumab in ABCP arm |

Abbreviations: PDC, platinum doublet chemotherapy; TTD, time to treatment discontinuation.

The acquisition and administration costs associated with the subsequent treatment options are presented in Table 57 and Table 58, respectively.

The total cost of second-line and third-line subsequent treatments in each arm is calculated by:

- Multiplying the duration of treatment with cost to work out total cost of each treatment/regimen as a subsequent treatment
- Multiplying the above by the estimated proportion of patients receiving each subsequent treatment

The cost of subsequent treatments is applied as a one-off cost to patients that discontinue treatment per cycle.



**Table 57: Subsequent treatment acquisition costs included in the economic model**

| Treatment | | Admin method | Dose per admin | Admins per cycle | Max. admins | Treatment cycle length | Strength per vial/cap | Vials/caps per pack | Cost per pack (incl. discount) | Cost per tx cycle | Cost per 30 days† |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PDC | Pemetrexed | IV | 500 mg/m$^2$ | 1 | N/A | 21 days | 100 | 1 | £24.52 | £209.74 | £375.37‡ |
| | Cisplatin | IV | 75 mg/m$^2$ | 1 | N/A | 21 days | 100 | 1 | £29.27 | £37.56 | |
| | Carboplatin | IV | 575 mg | 1 | N/A | 21 days | 600 | 1 | £71.44 | £68.47 | |
| Pemetrexed | | IV | 500 mg/m$^2$ | 1 | N/A | 21 days | 100 | 1 | £24.52 | £209.74 | £299.64 |
| Docetaxel | | IV | 75 mg/m$^2$ | 30 | 4 | 21 days | 20 | 4 | £3.67 | £5.89 | £8.41 |
| ABCP | Atezolizumab | IV | 1200 mg | 1 | N/A | 21 days | 1200 | 1 | £3,807.69 | £3,807.69 | £8,460.32 |
| | Bevacizumab | IV | 972 mg | 1 | N/A | 21 days | 100 | 1 | £205.00 | £1,992.60 | |
| | Carboplatin | IV | 575 mg | 1 | N/A | 21 days | 600 | 1 | £71.44 | £68.47 | |
| | Paclitaxel | IV | 342 mg/m$^2$ | 1 | N/A | 21 days | 100 | 1 | £9.13 | £53.47 | |

† Cost per 30-day cycle calculated as the cost per cycle multiplied by 30 (the model cycle length) divided by the treatment cycle length; ‡ Calculated as the cost per 30 days for pemetrexed plus the weighted average of the cost per 30 days for cisplatin and carboplatin.
Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; IV, intravenous; N/A, not applicable; PDC, platinum doublet chemotherapy; tx, treatment.

**Table 58: Administration costs associated with subsequent treatments**

| Cost per treatment cycle | Cost per treatment cycle | Cost per 30 days | Reference |
|---|---|---|---|
| Pemetrexed | £345.00 | £492.86 | NHS Payment Scheme2023/25:[104] average, SB13Z & SB15Z, Deliver more Complex Parenteral Chemotherapy at First Attendance & Deliver Subsequent Elements of a Chemotherapy Cycle |
| PDC | £345.00 | £492.86 | |
| Docetaxel | £345.00 | £492.86 | |
| ABCP | £345.00 | £492.86 | |

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; NHS, National Health Service; PDC, platinum doublet chemotherapy.

### B.3.6.2 Treatment monitoring costs

Costs related to drug monitoring were based on the EMA label information for each treatment (no monitoring specified for oral treatments) and the costs of lab tests were sourced from National Schedule of NHS 2021/22.[109] Since no frequency data was given in the EMA label information for PDC, it was assumed all tests were conducted once every treatment cycle. Table 59 presents a summary of the monitoring costs applied in the model. Monitoring costs are applied every 30 days to all patients whilst on treatment.

**Table 59: Monitoring costs included in the model**

| Treatment | Cost item | Number per treatment cycle | Unit cost | Cost per treatment cycle | Description |
|---|---|---|---|---|---|
| Osimertinib | N/A | N/A | N/A | N/A | No monitoring costs assumed for oral treatments (this approach was adopted in TA654[59]) |
| PDC | Liver function test | 1 | £1.64 | £9.18 | National Schedule of NHS 2021/22: DAPS04, Clinical biochemistry.[109] Inflated using PSSRU 2022/23 annual inflation rate[105] |
| | Renal function test | 1 | £1.64 | | |
| | Complete blood count | 1 | £3.14 | | National Schedule of NHS 2021/22: DAPS05, Haematology.[109] Inflated using PSSRU 2022/23 annual inflation rate[105] |
| Pemetrexed | Liver function test | 1 | £1.64 | £9.18 | National Schedule of NHS 2021/22: DAPS04, Clinical biochemistry.[109] Inflated using PSSRU 2022/23 annual inflation rate[105] |
| | Renal function test | 1 | £1.64 | | |
| | Complete blood count | 1 | £3.14 | | National Schedule of NHS 2021/22: DAPS05, Haematology.[109] Inflated using PSSRU 2022/23 annual inflation rate[105] |
| Docetaxel | Complete blood count | 1 | £3.14 | £4.49 | National Schedule of NHS 2021/22: DAPS05, Haematology.[109] Inflated using PSSRU 2022/23 annual inflation rate[105] |



| Treatment | Cost item | Number per treatment cycle | Unit cost | Cost per treatment cycle | Description |
|---|---|---|---|---|---|
| ABCP | Liver function test | 1 | £1.64 | £9.18 | National Schedule of NHS 2021/22: DAPS04, Clinical biochemistry.[109] Inflated using PSSRU 2022/23 annual inflation rate[105] |
| | Renal function test | 1 | £1.64 | | |
| | Complete blood count | 1 | £3.14 | | National Schedule of NHS 2021/22: DAPS05, Haematology.[109] Inflated using PSSRU 2022/23 annual inflation rate[105] |

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; N/A, not applicable; NHS, National Health Service; PDC, platinum doublet chemotherapy.

### B.3.6.3 Health-state unit costs and resource use

#### *B.3.6.3.1 Progression-free and progressed disease health state costs*

The health state resource use costs used in the model were sourced from the HTA study by Brown et al. (2013)[110] which has been used by the Assessment Group for the NICE multiple technology appraisal of erlotinib and gefitinib[111] and other recent single technology appraisals in NSCLC, including TA655, TA713, TA595, TA374, and TA654.[59, 86, 111-113] However, to ensure this source is reflective of current UK clinical practices, clinical expert feedback was sought. Clinicians stated that NSCLC patients receive an MRI scan every 3–6 months to monitor for CNS metastases; however, this key resource is not accounted for in the Brown et al. study[110]. Additionally, clinicians highlighted that patients with progressed disease might present in accident and emergency (A&E) departments due to the severity of their illness and difficulty accessing primary care services promptly. They also emphasised that routine practices do not typically include chest X-rays, GP surgeries, home visits, or therapist visits. In alignment with the clinician feedback, these resources were excluded from the progression-free and progressed disease health state costs, and MRI scans were added. A&E visits were also incorporated into the model for the progressed disease health state costs. The clinical nurse time required in the progressed disease health state was inflated from 0.99 to 1.33 based on clinician feedback.



The unit costs associated with each resource use item were sourced from NHS National Payment Schedule 2023 to 2025[104] and Personal Social Services Research Unit (PSSRU) (2022).[114] The progression-free and progressed disease health state costs are summarised in Table 60 and Table 61, respectively.

**Table 60: Progression-free health state costs**

| Cost item | Resource use per annum | Resource use per 30 days | Unit cost | Cost per 30 days† | Reference in submission |
|---|---|---|---|---|---|
| Outpatient visit | 9.61 | 0.79 | £141.00 | £111.29 | NHS Payment Scheme 2023/25:[104] WF01A, Non-Admitted Face-to-Face Attendance, First, Clinical oncology |
| MRI | 2.00 | 0.17 | £150.00 | £25.50 | NHS Payment Scheme 2023/25:[104] RD01A & RD02A, Magnetic Resonance Imaging Scan of One Area, without Contrast/ with Post-Contrast, 19 years and over |
| CT scan (chest) | 0.62 | 0.05 | £91.00 | £4.63 | NHS Payment Scheme 2023/25:[104] RD21A, Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over |
| CT scan (other) | 0.36 | 0.03 | £93.00 | £2.75 | NHS Payment Scheme 2023/25:[104] RD22Z, Computerised Tomography Scan of One Area, with Pre- and Post-Contrast |
| ECG | 1.04 | 0.09 | £135.00 | £11.53 | NHS Payment Scheme 2023/25:[104] EY51Z, Electrocardiogram Monitoring or Stress Testing (outpatient) |
| Clinical nurse specialist | 12 hours contact time | 0.99 | £52.00 | £51.25 | PSSRU 2023:[105] Cost per working hour band 6 hospital-based nurse |

† Calculated by multiplying the resource use per 30 days by the unit cost.
Abbreviations: CT, computer tomography; ECG, electrocardiogram; GP, general practitioner; HCHS, Hospital and Community Health Services; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.



**Table 61: Progressed disease health state costs**

| Cost item | Resource use per annum | Resource use per 30 days | Unit cost | Cost per 30 days† | Reference in submission |
|---|---|---|---|---|---|
| Outpatient visit | 7.91 | 0.65 | £141.00 | £91.61 | NHS Payment Scheme 2023/25:[104] WF01A, Non-Admitted Face-to-Face Attendance, First, Clinical oncology |
| MRI | 2.00 | 0.17 | £150.00 | £25.50 | NHS Payment Scheme 2023/25:[104] RD01A & RD02A, Magnetic Resonance Imaging Scan of One Area, without Contrast/ with Post-Contrast, 19 years and over |
| CT scan (chest) | 0.24 | 0.02 | £91.00 | £1.79 | NHS Payment Scheme 2023/25:[104] RD21A, Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over |
| CT scan (other) | 0.42 | 0.03 | £93.00 | £3.21 | NHS Payment Scheme 2023/25:[104] RD22Z, Computerised Tomography Scan of One Area, with Pre- and Post-Contrast |
| ECG | 0.88 | 0.07 | £135.00 | £9.76 | NHS Payment Scheme 2023/25:[104] EY51Z, Electrocardiogram Monitoring or Stress Testing (outpatient) |
| Clinical nurse specialist | 12 hours contact time | 1.33 | £52.00 | £69.16 | PSSRU 2023:[105] Cost per working hour band 6 hospital-based nurse |
| A&E visit | 17.16 consultations | 0.33 | £274.89 | £69.16 | NHS Payment Scheme 2023/25:[104] VB01Z:VB09Z, Emergency Medicine, Type 1 and 2 Departments |

† Calculated by multiplying the resource use per 30 days by the unit cost.
Abbreviations: CT, computer tomography; ECG, electrocardiogram; GP, general practitioner; HCHS, Hospital and Community Health Services; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 62 presents the total health state costs associated with the progression-free and progressed-disease health states.



**Table 62: Health state costs**

| Health state | Total cost per 30 days | Reference |
|---|---|---|
| PFS | £206.96 | Calculated as the sum of the cost per 30 days for all the cost items presented in Table 60 |
| PD | £291.74 | Calculated as the sum of the cost per 30 days for all the cost items presented in Table 61 |

Abbreviations: PD, progressed disease; PFS, progression-free survival.

### B.3.6.4 CNS metastases related costs

The health state costs associated with progression-free and progressed disease (as described in Section B.3.6.3.1) were inflated to account for the additional resource use associated with the management of CNS metastases. A study by Kong et al. (2021)[115] showed disease-related costs were 1.2 times higher in patients with NSCLC and brain metastases, compared with patients with NSCLC without brain metastases. Assuming that resource use for brain metastases is analogous to resource use for CNS metastases, a factor of 1.2 was applied to the disease management costs for the proportion of patients presenting with CNS metastases at baseline in each arm of the FLAURA2 trial (40%).[8] Table 63 presents the total health state costs for progression-free and progressed disease which account for CNS metastases-related costs. This approach is a conservative assumption that assumes that the proportion of patients presenting with CNS metastases is fixed over time, in the absence of literature displaying the change in the rate over time. The proportional increase in cost for patients with CNS metastases is an input in the model and is explored in sensitivity analyses, to fully assess the robustness of the assumption.

**Table 63: CNS metastases related costs**

| Health state | Proportion of patients with CNS metastases at baseline | Proportional increase in cost for patients with CNS metastases | Total cost |
|---|---|---|---|
| PFS | 40%[8] | 120%[115] | £223.46 |
| PD | | | £315.00 |

Abbreviations: CNS. Central nervous system; PD, progressed disease; PFS, progression-free survival.

The health state costs presented in Table 63 are used in the model base case.



### B.3.6.5 Terminal care/end of life costs

For patients who die in a given cycle, terminal care costs were applied as an instantaneous one-off cost on their transition to the death health state. Resource use for end-of-life/terminal care was based on information from a study by Brown et al. (2013)[110] which provides resource use for the time spent either in hospital, hospice, or at home. Costs were sourced from PSSRU 2022[114] and are presented in Table 64.

**Table 64: Terminal care/end of life costs**

| Items | Patients that died per setting | Unit cost | Total cost | Reference |
|---|---|---|---|---|
| Hospital | 55.8% | £10,782 | £6,016.36 | PSSRU 2023:[105] Hospital care |
| Hospice | 16.9% | £25,198 | £4,258.46 | PSSRU 2023:[105] Residential and nursing care |
| Home | 27.3% | £4,839 | £1,321.05 | PSSRU 2023:[105] Home care |
| **Total** | | | **£11,595.87** | - |

Abbreviations: PSSRU, Personal Social Services Research Unit

### B.3.6.6 Adverse reaction unit costs and resource use

A description of the AEs included in the model is presented in Section B.3.4.4. As per the approach used for AE disutilities, AE costs were applied in the model as fixed payoffs in the first cycle. The cost per AE event is presented in Table 65.

**Table 65: List of adverse reactions and summary of costs in the economic model**

| Adverse reactions | Cost per event | Reference in submission |
|---|---|---|
| Diarrhoea | £5,372.73 | NHS Payment Scheme 2023/25:[104] FD10A-M Non-Malignant Gastrointestinal Tract Disorders with/without (single/multiple) Interventions; Non-elective spell |
| Fatigue | £3,729.50 | NHS Payment Scheme 2023/25:[104] SA01G-SA01K Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia; Non-elective spell |
| Anaemia | £2,775.60 | NHS Payment Scheme 2023/25:[104] SA04G-L, Iron Deficiency Anaemia; Non-elective stay |
| Decreased appetite | £5,805.80 | NHS Payment Scheme 2023/25:[104] FD04A-E, Nutritional disorders with/without interventions; Non-elective spell |
| Pneumonia | £5,237.18 | NHS Payment Scheme 2023/25:[104] DZ11K-V, Lobar, atypical or viral pneumonia with/without single/multiple interventions; Non-elective spell |



| Adverse reactions | Cost per event | Reference in submission |
|---|---|---|
| Neutropenia | £2,629.67 | NHS Payment Scheme 2023/25:[104] SA08G-J. Other haematological or splenic disorders; Non-elective spell |
| Neutrophil count decreased | £2,629.67 | Assumed same as neutropenia |
| Platelet count decreased | £2,627.80 | NHS Payment Scheme 2023/25:[104] SA09G-K, Other red blood cell disorders; Non-elective spell |
| Thrombocytopenia | £3,241.75 | NHS Payment Scheme 2023/25:[104] SA12G-K, Thrombocytopenia with CC; Non-elective spell |
| Febrile neutropenia | £3,625.00 | NHS Payment Scheme 2023/25:[104] WJ07A-D, Fever of Unknown Origins with/without interventions; Non-elective spell |
| White blood cell count decreased | £2,629.67 | Assumed same as neutropenia |
| Ejection fraction decreased | £3,757.60 | NHS Payment Scheme 2023/25:[104] EB03A-E, Heart failure or shock; Non-elective stay |
| Leukopenia | £2,629.67 | Assumed same as neutropenia |
| Pulmonary embolism | £4,125.71 | NHS Payment Scheme 2023/25:[104] DZ09J-Q, Pulmonary Embolus with/without intervention; Non-elective spell |

### *B.3.7 Severity*

The severity modifier was deemed not to be applicable for this submission.

### *B.3.8 Uncertainty*

Uncertainty in the model is explored in Section B.3.12. Uncertainty relating to the model parameters is assessed through probabilistic sensitivity analysis (PSA) in Section B.3.12.1 and deterministic sensitivity analysis (DSA) in Section B.3.12.2. Scenario analyses are also used to analyse the impact of uncertainty on model input and assumptions are discussed in Section B.3.12.3.

### *B.3.9 Managed access proposal*

Not applicable.

### *B.3.10 Summary of base-case analysis inputs and assumptions*

Table 66 provides a list of all the base-case inputs which are varied in DSA and PSA and details the CI by which they were varied, and the distributions assumed.



**Table 66: Summary of variables applied in the economic model**

| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| **Model setup parameters** | | | |
| Time horizon | 20 years | Fixed | B.3.2.3 |
| Cycle length | 30 days | Fixed | |
| Discount rate - Costs | 3.5% | LCI: 3.5%, UCI: 3.85% (Normal) | |
| Discount rate - QALYs | 3.5% | | |
| **Baseline patient characteristics** | | | |
| Starting age (years) | 60.8 | LCI: 54.7 UCI: 66.9 (Log-normal) | B.3.2.1 |
| Body weight (kg) | 64.8 | LCI: 58.3 UCI: 71.3 (Log-normal) | B.3.6.1.1 |
| Height (cm) | 162.0 | LCI: 146.3 UCI: 178.9 (Log-normal) | |
| Proportion of female | 61.4% | LCI: 55.26% UCI: 67.54% (Beta) | B.3.2.1 |
| Proportion of patients on cisplatin | 50.0% | LCI: 45.00% UCI: 55.00% (Beta) | B.3.6.1.2.2 |
| Proportion of patients on carboplatin | 50.0% | LCI: 45.00% UCI: 55.00% (Beta) | |
| **Base case PFS curve parameters** | | | |
| **Osimertinib plus chemotherapy** | | Cholesky decomposition of variance-covariance matrix used | B.3.3.3 |
| Distribution | Weibull | | |
| Parameter 1 | 1.34 | | |
| Parameter 2 | 35.41 | | |
| **Osimertinib monotherapy** | | Cholesky decomposition of variance-covariance matrix used | |
| Distribution | Weibull | | |
| Parameter 1 | 1.22 | | |
| Parameter 2 | 25.41 | | |
| **Base case OS curve parameters** | | | |
| **Osimertinib plus chemotherapy** | | Cholesky decomposition of variance-covariance matrix used | B.3.3.2 |
| Distribution | 2 spline normal | | |
| Parameter 1 | -2.205 | | |
| Parameter 2 | 0.325 | | |
| Parameter 3 | 0.453 | | |



| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Parameter 4 | -1.118 | | |
| Parameter 5 | 0.000 | | |
| Parameter 6 | -2.029 | | |
| Parameter 7 | 2.583 | | |
| Parameter 8 | 3.238 | | |
| Parameter 9 | 3.701 | | |
| Parameter 10 | 0.000 | | |
| **Osimertinib monotherapy** | | | |
| Distribution | 2 spline normal | Cholesky decomposition of variance-covariance matrix used | B.3.3.2 |
| Parameter 1 | -2.577 | | |
| Parameter 2 | 0.316 | | |
| Parameter 3 | 0.226 | | |
| Parameter 4 | -0.631 | | |
| Parameter 5 | 0.000 | | |
| Parameter 6 | -0.371 | | |
| Parameter 7 | 2.834 | | |
| Parameter 8 | 3.223 | | |
| Parameter 9 | 3.653 | | |
| Parameter 10 | 0.000 | | |
| **Base case TTD curve parameters** | | | |
| **Osimertinib plus chemotherapy (osimertinib)** | | Cholesky decomposition of variance-covariance matrix used | B.3.3.4 |
| Distribution | Gompertz | | |
| Parameter 1 | 0.02 | | |
| Parameter 2 | 0.02 | | |
| **Osimertinib plus chemotherapy (pemetrexed)** | | | |
| Distribution | Exponential | | |
| Parameter 1 | 0.06 | | |
| Parameter 2 | 0.00 | | |
| **Osimertinib monotherapy** | | | |
| Distribution | Gamma | | |
| Parameter 1 | 1.37 | | |
| Parameter 2 | 0.05 | | |
| **Health state costs** | | | |



| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Progression free | [redacted] | LCI: 0.75 UCI: 0.91 (Beta) | B.3.4.4 |
| Progressed disease | 0.640 | LCI: 0.58 UCI: 0.70 (Beta) | |
| **Adverse event rates – osimertinib plus chemotherapy** | | | |
| Diarrhoea | 2.90% | LCI: 2.61% UCI: 3.19% (Beta) | B.3.4.5 |
| Fatigue | 2.90% | LCI: 2.61% UCI: 3.19% (Beta) | |
| Anaemia | 19.93% | LCI: 17.93% UCI: 21.92% (Beta) | |
| Decreased appetite | 2.90% | LCI: 2.61% UCI: 3.19% (Beta) | |
| Pneumonia | 2.17% | LCI: 1.96% UCI: 2.39% (Beta) | |
| Neutropenia | 13.41% | LCI: 12.07% UCI: 14.75% (Beta) | |
| Neutrophil count decreased | 11.23% | LCI: 10.11% UCI: 12.36% (Beta) | |
| Platelet count decreased | 7.61% | LCI: 6.85% UCI: 8.37% (Beta) | |
| Thrombocytopenia | 6.88% | LCI: 6.20% UCI: 7.57% (Beta) | |
| Febrile neutropenia | 3.99% | LCI: 3.59% UCI: 4.38% (Beta) | |
| White blood cell count decreased | 3.26% | LCI: 2.93% UCI: 3.59% (Beta) | |
| Ejection fraction decreased | 2.90% | LCI: 2.61% UCI: 3.19% (Beta) | |
| Leukopenia | 2.90% | LCI: 2.61% UCI: 3.19% (Beta) | |
| Pulmonary embolism | 2.17% | LCI: 1.96% UCI: 2.39% (Beta) | |
| **Adverse event rates – osimertinib monotherapy** | | | |
| Diarrhoea | 0.36% | LCI: 0.33% UCI: 0.40% (Beta) | B.3.4.5 |
| Fatigue | 0.36% | LCI: 0.33% UCI: 0.40% (Beta) | |



| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Anaemia | 0.36% | LCI: 0.33% UCI: 0.40% (Beta) | |
| Decreased appetite | 0.73% | LCI: 0.65% UCI: 0.80% (Beta) | |
| Pneumonia | 1.82% | LCI: 1.64% UCI: 2.00% (Beta) | |
| Neutropenia | 0.73% | LCI: 0.65% UCI: 0.80% (Beta) | |
| Neutrophil count decreased | 0.73% | LCI: 0.65% UCI: 0.80% (Beta) | |
| Platelet count decreased | 0.00% | LCI: 0.00% UCI: 0.00% (Beta) | |
| Thrombocytopenia | 1.09% | LCI: 0.98% UCI: 1.20% (Beta) | |
| Febrile neutropenia | 0.00% | LCI: 0.00% UCI: 0.00% (Beta) | |
| White blood cell count decreased | 0.36% | LCI: 0.33% UCI: 0.40% (Beta) | |
| Ejection fraction decreased | 1.09% | LCI: 0.98% UCI: 1.20% (Beta) | |
| Leukopenia | 0.00% | LCI: 0.00% UCI: 0.00% (Beta) | |
| Pulmonary embolism | 1.09% | LCI: 0.98% UCI: 1.20% (Beta) | |
| **Adverse event disutilities** | | | |
| Diarrhoea | -0.00013 | LCI: -0.00012 UCI: -0.00014 (Gamma) | B.3.4.6 |
| Fatigue | -0.00020 | LCI: -0.00018 UCI: -0.00022 (Gamma) | |
| Anaemia | -0.00020 | LCI: -0.00018 UCI: -0.00022 (Gamma) | |
| Decreased appetite | -0.00020 | LCI: -0.00018 UCI: -0.00022 (Gamma) | |
| Pneumonia | -0.00002 | LCI: -0.00002 UCI: -0.00002 (Gamma) | |
| Neutropenia | -0.00025 | LCI: -0.00022 UCI: -0.00027 (Gamma) | |
| Neutrophil count decreased | -0.00025 | LCI: -0.00022 UCI: -0.00027 (Gamma) | |



| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Platelet count decreased | -0.00025 | LCI: -0.00022 UCI: -0.00027 (Gamma) | |
| Thrombocytopenia | -0.00025 | LCI: -0.00022 UCI: -0.00027 (Gamma) | |
| Febrile neutropenia | -0.00025 | LCI: -0.00022 UCI: -0.00027 (Gamma) | |
| White blood cell count decreased | -0.00025 | LCI: -0.00022 UCI: -0.00027 (Gamma) | |
| Ejection fraction decreased | -0.00017 | LCI: -0.00016 UCI: -0.00019 (Gamma) | |
| Leukopenia | -0.00025 | LCI: -0.00022 UCI: -0.00027 (Gamma) | |
| Pulmonary embolism | -0.00017 | LCI: -0.00016 UCI: -0.00019 (Gamma) | |
| **Treatment acquisition cost per 30 days** | | | |
| Osimertinib plus chemotherapy (initial phase) | £23.47 | LCI: £21.13 UCI: £25.82 (Gamma) | B.3.6.1.1 |
| Osimertinib plus chemotherapy (maintenance phase - chemotherapy) | £320.11 | LCI: £288.09 UCI: £352.12 (Gamma) | |
| Osimertinib plus chemotherapy (maintenance phase - osimertinib) | £2,019.62 | LCI: £1817.65 UCI: £2221.58 (Gamma) | |
| Osimertinib monotherapy | £2,085.80 | LCI: £1877.22 UCI: £2294.38 (Gamma) | |
| **Administration costs** | | | |
| Cisplatin | £492.86 | LCI: £443.57 UCI: £542.14 (Gamma) | B.3.6.1.3 |
| Carboplatin | £492.86 | LCI: £443.57 UCI: £542.14 (Gamma) | |
| Pemetrexed | £492.86 | LCI: £443.57 UCI: £542.14 (Gamma) | |
| Osimertinib | £10.40 | LCI: £9.36 UCI: £11.44 (Gamma) | |
| **Monitoring costs** | | | |
| Monitoring costs - Cost per 30 days - Osimertinib plus Chemotherapy | £9.18 | LCI: £8.26 UCI: £10.10 (Gamma) | B.3.6.2 |
| Monitoring costs - Cost per 30 days - Osimertinib | £0.00 | LCI: £0.00 UCI: £0.00 (Gamma) | |



| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| **Distribution of patients across second-line treatments** | | | |
| **From osimertinib plus chemotherapy** | | | |
| PDC | [redacted] | LCI: 12.44% UCI: 15.20% (Dirichlet) | B.3.6.1.4 |
| Pemetrexed | [redacted] | LCI: 0.00% UCI: 0.00% (Dirichlet) | |
| Docetaxel | [redacted] | LCI: 16.10% UCI: 19.67% (Dirichlet) | |
| ABCP | [redacted] | LCI: 5.40% UCI: 6.60% (Dirichlet) | |
| **From osimertinib monotherapy** | | | |
| PDC | [redacted] | LCI: 42.32% UCI: 51.72% (Dirichlet) | B.3.6.1.4 |
| Pemetrexed | [redacted] | LCI: 0.00% UCI: 0.00% (Dirichlet) | |
| Docetaxel | [redacted] | LCI: 19.80% UCI: 24.20% (Dirichlet) | |
| ABCP | [redacted] | LCI: 8.10% UCI: 9.90% (Dirichlet) | |
| **Distribution of patients across third-line treatments** | | | |
| **From osimertinib plus chemotherapy** | | | |
| PDC | [redacted] | LCI: 1.46% UCI: 1.79% (Dirichlet) | B.3.6.1.4 |
| Pemetrexed | [redacted] | LCI: 0.00% UCI: 0.00% (Dirichlet) | |
| Docetaxel | [redacted] | LCI: 0.00% UCI: 0.00% (Dirichlet) | |
| ABCP | [redacted] | LCI: 3.66% UCI: 4.47% (Dirichlet) | |
| **From osimertinib monotherapy** | | | |
| PDC | [redacted] | LCI: 6.56% UCI: 8.01% (Dirichlet) | B.3.6.1.4 |
| Pemetrexed | [redacted] | LCI: 0.00% UCI: 0.00% (Dirichlet) | |
| Docetaxel | [redacted] | LCI: 6.56% UCI: 8.01% (Dirichlet) | |
| ABCP | [redacted] | LCI: 6.56% UCI: 8.01% (Dirichlet) | |



| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| **Subsequent treatment cost per 30 days** | | | |
| PDC | £877.41 | LCI: £793.07 UCI: £969.31 (Gamma) | B.3.6.1.4 |
| Pemetrexed | £801.68 | LCI: £0.00 UCI: £0.00 (Gamma) | |
| Docetaxel | £510.45 | LCI: £771.94 UCI: £943.48 (Gamma) | |
| ABCP | £8,962.36 | LCI: £459.43 UCI: £561.52 (Gamma) | |
| **CNS metastases related costs** | | | |
| Proportion of patients with CNS metastases at baseline | 120% | LCI: 108% UCI: 132% (Beta) | B.3.6.4 |
| Proportional increase in cost for patients with CNS metastases | 40% | LCI: 36% UCI: 44% (Beta) | |
| **Terminal care/end of life unit costs** | | | |
| Hospital | £10,782.00 | LCI: £9703.80 UCI: £11860.20 (Gamma) | B.3.6.5 |
| Hospice | £25,198.00 | LCI: £22678.20 UCI: £27717.80 (Gamma) | |
| Home | £4,839.00 | LCI: £4355.10 UCI: £5322.90 (Gamma) | |
| **Patients that died per terminal care/end of life setting** | | | |
| Hospital | 55.8% | LCI: 50.22% UCI: 61.38% (Beta) | B.3.6.5 |
| Hospice | 16.9% | LCI: 15.21% UCI: 18.59% (Beta) | |
| Home | 27.3% | LCI: 24.57% UCI: 30.03% (Beta) | |
| **Adverse event costs** | | | |
| Diarrhoea | £5,372.73 | LCI: £4835.45 UCI: £5910.00 (Gamma) | B.3.6.6 |
| Fatigue | £3,729.50 | LCI: £3356.55 UCI: £4102.45 (Gamma) | |
| Anaemia | £2,775.60 | LCI: £2498.04 UCI: £3053.16 (Gamma) | |
| Decreased appetite | £5,805.80 | LCI: £5225.22 UCI: £6386.38 (Gamma) | |
| Pneumonia | £5,237.18 | LCI: £4713.46 UCI: £5760.90 (Gamma) | |



| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Neutropenia | £2,629.67 | LCI: £2366.70 UCI: £2892.63 (Gamma) | |
| Neutrophil count decreased | £2,629.67 | LCI: £2366.70 UCI: £2892.63 (Gamma) | |
| Platelet count decreased | £2,627.80 | LCI: £2365.02 UCI: £2890.58 (Gamma) | |
| Thrombocytopenia | £3,241.75 | LCI: £2917.58 UCI: £3565.93 (Gamma) | |
| Febrile neutropenia | £3,625.00 | LCI: £3262.50 UCI: £3987.50 (Gamma) | |
| White blood cell count decreased | £2,629.67 | LCI: £2366.70 UCI: £2892.63 (Gamma) | |
| Ejection fraction decreased | £3,757.60 | LCI: £3381.84 UCI: £4133.36 (Gamma) | |
| Leukopenia | £2,629.67 | LCI: £2366.70 UCI: £2892.63 (Gamma) | |
| Pulmonary embolism | £4,125.71 | LCI: £3713.14 UCI: £4538.29 (Gamma) | |

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; CNS, central nervous system; LCI, lower confidence interval; OS, overall survival; PDC, platinum doublet chemotherapy; PFS, progression-free survival; QALY, quality-adjusted life year; UCI, upper confidence interval.

### B.3.10.1 Assumptions

The main assumptions of the economic model, alongside supporting justification, and scenario analyses are presented in Table 67. The focus of this table are the assumptions/inputs which are varied in scenario analyses.



**Table 67: Base case model assumptions and scenarios**

| Model input and cross reference | Source/assumption | Justification | Scenarios |
|---|---|---|---|
| **General** | | | |
| Patient characteristics | Patient characteristics (age and body surface area) were derived from FLAURA2 and were assumed to be representative of EGFRm NSCLC patients in the UK | Advisors in the UK advisory board agreed the FLAURA2 patient population was representative of the EGFRm NSCLC population in the UK[2] | N/A; patient characteristics were varied in the DSA |
| Time horizon | 20-year time horizon was utilised as <1% of patients were alive after 20 years | Preference specified in NICE reference case | 10 years |
| Discounting | Costs and health outcomes were discounted annually by 3.5% | Preference specified in NICE reference case | 1.5% discount rate applied to costs and health outcomes |
| **Intervention and comparators** | | | |
| Comparator | Osimertinib monotherapy was assumed to be the only relevant comparator | Osimertinib monotherapy represents the current SoC for patients in England who are receiving first-line treatment for locally advanced/metastatic NSCLC and is used in 86% of EGFRm patients.[1] The alternative treatments (dacomitinib, afatinib, erlotinib and gefitinib) are rarely used and osimertinib with pemetrexed and platinum-based chemotherapy is expected to displace osimertinib monotherapy only. This positioning was validated by UK clinical insight with, 9 UK-based clinical experts consulted as part of an advisory board unanimously stating that osimertinib monotherapy was their current first-line treatment of choice for metastatic EGFRm NSCLC. This is further supported by current clinical guidelines such as ESMO, where osimertinib is recommended as the preferable first-line treatment option for patients with a classical activating EGFR mutation (exon 19 deletion or exon 21 L858R), especially for patients with CNS metastases.[3] | N/A |

| Model input and cross reference | Source/assumption | Justification | Scenarios |
|---|---|---|---|
| Subsequent treatments | PDC, pemetrexed, docetaxel, and ABCP included as subsequent treatment options in the base case | Clinical experts review the distribution of patients across subsequent treatments observed in FLAURA2 and reweighted these values to reflect NHS clinical practice | N/A |
| | The cost of subsequent treatments was computed as a one-off cost, and includes drug acquisition, administration and monitoring. These costs were incorporated on discontinuation of first-line treatment | This approach has been adopted in previous NICE submissions (TA595 and TA654)[59, 86] | N/A |
| | The benefit associated with subsequent treatments is assumed to be implicitly accounted for in the extrapolated OS data from FLAURA2, including ABCP | Although ABCP was not listed as a subsequent treatment option in FLAURA2, components of the ABCP regimen were included. Therefore, it is assumed that these components serve as an adequate proxy for ABCP, thus allowing the assumption that ABCP's benefits are captured within OS to be made | N/A |
| Initial treatment phase | Proportion of patients receiving cisplatin and carboplatin | This was not reported within FLAURA2 study so a 50:50 assumption was made | Cisplatin = 25%; Carboplatin = 75%<br>Cisplatin = 75%; Carboplatin = 25% |
| PDC | The duration of PDC as a subsequent treatment was informed by published literature. | Published literature was utilised in the base case due to the immaturity of the PDC TTD data reported in FLAURA2 | N/A |
| RDI | RDI for osimertinib and pemetrexed was informed by FLAURA2 | FLAURA2 is the key evidence source for the osimertinib plus chemotherapy and osimertinib monotherapy arm | Assuming all treatments have a RDI of 100% |
| | RDI data was not available for cisplatin or carboplatin, so RDI 100% was conservatively assumed. | This data was not available from FLAURA2 so a conservative assumption was made | N/A |

| Model input and cross reference | Source/assumption | Justification | Scenarios |
|---|---|---|---|
| **Efficacy** | | | |
| Proportional hazards | Proportional hazards assumption is invalidated | The log cumulative hazard plots cross between the osimertinib monotherapy and osimertinib plus chemotherapy arms. | N/A |
| PFS source | PFS from FLAURA2 based on investigator assessment | There was a statistically significant and clinically meaningful improvement in PFS in patients randomised to osimertinib plus chemotherapy compared to osimertinib monotherapy based on Investigator-assessed per RECIST v1.1<br>TA654 also selected Investigator as the PFS source | PFS informed by BICR |
| TTD | TTD was not bounded by PFS, allowing patients to continue with their first-line treatment after progressing | To account for the time between the patient's disease progression and the initiation of alternative subsequent treatment | N/A |
| | TTD and PFS were informed by FLAURA2 data that had been extrapolated over the model time horizon. TTD informed the time on treatment. | Typically, oncology studies use TTD to inform time on treatment rather than PFS. This assumption allowed for situations that may occur in clinical practice. Patients in PFS health state may discontinue osimertinib. Similarly, patients that progress may continue taking osimertinib | |
| PDC TTD (subsequent treatment) | The treatment duration of PDC was informed by extrapolated TTD data collected in the FLAURA2 study | To be consistent with the rest of the model which uses extrapolated data to inform | N/A |
| **Costs** | | | |
| Treatment discount | Osimertinib in the osimertinib plus chemotherapy arm had a discount of [redacted] applied to its list price.<br>Osimertinib in the osimertinib monotherapy arm had a discount of [redacted] applied to its list price | [redacted] | N/A |

| Model input and cross reference | Source/assumption | Justification | Scenarios |
|---|---|---|---|
| Osimertinib drug acquisition cost | Calculated based on available formulations, pack sizes, unit costs, and price per mg, patients incur the cost of osimertinib for the duration of treatment | To account for the total cost of treating patients with osimertinib | The additional incremental background cost of osimertinib was removed to account for the high cost of osimertinib as background therapy as per NICE DSU guidance[116] |
| Chemotherapy drug acquisition costs | Pack prices obtained from eMIT are applied to cisplatin, carboplatin, and pemetrexed | Preference specified in NICE reference case | N/A |
| Chemotherapy administration costs | Cisplatin and carboplatin do not incur administration costs | This is because pemetrexed is administrated at the same time as cisplatin and carboplatin in the initial treatment phase. Therefore, applying administration costs to cisplatin and carboplatin would be double counting | Scenario that includes administration cost for cisplatin and carboplatin |
| PFS and PD health state costs | Items deemed relevant to expert opinions informed the health state costs | Clinical opinions informed the resource use considered relevant to clinical practice | N/A |
| Wastage | Wastage was excluded from the model | This approach was adopted in TA654 | Wastage included for IV treatments |

| Model input and cross reference | Source/assumption | Justification | Scenarios |
|---|---|---|---|
| **Utility** | | | |
| Health state utility values | HSUVs were assumed constant over time, treatment agnostic, and applied directly to health states.<br>FLAURA2 for informed the HSUV for PFS and Labbe 2017 informed the PD HSUV | The PD value based on UK conversions reported by Labbé et al. was more appropriate as most patients had multiple assessments over time, at various time points of their disease and treatment course. Furthermore, the PD utility value of 0.64 is similar to those used and accepted by ERGs in two previous NSCLC NICE submissions: TA309/TA402[91] and TA347[92]. TA654 also utilised PD value reported by Labbé et al. to inform its base case | FLAURA2 (PF & PD)[8] |

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; BICR, blinded independent central review; CT, computed tomography; DSA, deterministic sensitivity analysis; ECG, electrocardiogram; EGFRm, epidermal growth factor receptor mutation; ERG, evidence review group; GP, general practitioner; HSUV, health state utility value; HTA, health technology assessment; IV, intravenous; N/A, not applicable; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressed disease; PDC, platinum doublet chemotherapy; PF, progression free; PFS, progression-free survival; RDI, relative dose intensity; RECIST, Response Evaluation Criteria In Solid Tumors; SoC, standard of care; TTD, time to treatment discontinuation.

## *B.3.11 Base-case results*

### B.3.11.1 Base-case incremental cost-effectiveness analysis results

The base case results are presented in Table 68 and Table 69. Clinical outcomes and the disaggregated results are presented in Appendix J.

All results presented in Sections B.3.11 to B.3.12.3 use the commercial access agreement for osimertinib in both the osimertinib plus chemotherapy and the osimertinib monotherapy. List prices are used for all other treatments, including chemotherapy and subsequent treatments. The base case results show that osimertinib plus chemotherapy is associated with an increase of [redacted] life years, and [redacted] QALYs compared with osimertinib monotherapy. Osimertinib plus chemotherapy is associated with an increase in costs of [redacted] versus osimertinib monotherapy, resulting in an ICER of £27,280.04 versus osimertinib monotherapy.

The base case net health benefit at £20,000 and £30,000 WTP thresholds are shown in Table 69. The base case net health benefit shows a NHB of -0.158 at the £20,000 WTP threshold, and a NHB of 0.036 at the £30,000 WTP threshold, based on the [redacted].



**Table 68: Base-case results**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| Osimertinib + Chemotherapy | [redacted] | [redacted] | [redacted] | - | - | - | - | - |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £27,280.04 | £27,280.04 |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

**Table 69: Net health benefit**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | NHB at £20,000 | NHB at £30,000 |
|---|---|---|---|---|---|---|
| Osimertinib + Chemotherapy | [redacted] | [redacted] | - | - | - | - |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] | -0.155 | 0.039 |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit.

## *B.3.12 Exploring uncertainty*

### B.3.12.1 Probabilistic sensitivity analysis

PSA was performed by varying all parameters in the model simultaneously by sampling from probability distributions. The ranges and the distributions assumed are shown in Table 66. For parameters where CIs and/or standard deviations/standard errors of the mean (SDs/SEs) were available, these are used to estimate parameter uncertainty. For variables where no CIs and/or SDs/SEs were available, the CIs are assumed arbitrarily to be +/-10% of the base case value, or other plausible maximum/minimum plausible ranges if +/-10% is implausible.

The results of the pairwise PSA are shown in Table 70 and Figure 31. These results were generated based on 1,000 simulations (convergence of the ICER was achieved by approximately the 200$^{th}$ simulation). The PSA results show osimertinib plus chemotherapy to be cost effective at the £30,000 WTP threshold. The ICER is £28,318.23 in the probabilistic analysis, and £27,280.04 in the deterministic analysis when compared to osimertinib monotherapy.

The results were plotted in a cost-effectiveness acceptability curve (CEAC) which shows the probability of either treatment being the most cost-effective across a range of WTP thresholds (Figure 32). At a willingness to pay threshold of £30,000, osimertinib plus chemotherapy is associated with a 52% probability of being cost effective.



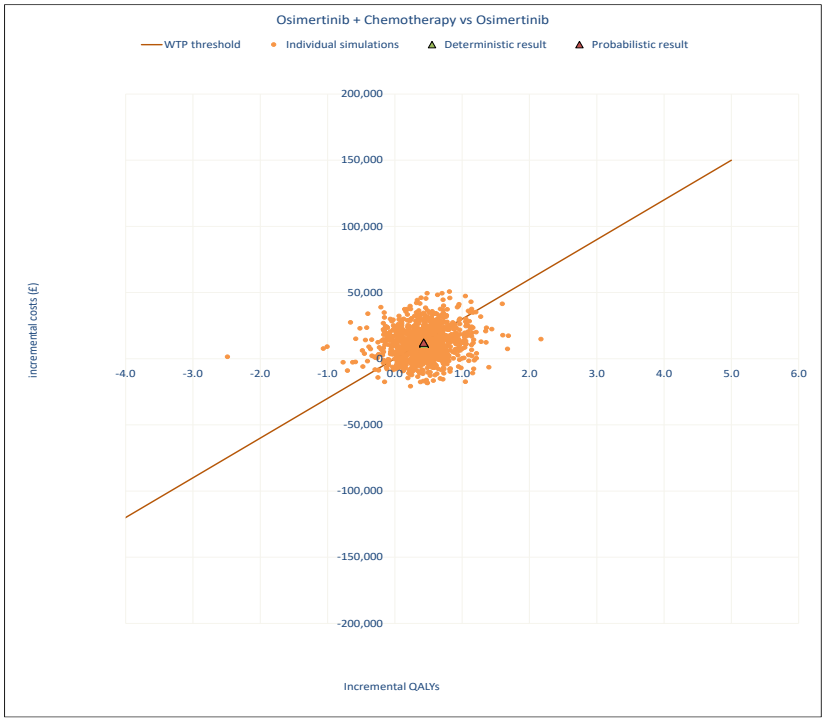
 

**Table 70: Base-case probabilistic incremental cost-effectiveness results**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| Osimertinib + Chemotherapy | [redacted] | [redacted] | [redacted] | - | - | - | - | - |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £28,318.23 | £28,318.23 |

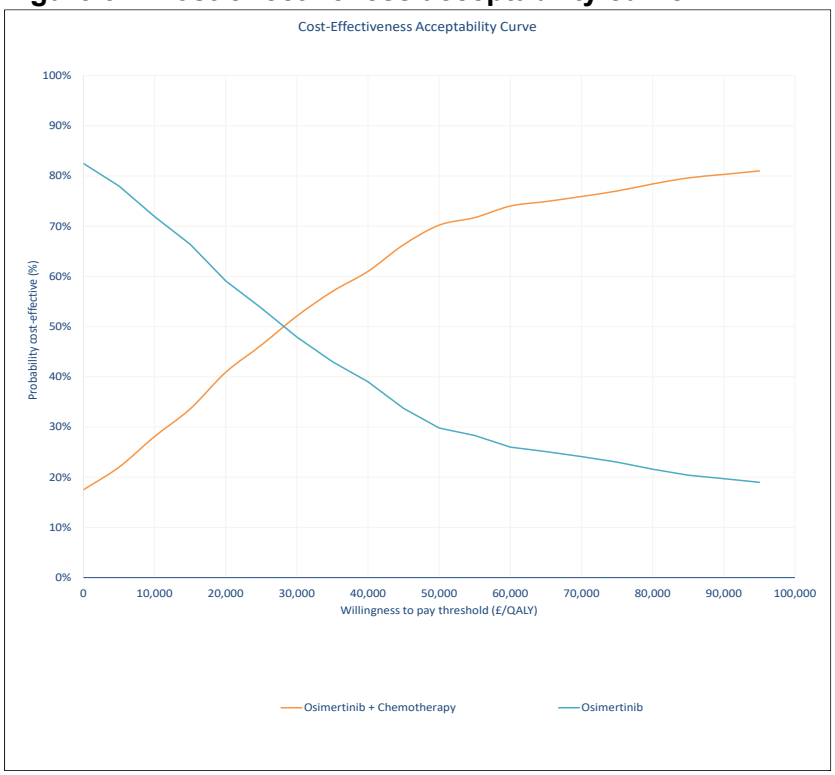
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

## Figure 31: Cost-effectiveness plane




Abbreviations: WTP, willingness-to-pay

## Figure 32: Cost-effectiveness acceptability curve





### B.3.12.2 Deterministic sensitivity analysis

In the DSA, each input parameter was varied +/-10% (or other plausible maximum/minimum plausible ranges if +/-10% is implausible) to explore the impact of each parameter on model outcomes. Parameters with no associated uncertainty, such as drug costs, are excluded from the analysis. Interdependent variables that cannot be varied individually, such as efficacy extrapolation parameters, were also excluded. All parameters included in the one-way sensitivity analysis are presented in Table 71 and the results presented graphically in Figure 33.

The results show that the most influential parameters on the model results are those that are related to the health state utilities, proportion of patients receiving ABCP as a second-line treatment, and the administration costs associated with pemetrexed. The progression-free health state utility value was the most influential parameter. This is driven by the improved PFS osimertinib plus chemotherapy has which results in more patients remaining on first-line treatments for longer which results in higher drug acquisition costs. Except for one analysis, all deterministic analyses were cost-effective at a WTP threshold of £30,000 per QALY gained

**Table 71: DSA results for osimertinib plus chemotherapy vs osimertinib monotherapy**

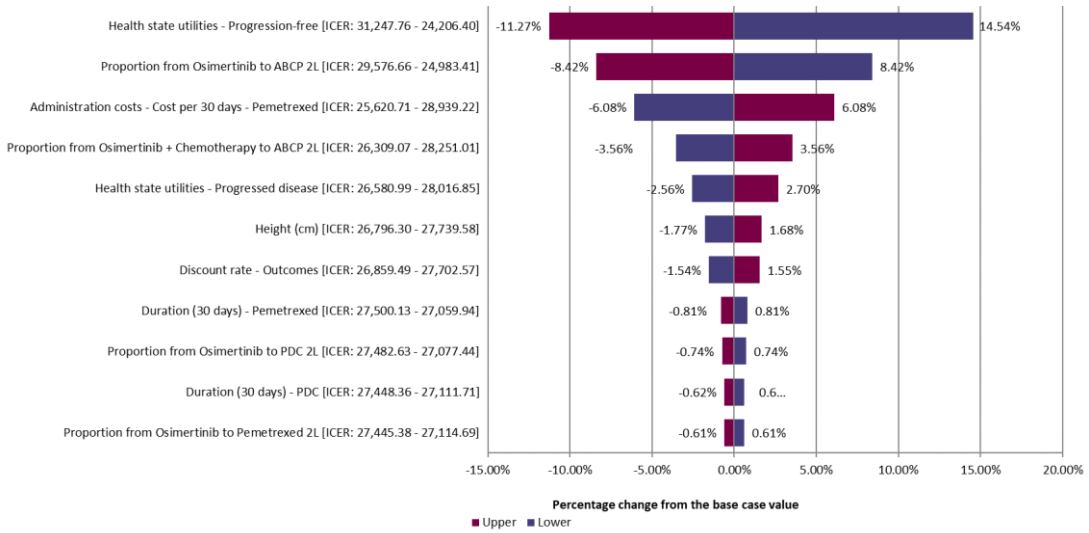
| Parameter | ICER with low value | ICER with high value | Difference (£) |
|---|---|---|---|
| Health state utilities - Progression-free | £31,247.76 | £24,206.40 | £7,041.36 |
| Proportion from Osimertinib to ABCP 2L | £29,576.66 | £24,983.41 | £4,593.25 |
| Administration costs - Cost per 30 days - Pemetrexed | £25,620.71 | £28,939.22 | £3,318.51 |
| Proportion from Osimertinib plus Chemotherapy to ABCP 2L | £26,309.07 | £28,251.01 | £1,941.94 |
| Health state utilities - Progressed disease | £26,580.99 | £28,016.85 | £1,435.86 |
| Height (cm) | £26,796.30 | £27,739.58 | £943.28 |
| Discount rate - Outcomes | £26,859.49 | £27,702.57 | £843.08 |
| Duration (30 days) - Pemetrexed | £27,500.13 | £27,059.94 | £440.20 |
| Proportion from Osimertinib to PDC 2L | £27,482.63 | £27,077.44 | £405.19 |
| Duration (30 days) - PDC | £27,448.36 | £27,111.71 | £336.65 |

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; PDC, platinum doublet chemotherapy.



**Figure 33: Tornado diagram**




Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; ICER, incremental cost-effectiveness ratio.

### B.3.12.3 Scenario analyses

To further explore the challenges relating to cost effectiveness of combination therapies and uncertainty around the modelled results, a series of scenario analyses were performed where specific alternative model assumptions were varied.

#### *B.3.12.3.1 Scenarios to address specific issues relating to combination therapies*

There are well understood challenges associated with the appraisal of combination therapies, particularly when add-on treatments result in improved survival and extend the use of background care. The NICE DSU previously identified circumstances where add-on medicines were unable to demonstrate cost effectiveness even at 'zero price' and the NICE Methods Guide recommends non-reference case analyses to be explored, in certain circumstances, where the costs of background care are removed.[116] This submission evaluates the addition of pemetrexed and platinum-based chemotherapy to the existing standard of care, osimertinib monotherapy, and results in an improvement in clinical outcomes and subsequent increase in background care costs. Given this, a scenario analysis was explored where the additional incremental background cost (i.e. osimertinib acquisition cost) was removed (Table 72).



Although the base case analysis presented in Section B.3.11.1 can be considered to be plausibly cost effective, and the situation identified by the NICE DSU (i.e. not cost effective at zero price) does not apply, removal of background care costs remains informative for Committee decision making. In this scenario, the incremental costs were reduced by £3,440.26 (3.2%), leading to an ICER of £19,183 per QALY gained (Table 72). Such a result is consistent with expectations and underlines the important conclusion that the addition of a well-established, generic chemotherapy regimen to existing standard of care can be considered a cost-effective use of NHS resources and improve patient outcomes.



**Table 72: Osimertinib drug acquisition cost scenarios**

| Scenario | Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| Removal of incremental osimertinib drug acquisition costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,183.61 | -29.7% |

#### *B.3.12.3.2 Base case scenario analyses*

The scenarios which were performed on are described in Table 67.

Scenarios were selected for inclusion in the model based on clinical expert input and identified areas of uncertainty in certain model inputs that required further analysis to improve the robustness of the model outputs. Key scenarios include the removal of treatment acquisition and administration costs associated with chemotherapy in the osimertinib plus chemotherapy arm as well as varying the extrapolation distribution associated with PFS, OS and TTD. Curve extrapolation selection for scenario analysis was based on both statistical fit and clinical plausibility. In the majority of the scenario analyses, osimertinib plus chemotherapy was considered cost-effective versus osimertinib monotherapy at a WTP threshold of £30,000 per QALY. Of note, the ICER when using PF and PD health state utility values, derived from FLAURA-2 data, was consistent with the base case analysis and below a WTP threshold of £30,000 per QALY. The ICER was highly sensitive to the removal of chemotherapy administration costs, resulting in a 60.8% decrease versus the base case analysis and an ICER of £10,687.23 per QALY gained.

The results of the scenario analyses are presented in Table 73.



**Table 73: Scenario analysis results for osimertinib plus chemotherapy vs osimertinib monotherapy**

| Scenario | Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| Time horizon of 10 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £29,721.55 | 8.9% |
| Inclusion of the cost of wastage | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,986.40 | 20.9% |
| Discount rate of 1.5% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £25,570.62 | -6.3% |
| Utility source - FLAURA2 (PF & PD) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £28,897.25 | 5.9% |
| Progression-free survival extrapolation – Gamma (osimertinib) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £27,911.26 | 2.3% |
| Progression-free survival extrapolation – Gompertz (osimertinib + chemotherapy) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £34,884.71 | 27.9% |
| Overall survival extrapolation – 2 spline odds (both arms) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,291.51 | 18.4% |
| Overall survival extrapolation – Weibull (both arms) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £14,605.34 | -46.5% |
| Overall survival extrapolation – Gamma (both arms) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £14,560.46 | -46.5% |
| TTD survival (osimertinib + | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £15,009.14 | -45.0% |



| Scenario | Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| chemotherapy (osimertinib)) extrapolation – Gen gamma | | | | | | | | |
| TTD survival (osimertinib) extrapolation - Weibull | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £31,500.45 | 15.5% |
| Progression-free survival source - BICR | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £22,994.98 | -15.7% |
| Removal of administration cost of chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £10,687.23 | -60.8% |
| Relative dose intensity - 100% for all treatments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £33,890.57 | 24.2% |

Abbreviations: BICR, blinded independent central review; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OS, overall survival; PD, progressed disease; PDC, platinum doublet chemotherapy; PF, progression free; PFS, progression-free survival; QALYs, quality-adjusted life years, RDI, relative dose intensity; TTD, time to treatment discontinuation.

### *B.3.13 Subgroup analysis*

No subgroup analyses for osimertinib plus chemotherapy were considered to be relevant for the submission.

### *B.3.14 Benefits not captured in the QALY calculation*

Patients diagnosed with advanced or metastatic NSCLC may require the support of informal caregivers for symptom management, and psychological support.[117] This can pose a physical, emotional and financial challenge for caregivers, which is not reflected in the model QALY calculation. Informal caregivers for patients with advanced NSCLC report a detrimental impact on their quality of life, particularly as patient health deteriorates.[118] Furthermore, a study of caregiver burden in Europe reported that carers for patients receiving first-line treatment for advanced disease were providing a mean of 29.5h support per week with overall work impairment ranging from 21.1% to 30.4%.[119] Osimertinib plus chemotherapy significantly improves PFS compared with osimertinib monotherapy, and there may therefore be an associated reduction in the burden to caregivers in terms of their quality of life, time and effort required and work productivity.

### *B.3.15 Validation*

#### B.3.15.1 Validation of cost-effectiveness analysis

### *B.3.16 Interpretation and conclusions of economic evidence*

This *de novo* economic evaluation has estimated the cost-effectiveness of osimertinib plus chemotherapy versus osimertinib monotherapy for patients with unresectable locally advanced or metastatic EGFRm NSCLC. The results of the evaluation show that osimertinib plus chemotherapy is associated with an increase in life years of [redacted] additional years, and [redacted] additional QALYs compared to osimertinib monotherapy. Osimertinib plus chemotherapy is associated with an increase in costs of [redacted] versus osimertinib monotherapy. This results in an ICER of £27,280.04 versus osimertinib monotherapy.



Scenarios to address the challenge of combination treatments which remove increased treatment acquisition costs associated with background osimertinib, or administration costs of chemotherapy, in the osimertinib plus chemotherapy arm had a large influence on the ICER, and when these costs were excluded, the ICER reduced to £19,183.61 and £10,687.23 per QALY gained, respectively. Scenario analyses that varied the extrapolation distribution associated with OS and TTD also impacted the ICER; however, the results were largely consistent with the base case analysis.

The one-way sensitivity analyses showed that the main drivers of cost-effectiveness are the progression-free health state utility, the proportion of patients that receive ABCP as a second-line therapy in both arms, and the administration cost associated with pemetrexed. Except for one analysis, all deterministic analyses were cost-effective at a WTP threshold of £30,000 per QALY gained.

The PSA showed that the probabilistic results are consistent with the deterministic results and that osimertinib plus chemotherapy is associated with 52% probability of being cost-effective at a WTP threshold of £30,000 per QALY gained.

#### B.3.16.1 Strengths and limitations

The CEA presented as part of this submission leverages an established model framework widely used and accepted in oncology and used in previous NICE appraisals for NSCLC, including that for osimertinib monotherapy (TA654), the key relevant comparator in this appraisal. In addition, clinical efficacy and safety data for the CEA was informed from the FLAURA2 trial, which is a robust, randomised, open-label, multi-centre, global, phase 3 clinical trial, providing direct evidence for osimertinib plus chemotherapy versus osimertinib monotherapy in the treatment of locally advanced/metastatic EGFRm NSCLC. The economic evaluation also benefitted from clinical input which validated several of the modelling assumptions through an advisory board and external stakeholder engagements.

One limitation of the CEA is the uncertainty surrounding the long-term extrapolation of efficacy data. However, the choice of extrapolation distributions was validated with

UK clinical experts. Additionally, there is uncertainty about how subsequent treatments will affect survival. Although the model assumes that all survival gains are captured within overall survival, it also includes ABCP as a subsequent treatment option, despite it not being explicitly a subsequent treatment in the FLAURA2 trial. However, several components of the ABCP regimen (atezolizumab, bevacizumab, and carboplatin) were included as treatment options in FLAURA2, which reduces uncertainty as these components are assumed an adequate proxy for ABCP. To address uncertainty in the model, extensive sensitivity analyses, including PSA, DSA, and scenario analyses, were conducted.

### B.3.16.2 Conclusions

The results of this CEA indicate that osimertinib plus chemotherapy is a cost-effective treatment when assessed against the NICE WTP threshold of £30,000 per QALY gained. It can be considered a cost-effective option versus osimertinib monotherapy for the treatment of EGFRm locally advanced (stage IIIB-IIIC) or metastatic (stage IV) NSCLC from the perspective of the UK NHS and PSS. This conclusion was consistent across the PSA, deterministic analyses and the majority of the scenario analyses.



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## B.5 Appendices

**Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)**

**Appendix D: Identification, selection and synthesis of clinical evidence**

**Appendix E: Subgroup analyses**

**Appendix F: Adverse reactions**

**Appendix G: Published cost-effectiveness studies**

**Appendix H: Health-related quality-of-life studies**

**Appendix I: Cost and healthcare resource identification, measurement and valuation**

**Appendix J: Clinical outcomes and disaggregated results from the model**

**Appendix K: Price details of treatments included in the submission**

**Appendix L: Checklist of confidential information**

**Appendix M: Additional supporting data from the FLAURA2 study**



# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

## Summary of Information for Patients (SIP)

**May 2024**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6328 Osimertinib FLAURA2 SIP 150524 | 1.0 | No | 15th May 2024 |

# Summary of Information for Patients (SIP):

## The pharmaceutical company perspective

### What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

### SECTION 1: Submission summary

**1a) Name of the medicine** (generic and brand name):

| |
|---|
| Osimertinib (TAGRISSO®), to be administered in combination with pemetrexed and platinum-based chemotherapy (either carboplatin or cisplatin) |

**1b) Population this treatment will be used by.** Please outline the main patient population that is being appraised by NICE:

| |
|---|
| Adults with previously untreated EGFR mutation-positive advanced or metastatic non-small-cell lung cancer (NSCLC) |

**1c) Authorisation:** Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

| |
|---|
| The marketing authorisation for osimertinib in this indication is pending. Please refer to Section B.1.2 of the main submission document for more information. |

**1d) Disclosures.** Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AstraZeneca UK Limited engages with the following patient advocacy groups in lung cancer, with the aims of strengthening patient insights and responding to requests for information: EGFR Positive UK and Roy Castle Lung Cancer Foundation.

AstraZeneca UK is also a corporate supporter of UK Lung Cancer Coalition, which includes patient advocacy groups.

Funding provided to UK patient groups is published annually on our website: https://www.astrazeneca.co.uk/partnerships/working-with-patient-groups

## SECTION 2: Current landscape

### 2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Lung cancer is the third most common cancer and the most common cause of cancer deaths in the UK.[1] NSCLC is the most common type of lung cancer, accounting for 86% of all cases.[2] Approximately 10% of NSCLC have changes (also known as mutations) within the EGFR gene;[3] this gene produces a protein which controls the growth and multiplication of healthy cells. Mutations in the EGFR gene can result in more EGFR protein being produced than is needed, leading to faster cell growth and multiplication, which can in turn cause cancer. Two of the most common mutations in the EGFR gene are exon 19 deletions and exon 21 L858R point mutations; these account for ~90% of all cases of NSCLC with EGFR mutations;[4, 5] and are the focus of this appraisal. These changes are referred to as EGFRm throughout the submission documents. Compared with tumours without EGFRm, the presence of EGFRm is associated with faster disease progression and a higher rate of brain metastases.[6, 7]

NSCLC is hard to detect in its early stages and more than 65% of people with lung cancer in England are diagnosed with cancer that has spread and can't be removed with surgery. Cancer that has spread into nearby tissues or lymph nodes is described as locally advanced, and cancer that has spread to other organs in the body is described as metastatic.[8] There is no cure for metastatic NSCLC, and fewer than 5% of people diagnosed with this type of disease survive for 5 years.[9]

Typical symptoms of locally advanced or metastatic disease include a persistent cough, chest pain, dyspnoea, fatigue, loss of appetite and weight loss[10, 11] and these can have a substantial impact on the quality of life of people with NSCLC. As the disease progresses and symptoms get worse, quality of life can continue to decrease .[10, 11] People may experience other symptoms, which depend on where the cancer has spread.[12] Treatments for advanced or metastatic NSCLC can have side effects which can further worsen quality of life.[13, 14]

**2b) Diagnosis of the condition (in relation to the medicine being evaluated)**

| Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment? |
| --- |
| People may be diagnosed with lung cancer after seeing their GP about their symptoms.[15] In cases where the GP thinks symptoms could be caused by lung cancer, they will arrange tests to help make a diagnosis, including a chest x-ray and a CT (computed tomography) scan.[15] If these tests show anything abnormal, the GP will request a referral to a chest specialist.[15]<br><br>At the hospital, the specialist will explain any other tests that may be needed; these may include a PET-CT (positron emission tomography-computed tomography) scan and a biopsy.[15] In cases where a positive diagnosis for NSCLC is received, further examinations may be required to describe the size and position of the tumour, identify certain mutations in the cancer cells (such as EGFRm), and establish whether the cancer has spread outside of the lungs.[15] These tests will also help to determine the best treatment for the patient. |

**2c) Current treatment options:**

| The purpose of this section is to set the scene on how the condition is currently managed:<br>• What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.<br>• Please also consider:<br>o if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.<br>o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are. |
| --- |
| There is no cure for locally advanced or metastatic EGFRm NSCLC; therefore, treatment goals are focused on slowing down disease progression, prolonging survival and improving quality of life. The potential benefits of any treatment should be balanced with the risk of side effects.[16]<br><br>NICE currently recommends a range of treatment options for previously untreated locally advanced or metastatic EGFRm NSCLC, including platinum-based chemotherapy and targeted therapies called tyrosine kinase inhibitors (TKIs) which specifically block the EGFR protein and slow down cancer cell growth and multiplication. Currently, there are several TKIs that are recommended by NICE, these are afatinib, dacomitinib, erlotinib, gefitinib and osimertinib.<br><br>Osimertinib is the preferred treatment in the UK for untreated locally advanced or metastatic EGFRm NSCLC in adults.[17] Osimertinib has demonstrated improved outcomes compared with other TKIs, with a significant improvement in the median length of time that people remain alive without their disease getting worse (also known as progression-free survival [PFS]; 18.9 vs 10.2 months; $p<0.001$)[18] and significantly longer median overall survival (OS; 38.6 versus 31.8 months; $p=0.0446$)[19] than erlotinib and gefitinib demonstrated in a clinical trial. Osimertinib can also get |

into the brain[20, 21] and has been shown to significantly delay disease progression to the central nervous system (CNS), compared with erlotinib and gefitinib.[22]

In the management of locally advanced or metastatic NSCLC, it is important that people receive the most effective treatment possible as their first treatment after they receive a diagnosis.[17] Many people will not go on to receive a second treatment; some may not be suitable for additional treatments due to the severity of their disease, they may choose not to receive any further treatment, or they may die before receiving a second treatment.[23-25]

Despite the significant improvement in outcomes observed with osimertinib monotherapy, those receiving treatment eventually develop treatment resistance (meaning that osimertinib stops working as well) and their disease gets worse.[5] There is therefore a need for additional treatments to further improve outcomes for people with advanced or metastatic EGFRm NSCLC.

**2d) Patient-based evidence (PBE) about living with the condition**

**Context:**

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Advanced or metastatic NSCLC negatively affects quality of life due to the symptoms experienced as a result of the cancer and its treatment.[10, 11]

Studies that have looked into lived experiences showed that people with metastatic NSCLC consider fatigue, pain and discomfort, shortness of breath, and cough to be their most important symptoms.[26-28] Participants in these studies indicated that symptoms have a negative impact on their physical and emotional wellbeing and affect their ability to carry out daily activities. Difficulty walking, anxiety/depression, impact on personal relationships, impact on sleep, and difficulty doing daily tasks have been identified as the most impactful for their lives.[26-28]

In addition, people with advanced or metastatic NSCLC may require physical or emotional support from caregivers.[29] This may be challenging for caregivers, physically, emotionally and financially, negatively affecting their ability to work[30] and reducing their overall quality of life.[31] People with metastases may experience other negative symptoms that affect their quality of life; for example, people with brain metastases may need assistance with daily tasks such as bathing, walking and driving.[32]

## SECTION 3: The treatment

### 3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

The Summary of Product Characteristics for osimertinib is available here: https://www.medicines.org.uk/emc/product/7615/smpc

Osimertinib is has been developed to permanently attach to mutated EGFR protein only. This can reduce growth and multiplication of the cancer cells. Osimertinib does not target normal EGFR protein on non-cancerous cells and so does not damage normal cells.[33]

Pemetrexed is a type of chemotherapy which stops cells from being able to multiply.[34]

Cisplatin and carboplatin are platinum-based chemotherapies that bind to DNA and destroy cells that are multiplying.[35, 36]

### 3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

**If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**

Osimertinib is intended to be used in combination with pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin). Osimertinib alone is already approved by NICE[37] and is currently the most commonly used treatment in the UK for previously untreated locally advanced or metastatic EGFRm NSCLC in adults.[17] Those receiving treatment, however, eventually develop treatment resistance (osimertinib stops working as well) and their disease gets worse.[5] Clinical trials have shown that the addition of chemotherapy to TKIs can delay worsening of NSCLC alongside a manageable side effect profile when compared with treatment with a TKI alone.[38] Studies were therefore performed to see whether adding pemetrexed plus platinum-based chemotherapy (carboplatin or cisplatin) to osimertinib could offer improved efficacy, delaying treatment resistance.

**3c) Administration and dosing**

| How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.<br><br>How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments? |
|---|
| Osimertinib is available as 40 mg or 80 mg oral tablets, which can be taken at home. The recommended dose is 80 mg once a day when taken with pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin).<br><br>The recommended dose of pemetrexed is 500 mg/m$^2$ of body surface area administered in hospital intravenously over 10 minutes once every 21 days.[34]<br><br>Both carboplatin and cisplatin are given in hospital after completion of the pemetrexed infusion once every 21 days, for the first four treatments only.[34] The recommended dose of carboplatin is 5–7 mg/ml/min, administered intravenously.[35] The recommended dose of cisplatin is 75 mg/m$^2$ body surface area infused intravenously over two hours approximately 30 minutes after completion of pemetrexed infusion. [34] |

**3d) Current clinical trials**

| Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials. |
|---|
| FLAURA2 is a global clinical trial which has compared the efficacy and safety of osimertinib in combination with pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin) versus osimertinib alone in participants with untreated locally advanced or metastatic EGFRm NSCLC (**Error! Reference source not found.**). Although some results from the trial are available, the trial is still ongoing and is expected to be completed in the second half of 2025. Results presented in this submission were based on the data analysis conducted in April 2023 and an additional overall survival analysis conducted in January 2024.<br><br>FLAURA2 included participants with EGFRm NSCLC whose cancer had spread to nearby tissues or lymph nodes (locally advanced disease) or to other organs in the body (metastatic disease). To be included in the study, participants must not have received any previous treatment for advanced or metastatic EGFRm NSCLC. Participants also had to be in good general health.<br><br>In total, 279 participants received treatment with osimertinib in combination with pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin) and 278 participants received treatment with osimertinib alone.<br><br>The outcomes measured in the trial included how long participants remained alive without their cancer getting worse (called progression-free survival in the trial), how long participants remained alive (called overall survival in the trial) and how many participants experienced a decrease in the size of their tumour or whose cancer disappeared (called the objective response rate in the trial). Quality of life was also measured using a number of different questionnaires that were completed |

by the participants at different points during the trial. Any side effects reported by participants were also recorded.

Furter details on the study design and results from the FLAURA2 trial are available from the following sources:

1. Planchard D, Jänne PA, Cheng Y, Yang JC, Yanagitani N, Kim SW, et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. The New England journal of medicine. 2023;389(21):1935-48.[39]
2. Jänne PA, Planchard D, Kobayashi K, Cheng Y, Lee CK, Valdiviezo N, et al. CNS Efficacy of Osimertinib With or Without Chemotherapy in Epidermal Growth Factor Receptor-Mutated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2023:Jco2302219.[40]
3. Valdiviezo N, Okamoto I, Hughes BGM, Ahmed S, Wu l, Hu J, et al. First line osimertinib platinum pemetrexed in EGFRm advanced NSCLC: FLAURA2 post progression outcomes. Presented at the European Lung Cancer Congress 2024. 2024.[41]

**3e) Efficacy**

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The FLAURA2 study showed that participants treated with osimertinib in combination with pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin) lived significantly longer without their disease getting worse (median 25.5 months) than participants treated with osimertinib alone (median 16.7 months). In addition, there was a trend towards an improvement in how long participants remained alive with osimertinib in combination with pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin) treatment; however, a lot of participants are still alive in both treatment groups and the trial will need to continue for longer for a final analysis of the difference in survival between the two treatments to be performed.

For participants who had CNS metastases when starting treatment in the FLAURA2 study, osimertinib, pemetrexed and platinum-based chemotherapy provided a reduction (42%) in the risk of CNS disease progression or death.

More participants in the osimertinib in combination with platinum-based chemotherapy (pemetrexed plus carboplatin or cisplatin) group experienced a decrease in the size or a disappearance of their tumour (83.2%) compared with participants who received osimertinib alone (75.5%).

**3f) Quality of life impact of the medicine and patient preference information**

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life in FLAURA2 was assessed using a number of different questionnaires that were completed by the participants at different time points during the study. These included questionnaires on general health (EQ-5D), the impact of having cancer (EORTC-QLQ-C30), and on specific issues that are known to affect people with lung cancer (EORTC QLQ-L13).

Results showed that there was a small improvement in global health status/quality of life and physical functioning following treatment with either osimertinib in combination with pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin) or osimertinib alone. Importantly, adding chemotherapy to osimertinib did not have a negative impact on quality of life. Of note, treatment osimertinib in combination with pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin) resulted in small improvement in coughing, difficulty breathing and chest pain, but a slight worsening in appetite loss.

**3g) Safety of the medicine and side effects**

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, osimertinib, pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin) are associated with side effects. During the FLAURA2 trial, nearly all participants experienced side effects (also called adverse events) of treatment. The most commonly reported adverse events (AEs) for participants receiving osimertinib in combination with platinum-based chemotherapy (pemetrexed plus carboplatin or cisplatin) were anaemia (46.4% of participants), diarrhoea (43.5% of participants), and nausea (43.1% of participants). The most common AEs with osimertinib alone were diarrhoea (40.7% of participants), paronychia, which is an infection of the skin around the nails (26.5% of participants), and dry skin (24.0% of participants). A summary of AEs which occurred in 10% or more of either treatment group is presented in Table 1.

Rates of osimertinib discontinuation were low in both treatment arms (10.9% for osimertinib plus pemetrexed and platinum-based chemotherapy vs 6.2% for osimertinib alone).

The proportions of participants who had an AE with outcome of death were low in both treatment arms (6.5% for osimertinib plus platinum-based chemotherapy and 2.9% for osimertinib alone).

**Table 1: Adverse events occurring in ≥10% of participants in the FLAURA2 trial**

| Adverse events | Osimertinib + chemotherapy (N=276) | Osimertinib monotherapy (N=275) |
|---|---|---|
| Participants with any AE | 276 (100) | 268 (97.5) |
| Anaemia | 128 (46.4) | 22 (8.0) |
| Diarrhoea | 120 (43.5) | 112 (40.7) |
| Nausea | 119 (43.1) | 28 (10.2) |
| Decreased appetite | 85 (30.8) | 26 (9.5) |
| Constipation | 81 (29.3) | 28 (10.2) |
| Rash | 77 (27.9) | 57 (20.7) |
| Fatigue | 76 (27.5) | 26 (9.5) |
| Vomiting | 73 (26.4) | 17 (6.2) |
| Neutropenia | 68 (24.6) | 9 (3.3) |
| Stomatitis | 68 (24.6) | 50 (18.2) |
| Paronychia | 65 (23.6) | 73 (26.5) |
| Neutrophil count decreased | 62 (22.5) | 16 (5.8) |
| COVID-19 | 57 (20.7) | 39 (14.2) |
| Alanine aminotransferase increased | 56 (20.3) | 21 (7.6) |
| Platelet count decreased | 51 (18.5) | 19 (6.9) |
| Thrombocytopenia | 51 (18.5) | 12 (4.4) |
| Dry skin | 50 (18.1) | 66 (24.0) |
| Aspartate aminotransferase increased | 48 (17.4) | 13 (4.7) |
| Blood creatinine increased | 46 (16.7) | 12 (4.4) |
| White blood cell count decreased | 44 (15.9) | 18 (6.5) |
| Oedema peripheral | 42 (15.2) | 12 (4.4) |
| Dermatitis acneiform | 37 (13.4) | 36 (13.1) |
| Urinary tract infection | 36 (13.0) | 28 (10.2) |
| Leukopenia | 35 (12.7) | 11 (4.0) |
| Insomnia | 34 (12.3) | 18 (6.5) |
| Dizziness | 32 (11.6) | 16 (5.8) |
| Weight decreased | 32 (11.6) | 22 (8.0) |
| Cough | 31 (11.2) | 29 (10.5) |
| Pyrexia | 31 (11.2) | 15 (5.5) |
| Arthralgia | 28 (10.1) | 32 (11.6) |
| Pruritus | 22 (8.0) | 31 (11.3) |

**3h) Summary of key benefits of treatment for patients**

| Issues to consider in your response:<br>• Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.<br>• Please include benefits related to the mode of action, effectiveness, safety and mode of administration |
|---|
| The FLAURA2 study showed that for people with untreated advanced or metastatic EGFRm NSCLC, adding pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin) to osimertinib significantly improves the time that people remain alive without their disease getting worse, with a trend towards an improvement in life expectancy and no negative impact on HRQoL, compared with using osimertinib alone. in. In addition, osimertinib in combination with platinum-based chemotherapy demonstrated manageable side effects.<br><br>Peoples with EGFRm have a higher rate of CNS metastases than patients without EGFRm (70% vs 38%).[7] CNS metastases can have a substantial impact on symptom burden and QoL[12] and are associated with poor survival.[42] Osimertinib is able to cross the blood-brain barrier, and therefore target CNS metastases.[20, 21] The FLAURA2 data indicate that for patients who have CNS metastases when starting treatment, osimertinib, pemetrexed and platinum-based chemotherapy provides a reduction (42%) in the risk of CNS disease progression or death. |

**3i) Summary of key disadvantages of treatment for patients**

| Issues to consider in your response:<br>• Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?<br>• Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration<br>• What is the impact of any disadvantages highlighted compared with current treatments |
|---|
| Nearly all participants in both treatment arms experienced side effects. The proportion of participants that experienced a side effect that was considered to be caused by the treatment was higher with osimertinib in combination with pemetrexed plus platinum-based chemotherapy (97.5%) compared with treatment with osimertinib alone (87.6%). The increase in side effects with osimertinib in combination with pemetrexed plus platinum-based chemotherapy were considered to be caused by the addition of chemotherapy treatments which work in a different way to osimertinib.<br><br>People who are treated with pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin) will need to visit a hospital for intravenous infusions every 21 days; however, osimertinib can be taken orally at home. |

### 3i) Value and economic considerations

**Introduction for patients:**

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

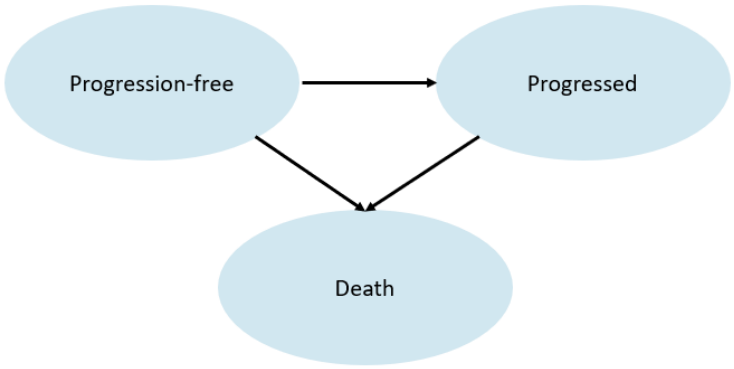
In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

**How the model reflects the condition**

- An economic model was designed to simulate locally advanced or metastatic EGFRm NSCLC by modelling the different stages of the disease using categories called 'health states' (Figure 1). The health states used in the model were:
  - Progression-free – the cancer is not getting worse
  - Progressed – the cancer has got worse
  - Death.
- In the model, patients start in the progression-free state, and then may either die, or experience worsening of the disease; once the patient has experienced worsening of the disease, they remain in this health state until they die. This reflects the real-life disease course.
- The model assessed the cost effectiveness of osimertinib plus pemetrexed plus platinum-based chemotherapy (carboplatin or cisplatin) compared with osimertinib alone in the first-line treatment of patients with locally advanced or metastatic EGFRm NSCLC.
- Patients experience different quality of life and accrue different costs depending on the health state they are in, with those in 'Progression-free' experiencing the best quality of life and lowest costs, and those in the 'Progressed' health state experiencing the worst quality of life and higher costs.
- The model works by simulating how patients move between the health states when they are given different treatments; the more effective the treatment, the more time patients will spend in the 'Progression-free' health state.

**Figure 1. Model structure**




**Modelling how much a treatment extends life**

- Data from the FLAURA2 clinical trial were used to inform the efficacy of osimertinib plus pemetrexed and platinum-based chemotherapy versus osimertinib alone (i.e. how long patients remained in the 'Progression-free' or 'Progressed' health state) in the cost-effectiveness model.
- As data from the clinical trial were only available for a relatively short length of time, statistical models were used to estimate the proportion of patients who would be in the 'progression-free' and 'progressed' health states over the course of 15 years.

**Modelling how much a treatment improves quality of life**

- In the model, quality of life was determined by the health state that patients are in rather than the treatment they receive; patients in the 'Progression-free' health state have a better quality of life than patients in the 'Progressed' health state.
- EQ-5D data from the FLAURA2 trial were used to estimate the quality of life for patients in the 'Progression-free' and 'Progressed' health states.
- The model also considered that side effects may have a negative impact on quality of life. The types of side effects and the number of patients experiencing them was informed by the FLAURA2 trial, and the impact of these side effects on quality of life was estimated from the published literature.

**Modelling how the costs of treatment differ with the new treatment**

- Costs that were considered in the cost-effectiveness model include treatment, treatment administration, resource use (costs for healthcare professionals and hospitals), costs of treating side effects, and costs of any subsequent treatments that patients receive after they stop treatment with osimertinib in combination with pemetrexed plus platinum-based chemotherapy or osimertinib alone.
- CNS metastases are associated with increased resource use and costs. The health state costs associated with progression-free and progressed disease were inflated to account for the additional costs associated with the management of CNS metastases.
- Osimertinib plus platinum-based chemotherapy displays better efficacy compared to osimertinib alone. This translates into patients spending more time in the 'Progression-free' health state, with a lower resource requirement on the healthcare professionals used when

patients progress, and a lower proportion of patients dying, with patients progressing to the death health state assumed to receive terminal care

**Uncertainty**

- Uncertainty in the model inputs and structure was explored using sensitivity and scenario analyses; these analyses assessed the impact on the model outputs when inputs are varied by a defined amount.

**Cost-effectiveness result**

- Osimertinib plus platinum-based chemotherapy was found to have an ICER of £27,280.04 compared with osimertinib alone.
- For full details on the modelled benefit in overall survival, progression-free survival, QALYs gained, and the incremental cost-effectiveness ratio, see the Company NICE Submission Document B, Section B.3.9.

## 3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

The combination of osimertinib with pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin) provides an opportunity to build on the efficacy of the current standard of care, treatment with osimertinib alone, with a more intensified treatment regimen that can maximise long-term outcomes for adults with previously untreated locally advanced or metastatic EGFRm NSCLC. The addition of pemetrexed and platinum-based chemotherapy to osimertinib can delay disease progression and reduce tumour size for patients with locally advanced or metastatic EGFRm NSCLC, including people who are considered higher risk such as those with CNS metastases.

## 3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

| |
|---|
| More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br><br>Find more general information about the Equality Act and equalities issues here |
| Use of osimertinib with pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin) is not expected to raise any equality issues. |

## **SECTION 4:** Further information, glossary and references

### 4a) Further information

| |
|---|
| Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.<br>Where possible, please provide open access materials or provide copies that patients can access. |
| Useful resources for NSCLC:<br><br>• Cancer Research UK: https://www.cancerresearchuk.org/about-cancer/lung-cancer<br>• Macmillan Cancer Support: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/non-small-cell-lung-cancer<br>• NHS UK: https://www.nhs.uk/conditions/lung-cancer/<br>• Patient UK: https://patient.info/doctor/lung-cancer-pro<br>• EGFR+ UK https://www.egfrpositive.org.uk/what-is-egfr<br><br>Further information on NICE and the role of patients**:**<br><br>• Public Involvement at NICE Public involvement \| NICE and the public \| NICE Communities \| About \| NICE<br>• NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance \| Help us develop guidance \| Support for voluntary and community sector (VCS) organisations \| Public involvement \| NICE and the public \| NICE Communities \| About \| NICE<br>• EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/<br>• EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf<br>• National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/<br>• INAHTA: http://www.inahta.org/<br>• European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp- |

content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

**4b) Glossary of terms**

- EGFR gene: A gene that makes a protein on cells that helps them grow
- EGFRm: Changes within the EGFR gene that can make cells grow too much and cause cancer
- First-line treatment: The first treatment given for a disease
- Locally advanced cancer: Cancer that has spread into nearby tissues or lymph nodes
- Metastatic cancer: Cancer that has spread to other organs in the body
- Non-small cell lung cancer (NSCLC): One of two primary types of lung cancer and the most common kind
- Objective response rate (ORR): The percentage of patients whose cancer shrinks or disappears after treatment
- Overall survival: The average length of time patients are alive after the start of treatment
- Progression-free survival: The average length of time after the start of treatment in which a person is alive, and their cancer does not grow or spread
- Resource use: Costs for healthcare professionals and hospitals
- Tyrosine kinase inhibitor (TKI): A therapy that can identify and attack the EGFR gene within cancer cells.

**4c) References**

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:


1. Cancer Research UK. Lung cancer statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero. Accessed on: 29th Febrary 2024.
2. National Lung Cancer Audit. Annual Report. London: Royal College of surgeons of England https://wwwlungcanceraudit orguk/wp-content/uploads/2024/03/NLCA-Patient-Summary_SotN-report-2023_final-120423pdf#:~:text=The%20number%20of%20patients%20diagnosed,and%2010%25%20had%20never%20smoked. 2023.
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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Single Technology Appraisal

# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

# Clarification questions

**June 2024**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6328 Osimertinib EAG clarification questions final[CON] – Response-21062024.docx | 1.0 | Yes | 24/06/2024 |

**Notes for company**

**Highlighting in the template**

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# Section A: Clarification on effectiveness data

## *Data/Results*

**A1. Priority question: Please can you provide the progression free survival (PFS) curves and results at the later Data Cut-Off of 8th Jan 2024. See also question B9 below.**

**Response:**

The data cut-off (DCO) of 8th Jan 2024 was an ad-hoc analysis of the overall survival (OS) outcome provided as part of US Food and Drug Administration (FDA)-specific regulatory procedures. This DCO was focused on providing OS data and the PFS outcome was not assessed as part of this data request.

**A2. Priority question: Document B, Table 1, pg 10: The submission states that the market share for osimertinib monotherapy is [redacted], with justification for excluding the other four comparators from the NICE scope being that they are used 'rarely' as first-line treatment (dacomitinib, afatinib, erlotinib and gefitinib). Please could the company explain why treatments with a collective**

**share of [redacted] are considered 'rare' and not of relevance to the current appraisal?**

**Response:**

The four comparators from the NICE final scope that were excluded from the company submission are not representative of UK care. The remaining 14% market share is made up of a very small amount of individual usage when broken down across the excluded comparators. The individual shares of dacomitinib, afatinib, erlotinib and gefitinib are depicted in Table 1 below.

**Table 1: Market share in first-line metastatic EGFRm NSCLC**

| Therapy | UK Market Share (February 2024) |
|---|---|
| Osimertinib | [redacted] |
| Dacomitinib | [redacted] |
| Afatinib | [redacted] |
| Erlotinib | [redacted] |
| Gefitinib | [redacted] |

Abbreviations: EGFRm, epidermal growth factor receptor mutation positive; NSCLC, non-small cell lung cancer
Source: AstraZeneca data on file(1)

Not only is the percent usage of each of the tyrosine kinase inhibitors (TKIs) listed in the NICE final scope negligible, but their usage has been decreasing over time as osimertinib has become the established UK standard of care. This is depicted in the 2020-2024 UK market share data presented in Figure 1.

To support the company response the EAG clarification questions, five further one to one interviews were conducted with the clinical experts previously consulted for the clinical validation described in Section B.2.3.5 of the company submission. All 5 clinicians confirmed osimertinib as standard of care and that the other comparators listed in the NICE draft scope were not considered relevant comparators within UK clinical practice.

**Figure 1: First-line metastatic EGFRm NSCLC UK market share over time**

Abbreviations: EGFRm, epidermal growth factor receptor mutation positive; NSCLC, non-small cell lung cancer
Source: AstraZeneca data on file(1)

**A3.** Further justification for focusing only on osimertinib monotherapy is informed by the expert opinion of 9 clinicians. On pg 10 (Document B, Table 1), the company submission states that all 9 agreed that osimertinib monotherapy is the current standard of care and that osimertinib with pemetrexed and platinum-based chemotherapy would displace osimertinib only. The supplement "FLAURA2 Advisory Board" provided by the company reports the detail of the advisory board/ expert discussion (dated 9/11/2023). Please can you point to the sections of this supplementary report that support this claim in Document B, pg 10 (decision problem)?

**Response:**

Page 18 of the supplementary report describes that the advisors all currently use osimertinib as their 1L treatment of choice for patients with metastatic EGFRm NSCLC. This was a unanimous response from all 9 participating clinicians when asked what was the current 1L treatment of choice.(2)

### *Systematic review of clinical effectiveness*

**A4.** The criteria for including interventions and comparators in the systematic review align with the decision problem as specified in the NICE scope, but are inconsistent with the decision problem as subsequently framed in the company submission (please see Clarification Table 1 below at end of document). Please can you clarify the reasons for this discrepancy? As the systematic review should underpin the selection of evidence presented in the company submission, please can you explain why the systematic review includes a broader range of comparators (aligning with the NICE scope) but that the evidence presented in the company submission focuses on a narrower comparison of osimertinib with pemetrexed and platinum-based chemotherapy versus osimertinib?

**Response:**

The Clinical systematic literature review (SLR) was initially conducted using broad inclusion criteria to assure that it sufficiently captured treatments available globally for the treatment of metastatic or locally advanced NSCLC and relevant data. After publication of the NICE scope final scope, the gathering of UK clinical insight, and the consideration of current clinical guidelines such as ESMO, the company concluded that osimertinib monotherapy was the only relevant comparator for the osimertinib plus chemotherapy regimen.(2),(3)

**A5.** The EAG could not locate the protocols for the systematic reviews in the submission. Please can you provide protocols for all systematic reviews – ensuring that any post-protocol amendments are clearly marked?

**Response:**

The protocols for all systematic reviews have been provided in confidence in an updated reference pack. Please note, for the economic and quality of life SLRs, the same protocol was used for both the original and updated SLR. Any post-protocol amendments have been flagged as comments within the provided documents.

**A6.** Document B, Appendices, pg 30: You identify and report the OPAL study which you rely upon for adverse events data. Please can you clarify how you identified the OPAL study, and why it was not identified by the systematic review?

**Response:**

The OPAL study is a phase II study of osimertinib in combination with platinum and pemetrexed in patients with previously untreated EGFRm advanced non-squamous NSCLC. The lack of randomisation in the study design meant it was excluded from the systematic literature review and not considered for the provision of further efficacy data. However, it is an AstraZeneca sponsored trial and the company provided it to share further safety data on the osimertinib plus chemotherapy regimen to further support decision making.(4)

**A7.** Document B, Appendices, p25: please can you explain why you did not use the Cochrane RoB 2 tool for the risk of bias assessment of the FLAURA-2 trial? RoB 2.0 focuses on outcomes and therefore gives a clearer sense of the risk of bias per outcome specifically. This helps to guide interpretation of clinical effect and any possible implications where data are used in the model.

**Response:**

The quality assessment of the FLAURA2 trial was conducted using the standard NICE single technology assessment (STA) checklist for randomised controlled trials (RCTs). This tool was selected as it had previously been recommended as part of the NICE STA methodological guidance and covers similar methodological domains to the Cochrane Risk of Bias 2 tool. As reported in Document B, Appendices, p25 (Table 2 below), no major quality issues or risk of bias were identified in the quality assessment of the FLAURA2 trial.

**Table 2: Quality assessment results for FLAURA2**

| Trial number (acronym) | yes/no/not clear/N/A | Justification |
|---|---|---|
| Was randomisation carried out appropriately? | Yes | Patients were randomised in a 1:1 ratio to receive either osimertinib + chemotherapy or osimertinib monotherapy. Treatment was assigned using an IVRS/IWRS. |
| Was the concealment of treatment allocation adequate? | Yes | Blinded and unblinded access and notifications were controlled using the IVRS/IWRS. The Sponsor was blinded to treatment assignment and did not have access to any aggregate summaries by treatment arm during the study. |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Yes | Overall, baseline demographics, patient characteristics and disease characteristics were well balanced between treatment arms |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | No | The study was open label to avoid placing an undue burden on patients. Investigators and patients were not blinded to study treatment.<br>A sensitivity analysis of the primary PFS endpoint was conducted by BICR to assess ascertainment bias. |
| Were there any unexpected imbalances in drop-outs between groups? | No | Overall, the number and reasons for discontinuations from treatment were not unexpected, and no patients were lost to follow-up during the study. |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | No | The primary and key secondary outcomes listed in the methodology section are consistent with those reported in the results section. |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Yes | Analyses in the overall population were conducted on the FAS (i.e., ITT), comprising all patients randomised to treatment. No patients were lost to follow-up during the study. |

**A8.** Document B, Appendices, pg 18: the submission states: '*In addition, the FLAURA SLR conducted in 20189 was also leveraged and a de-duplication was conducted with the records which were included or excluded for not having population, outcomes, study type of interest, or timeframe of publishing after full-text review.'* Please can you clarify what 'leveraged' means here and explain why de-

duplication was needed between the systematic review underpinning appraisal TA654 and the review underpinning the current submission?

**Response:**

The eligibility criteria of the clinical SLR underpinning TA654 were very similar to the eligibility criteria in the clinical SLR conducted in support of the current appraisal however, the latter clinical SLR has a broader scope with expanded interventions and comparators of interest.(5) Consequently, the search strategy was amended for the clinical SLR underpinning this appraisal.

To minimise duplication of work between the two SLRs, given their similarity, the TA654 SLR was used to inform the clinical SLR in this appraisal. The full libraries of the clinical SLRs for TA654 and the current appraisal were de-duplicated and decisions made in the TA654 SLR were carried forward to the SLR in this appraisal. However, to reflect the differences in scope between the two SLRs, decisions were not carried forward for articles excluded on the basis of intervention or comparator, and these studies were re-screened against the eligibility criteria of the current SLR.

**A9.** Document B, Appendices, p6: you report searching DARE and HTA via the Cochrane Library. As it is not possible to search these databases via the Cochrane Library, please can you clarify if DARE and HTA were searched and how?

**Response:**

AstraZeneca agree that it is no longer possible to search DARE and HTAD via the Cochrane Library; the records from these databases have been migrated to PubMed. We would like to clarify that these databases were not searched via the Cochrane Library, but we are confident that any relevant records previously housed within HTAD or DARE will have been identified by the comprehensive searches in other databases.

**A10.** Document B, Appendices p19: Please can you confirm how many articles you excluded because “inclusion criteria was unclear” and clarify if study authors were contacted to seek clarification before exclusion, as per best practice in reviewing?

**Response:**

As reported in the PRISMA diagrams for the original SLR and SLR update (Document B, Appendices Figures 1 and 2; p22 and 23, respectively), which detail

the rationale for exclusion of reports following full-text review, no studies were excluded based on inclusion criteria being unclear. Consequently, there was no need to contact authors to seek clarification before exclusion.

**A11.** The systematic review does not describe methods for data extraction. Please can you provide a report of data collection process, for example:

- if you used a pre-defined and piloted tool to manage data extraction;
- how data extraction was performed (e.g. independently by two reviewers with a third reviewer available as needed);
- how you handled missing or unclearly reported data (e.g. you contacted study authors or made imputations)

**Response:**

Prior to data extraction, a data extraction grid was prepared in Microsoft Excel®, comprising the following fields for extraction:

- **Publication details:** Title, authors, publication year, sponsor, journal, volume, page numbers
- **Study characteristics:** Objective, study design, sample size, intervention/comparators (including dose and mode of administration), blinding, length of follow-up, sample size, treatment duration, setting and locations, type of trials, statistical methods of data analysis, relevant biases
- **Patient characteristics**: Age, gender distribution (% female), inclusion/exclusion criteria, baseline characteristics (comorbidities, current and prior treatments, medical history, levels of biomarkers)
- **Efficacy outcome data:** Progression-free survival; overall survival; post-progression survival; response rates, time to progression, time to treatment failure, time to disease progression or death on subsequent therapy, time to death or distant metastasis, time to brain metastases, proportion of patients with brain metastases, CNS response rates, health related quality of life, other PROs and any other outcomes related to clinical efficacy; for each outcome, data on number of subjects, percentages, hazard ratios/odds ratios/relative risk, mean, standard deviation, standard errors, 95% confidence intervals, time unit and p values, where applicable, were extracted

- **Safety outcome data:** Grade 3/4/5 adverse events, specific key adverse events of interest, adverse events of special interest, time to treatment discontinuation, and any other outcomes related to safety profile; for each outcome data on number of subjects, percentages, hazard ratios/odds ratios/relative risk, mean, standard deviation, standard errors, 95% confidence intervals, time unit and p values, where applicable, were extracted

Information for each included article was extracted by a single reviewer in the first instance. A senior reviewer independently verified the extracted information and ensured that no relevant information had been missed. Any discrepancies or missing information identified by the senior reviewer were discussed until a consensus was reached and the missing data extracted.

Where missing data could be calculated based on other available data (e.g. percentages from N and n numbers), such calculations were conducted. Similarly, where relevant graphs corresponding to the missing data were available, these were digitised in order to obtain these missing data. Authors were not contacted to obtain missing data as the quality assessment of the included studies identified that none of the included studies stood out in terms of missing data, clarity or reporting.

## Section B: Clarification on cost-effectiveness data

### *Utilities*

**B1. Priority Question: Page 134 of the CS, section B.3.4.2. Mapping, states: "*The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression. Due to censoring, the EQ-5D-5L observations obtained during this period have an unknown/missing health status and therefore, were omitted from the analysis.*" Can you please provide clarity on what is meant by excluding observations with an unknown/missing health status? Does this mean that when calculating the PFS utility scores it includes observations from the PFS period for patients who progressed as well as for those who did not progress? Or is it calculating the PFS scores using only the available data for patients who never**

**progressed? Can you please also elaborate on the rationale for using the MMRM analysis model?**

**Response:**

Records for any patients with quality of life (QoL) data were included in the mixed model for repeated measures (MMRM) regardless of whether they were censored for progression. However, for patients who were censored for progression, records that occur after patients were censored for progression were not included in the MMRM analyses. This is because these records cannot be attributed to a health state of pre- or post-progression.

The MMRM method was selected as it can be used to estimate the differences in QoL across different health states and treatment (model dependent) accounting for the correlation in utility scores that occurs due to the repeated measurements for each subject. In addition, the MMRM method also provides valid results when missing data occur (as is the case for FLAURA2) and where missing utility data are missing at random; this is consistent with the EMA guideline on missing data in confirmatory clinical trials (EMA 2009) which describes MMRM as a possible approach to handling missing data without formal imputation.(6) The use of MMRM methodology is also consistent with the pre-specified analysis of patient reported outcomes for FLAURA2 detailed in the clinical trial SAP and applied in the clinical study report (CSR).

**B2. Priority Question: The regression model used to estimate PFS utilities is unclear. Could you please specify the regression model and confirm it has adjusted for baseline utility values in the calculation both of PFS and PD utilities? Although not significant, the differences in utility at baseline between the groups are important and favour the intervention group. If the current regression model to estimate PFS and PD utilities does not adjust for baseline utility, please provide new estimates of PFS and PD utilities by treatment group adjusting for baseline utility and recalculate the ICERs.**

**Response:**

The final MMRM model selected based on AIC was the model with a fixed effect for progression status (pre / post-progression). Estimation was based on restricted maximum likelihood method (REML).

There are N subjects indexed by i (i=1,...,N).

The model equation is as follows:

$y_i=X_i \beta+\epsilon_i$

Where β represents the coefficients for pre/post-progression, and $X_i$ is a design matrix for subject i.

The vector of within-subject residuals, $\epsilon_i$, is assumed to have a multivariate normal distribution, where the variance-covariance matrix accommodates correlations between residuals. Vectors of residuals are assumed to be independent between subjects.

The correlation of repeated utility measurements for each subject was captured by the specification of a covariance structure for the MMRM. The selection of the appropriate covariance structure was determined by first fitting a flexible unstructured covariance structure. As the unstructured covariance model failed to converge, more restrictive covariance structures were considered and results presented for the first covariance structure in the sequence that successfully converges.

The hierarchy of covariance structures tested, in order of most to least flexible, is shown below:

- Unstructured – each visit is allowed to have a different variance, and each combination of visits is allowed to have a different covariance.
- Toeplitz with heterogeneity – each visit is allowed to have a different variance, covariances between measurements depend on how many visits apart they are.
- Autoregressive, order 1 (AR(1)) with heterogeneity – each visit is allowed to have a different variance, and covariances decrease based on how many visits apart they are. Covariances decrease towards zero as the number of visits between observations increases.
- Toeplitz – as above for number 2, but each visit shares the same variance.

- Autoregression, order 1 (AR(1)) – as above for number 3, but each visit shares the same variance.

In the selected MMRM model an autoregressive, order 1 with heterogeneity covariance structure was utilised.

The selected model does not include a covariate for baseline utility. As such, an MMRM model was fitted including a fixed covariate for baseline utility in addition to progression status, results for this model are presented below.

Patients are only included in this analysis if there is a baseline utility record recorded, leading to 500 patients out of a total 535 with baseline QOL data, of these 8 only had a baseline record and as such 492 patients are included in the fitted model. Given that the patient data used to fit the extended MMRM model, AIC cannot be compared between this extended model and the previously selected model).

With the addition of the covariate for baseline utility the model did not converge with the previously selected correlation structure (AR(1) with heterogeneity) and the AR(1) structure was used to fit the model. The results for two MMRM models

- Progression status + Baseline utility
- Progression status * Baseline utility

are presented in Table 3. The AIC for the additive model was the lowest of the two and is therefore selected. The marginal means for progression status of the fitted model are presented in

Table ***4***, results are similar to the previous utility estimates by health state.

**Table 3: Results of fitted MMRM model with covariates for progression status and baseline utility**

| Parameter | Progression status + Baseline utility score | Progression status * Baseline utility score |
|---|---|---|
| (Intercept) | [redacted] | [redacted] |
| Post progression | [redacted] | [redacted] |
| Baseline utility | [redacted] | [redacted] |
| Post progression*Baseline utility | [redacted] | [redacted] |

| | | |
|---|---|---|
| AIC score | [redacted] | [redacted] |
| BIC score | [redacted] | [redacted] |

**Table 4: Marginal means for Progression Status + Baseline utility fitted MMRM model by progression status**

| Progression status | Estimate | SE | DF | 95% LCL | 95% UCL |
|---|---|---|---|---|---|
| Pre-progression | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Post progression | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

The current model is extended from previously selected best fitting model (which included a covariate for progression status only). The inclusion of treatment as a covariate into the MMRMs was not found to provide an improvement in statistical fit versus the model with progression status alone, and covariate estimates for treatment were not significant in any of the models tested. As such, results are not provided by treatment arm as the fitted model does not include a covariate for treatment.

Whilst results by treatment arm are not provided, the CEM does account for differences in the incidence of adverse events (AE)s between treatment arms and therefore reflects the treatment-specific impact of AEs on patient utility. As described in the original submission, Grade ≥3 AEs occurring in at least 2% of patients in one arm of FLAURA2 are captured in the model; a disutility is applied for the duration over which the AE was assumed to last, and the resulting utility decrement was applied to the percentage of patients experiencing the AE in the FLAURA2 trial in the first model cycle.

**B3. Priority Question: Missing EQ-5D data from the FLAURA2 trial may be biasing upwards the utilities based on the FLAURA 2 patient PROMS data, as we know that people who feel poorly complete less. Could you please re-estimate the EQ-5D utilities (after using the Hernandez Alava model), but now also using multiple imputation models for missing scores adjusting for known confounding factors, such as socio-demographics, disease and treatment characteristics, and the remaining available outcome measures? Please provide the new utility estimates for PFS and PD with multiple imputation by**

**treatment group, and provide a scenario with PFS utilities depending on treatment.**

**Response:**

The overall compliance rate for EQ-5D-5L was high and consistent between treatment arms. As anticipated, the number of expected and received questionnaires decreased over time, but compliance in both arms remained ≥80% up to 46 weeks, and ≥75% up to 94 weeks. Overall, compliance rate was also approximately equivalent between arms (78.5% and 78.3% for Osi + Chemo and Osi respectively. Post disease progression, compliance was lower but broadly consistent between the treatment arms up to 40 weeks post-progression (Table 14.2.10.8.1b of D5169C00001-FLAURA2-Final-PSC-V2-Tables-20230802).(7)

The analysis of patient reported outcomes (PROs) conducted for FLAURA2 utilised MMRM as this approach can be utilised to account for missing data as described previously. Both MMRM and multiple imputation can be utilised as methods to account for data that are MCRA or MAR (Twisk 2013, Rosel 2022).(8),(9) However, Twisk (2013) found that using multiple imputation (MI) to account for missing data was not required when a mixed model analysis of longitudinal date was performed.(8) This is further supported by Rosel 2022, who found that mixed models without multiple imputation did not lead to any loss of accuracy when included baseline covariates were complete.(9)

In addition, Rosel 2022 also highlight that approaches to MI are challenging in the case of PROs where there are multiple items that may result in a missing record, as such determining one appropriate approach to MI may be challenging in this case.(9) As such, given the above and time available, analysis using multiple imputation has not been conducted.

**B4.** Can you please provide clarity on which patients constitute the group of “unknowns” in annex PAY0453 - FLAURA2 - EQ5D MMRM Analysis - - ITT, utility summary statistics table (page 4, unmarked).

**Response:**

The summary statistics table provided in annex PAY0453 - FLAURA2 - EQ5D MMRM Analysis - - ITT summarises all available utility records that are available for

FLAURA2. Records included in the unknown category are those that are described in Question B.1 that cannot be attributed to either health state given they occur after the patient is censored for progression. As described in B.1 these records are not utilised to fit the MMRM models.

**B5. Priority Question: The FLAURA2 trial population is on average 61 years of age with advanced lung cancer. After treatment with osimertinib monotherapy or with osimertinib +chemotherapy, the utility score in the PFS state (using the EQ-5D mapped scores) is 0.828.**

a. **Please can you comment on the validity of the PFS utility value used in the submission and why it is superior to the average UK population norm of 0.799 for 55-64 year olds.**

**Response:**

AstraZeneca understand that the utility value referred to in the question is obtained from Janssen et al. 2019.(10) The utility value of 0.799 is calculated from a country-specific dataset of EQ-5D-3L survey responses. The observed differences between utility values reported in Janssen et al. 2019 and those derived from FLAURA2 may be accounted for by key differences in the data and methodology underpinning these estimates:

- FLAURA2 utilised the 5L version of the EQ-5D, whereas Janssen et al. 2019 used the 3L version. It has been reported that use of the EQ-5D-5L results in an upward shift in utility values versus use of the EQ-5D-3L, as respondents using the 5L can report ill health more frequently but with less severity.(11)

The derived utility value is further supported by Nafees 2017, which derived the utility of NSCLC patients of adult patients with stable disease and no adverse events for patients in the UK to be 0.84.(12). Patients in the FLAURA2 trial were as young as 26, this publication is therefore useful to inform PFS utility. The PFS utility value derived from Nafees 2017 is higher than the utility value used for the PFS health state in the current model and offers validation of the choice of utility value.

AstraZeneca believe that health state utility values derived from FLAURA2 EQ-5D-5L mapped to EQ-5D-3L best reflect the HRQoL of the target population for the current decision problem. This is aligned with the NICE Process and Methods Guide (PMG) 36, which indicates a preference for estimating utility values based on EQ-5D data collected in relevant clinical trials in the first instance.(13) A PFS utility score of 0.828 is therefore more appropriate for decision making.

b. **There are a number of mapping models developed to derive EQ-5D-3L utilities from PROs such as the EORTC-QLQ-C30, some of which developed specifically on non-small cell lung cancer populations (please consult, for example HERC database of mapping studies — Health Economics Research Centre (HERC) (ox.ac.uk)). Please derive alternative estimates for PFS using a range of mapping models and present these utility results, and the resulting ICERs, as scenario analysis. Global – are we able to provide these scenarios?**

**Response:**

As stated in the NICE PMG 36, the EQ-5D is NICE's preferred measure of health-related quality of life (HRQoL) and other HRQoL measures may be used when EQ-5D data are not available.(13) Consequently, the economic analysis for the current appraisal utilises health state utility values derived from FLAURA2 EQ-5D-5L data. In accordance with the NICE position statement on use of the EQ-5D-5L, health state utility values were calculated by mapping the 5L descriptive system data onto the 3L value set.(14)

AstraZeneca acknowledge that this differs from the approach taken in TA654. In TA654, health state utility values were instead estimated by mapping EORTC QLQ-C30 data from the FLAURA trial to the EQ-5D-3L.(5) EQ-5D data were not collected in the FLAURA trial, therefore this was deemed the most appropriate approach to estimate health state utility values in this specific instance.

Utility values derived from other HRQoL measures recorded in FLAURA2, such as the EORTC QLQ-C30, are not available. The requested scenario analyses have therefore not been performed. However, the utility values provided in the original company submission were estimated following the preferred methods of the NICE

and a scenario analysis has been conducted utilising the health state utility values derived from the FLAURA trial EORTC QLQ-C30 data (see Question B.5.c). Deriving utilities using alternative methodology represent a departure from the NICE guidelines, and therefore is not appropriate for decision making within the NICE reference case.

c. **In TA654 for osimertinib monotherapy for the same patient group, the company uses mapped utilities from PROs from the FLAURA trial (FLAURA1) for the PFS and PD (1 treatment) health states [these were reproduced in Table 28 of the EAG report]. Could the company also make these mapped utilities available for the present submission and re-run a scenario analysis with them?**

**Response:**

While utility values aim to standardise quality of life measurements, numerous factors can introduce variability between trials within the same patient population. The health state utility values included within this submission were derived directly from the FLAURA-2 trial, as the most relevant evidence base to this submission. The utility values from TA654 were derived from the FLAURA trial. The mapped utility values from TA654 are presented in **Table *5*: Mapped utility values (TA654)**Table 5, and a scenario analysis using these utility values is presented in Table 6. The utilities used within this scenario represent a departure from the NICE guidelines and therefore are not appropriate for decision making within the NICE reference case.

**Table 5: Mapped utility values (TA654)**

| Health state | Utility value | Source/description |
|---|---|---|
| Progression-free | 0.794 | Mapped from FLAURA EORTC |
| Progressed disease (1L treatment) | 0.704 | Mapped from FLAURA EORTC |

**Table 6:Scenario analysis of TA654 utilities**

| Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base case ICER (%) |
|---|---|---|---|---|---|---|---|
| Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £29,619 | 8.58% |

d. **In TA654 for osimertinib monotherapy, the company argued that the Labbe 2017 0.64 utility value for PD (subsequent treatment or BSC) was too low and did not represent the true quality of life of patients in this health state. This claim was corroborated by clinical advice and the final value used was 0.678. Could the company explain the rationale for not using the utility value of 0.678 for PD in this submission?**

**Response:**

The estimated PD health utility from FLAURA2 was inconsistent with previous appraisals in NSCLC (TA654/309/402/347). This may have been due to the limited number of measurements for post-progression health utilities, most of which occurred immediately after progression. As a result, an alternative source of PD utility was identified.

The base case utility was based on Labbe et al. (2017), a longitudinal cohort study conducted in Canada. Labbe et al. provided utility values for PD based on assessments conducted over multiple occasions, capturing patients' long-term deterioration of HRQoL. Although the study was not conducted in a UK setting, results based on UK conversions were reported and PD value was considered more appropriate than the one reported in FLAURA2.

Furthermore, this study was used to inform the PD health state utility in TA654 and the PD utility value reported by Labbe et al. was very similar to those used and accepted by ERGs in two previous NSCLC NICE submissions; TA309/TA402 and TA347. Labbe et al. therefore is an appropriate PD utility value that is considered suitable for decision making.

## *Model structure and assumptions*

**B6.** In section B.3.2.4 of the submission you explain that *"patients in both arms were treated until death or another discontinuation criterion was met, in line with the*

*FLAURA2 trial*". Could you clarify which of the FLAURA2 discontinuation criteria were adopted in the economic model?

Treatment duration for both treatment arms was estimated based on time to treatment discontinuation (TTD) data from the FLAURA2 clinical trial. In FLAURA2, randomised treatment was continued until disease progression (investigator assessed, per Response Evaluation Criteria in Solid Tumours [RECIST] 1.1) or another treatment discontinuation criterion was met. Patients could continue to receive study treatment with osimertinib beyond RECIST 1.1-defined progression if, in the judgement of the investigator, they were receiving clinical benefit and did not meet any discontinuation criteria. However, if the patient was deemed to have clinically significant unacceptable or irreversible toxicities, rapid tumour progression, or symptomatic progression requiring urgent medical intervention, study treatment was discontinued. (15),(16) Standard parametric models were fitted to the FLAURA2 TTD data, based on the discontinuation criteria, in order to incorporate treatment duration accurately into the economic model. Treatment duration was modelled separately for osimertinib monotherapy, osimertinib in combination with chemotherapy and pemetrexed to accurately reflect time on treatment for each regimen.

## *Model results*

**B7. Priority Question. The PSA results in the submitted executable model file (ICER of £31,348) differ from the PSA results reported in Document B (ICER of £27,280), and the EAG has been unable to replicate the results reported in Document B. Please could you provide the version of the model with the iterations from the reported results saved, or update the results in the report to match the submitted model.**

**Response:**

The correct version of the cost-effectiveness model has been uploaded to NICE Docs alongside this response document. The model has a probabilistic ICER of £28,318 and a deterministic ICER of £27,280.

**B8.** In section B.3.11.1 of the submission you explain that convergence of the ICERs in the PSA was achieved by approximately the 200$^{th}$ simulation. How did you assess

model convergence? The EAG found that more simulations were required for stable results.

**Response:**

Since NICE does not prescribe a specific methodology for assessing convergence, the convergence of the ICER in the PSA was evaluated by visually inspecting the ICER convergence plot within the Excel model. After 200 simulations, fluctuations around the mean probabilistic ICER were approximately within £1,000-£2,000 per QALY, therefore it was considered convergence had occurred from this simulation onwards.

## *Model clinical parameters*

**B9. Priority question: Please provide fitted survival curves and model fit for progression free survival (PFS) using the later Data Cut-Off of 8th Jan 2024 (Also see question A1), and updated cost-effectiveness results using the later Data Cut-Off.**

**Response:**

As described above in response to question A1, the data cut-off (DCO) of 8th Jan 2024 was an ad-hoc analysis of the overall survival (OS) outcome provided as part of US Food and Drug Administration (FDA)-specific regulatory procedures. This DCO was focused on providing OS data and did not include the PFS outcome.

## *Subgroups*

**B10. Priority question. Can you provide cost-effectiveness results for subgroup analyses for those with and without CNS metastases?**

**Response:**

To model efficacy in the CNS metastases group, survival analysis was performed on time-to-event outcomes using parametric modelling. Curve selection was based on the following criteria.

- Assessment of whether the proportional hazards assumption
- Akaike information criterion (AIC) and Bayesian information criterion (BIC)
- Visual inspection of modelled curves vs KM curves

- Clinical validity

## Overall Survival

Proportional Hazards

The first step in selecting the choice of parametric survival model for OS was to assess whether the PHA was upheld for the CNS metastases subgroup within the FLAURA2 data. Figure 1**: First-line metastatic EGFRm NSCLC UK market share over time** show that the plot of the Schoenfeld residuals against time did not show a pattern of changing residuals and the p-value for Schoenfeld residuals test is non-significant (p=0.1929), indicating that the PHA could be considered reasonable. However, the log cumulative hazard curves (Figure 3) were not parallel over time, indicating that the treatment effect varied over the trial period.

On this basis it was considered that there was a violation of the PHA.

**Figure 2: Plot of Schoenfeld residuals (OS)**

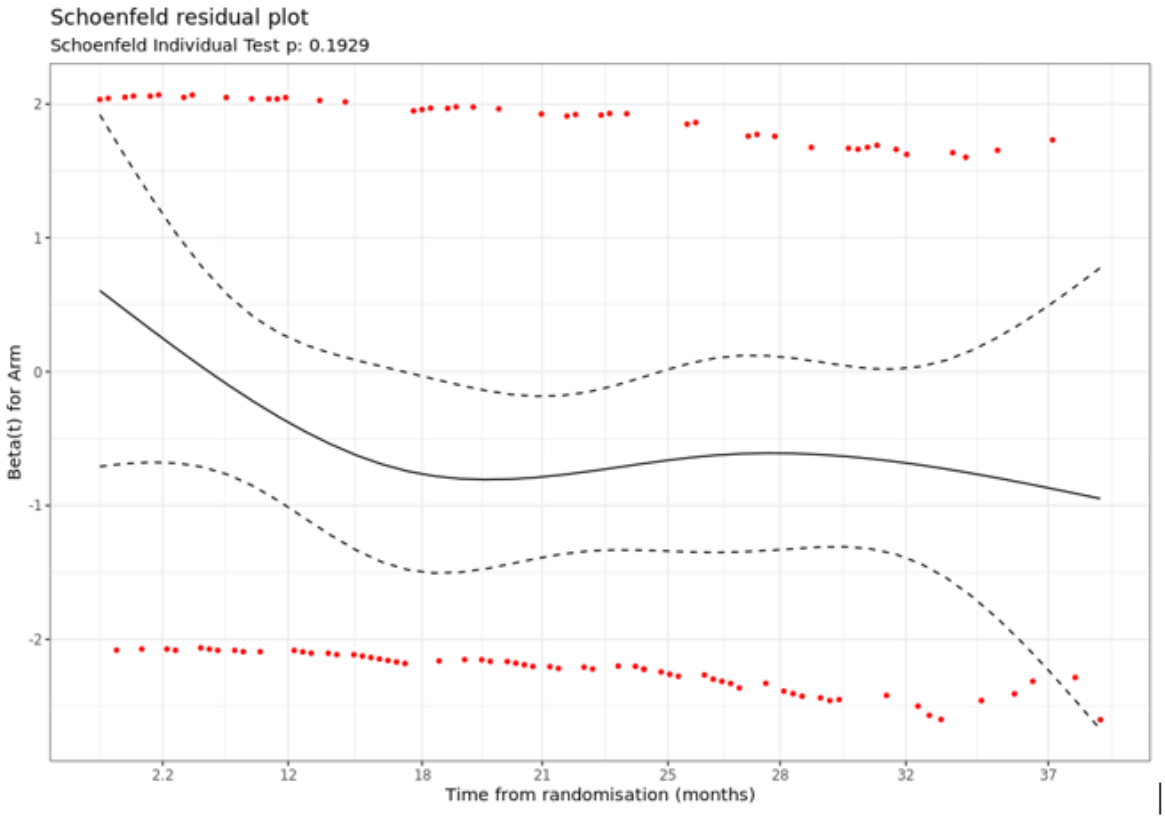
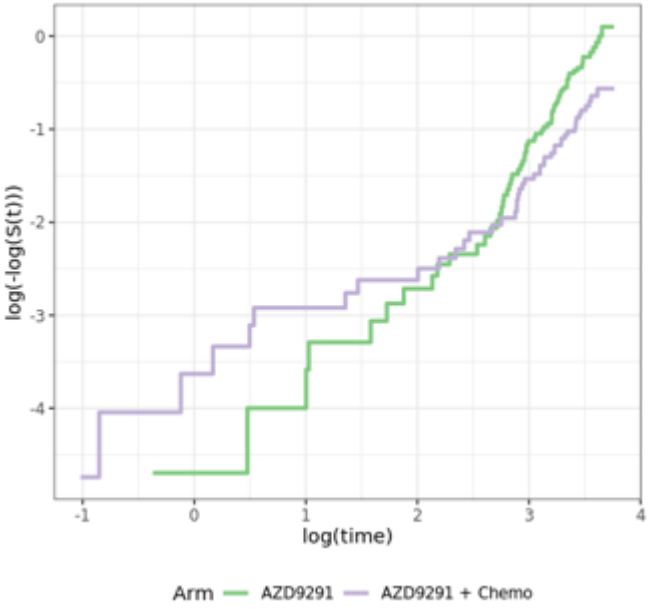


**Figure 3: Log cumulative hazard curves (OS)**




As the PHA was not considered to be a reasonable assumption, parametric models were fitted separately to both arms. In accordance with NICE DSU TSD 14 seven standard parametric distributions (exponential, gamma, generalised gamma, log-normal, log-logistic, Weibull, Gompertz) were fitted to the observed OS data from the FLAURA2 clinical trial.(17) Furthermore, as specified in NICE DSU TSD 21, flexible models (such as spline-based models) should also be considered where complex hazard functions exist and cannot be represented well by standard parametric models.(18) Spline models were therefore also considered, as consistent with the approach taken in the original submission dossier.

Statistical fit

The AIC and BIC statistics indicating the within-trial goodness-of-fit of each standard parametric survival model for osimertinib plus chemotherapy and osimertinib monotherapy are provided in Table 7 and Table 8, respectively.

For the osimertinib plus chemotherapy arm, the exponential and Gompertz distributions provided the best fits based on AIC and BIC statistics. The remaining curves all provide inferior fits, however the difference in the range of AIC/BIC criteria is relatively narrow. All of the spline-based models had similar AIC values.

For the osimertinib monotherapy arm, similarly the exponential and Gompertz distributions provided the best fits based on AIC and BIC statistics. The 1-knot and

2-knot model on the odds scale provided the best fitting models of the splines based on AIC/BIC. However, the majority of spline models provided relatively reasonable fits according to these statistics, with the difference in the range of AIC/BIC criteria being relatively narrow.

**Table 7: AIC and BIC statistics for OS in the osimertinib plus chemotherapy arm**

| Distribution | AIC | BIC |
|---|---|---|
| Exponential | 469.3 | 472.1 |
| Weibull | 470.9 | 476.4 |
| Log-normal | 479.5 | 485.1 |
| Log-logistic | 473.5 | 479.0 |
| Gompertz | 468.4 | 473.9 |
| Generalised Gamma | 470.9 | 479.2 |
| Gamma | 471.2 | 476.7 |
| Scale=hazard (1 knots) | 469.2 | 477.5 |
| Scale=hazard (2 knots) | 470.7 | 481.7 |
| Scale=hazard (3 knots) | 469.9 | 483.7 |
| Scale=normal (1 knots) | - | - |
| Scale=normal (2 knots) | 470.7 | 481.7 |
| Scale=normal (3 knots) | 469.1 | 482.9 |
| Scale=odds (1 knots) | 470.0 | 478.3 |
| Scale=odds (2 knots) | 470.7 | 481.7 |
| Scale=odds (3 knots) | 469.8 | 483.5 |

**Table 8: AIC and BIC statistics for OS in the osimertinib monotherapy arm**

| Distribution | AIC | BIC |
|---|---|---|
| Exponential | 469.3 | 472.1 |
| Weibull | 470.9 | 476.4 |
| Log-normal | 479.5 | 485.1 |
| Log-logistic | 473.5 | 479.0 |
| Gompertz | 468.4 | 473.9 |
| Generalised Gamma | 470.9 | 479.2 |
| Gamma | 471.2 | 476.7 |
| Scale=hazard (1 knots) | 585.7 | 593.8 |
| Scale=hazard (2 knots) | 587.1 | 597.9 |
| Scale=hazard (3 knots) | 588.8 | 602.3 |

| | | |
|---|---|---|
| Scale=normal (1 knots) | - | - |
| Scale=normal (2 knots) | 588.4 | 599.2 |
| Scale=normal (3 knots) | 589.8 | 603.3 |
| Scale=odds (1 knots) | 585.4 | 593.5 |
| Scale=odds (2 knots) | 587.4 | 598.2 |
| Scale=odds (3 knots) | 589.2 | 602.7 |

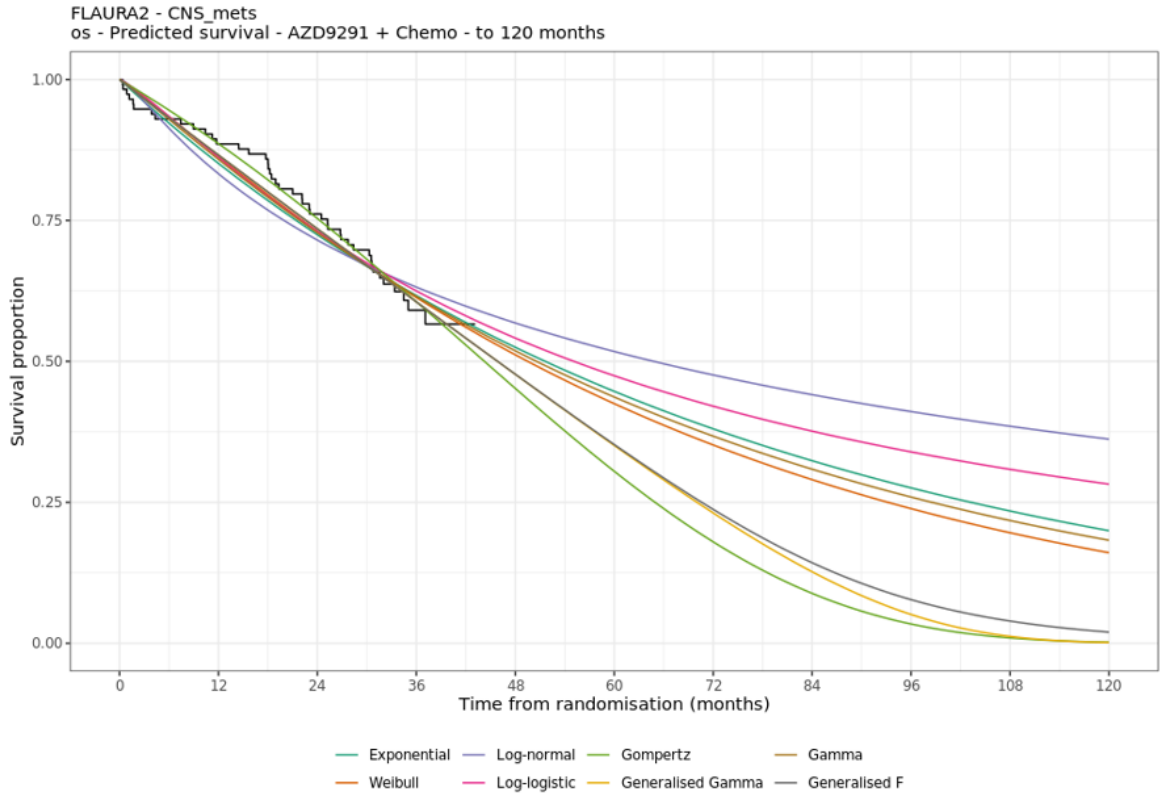
Standard parametric models: Visual inspection of extrapolations vs. observed data

Figure 5 and Figure 4 displays the standard parametric models extrapolated over a 10-year period with the KM overlaid.

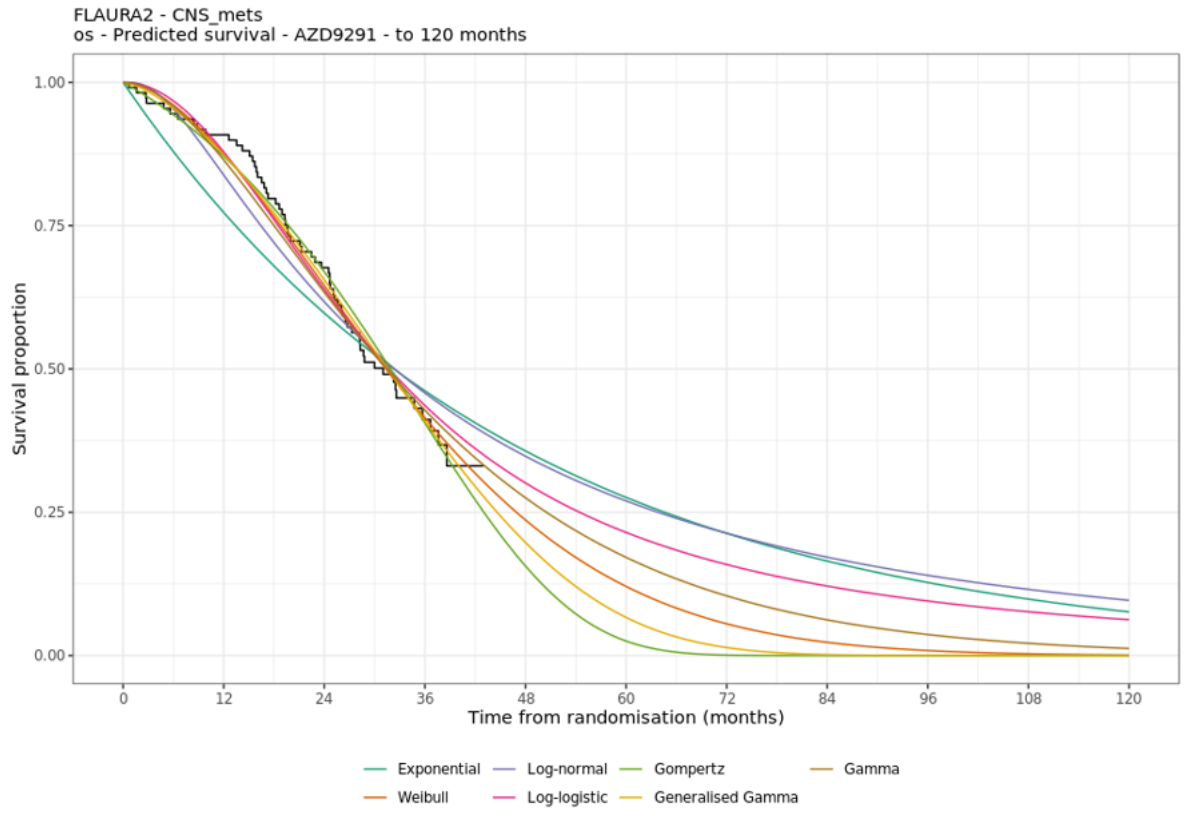
For osimertinib plus chemotherapy, all of the standard parametric models provided a poor fit to the KM curve data, with all models apart from Gompertz, under predicting survival between 6 and 30 months. At 30 months, all models align closely to the KM curve. The Gompertz provides the best visual fit of all standard parametric distributions, however the overall fit was still poor. The model failed to capture the increase in hazards between 0 and 6 months and the decrease in hazards between month 12 and 18. Spline modelling was therefore explored for the osimertinib chemo arm OS extrapolation.

For the osimertinib monotherapy arm, all of the standard parametric models provided a poor fit to the KM curve data. The Weibull and the generalised gamma appeared to provide the best visual fit to the KM curve, although under predicting survival between 12 and 18 months. All standard parametric models fail to capture the decrease in hazards at approximately 10 months. The exponential, lognormal, loglogistic and gamma distributions all fail to fit the data after 36 months onwards and are considered to overestimate long term survival. Spline modelling was therefore explored for the osimertinib plus chemotherapy arm OS extrapolation.

## Figure 4: CNS metastases OS KM and extrapolations for osimertinib plus chemotherapy




## Figure 5: CNS metastases OS KM and extrapolations for osimertinib monotherapy



Spline models: Visual inspection of extrapolations vs. observed data

Figure 6, Figure 7 and Figure 8 show the spline-based models extrapolated over a 10-year period with the KM overlaid (on the normal, odds and hazard scale, respectively).

For osimertinib plus chemotherapy, all 3-knot models were the best at capturing the decreasing hazards at month 18, however the 3-knots provided the most optimistic assumptions on the normal and hazards scale in the long term, and the second most optimistic on the odds scale. Across all scales, the 2-knot models were the best visual fit to the KM data after 24 months.

For osimertinib monotherapy, on the normal scale, both the 2-knot and the 3-knot were broadly equivalent, with neither capturing the decreasing hazards around month 12; however, both models predicted the KM data well after 12 months. The extrapolations were broadly equivalent between the normal scale and the odds scale, with all models providing similar results. On both scales, the 3-knot models predicted more optimistic survival estimates in the long-term, highlighting the importance of clinical validation.

**Figure 6: CNS metastases OS curves and extrapolations (spline-based models on normal scale): osimertinib plus chemotherapy and osimertinib monotherapy**

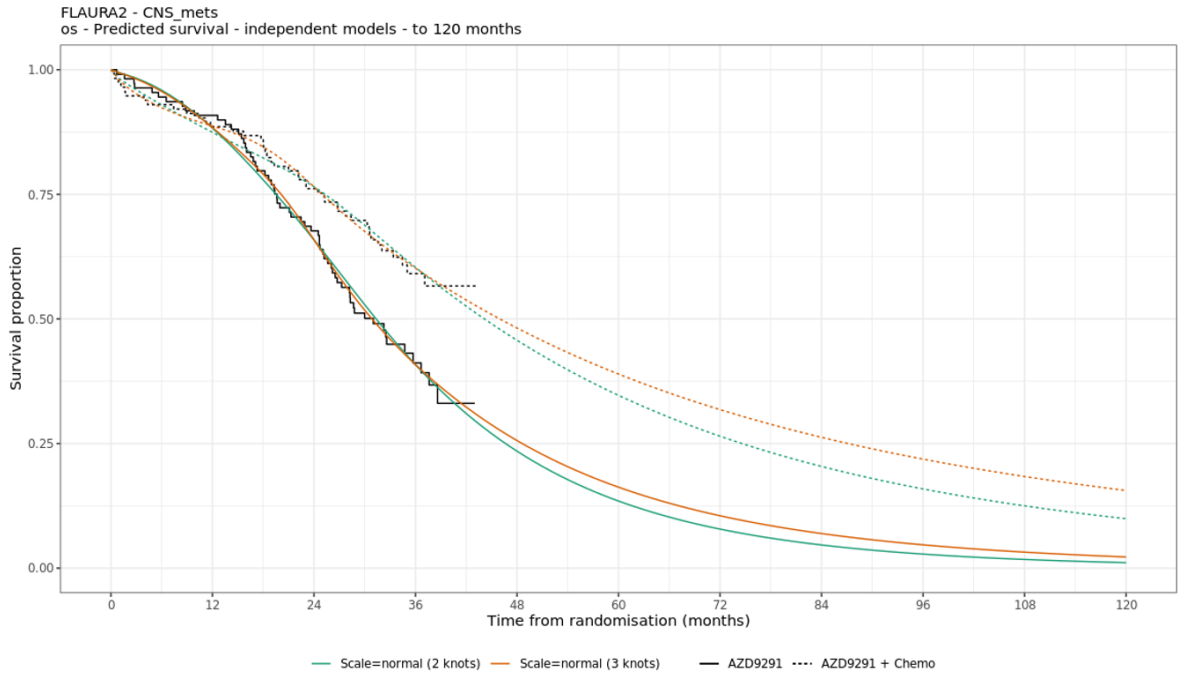


**Figure 7: CNS metastases OS curves and extrapolations (spline-based models on odds scale): osimertinib plus chemotherapy and osimertinib monotherapy**

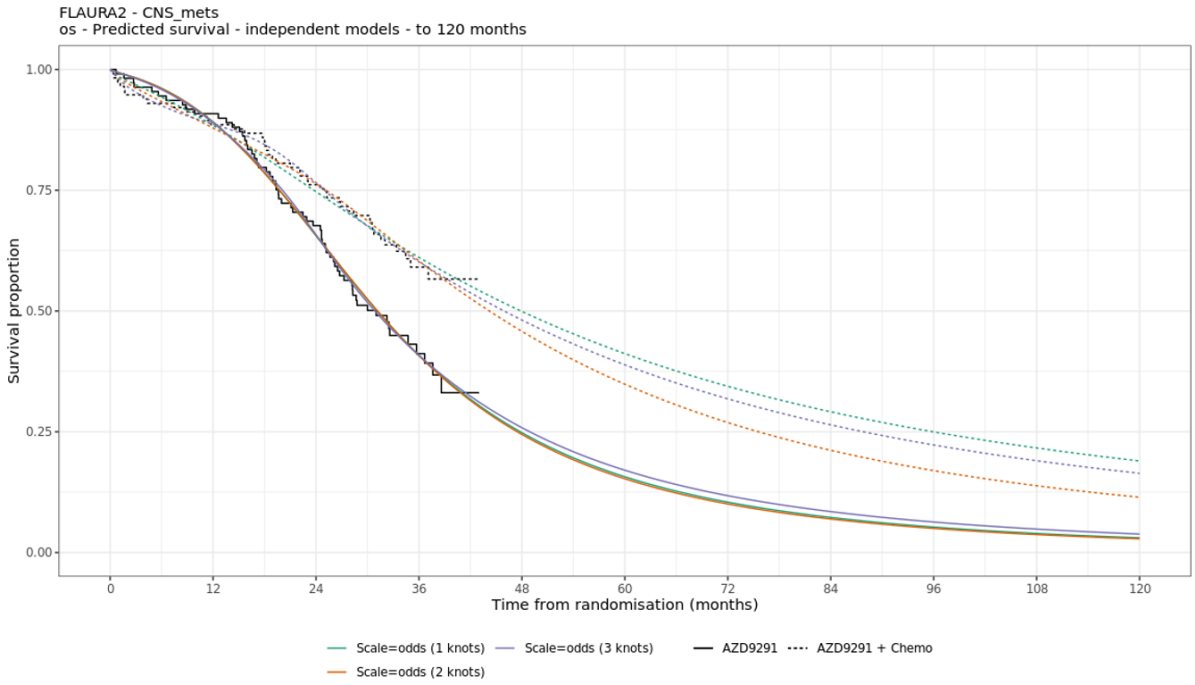
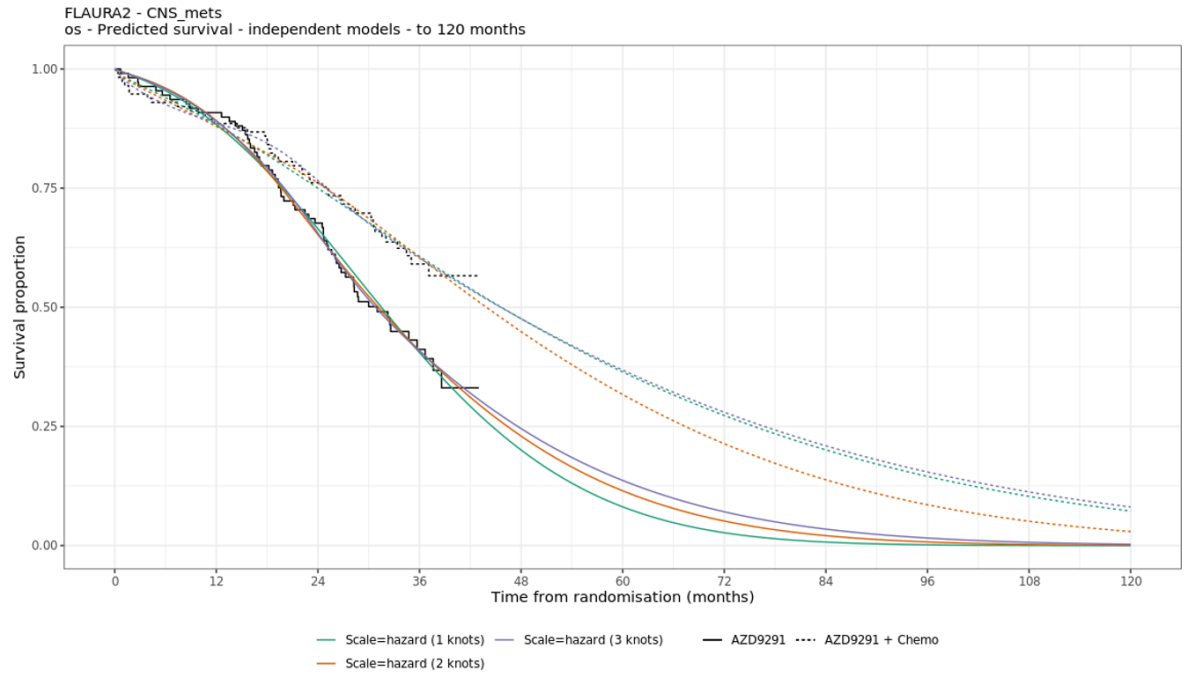



**Figure 8: CNS metastases OS curves and extrapolations (spline-based models on hazard scale): osimertinib plus chemotherapy and osimertinib monotherapy**




## Clinician validation

To support the company response the EAG clarification questions, five further one to one interviews were conducted with the clinical experts previously consulted for the clinical validation described in Section B.2.3.5 of the company submission.

Clinician validation was sought for OS extrapolations in the CNS metastases subgroup. The KM data for both arms from FLAURA2 and standard parametric models over a 10-year time period were provided to clinicians and they were asked to comment on the proportion of patients they would expect to be alive at different time points.

For OS, clinicians stated that at 10 years, they expected 2% of patients on osimertinib monotherapy to be alive. For patients on osimertinib plus chemotherapy, clinicians expected 10% of patients to be alive. Half of clinicians deemed the 2-knot odds model for both trial arms to be the most plausible distribution. The remaining half deemed the 2-knot normal model to be the most plausible for both trial arms.

Base case selection

In the base case, independently fit 2-knot models on the normal scale were selected for both the osimertinib plus chemotherapy arm and the osimertinib monotherapy arm. The 2-knot model on the normal scale was a good visual fit to the trial data. The 2-knot model on the normal scale predicted 1.0% and 9.8% of patients on osimertinib and osimertinib plus chemotherapy, respectively, would be alive at 10 years. The 2-knot model on the normal scale predicted 10-year survival that was more consistent with clinical opinion, compared to the 2-knot model on either the hazard or odds scale.

**Progression Free Survival**

Proportional Hazards

The first step in selecting the choice of parametric survival model for PFS was to assess whether the PHA was upheld for the CNS metastases subgroup data in FLAURA2. Figure 9 shows that the plot of the Schoenfeld residuals against time does not show a pattern of changing residuals but the p-value for Schoenfeld residuals test is non-significant (p=0.1821), indicating that the proportional hazards assumption may be reasonable. However, the log cumulative hazard curves (Figure 10**Error! Reference source not found.**) were not parallel over time, indicating that the treatment effect varied over the trial period. On this basis it was considered that there was a violation of the PHA.

**Figure 9: Plot of Schoenfeld residuals (PFS)**

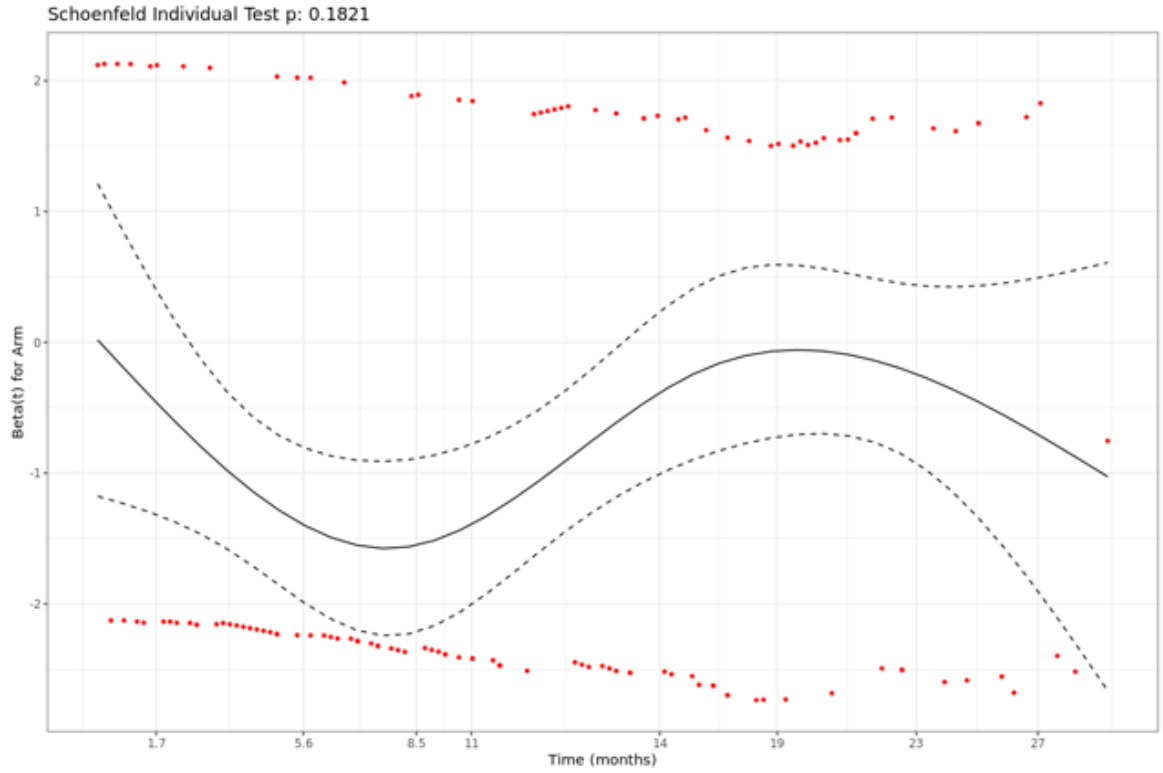
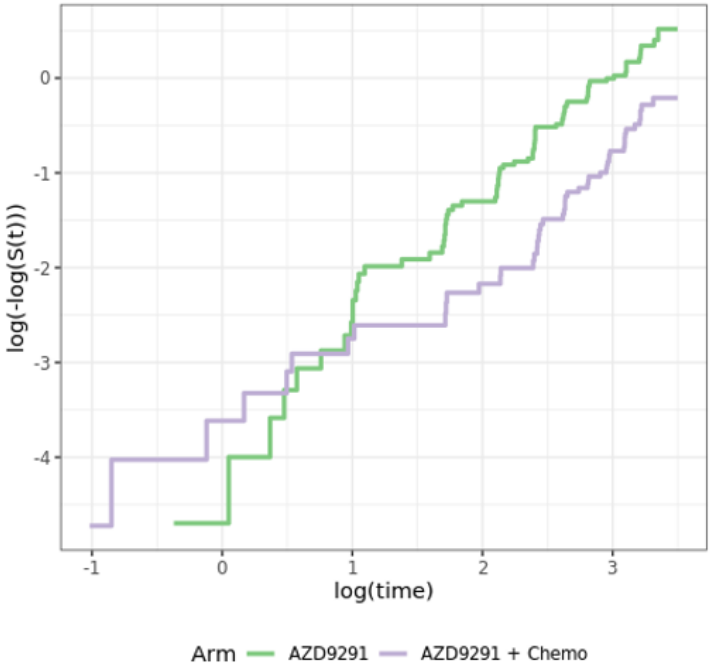



**Figure 10: Log cumulative hazard curves (PFS)**




As the PHA was not considered to be a reasonable assumption, parametric models were fitted separately to both arms. As with OS, and in accordance with NICE DSU TSD 14(17) seven standard parametric distributions (exponential, gamma,

generalised gamma, log-normal, log-logistic, Weibull, Gompertz) were fitted to the observed PFS data from the FLAURA2 clinical trial.

Statistical fit

The AIC and BIC statistics indicating the within-trial goodness-of-fit of each standard parametric survival model for osimertinib plus chemotherapy and osimertinib monotherapy are provided in Table 9 and Table 10, respectively. All curves for PFS provided a good visual fit and therefore flexible models were not explored further.

For the osimertinib plus chemotherapy arm, the Gompertz, generalised gamma and the Weibull distribution provided the best fits based on the AIC and BIC statistics. However, considering the relatively narrow range of AIC/BIC values, there were multiple models that provided reasonable fits based on the AIC statistic. Most distributions provided a reasonable statistical fit to the trial data, with the exception of log-normal and log-logistic distribution.

For the osimertinib monotherapy arm, the Weibull, log-normal, log-logistic and gamma distribution provided the best fits based on both AIC and BIC statistics. The exponential, Gompertz and generalised gamma provided poor statistical fits to the data based on AIC/BIC.

**Table 9: AIC and BIC statistics for PFS in the osimertinib plus chemotherapy arm**

| Distribution | AIC | BIC |
|---|---|---|
| Exponential | 490.0 | 492.8 |
| Weibull | 488.0 | 493.5 |
| Log-normal | 500.3 | 505.8 |
| Log-logistic | 492.3 | 497.9 |
| Gompertz | 483.3 | 488.8 |
| Generalised Gamma | 486.5 | 494.8 |
| Gamma | 489.2 | 494.7 |

**Table 10: AIC and BIC statistics for PFS in the osimertinib monotherapy arm**

| Distribution | AIC | BIC |
|---|---|---|
| Exponential | 635.1 | 637.8 |
| Weibull | 632.1 | 637.5 |
| Log-normal | 631.7 | 637.1 |
| Log-logistic | 631.2 | 636.6 |

| | | |
|---|---|---|
| Gompertz | 635.0 | 640.4 |
| Generalised Gamma | 632.4 | 640.5 |
| Gamma | 631.3 | 636.7 |

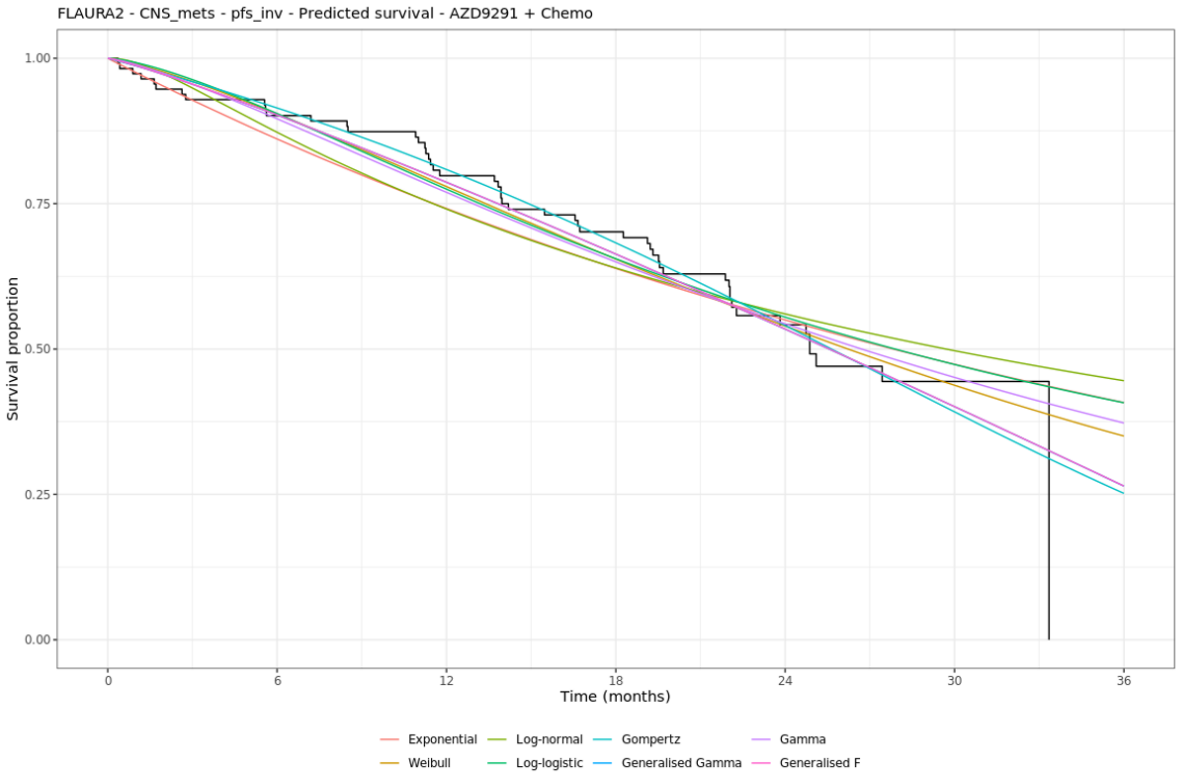
Visual inspection of extrapolations vs. observed data

Figure 11 and Figure 12 display the standard parametric models extrapolated over a 36-month period with the KM overlaid for PFS in the CNS metastases subgroup.

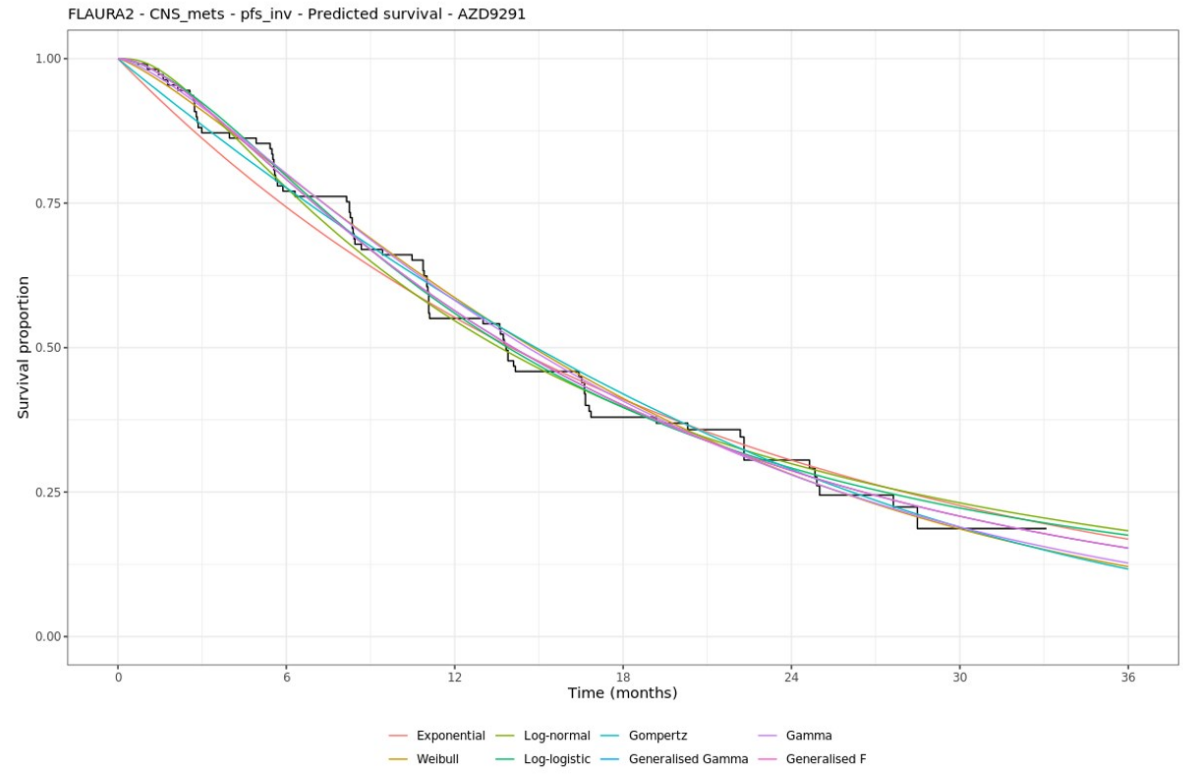
For osimertinib plus chemotherapy, the Weibull and the gamma appeared to provide a reasonable visual fit to the KM curve. The exponential and log-normal provide poor fits to the KM curve. The log-logistic curve provides a good fit to the KM data up until 24 months where the curve begins to plateau. This may lead to an overestimation of long term PFS.

For osimertinib monotherapy, all of the curves provided a reasonable visual fit to the KM curve. For the osimertinib monotherapy arm, the Weibull, gamma, generalised gamma and the Gompertz appeared to provide a reasonable visual fit to the KM curve.

## Figure 11: CNS metastases PFS KM and extrapolations for osimertinib plus chemotherapy




## Figure 12: CNS metastases PFS KM and extrapolations for osimertinib monotherapy



Clinician validation

Clinician validation was sought for PFS extrapolations in the CNS metastases subgroup. The KM data for both arms from FLAURA2 and standard parametric models over a 5-year time period was provided to clinicians and they were asked to comment on the proportion of patients they would expect to be alive at different time points.

For osimertinib monotherapy, clinicians stated that they would expect 1% of osimertinib to be progression free at 5 years. For osimertinib plus chemotherapy, clinicians stated that they would expect PFS to be up to 5% at 5 years.

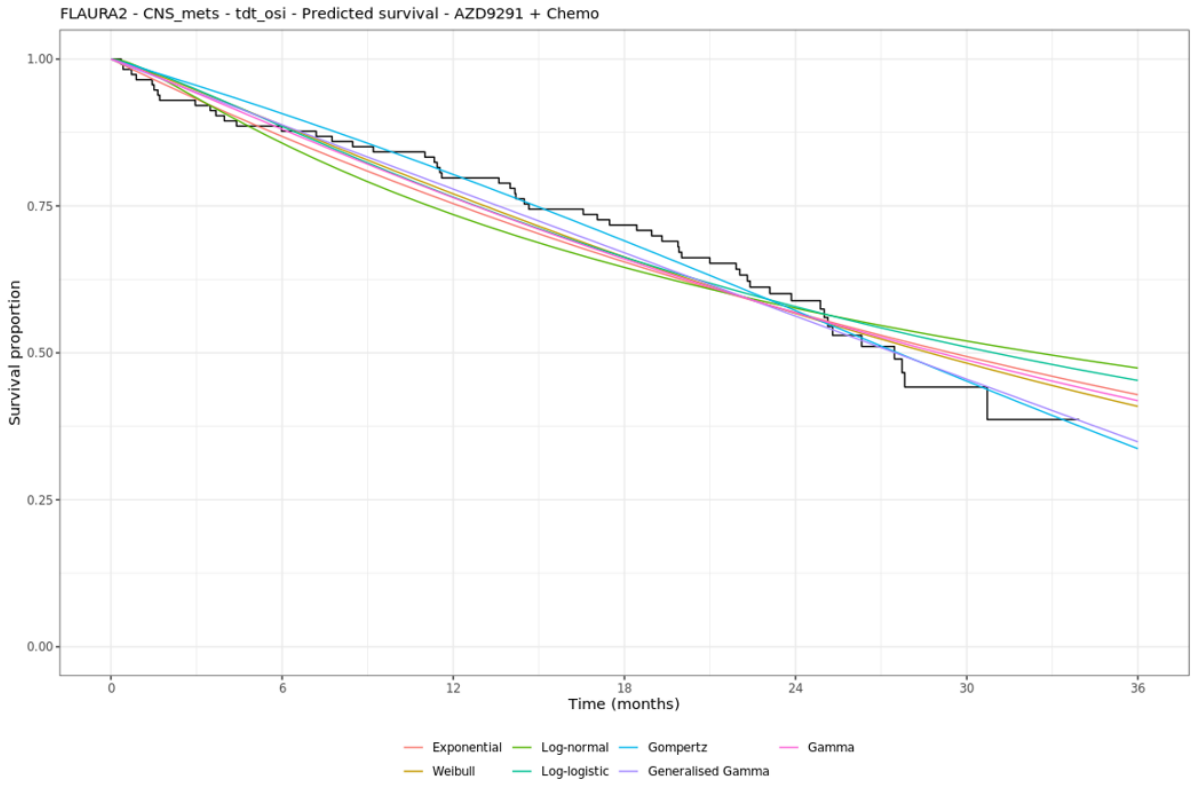
Base case selection

In the base case, independently fit Weibull distributions were selected for both the osimertinib plus chemotherapy arm and the osimertinib monotherapy arm based on good statistical and visual fit. The Weibull model predicted 1.2% and 3.0% of patients on osimertinib and osimertinib plus chemotherapy, respectively, would be progression free at 5-years. These survival estimates were consistent with clinical opinion.

**Time to treatment discontinuation**

**Figure *13*** presents the parametric models fitted to the FLAURA2 TTD data for osimertinib in the osimertinib plus chemotherapy arm in the CNS metastases subgroup, Table 11 shows the corresponding AIC and BIC ranks.

## Figure 13: CNS metastases FLAURA2 TTD KM and extrapolations for osimertinib plus chemotherapy (osimertinib)




## Table 11: AIC and BIC for TTD parametric modes for osimertinib plus chemotherapy (osimertinib)

| Parametric model | AIC | BIC |
|---|---|---|
| Exponential | 515.0 | 517.7 |
| Weibull | 516.2 | 521.7 |
| Log-normal | 525.7 | 531.2 |
| Log-logistic | 520.5 | 526.0 |
| Gompertz | 512.4 | 517.9 |
| Generalised Gamma | 514.4 | 522.7 |
| Gamma | 516.6 | 522.1 |

The AIC and BIC scores show that the Gompertz is the best statistically fitting distribution. Based on a visual comparison of the KM curve to the extrapolations, only the Gompertz and generalised gamma distributions captured the tail of the KM curve and were considered clinically plausible estimates in the long term. Therefore, due to best statistical and good visual fit, the Gompertz distribution was considered the most appropriate extrapolation in the base case.

Figure 14 and

Table ***12*: AIC and BIC for TTD parametric modes for osimertinib monotherapy** show the parametric models fitted to the osimertinib monotherapy FLAURA2 TTD data and their corresponding AIC and BIC ranks.

**Figure 14: CNS metastases TTD KM and extrapolations for osimertinib monotherapy**

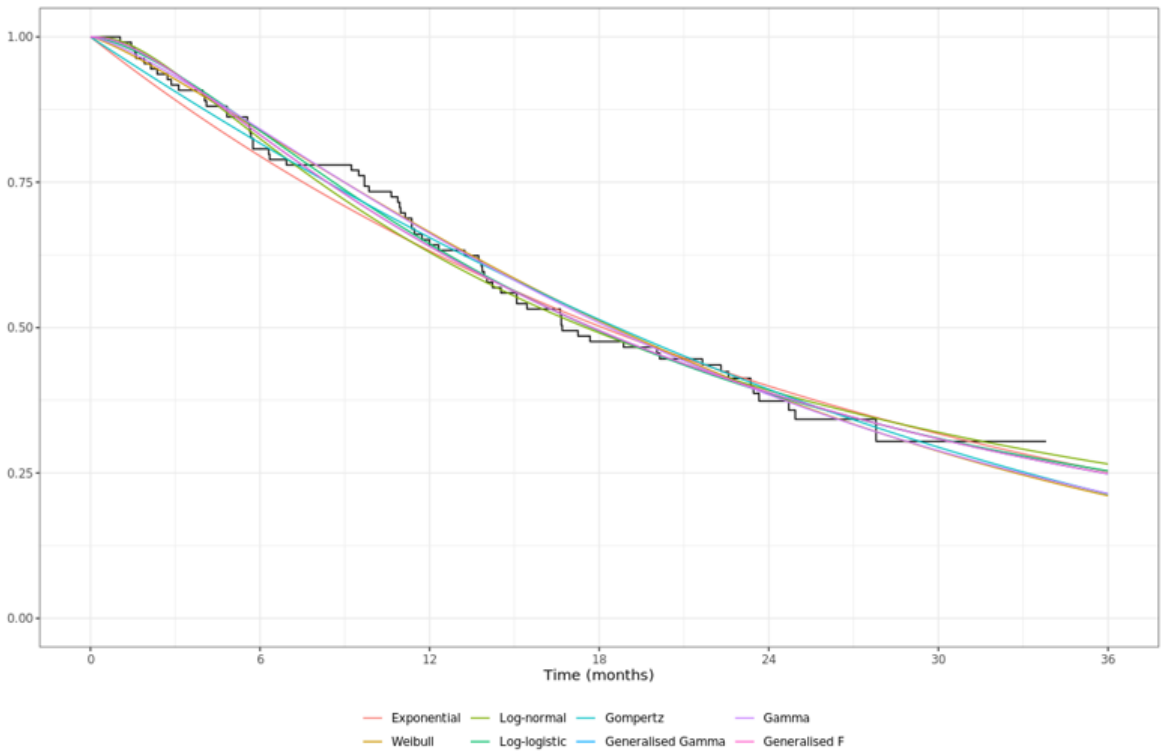



**Table 12: AIC and BIC for TTD parametric modes for osimertinib monotherapy**

| Parametric model | AIC | BIC |
|---|---|---|
| Exponential | 598.9 | 601.6 |
| Weibull | 597.7 | 603.1 |
| Log-normal | 596.1 | 601.6 |
| Log-logistic | 596.4 | 601.8 |
| Gompertz | 599.9 | 605.3 |
| Generalised Gamma | 597.8 | 605.9 |
| Gamma | 597.1 | 602.5 |

The AIC and BIC scores show that all parametric distributions provide a reasonable fit to the observed data. Based on the AIC and BIC rankings, lognormal extrapolation was the most suitable distribution for TTD extrapolation in the osimertinib monotherapy arm. However, the lognormal extrapolation predicts a decreasing hazard ratio, and it was therefore considered that it may overpredict treatment duration. The loglogistic distribution was the second-best fitting, however the loglogistic distribution also predicts a decreasing hazard ratio and will therefore likely over predict time on treatment. The gamma distribution was the next best fitting, with

a close AIC/BIC score to the loglogistic distribution, and was not considered to overpredict treatment duration compared with the loglogistic and lognormal distributions in the long-term. Therefore, the gamma distribution was selected for the base case.

Figure ***15*** presents the parametric models fitted to the FLAURA2 TTD data for pemetrexed in the osimertinib plus chemotherapy arm.

Table ***13*** shows the corresponding AIC and BIC ranks.

**Figure 15: CNS metastases TTD KM and extrapolations for osimertinib plus chemotherapy (pemetrexed)**

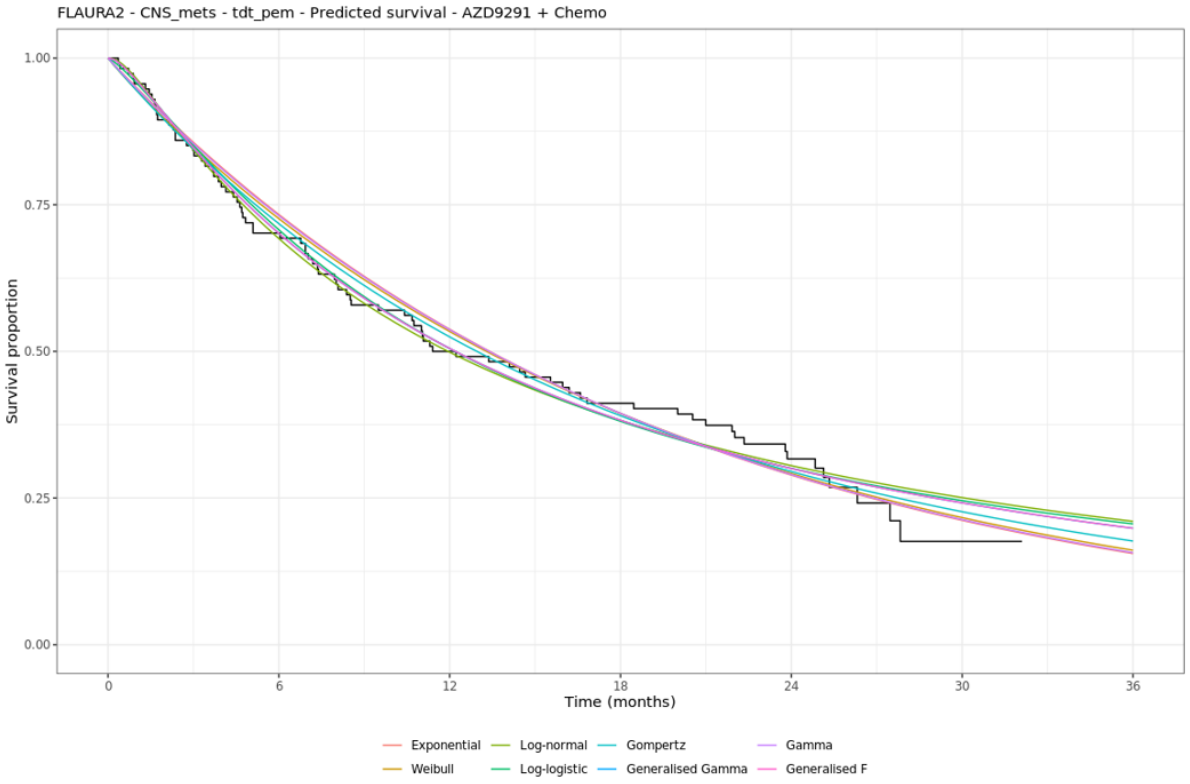



**Table 13: AIC and BIC for TTD parametric modes for osimertinib plus chemotherapy (pemetrexed)**

| Parametric model | AIC | BIC |
|---|---|---|
| Exponential | 651.8 | 654.6 |
| Weibull | 653.7 | 659.2 |
| Log-normal | 651.2 | 656.7 |
| Log-logistic | 652.8 | 658.3 |
| Gompertz | 653.4 | 658.9 |
| Generalised Gamma | 653.0 | 661.2 |
| Gamma | 653.8 | 659.3 |
| Generalised F | 655.0 | 666.0 |

Given the narrow range of the AIC and BIC scores, all the parametric distributions were considered to provide similar fits to the observed data. Of the distributions, the AIC and BIC rankings suggest that the exponential and lognormal distributions were the best statistically fitting extrapolations for the pemetrexed TTD data. Furthermore, it was considered implausible to expect patients to be receiving treatment beyond 5 years; of the standard distributions, the exponential distribution predicted the lowest proportion on therapy at 5 years. Considering the exponential distribution was one of the best fitting to the observed data, and the exponential survival distribution predicted the lowest proportion on therapy at 5 years, this extrapolation was considered the most appropriate to model pemetrexed TTD data.

### Resource use

A study by Kong et al. (2021) showed disease-related costs were 1.2 times higher in patients with NSCLC with brain metastases, as compared to patients with NSCLC without brain metastases.(19) On the assumption that resource use for brain metastases is analogous to resource use for CNS metastases, in the subgroup analysis of the model, this factor of 1.2 reported in Kong et al. (2021) was applied to the disease management costs.

### Results

The CNS metastases subgroup results using the base case extrapolations outlined are presented below in Table 14. The results from this analysis in the CNS metastases subgroup, a patient population with high-unmet need, are highly cost-effective at a willingness-to-pay threshold of 30,000 per QALY gained. Moreover, the

results remain broadly consistent with ITT analysis, which remains the population of interest for decision making in this appraisal.

**Table 14: CNS metastases subgroup**

| Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £18,834.80 |

## *Costs*

**B11. Priority question. Please provide a scenario where all subsequent treatments are the same, regardless of 1st line treatment, with the exception that pemetrexed maintenance would not be used following osimertinib+chemotherapy**

**Response:**

To ensure that the cost-effectiveness analysis accurately reflected NHS clinical practice, the distribution of subsequent therapies in the initial submission were validated by clinical experts. Of note, clinicians were asked to validate the type and proportion of subsequent treatments patients within each arm of the trial and confirmed that the proportion and type of subsequent treatment would likely differ according to trial arm.

A scenario equalising subsequent treatments is therefore not considered plausible or likely representative of NHA clinical practice, as patients receiving osimertinib plus chemotherapy are receiving a new comprehensive combination regimen up-front and will therefore receive different therapies in later lines compared with patients receiving osimertinib monotherapy. Specifically, clinicians highlighted that osimertinib+chemotherapy effectively combines the current first line and second-line treatment options, giving them concurrently rather than sequentially.(2) A scenario where all subsequent treatments are the same is therefore not considered informative for decision making.

**B12. Priority question. What was the source for the assumed 17.16 A&E consultations for the progressed disease health-state (Table 61 of CS)? Why**

**not include A&E consultations for the PFS health state for the chemotherapy group?**

**Response:**

Clinical expert feedback was sought to ensure that resource use in the cost-effectiveness model accurately reflected current UK clinical practice. Clinicians were shown the resource use estimated from Brown et al., that has been used to inform previous technology appraisals in the NSCLC.(20) Clinicians were asked to comment on whether the amount of resource utilisation was accurate, and whether any resource was missing from the list shown.

Clinicians highlighted that patients with progressed disease may present in accident and emergency (A&E) departments due to the severity of their illness and difficulty accessing primary care services promptly. A&E visits were therefore incorporated into the model for the progressed disease health state costs. Clinicians said that they would expect a patient in the progressed disease state to present in A&E on average once every three months.

AstraZeneca would like to highlight that there is a typographical error in Table 61, whereby the 17.16 annual A&E consultations should be corrected to 3.96 annual A&E consultations. This is an error in this table of the submission document only and does not impact the results of the cost-effectiveness model or the reported results in the results section of the submission document.

**B13.** Can you give more rationale for the scenario removing the osimertinib acquisition cost?

**Response:**

NICE determines whether a combination therapy is cost effective using the same framework as it does for monotherapy medicines. However, there are fundamental challenges with this methodology when considering combination therapies, some of which are technically complex.

A key challenge is that by extending patients' lives when they are treated with a combination therapy including one treatment that is the current standard of care, the patient receives the currently available treatment for longer and the costs to the NHS

increase. This increase in costs is not always considered cost effective, in some cases even when the new treatment in the combination therapy costs £0.

This submission evaluates the addition of pemetrexed and platinum-based chemotherapy to the existing standard of care, osimertinib monotherapy, and results in an improvement in clinical outcomes and subsequent increase in background osimertinib monotherapy costs. We therefore presented an exploratory scenario analysis where the *additional incremental background cost* (i.e. osimertinib drug acquisition cost) was removed. This scenario is consistent with that outlined in the NICE DSU, that previously identified circumstances where add-on medicines were unable to demonstrate cost effectiveness even at 'zero price'.(21) This DSU guidance recommends non-reference case analyses to be explored, in certain circumstances, where the costs of background care are removed.

Although the base case analysis presented within the original submission can be considered to be plausibly cost effective, and the situation identified by the NICE DSU (i.e. not cost effective at zero price) does not apply, removal of background care costs remains informative for committee decision making. In this scenario, the incremental costs were reduced by £4,854, leading to an ICER of £19,184 per QALY gained. Such a result is consistent with expectations and underlines the important conclusion that the addition of a well-established, generic chemotherapy regimen to existing standard of care is highly likely to be considered a cost-effective use of NHS resources.

**B14.** Could the company please provide a sensitivity analysis to resource use costs estimated using the NHS reference costs (national collection of costs), instead of tariffs?

**Response:**

A scenario using NHS reference costs is displayed in Table 18**Error! Reference source not found.** below. This scenario leads to a reduction in the ICER, due to lower adverse event costs derived when using NHS reference costs. Details of the unit cost inputs based on NHS reference costs for each resource type is provided in in Table 15, Table 16 and Table 17.

**Table 15: Resource unit costs**

| Resource use | | |
|---|---|---|
| Outpatient visit | £203 | *NHS Reference Costs 2022: OPROC, Average unit cost outpatient procedures* |
| MRI | £198 | *NHS refernce Cost 2022: RDO2A 19 years and over Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over* |
| CT scan (chest) | £142 | *NHS Reference Costs 2022: RD21A, Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over* |
| CT scan (other) | £141 | *NHS Reference Costs 2022: RD22Z, Computerised Tomography Scan of One Area, with Pre- and Post-Contrast* |
| ECG | £159 | *NHS Reference Costs 2022: EY51Z, Electrocardiogram Monitoring or Stress Testing* |
| A&E | £158 | *NHS Reference Costs 2022: 180, Emegerncy Medicine Service, Consultant led* |
| Clinical nurse specialist | £119 | *NHS Reference Costs 2022: N10AF, Specialist Nursing, Cancer Related, Adult, Face to face* |

**Table 16: Administration unit cost**

| Administration costs | | |
|---|---|---|
| Deliver complex chemo | £364 | *SB13Z-SB15Z, deliver complex chemotherapy weighted average, outpatient. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022.* |

**Table 17: Adverse event unit costs**

| Adverse Event Costs | | |
|---|---|---|
| Diarrhoea | £589 | *Calculated, weighted average- FD10A-M Non-Malignant Gastrointestinal Tract Disorders with/without (single/multiple) Interventions, Non-elective short stay. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022.* |
| Fatigue | £770 | *Calculated, weighted average- SA01G-SA01K Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia – non-elective short stay (Weighted Average); Non-elective short stay. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022.* |
| Anemia | £770 | *Assumed same as fatigue* |
| Decreased appetite | £876 | *Calculated (weighted average), FD04A-E, Nutritional disorders with/without interventions, all CC scores, Non-elective short stay. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022.* |
| Pneumonia | £669 | *Calculated- DZ11K-N, P-V Lobar, atypical or viral pneumonia with/without single/multiple interventions – non-elective long stay (Weighted Average). NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022.* |
| Neutropenia | £543 | *Calculated, weighted average- SA08G, SA08H, SA08J. Other haematological or splenic disorders, with CC score 0-6+, non-elective short stay. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022.* |
| Neutrophil count decreased | £543 | *Assumed same as neutropenia* |
| Platelet count decreased | £676 | *Calculated, weighted average- SA09G, SA09H, SA09J-L, Other red blood cell disorders with CC score 0-14+. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022.* |
| Thrombocytopenia | £699 | *Calculated, weighted average SA12G-K Thrombocytopenia with CC Score 0-8+, non-elective short stay. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022.* |
| Febrile neutropenia | £2,975 | *Calculated, inflated from 2007/2008 to 2021/2022 (2286*334.5/257). Morgan et al. 2007 (DSU report), inflated using Pay & Price Index* |
| White blood cell count decreased | £543 | *Assumed same as neutropenia* |

| | | |
|---|---|---|
| Ejection fraction decreased | £666 | *Calculated, weighted average, EB03A-E, Heart failure or shock, with CC score 0-14+, non-elective short stay. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022.* |
| Leukopenia | £543 | *Assumed same as neutropenia* |
| Pulmonary embolism | £773 | *Calculated, weighted average, DZ09J-Q, Pulmonary Embolus with/without intervention; Non-elective spell. National schedule of reference costs: the main schedule 2021 to 2022.* |

**Table 18: NHS reference cost scenario**

| Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base case ICER (%) |
|---|---|---|---|---|---|---|---|
| Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £23,207 | -17.55% |

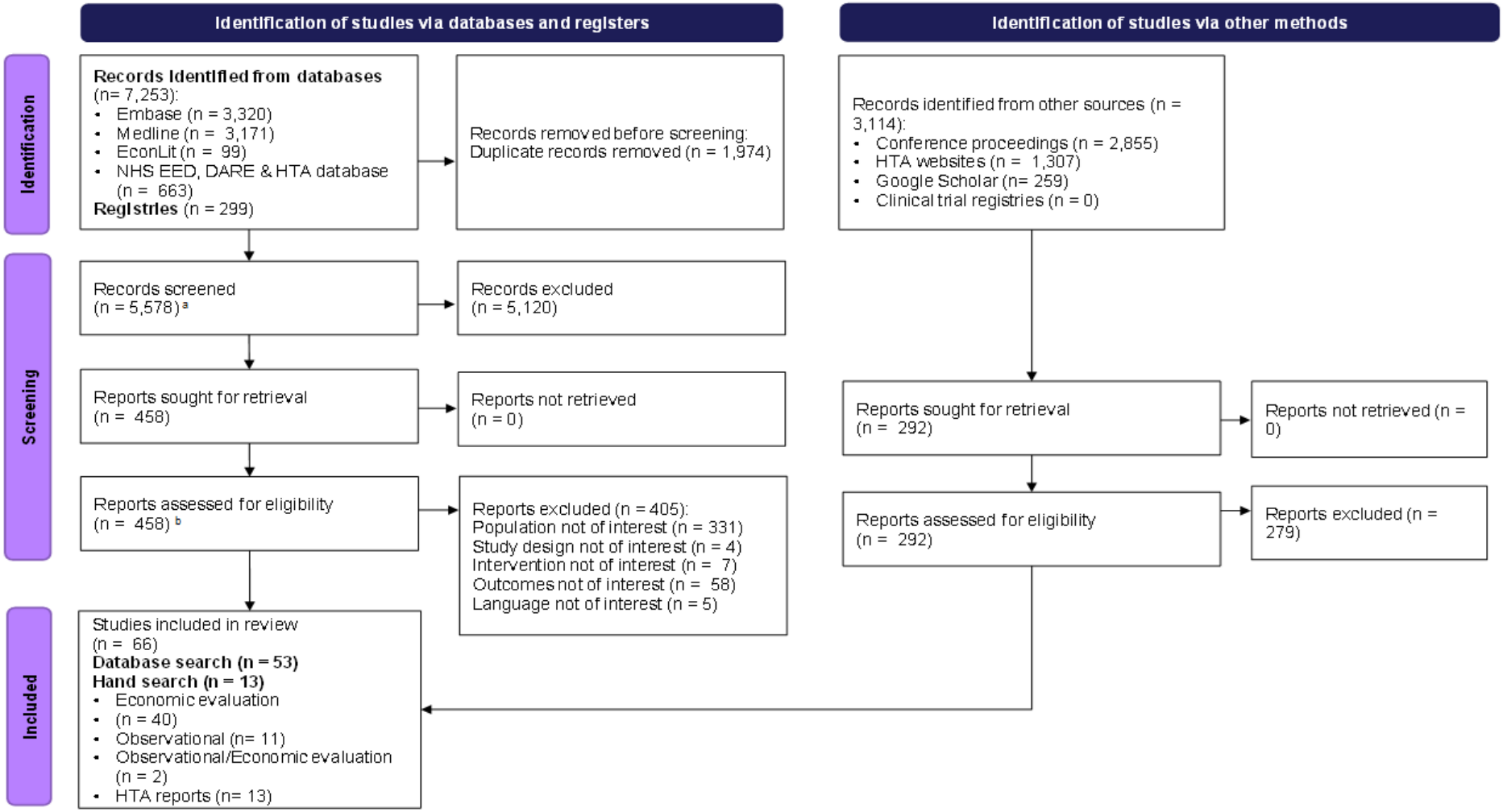
## *Literature searches for economic studies*

**B15.** Document B, Appendices, Figure 4 (pg 49): please can you provide a clearer version of the PRISMA flowchart as data is not clear in its current form.

**Response:**

The specified PRISMA flowchart (that from the original economic SLR) is provided in Figure 16.

*Figure 16. PRISMA flow diagram – original economic SLR*




[a] number of publications assessed at title and abstract screening stage; [b] number of publications assessed for eligibility as full text.
Abbreviations: SLR, systematic literature review.

**B16.** Please can you clarify whether the economic studies identified from the literature review were assessed for quality and, if so, what tool was used. Please can you also provide more detail on the methods and process of data extraction.

**Response:**

Model-based economic evaluations identified in the economic SLR were assessed for quality using the Drummond checklist.(22) An assessment of quality was not conducted for observational studies identified in the economic SLR.

Regarding methods and process for data extraction, please find a summary in the below paragraphs.

Prior to data extraction, a data extraction grid was prepared in Microsoft Excel®, comprising the following fields for extraction:

- Publication details (title, authors, date of publication, journal, sponsor, supplementary material (if any), trial name and number, etc.)
- Study characteristics (objective, study type, study design, settings, data source, study period, follow-up, sample size, subgroup details, statistical method, intervention(s), comparator(s), study biases and limitations, key conclusions, etc.)
- Patients' characteristics (overview of study population, NSCLC stage and mutation type, medical history, treatment history, age, age of disease onset, disease duration, inclusion/exclusion criteria, etc.)
- Outcomes of interest (including but not limited to):
    - Model-based economic evaluations
        - Methodology (modelling approach, model structure, perspective, time horizon, method of indirect cost estimation, discount rate, cost year, currency, time to endpoint, key data sources to estimate the progression of disease, cost and utility inputs, type of sensitivity analyses)
        - Results (outcomes measured, base case results and results from the sensitivity analyses)
        - Limitations of the model as acknowledged by the authors (or raised by reviewers in HTA reports)
    - Observational real-world and costing studies
        - Direct medical and non-medical costs (e.g., cost of treatments, hospital care, consultation, laboratory and medical procedures, transportation, home care and nursing)

- Indirect costs (e.g., productivity loss, disability, loss of leisure time, caregiver time)
- HCRU (e.g., hospitalization rate, length of stay, number of admissions or visits, inpatient and outpatient care, physician time)

Information for each included article was extracted by a single reviewer in the first instance. A senior reviewer independently verified the extracted information and ensured that no relevant information had been missed. Any discrepancies or missing information identified by the senior reviewer were discussed until a consensus was reached and the missing data extracted.

The quality of data reporting was assessed during the quality appraisal process, which was done for economic evaluations. Beyond the conclusions of the quality appraisal, during our review, we did not identify any individual study which stood out in terms of clarity of reporting or missing outcomes. Therefore, it was not deemed necessary to contact authors or make further assumptions about the reported results.

## Section C: Textual clarification and additional points

### *No further clarification*

Clarification Table 1.

| **Systematic review inclusion criteria: Document B appendices (Table 1, pg. 19-20)** | | **Company Decision Problem: Document B, table 1, pg. 10-11).** | |
|---|---|---|---|
| *Intervention* | First-line treatments approved by FDA, EMA, China, or other countries:<br>• Osimertinib<br>• TKI as monotherapy, including:<br>– Imatinib<br>– Gefitinib<br>– Erlotinib<br>– Dacomitinib<br>– Afatinib<br>– Dasatinib<br>– Sunitinib<br>– ASP8273<br>– Nilotinib<br>– Crizotinib<br>– Ceritinib<br>– Alectinib<br>– Lazertinib<br>– Aumolertinib<br>– Furmolertinib<br>– Amivantamab<br>– Mobocertinib<br>• Emerging first-line therapies in their development programmes<br>• TKI monotherapy in combination with other targeted therapies, including:<br>– Erlotinib + ramucirumab<br>– Erlotinib + bevacizumab<br>• TKI monotherapy in combination with chemotherapy<br>• Immunotherapies<br>• Platinum-based chemotherapy, including:<br>– Cisplatin<br>– Carboplatin | *Intervention* | Osimertinib with pemetrexed and platinum-based chemotherapy<br><br>[Rationale if different from the NICE scope:<br>Osimertinib monotherapy represents the current SoC for patients in England who are receiving first-line treatment for locally advanced/metastatic NSCLC and is used in 86% of EGFRm patients.(1) The alternative treatments (dacomitinib, afatinib, erlotinib and gefitinib) are rarely used and osimertinib with pemetrexed and platinum-based chemotherapy is expected to displace osimertinib monotherapy only. This positioning was validated by UK clinical insight, with 9 UK-based clinical experts consulted as part of an advisory board unanimously stating that osimertinib monotherapy was their current first-line treatment of choice for metastatic EGFRm NSCLC.(2) This is further supported by current clinical guidelines such as ESMO, where osimertinib is recommended as the preferable first-line treatment option for patients with a classical activating EGFR mutation (exon 19 deletion or exon 21 L858R), especially for patients with CNS metastases.(3) ] |
| *Comparators* | • Placebo<br>• Any treatment from the above list<br>• Any other pharmacological treatment | *Comparator(s)* | Osimertinib |

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

# Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

## About you

| | |
|---|---|
| **1.Your name** | [redacted] |
| **2. Name of organisation** | Roy Castle Lung Cancer Foundation |
| **3. Job title or position** | [redacted] |
| **4a. Brief description of the organisation (including who funds it). How many members does it have?** | Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, work in lung cancer patient care (information, support and advocacy activity) and raise awareness of the disease and issues associated with it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts.<br><br>Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer. |
| **4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in** | **RCLCF has received the following funding :**<br>- Amgen (£30,000 for 1 year funding of Global Lung Cancer Coalition (GLCC) project; £15,000 grant for Information Services; £165 Advisory Meeting Honorarium)<br>- BMS (£30,000 for 1 year funding of GLCC project; £1100 for Advisory board Honorarium)<br>- Lilly (£30,000 for 1 year funding of GLCC project)<br>- Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project; £1040 Advisory board Honorarium)<br>- Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations)<br>- Sanofi (£30,000 for1 year funding of GLCC project)<br>- Pfizer (£30,000 for 1 year funding of GLCC project) |

| | |
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| **the appraisal stakeholder list.]**<br>**If so, please state the name of the company, amount, and purpose of funding.** | - Astra Zeneca (£30,000 for 1 year funding of GLCC project; £19,500 for GLCC Project Translation; £300 for Advisory Board Honorarium)<br>- Daiichi Sankyo (£30,000 for 1 year funding of GLCC project; £131.50 for Advisory Board Honorarium)<br>- Takeda (£30,000 for 1 year funding of GLCC project; £260 Speaker Fee)<br>- Janssen (£24,000 grant funding for Ask The Nurse Service) |
| **4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |
| **5. How did you gather information about the experiences of patients and carers to include in your submission?** | The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, Patient Information Days, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline. |

## Living with the condition

| | |
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| **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?** | EGFR mutation is found in about 10 to15% of US/European lung cancer patients. These patients tend to be younger and more likely to be light/non-smokers, as compared to the general lung cancer population. With that in mind, it is our observation that, though a younger, fitter patient group (fewer co-morbidities), EGFR mutation patients tend to be diagnosed later, as they do not fit the 'typical' lung cancer patient profile.<br>Symptoms of advanced lung cancer, such as breathlessness, cough and weight loss are often difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe.<br>Recent years, with the development of Targeted Therapies for this EGFR mutation group has resulted in very much improved treatments.<br>From a carer's perspective, it is, of course difficult to have a loved one diagnosed with advanced lung cancer. |

## Current treatment of the condition in the NHS

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| **7. What do patients or carers think of current treatments and care available on the NHS?** | The third generation EGFR TKI, Osimertinib is NICE approved in several indications, including in first line treatment of EGFR mutation positive lung cancer. The development of such targeted therapies has been a major step forward in the treatment of lung cancer. These oral therapies have been much better tolerated than traditional chemotherapy, with less time spent in hospital.<br>Despite the high response rate, however, disease progression is likely to occur eventually. There is therefore a need to delay the emergence of Osimertinib resistance. |
| **8. Is there an unmet need for patients with this condition?** | Yes |

## Advantages of the technology

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| **9. What do patients or carers think are the advantages of the technology?** | Outcomes of treatment are seen as an advantage of this technology. We do not have any additional data, beyond that publicly available.<br><br>We are aware of the FLAURA2 Study, published in the NEJM. This study randomly assigned patients with EGFR mutated advanced NSCLC, who had not previously had treatment, to receive Osimertinib with chemotherapy (Pemetrexed and either Cisplatin or Carboplatin) or Osimertinib alone. Progression free survival was found to be significantly longer in the combination arm. At 24 months, 57% of the patients in the combination arm and 41% of the Osimertinib alone arm, were alive and progression free. The median response duration was 24 months in the combination arm and 15.3 months in the Osimertinib monotherapy arm. |

## Disadvantages of the technology

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| **10. What do patients or carers think are the disadvantages of the technology?** | Side effects associated with the addition of chemotherapy to the Osimertinib. This would also require IV treatment and more time spent at hospitals. |

## Patient population

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| **11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.** | |

## Equality

| | |
|---|---|
| **12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?** | |

## Other issues

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| **13. Are there any other issues that you would like the committee to consider?** | |

## Key messages

| | |
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| **14. In up to 5 bullet points, please summarise the key messages of your submission.** | • Osimertinib is the current treatment for patients with advanced EGFR mutation positive lung cancer (NICE TA654)<br>• Despite the efficacy of Osimertinib, most patients will have progression.<br>• First line treatment with Osimertinib plus chemotherapy shows significantly longer progression free survival than Osimertinib alone.<br>• Side effects of the combination are increased and are those of the chemotherapy<br>• |

Thank you for your time.

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# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]
# A Single Technology Appraisal

Produced by: Bristol Technology Assessment Group, University of Bristol

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None of the authors has any conflicts of interest to declare.

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**Rider on responsibility for report**
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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**Contributions of authors**

JC, EM, & NJW critiqued the health economic analysis submitted by the company. DMC, CC, & ET summarised and critiqued the clinical effectiveness data reported within the company's submission. NJW critiqued the statistical aspects of the submission. CC critiqued the company's search strategy. DC and HR provided clinical advice. All authors were involved in drafting and commenting on the final report.

[redacted]

# Abbreviations

| Abbreviation | Definition |
|---|---|
| 1L | First line |
| 2L | Second line |
| 3L | Third line |
| ABCP | Atezolizumab + bevacizumab + carboplatin + paclitaxel |
| AEs | Adverse Events |
| AIC | Akaike Information Criterion |
| BIC | Bayesian Information Criterion |
| BICR | Blinded Independent Central Review |
| BMI | Body Mass Index |
| CNS | Central Nervous System |
| CRD | Centre for Reviews and Dissemination |
| CS | Company Submission |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DSP | Disease Specific Programme |
| DSU | Decision Support Unit |
| EAG | Evidence Assessment Group |
| EGFR | Epidermal Growth Factor Receptor |
| EGFRm | Epidermal Growth Factor Receptor mutation |
| EMA | European Medicines Agency |
| eMIT | electronic Market Information Tool |
| EORTC QLQ-LC13 | European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Lung Cancer supplement to EORTC QLQ-C30 |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 |
| EQ-5D-3L | EuroQol 5 dimensions 3 level questionnaire |
| EQ-5D-5L | EuroQol 5 dimensions 5 level questionnaire |
| ESMO | European Society of Medical Oncology |
| Ex19del | Exon 19 deletion mutation |
| FAS | Full Analysis Set |
| HR | Hazard Ratio |
| HRQoL | Health-Related Quality of Life |
| ICER | Incremental Cost Effectiveness Ratio |
| L858R | Exon 21 substitution mutation |
| MRI | Magnetic Resonance Imaging |
| MMRM | Mixed Model for Repeated Measures |
| NSCLC | Non-Small Cell Lung Cancer |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |

| | |
|---|---|
| NR | Not Reported |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PD | Progressed Disease |
| PDC | Platinum Doublet Chemotherapy |
| PF | Progression-Free |
| PFS | Progression-Free Survival |
| PSM | Partitioned Survival Model |
| PSS | Personal Social Services |
| PSSRU | Personal Social Services Research Unit |
| QALY | Quality-Adjusted Life Year |
| RCT | Randomised Controlled Trial |
| RECIST v1.1 | Response Evaluation Criteria in Solid Tumours version 1.1 |
| RoB2 | Risk of Bias 2 tool |
| ROBIS | Risk Of Bias In Systematic reviews |
| SAS | Safety Analysis Set |
| SLR | Systematic Literature Review |
| TA | Technology Appraisal |
| TKI | Tyrosine Kinase Inhibitors |
| TTD | Time To Treatment Discontinuation |
| WHO PS | World Health Organisation Performance Status |

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# 1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

- Section 1.1 provides an overview of the key issues.
- Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER.
- Sections 1.3 to 1.6 explain the key issues in more detail.

Background information on the condition and the technology are provided in the company submission.[1, 2] Background evidence and further information on non-key issues are in the main EAG report.

## 1.1 Overview of the EAG's key issues

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE). Table 1 provides an overview of the EAG's key issues:

**Table 1: Summary of key issues for ID6328**

| ID6328 | Summary of issue | Report sections |
|---|---|---|
| **Key issue 1** | Subgroups according to central nervous system (CNS) metastases | Sections 3.2.4.2, 4.2.4.1 and 4.2.6.4 |
| **Key issue 2** | Potential for bias in key clinical outcomes feeding into the economic model | Sections 3.2.1, 3.2.3 and 4.2.7 |
| **Key issue 3** | Generalisability to NHS setting | Sections 3.2.2, 3.2.3, and 3.2.4 |
| **Key issue 4** | Missing data for health-related quality of life in the FLAURA2 trial | Sections 3.2.4.3 and 4.2.7.1.1 |
| **Key issue 5** | Extrapolation of overall survival | Section 4.2.6.1 |
| **Key issue 6** | Extrapolation of time to treatment discontinuation | Section 4.2.6.3 |
| **Key issue 7** | Baseline imbalances in HRQoL scores for the FLAURA2 trial and pooled estimates between groups | Sections 4.2.7.1.1, 4.2.7.1.2, and 4.2.7.1.3 |
| **Key Issue 8** | Plausibility of the progression free and progressed disease health state utilities | Section 4.2.7.1.4 and 4.2.7.2.1 |
| **Key issue 9** | Assumptions on resource use for progression-free and progressed disease states | Section 4.2.8.3 |
| **Key issue 10** | Assumptions on subsequent treatments at second line (2L) | Sections 3.2.3.1 and 4.2.8.2 |

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- different assumptions about the treatments that patients would receive at second line (the EAG assumes patients do not receive Atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP))
- choice of extrapolation model for overall survival
- choice of extrapolation model for time until treatment discontinuation of osimertinib monotherapy
- different assumptions about resource use and source for unit costs
- approach to modelling disutility, where the EAG prefers to use the disutility [redacted] from the FLAURA2 trial for osimertinib plus chemotherapy, rather than model disutility of individual adverse events
- assumed utilities for the progression free health-state (EAG assumes 0.794 compared with [redacted] in the company's base-case) and progressed disease health-state (EAG assumes 0.678 compared with 0.64 in company's base-case)

## 1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival (OS)) and health-related quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- increased time spent in the progression free state
- increased overall survival

Overall, the technology is modelled to affect costs by:

- higher administration and acquisition costs for osimertinib in the osimertinib plus chemotherapy group
- lower subsequent treatment costs for osimertinib plus chemotherapy compared with osimertinib monotherapy
- higher costs of managing adverse events for osimertinib plus chemotherapy compared with osimertinib monotherapy
- increased time spent in the progression free state
- increased overall survival

The modelling assumptions that have the greatest effect on the ICER are:

- choice of extrapolation model for time until treatment discontinuation of osimertinib monotherapy
- assumptions about the treatments that patients would receive at second line
- choice of extrapolation model for overall survival
- assumed utilities for the progression free and progressed disease health-states
- assumptions about resource use

## 1.3 The decision problem: summary of the EAG's key issues

**Key Issue 1: Subgroups according to central nervous system (CNS) metastases**

| Report section | Sections 3.2.4.2, 4.2.4.1, and 4.2.6.4 |
|---|---|
| Description of issue and why the EAG has identified it as important | No subgroups are identified in the NICE scope nor in the company's submission. The EAG notes however, that there is a difference (albeit not statistically significant) in the hazard ratio for both PFS and OS by CNS metastases subgroup, with a greater benefit for those with CNS metastases. The EAG considered it useful to see results for patients with and without CNS metastases. |
| What alternative approach has the EAG suggested? | The EAG requested the company to provide cost-effectiveness results for patients with and without CNS metastases. The company provided results for the subgroup with CNS metastases. |
| What is the expected effect on the cost-effectiveness estimates? | The company's deterministic ICER falls from £27,280 in the combined population to £18,835 in the CNS metastases subgroup.<br><br>Results are not presented for the group with no CNS metastases, however in order to obtain the results above, the ICER would have to be higher in the no CNS metastases subgroup than in the combined population. |
| What additional evidence or analyses might help to resolve this key issue? | N/A |

## 1.4 The clinical effectiveness evidence: summary of the EAG's key issues

**Key Issue 2: Potential for bias in FLAURA2 clinical outcomes**

| Report section | Sections 3.2.1, 3.2.3, and 4.2.7.1.1 |
|---|---|
| Description of issue and why the EAG has identified it as important | Risk of bias should be assessed at both the study and outcome-specific level, for outcomes feeding into the economic model. There is potential for bias in key clinical outcomes, due to the study design of FLAURA2 and missing outcome data. |
| What alternative approach has the EAG suggested? | The EAG used the Risk of Bias 2 tool to assess the potential for bias at the outcome level, as well as overall study level bias. |

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| What is the expected effect on the cost-effectiveness estimates? | The anticipated impact on the ICER for HRQoL and TTD are discussed in Key Issues 4 and 6. For PFS and OS, the impact is unknown, but likely to be small. |
| What additional evidence or analyses might help to resolve this key issue? | Clarification of TTD estimates, how they were estimated and from which FLAURA2 outcomes they were derived should be provided in the CS. For concerns regarding subsequent treatments during the randomised period for reasons other than progression, the company should provide clarification of the subsequent treatments used by those discontinuing due to progression and for other reasons (for PFS and OS). Appendix 16, Table 16.2.4.4.3b provides a per patient listing but was not included as part of the company's submission. HRQoL is discussed in Key Issues 4, 7, and 8. |

### Key Issue 3: Generalisability of findings to the NHS in England, considering currently available 2L and 3L treatments and patient demographics

| | |
|---|---|
| Report section | Sections 3.2.2, 3.2.3 and 3.2.4 |
| Description of issue and why the EAG has identified it as important | The EAG has identified three issues relating to the external validity of the FLAURA2 study:<br>(i) Generalisability of FLAURA2 results to the NHS in England. FLAURA2 participants were younger and more likely to be diagnosed at stage IVA compared to published UK survey data (Molife *et al.*).[3]<br>(ii) Lack of clarity regarding the proportion of patients who received second- and third-line therapies in FLAURA2 and whether these treatments are routinely available on NHS.<br>(iii) Proportion of FLAURA2 participants with CNS metastases at baseline, not representative of UK clinical practice. As subgroup analyses indicate the technology may be more effective in those with CNS metastases at baseline, FLAURA2 effect estimates may overestimate benefit compared to routine NHS use in England. |
| What alternative approach has the EAG suggested? | N/A |

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| What is the expected effect on the cost-effectiveness estimates? | (i) Estimates from FLAURA2 may over-estimate effects compared to a routine NHS setting.<br>(ii) Costs are sensitive to the assumed subsequent treatments after 1L.<br>(iii) The ICER will be higher in the no CNS metastases subgroup. |
| What additional evidence or analyses might help to resolve this key issue? | (i) Scenario analyses using utility estimates from external sources (see Key Issue 8).<br>(ii) Clarification of the subsequent treatments and regimens used in FLAURA2 (including specific combinations and line). Scenarios considering national NHS data on subsequent treatments (after osimertinib) (see Key Issue 10).<br>(iii) Baseline data on previous treatment status by CNS metastatic status. Views of clinical experts on routine practice for screening/identifying CNS metastases in NSCLC patients (see Key Issue 1). |

### Key Issue 4: Missing health-related quality of life (HRQoL) data in the FLAURA trial

| Report section | Sections 3.2.4.3 and 4.2.7.1.1 |
|---|---|
| Description of issue and why the EAG has identified it as important | Missing health-related quality of life (HRQoL) data from FLAURA2 and no adjustment for predictors of missing data in the linear mixed model for repeated measures (MMRM) estimating PFS utilities values, could bias HRQoL estimates informed by the FLAURA2 trial.<br><br>Missing HRQoL data in FLAURA2 were higher in the intervention group, and particularly in the first 16 weeks of the trial (during chemotherapy and when likely to have lower HRQoL scores). A higher proportion of intervention arm participants had unknown progression status and were excluded from analysis. This 'unknown status' group also had lower HRQoL scores than the control group.<br><br>HRQoL scores are analysed using a linear MMRM and inform PFS utilities. The company assumed differences between groups were small and removed group allocation from the regression model, pooling results for both groups. Using a linear mixed model to adjust for missingness would be appropriate if the model adjusted for all covariables that predict missingness, which is not the case in the company's MMRM. |

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| | Missing HRQoL data could:<br>(i) overestimate utility for the PFS health state, and<br>(ii) overestimate utility for the PFS health state for the intervention group by more than in the control group, causing the differential between the groups to be larger than that estimated by the company's MMRM model.<br><br>These would bias utility estimates upwards, in favour of osimertinib plus chemotherapy. |
| What alternative approach has the EAG suggested? | In their clarification response, the company provided a scenario with adjustment for baseline utility but without adjustment by treatment group.<br><br>PFS utilities based on FLAURA2 trial may be biased upwards for other reasons (see key issue 8). The EAG has therefore suggested:<br>(i) Using data for the PFS utility from a previous TA for the same population<br>(ii) Apply [redacted] in utility for the intervention group in the PFS health state, estimated using the difference between group [redacted] from baseline, for the pre-progressed FLAURA2 trial patients. |
| What is the expected effect on the cost-effectiveness estimates? | Although it is not possible to exactly estimate the effect on the ICER of missing data, applying the EAG suggestions of a lower PFS utility and [redacted] in utility for the intervention group in the PFS health, [redacted] the number of accrued QALYs and the ICER increases 20% from £27,280 to £32,227. |
| What additional evidence or analyses might help to resolve this key issue? | Adjusting for all predictors of missingness in the MMRM or using a multiple imputation model with chained equations adjusting for all known covariables explaining missingness could aid in estimating this impact.<br><br>However, given the lack of face-validity of the FLAURA2 estimates described in Key Issue 8, it is unlikely that such a model, even if adequately adjusted for missing data, would produce PFS estimates appropriate for this appraisal. |

## 1.5 The cost-effectiveness evidence: summary of the EAG's key issues

**Key Issue 5: Extrapolation of overall survival**

| Report section | Section 4.2.6.1 |
|---|---|
| Description of issue and why the EAG has identified it as important | The company extrapolated overall survival beyond the follow-up period of the FLAURA2 trial, which is an important input of the model. The company selected the 2-knot spline on a normal scale for both treatments in their base-case based on this giving the best spline fit to the osimertinib plus chemotherapy arm and giving a potentially conservative estimate of survival in the long-term in line with feedback from their clinicians. However, different survival models have different extrapolations and there is uncertainty as the most appropriate survival model. |
| What alternative approach has the EAG suggested? | The EAG prefers to use a 1-knot model for osimertinib monotherapy and a 2-knot model for osimertinib plus chemotherapy, on the odds scale, based on: model fit and plausibility of extrapolations for osimertinib monotherapy in line with findings from the FLAURA study, and a registry study from the Netherlands, and in line with the EAG's clinical advisors. |
| What is the expected effect on the cost-effectiveness estimates? | The deterministic ICER varies from £27,280 in the company's base-case to £34,616 in the EAG's base-case. |
| What additional evidence or analyses might help to resolve this key issue? | To resolve this issue, longer term follow-up data from FLAURA2 would be required. |

**Key Issue 6: Extrapolation of time to discontinuation of osimertinib**

| Report section | Section 4.2.6.3 |
|---|---|
| Description of issue and why the EAG has identified it as important | The duration of time spent on treatment has an impact on the overall cost of treatment. To estimate this, the company extrapolated the time-to-treatment discontinuation (TTD) beyond the follow-up period of their trial using survival models. Results are particularly sensitive to the extrapolation of TTD for osimertinib in both arms because patients stay on osimertinib for longer when given in combination with chemotherapy. The company assumed a Gompertz distribution for osimertinib when used in combination with chemotherapy and a Gamma distribution for osimertinib monotherapy. |

| | |
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| | The EAG agrees with the choice of the Gompertz for osimertinib when used in combination with chemotherapy but consider the Gamma to be implausible for osimertinib monotherapy because it predicts patients staying on treatment beyond disease progression. |
| What alternative approach has the EAG suggested? | The EAG prefers to use the Gompertz model for TTD of osimertinib monotherapy, because the visual fit appears to be good, the extrapolations are plausible compared with the curve used for PFS, and it is the same parametric model used for TTD for the osimertinib component of osimertinib plus chemotherapy. The company also provided functionality to impose a constraint on their base-case model where TTD does not exceed PFS. This gives similar results to the EAG preferred extrapolation. |
| What is the expected effect on the cost-effectiveness estimates? | The deterministic ICER with the EAG's preferred TTD extrapolation is £40,348 compared with the company's base-case of £27,280. Running the company's base-case with TTD bounded by PFS gives an ICER of £46,780. |
| What additional evidence or analyses might help to resolve this key issue? | Clinical input on the plausibility of continued treatment beyond disease progression, and further follow-up data from FLAURA2. |

### Key Issue 7: Baseline imbalances in FLAURA2 HRQoL scores and pooled estimates between groups

| Report section | Sections 4.2.7.1.1, 4.2.7.1.2, and 4.2.7.1.3 |
|---|---|
| Description of issue and why the EAG has identified it as important | Patients in the intervention group of the FLAURA2 trial have a [redacted] utility score at baseline ([redacted]) compared with patients in the control group ([redacted]).<br><br>The company argued that HRQoL scores for both groups in the FLAURA2 trial are similar in the pre-progression period but, as raised in Key Issue 4, this "similarity" may be caused by bias due to more missing data in the first 16 weeks of the intervention group.<br><br>The CS model includes utility decrements for adverse events (AEs), but these are included only in the first cycle and for a few days. Clinical advice to the EAG suggested that patients treated with |

| | |
|---|---|
| | chemotherapy in the PFS health state would have lower quality of life throughout the whole chemotherapy period and potentially spill over beyond this. |
| What alternative approach has the EAG suggested? | The EAG suggests using a utility decrement applied to the osimertinib plus chemotherapy group, compared with the osimertinib monotherapy group for the mean duration of the PFS health state.<br><br>Patients in the control group of the FLAURA2 trial had a [redacted] utility [redacted] from a mean score of [redacted] at baseline to [redacted] in the pre-progression period. In the intervention group, patients had a [redacted] mean [redacted] from [redacted] at baseline to [redacted] at pre-progression. We therefore applied a [redacted] of [redacted] to the intervention group. This estimate is robust to using median utility scores in reported in Table 28 (CS).<br><br>Given the [redacted] applied to the whole PFS health state encompasses disutility from AEs experienced in the period, the EAG changed the adverse events disutilities to zero in the model to avoid double-counting but kept the costs to reflect the additional costs of treating AEs. |
| What is the expected effect on the cost-effectiveness estimates? | Applying a [redacted] in utility for the whole PFS period reduces the number of accrued QALY gains in the intervention group and increases the deterministic ICER by 11% from £27,280 to £30,339. |
| What additional evidence or analyses might help to resolve this key issue? | Alternative statistical models to estimate the difference in utility per treatment arm, including, for example, multiple imputation models to impute missing data or a different specification of the MMRM model. |

### Key Issue 8: Plausibility of PFS and PD utilities

| | |
|---|---|
| Report section | Sections 4.2.7.1.4 and 4.2.7.2.1 |
| Description of issue and why the EAG has identified it as important | The utility value for the PFS and PD health states lacks face validity.<br><br>For the PFS health state, the utility estimates derived from the FLAURA2 trial, by applying the Hernandez-Alava mapping model[4] to the EQ-5D-5L responses as per NICE position statement,[5] yield |

| | |
|---|---|
| | estimates that are too high - an average utility score of [redacted] when the UK general population norm ages of 55 to 64 is 0.799 and 65-74 is 0.779.[6] Clinical advice to the EAG suggests that although it is fair to assume that patients improve their HRQoL from baseline in the PFS period, particularly those in the osimertinib monotherapy group, their quality-of-life score would not be [redacted] than that of the average UK population for the same age.<br><br>For the PD health state, the company agreed that estimates from FLAURA2 are too high, and uses estimates obtained from a 2017 Canadian study in the NSCLC population[7] and used in TA654[8]. However, this value may be too low. The CS model assumes [redacted] between the PFS and PD health states of [redacted], from [redacted] to 0.64, which is [redacted] than differences between health-states from other TAs and the literature. The PD utility estimated from mapping to EQ-5D-3L values from the EORTC questionnaires in the FLAURA trial[9] for TA654 was 0.704. The value accepted by NICE at TA654 was 0.678.<br><br>The model is very sensitive to the utility value of the PFS health state, and to a lesser extent also sensitive to PD health-state utility value. |
| What alternative approach has the EAG suggested? | In clarification question B5 the EAG asked for comment on the validity of the utility value and requested data from the EORTC-QLC-30 in the FLAURA2 trial to be mapped onto EQ-5D-3L utilities to check robustness of results. The EAG suggested a PFS value of 0.794, which is used in TA654, obtained from mapping responses from the EORTC-QLQ-c30 questionnaire in the FLAURA trial[9]. For the PD health state, the EAG suggests using the value of 0.678 as accepted by the committee for TA654. However, the company considered FLAURA2 estimates to be more appropriate because they follow NICE's position statement on the EQ-5D-5L value sets. |
| What is the expected effect on the cost-effectiveness estimates? | Changing the PFS utility to 0.794 and the PD utility to 0.678 [redacted] the accrued QALY gains and increases the deterministic ICER to £29,280 compared with £27,280 in the company's base-case. |

| | |
|---|---|
| What additional evidence or analyses might help to resolve this key issue? | It is unlikely that the utility values derived from the FLAURA2 trial data would have face validity, even after adjusting for confounding factors in the statistical model. This is due to the upward biases due to missing data (see Key Issue 4) and as the company pointed out, the Hernandez-Alava mapping model is producing higher than expected valuations for this population. It is therefore more suitable to use utility values from other TAs on the same population. |

### Key Issue 9: Measurement and valuation of resource use

| Report section | Section 4.2.8.3 |
|---|---|
| Description of issue and why the EAG has identified it as important | Measurements of resource use, including those required by patients with brain metastases, may not be representative of the current UK clinical practice. Resource use estimates were primarily sourced from Brown *et al*. (2013)[10] with some adaptations based on the company's clinical advisors. This is an old study and may not reflect current NHS practice.<br><br>In addition, resource use was valued using the NHS payment tariffs, which less accurately portray the true opportunity cost of the resource use, compared with reference costs. |
| What alternative approach has the EAG suggested? | The EAG's clinical advisors clarified that resource use was too high and not reflective of current NHS practice and proposed alternative average units of resource use. The EAG valued resources using the NHS national collection of costs, as these are more indicative of the true opportunity cost of resources than the NHS tariffs. |
| What is the expected effect on the cost-effectiveness estimates? | The EAG assumes lower units of resource use, and these are generally valued at higher prices. This has increased the deterministic ICER to £31,268 compared with the company's base-case of £27,280. |
| What additional evidence or analyses might help to resolve this key issue? | Further explorations could include a more in-depth systematic review of the literature identifying trials in the advanced NSCLC population including trial-based economic evaluations in the UK setting, where trial patients resource use is measured during a follow-up period. |

**Key Issue 10: Assumptions on subsequent treatments at second line (2L)**

| Report section | Sections 3.2.3.1 and 4.2.8.2 |
|---|---|
| Description of issue and why the EAG has identified it as important | The company's model includes the costs of treatments that would be received at 2L, and these are assumed to differ according to whether a patient received osimertinib plus chemotherapy or osimertinib monotherapy at 1L. The company assumed that patients will receive Atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP) at 2L, and that the proportions will be higher for osimertinib monotherapy, based on expert opinion from the company's clinical advisors. The EAG however heard that only a small proportion of this patient group would be fit enough for ABCP at 2L. Also, the only differences in subsequent treatments expected between osimertinib plus chemotherapy and osimertinib monotherapy would be that pemetrexed would not be used at later lines following osimertinib plus chemotherapy at 1L. The EAG acknowledges that there is uncertainty around the proportion of patients receiving ABCP treatments at 2L, and that incremental costs are sensitive to the assumed subsequent treatments at 2L. |
| What alternative approach has the EAG suggested? | The EAG has presented scenarios with different distributions of subsequent treatments at 2L. In those that receive 2L treatment, Scenario 1a assumes 0% receive ABCP, and Scenario 1b assumes approximately 11% receive ABCP (compared with 15% for the company's base-case). |
| What is the expected effect on the cost-effectiveness estimates? | The deterministic ICER under the EAG's Scenario 1a is £40,029 and under Scenario 1b is £30,530,in comparison with £27,280 in the company's base-case. |
| What additional evidence or analyses might help to resolve this key issue? | National data on subsequent treatments used following osimertinib monotherapy would be helpful. However, there will not be evidence currently available on subsequent treatments following osimertinib plus chemotherapy. |

## 1.6 Other key issues: summary of the EAG's view

The EAG did not identify any other key issues.

## 1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 2 describes the company's deterministic and probabilistic results, as presented in the CS and with the EAG running 50,000 iterations of the company's base-case probabilistic

results for convergence. The EAG's assumptions are added incrementally to the company's base-case results and reported in deterministic analysis. The full EAG base-case probabilistic results with 50,000 iterations are then reported. Proportional changes reported in brackets are computed from the company's deterministic ICER.

The EAG's assumptions are:

- Alternative assumptions about the distribution of 2L treatments after discontinuing 1L treatment (see section 4.2.8.2) as set out in Table 9 (EAG Scenario 1a)
- 100% of patients on the osimertinib plus chemotherapy receive carboplatin, compared to 50% in company's base-case (EAG Scenario 2)
- Average age of 65.6y, compared to 61y in company's base-case (EAG Scenario 3)
- 1-knot model on odds scale for osimertinib monotherapy group and 2-knot model on odds scale for osimertinib plus chemotherapy group for OS (EAG Scenario 4d)
- Gompertz for TTD of osimertinib monotherapy (EAG Scenario 5)
- RDI 96.4% for carboplatin and cisplatin (EAG Scenario 6)
- EAG's resource use assumptions (Table 11) with alternative unit costs (EAG Scenario 7)
- Disutility [redacted] in the PFS health state for the osimertinib plus chemotherapy group and AEs to zero, 0.794 for PFS, and 0.678 for PD (EAG Scenario 8c)

For further details of the exploratory and sensitivity analyses run by the EAG, see sections 6.2 and 6.3 of this report. The EAG identified an error in the formulae for the 2-knot spline on the odds scale for OS in the osimertinib plus chemotherapy group, which it corrected. The EAG also found that the results from the probabilistic analyses were not based on sufficient numbers of samples for convergence (see sections 5.1.1 and 5.3). The EAG increased the number of samples to 50,000 iterations, as reported below, to ensure results had converged. In response to clarification questions from the EAG the company provided a scenario for the subgroup population with CNS metastases (see section 5.2.1).

**Table 2: Summary of EAG's preferred assumptions and ICER**

| Scenario | Incremental cost | Incremental QALYs | ICER (change from company base-case deterministic results) |
|---|---|---|---|
| **Company's base-case deterministic results as reported in CS** | [redacted] | [redacted] | £27,280 |
| Company's base-case probabilistic results with 1,000 iterations as reported in CS | [redacted] | [redacted] | £28,318 |
| Company's base-case probabilistic results with 50,000 iterations run by EAG | [redacted] | [redacted] | £30,113 |
| **Introducing EAG's preferred assumptions** | | | |

| Scenario | Incremental cost | Incremental QALYs | ICER (change from company base-case deterministic results) |
|---|---|---|---|
| + EAG assumptions about the distribution of 2L treatments | [redacted] | [redacted] | £40,029 (+47%) |
| + 100% of patients on the osimertinib plus chemotherapy receive carboplatin | [redacted] | [redacted] | £40,142 (+47%) |
| + average age of 65.6y | [redacted] | [redacted] | £40,208 (+47%) |
| +1-knot model on odds scale for osimertinib monotherapy and 2-knot model on odds scale for osimertinib plus chemotherapy for OS | [redacted] | [redacted] | £48,162 (+77%) |
| + Gompertz for TTD of osimertinib monotherapy | [redacted] | [redacted] | £64,282 (+136%) |
| + RDI 96.4% for carboplatin / cisplatin | [redacted] | [redacted] | £64,253 (+136%) |
| + EAG's resource use assumptions (Table 10) | [redacted] | [redacted] | £68,826 (+152%) |
| + PFS utility of 0.794; PD utility 0. 678, and disutility of [redacted] PFS on osimertinib plus chemotherapy (instead of AE disutilities)<br><br>=<br>**EAG's preferred base-case deterministic results** | [redacted] | [redacted] | £88,444 (+224%) |
| EAG's preferred base-case probabilistic results with 50,000 iterations | [redacted] | [redacted] | £84,177 (+209%) |

# 2 INTRODUCTION AND BACKGROUND

This report provides a critique of the evidence submitted by the company (AstraZeneca) in support of osimertinib with pemetrexed and platinum-based chemotherapy for untreated epidermal growth factor receptor mutation-positive (EGFRm) advanced non-small-cell lung cancer (NSCLC). It considers the company's evidence submission and executable model received on 17/05/2024.[1, 2, 11] It also considers the company's response to clarification questions from the EAG received on 25/06/2024.

## 2.1 Critique of the company's proposed place of the technology in the treatment pathway and intended positioning of the intervention.

Full details of the technology and the mechanisms of action are described in sections B.1.2 and B.1.3 of the company submission (CS). The EAG considers section B.1.3 of the CS to provide an accurate overview of NSCLC.[1, 2]

European Medicines Agency (EMA) marketing authorisation for osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced NSCLC was approved on 30/05/2024.[12] The company have proposed that [redacted] As of 15/07/2024 no marketing authorisation was currently held for the technology in the UK.

The company's description of the proposed place of osimertinib with pemetrexed and platinum-based chemotherapy in the treatment pathway is considered appropriate by the EAG. The CS also positions osimertinib monotherapy as the current standard of care for NSCLC patients. As such, the company anticipated that osimertinib in combination with pemetrexed and platinum-based chemotherapy to displace osimertinib monotherapy only. The CS states this position was validated by nine UK-based clinical experts and is supported by specialty guidelines (e.g. European Society of Medical Oncology (ESMO)). Data provided by the company indicated that [redacted] of EGFRm patients in the UK currently receive osimertinib monotherapy. The CS states that, of the [redacted] of patients not prescribed osimertinib monotherapy in a first-line metastatic setting for EGFR mutation positive NSCLC, [redacted] (a monoclonal antibody). Erlotinib and gefitinib are first generation tyrosine kinase inhibitors (TKI) and afatinib and dacomitinib are second generation TKIs. Osimertinib is a third generation TKI.

Comments from the EAG's clinicians support this market share data, and they stated they did not prescribe first or second generation TKIs as first line (1L) therapy for EGFR mutation positive Ex19del or L858R mutations (although they may still use them for other EGFR

mutations). EAG clinical experts agreed that osimertinib in combination with pemetrexed and platinum-based chemotherapy would be most likely to displace osimertinib monotherapy. EAG clinicians observed that there would be some patients who would not be fit enough to receive osimertinib plus chemotherapy due to an increased risk of toxicities associated with chemotherapy, but that such patients would still be eligible for osimertinib monotherapy. EAG clinical experts also noted that, following NICE recommended options, pemetrexed plus cisplatin or carboplatin is currently considered a second line (2L) treatment in the UK. However, for patients prescribed osimertinib with pemetrexed and platinum-based chemotherapy at 1L they would not re-treat with pemetrexed at 2L. As such, it was noted that these patients may be more likely to receive 2L platinum doublet without pemetrexed maintenance.

Throughout the remainder of the EAG report 'osimertinib in combination with pemetrexed and platinum-based chemotherapy' will be shortened to 'osimertinib plus chemotherapy', for convenience.

## 2.2 Critique of company's definition of decision problem

Table 3 summarises the decision problem as outlined in the NICE scope and provides a summary of how this was addressed in the company submission. The EAG agrees with the company's definition of the decision problem as defined in the CS, although it is noted that it does not match NICE's final scope with regards to comparator interventions.

**Table 3: Summary of decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| Population | Adults with untreated advanced EGFR mutation-positive NSCLC | [redacted] | The company stated NICE's decision problem is in line with the population in the FLAURA2 trial and consistent with the anticipated licensed indication for the intervention (submission planned June 2024). | EAG has no concerns regarding the population, however the following issues are noted:<br>- The CS extends the decision problem to include patients with locally advanced disease. The EAG is content with this extension, as EAG clinical experts reported that they would want to use this treatment in those patients.<br>- The CS focuses on the most common forms of EGFR mutation-positive tumours only. The CS states that 90% of EGFR mutation-positive tumours [redacted] However, EAG clinical experts noted patients with other mutations may also benefit from this treatment. |
| Intervention | Osimertinib with pemetrexed and platinum-based chemotherapy | As per NICE scope | NA | The EAG has no concerns. |
| Comparator(s) | Established clinical management without osimertinib with pemetrexed and platinum-based chemotherapy including: | Osimertinib monotherapy | The CS states that osimertinib monotherapy is the current standard of care for patients in England who are receiving first-line | The EAG has no concerns regarding the choice of comparator. |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | • Osimertinib<br>• Dacomitinib<br>• Afatinib<br>• Erlotinib<br>• Gefitinib | | treatment for locally advanced or metastatic NSCLC. They said that osimertinib monotherapy is given to [redacted] of EGFRm patients. As such the company expected the intervention to replace osimertinib monotherapy only. The CS states this position was validated by 9 UK-based clinical experts and is supported by specialty guidelines (e.g. ESMO). | |
| Outcomes | • overall survival<br>• progression-free survival<br>• response rates<br>• duration of response<br>• time to treatment discontinuation<br>• adverse effects of treatment | As per NICE scope | NA | The outcomes reported in the CS match the NICE scope. The EAG notes that time to treatment discontinuation was a post hoc analysis in FLAURA2. |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | • health related quality of life (HRQoL). | | | |
| Economic analysis | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal | As per NICE scope | NA | The EAG has no concerns. A commercial arrangement is in place for osimertinib monotherapy. [redacted] |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | Social Services perspective.<br><br>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account. | | | |
| Subgroups | No subgroups are identified in the NICE scope. | No subgroups were identified by the company in the decision problem. | NA | Although no subgroups were identified in the NICE scope, a non-statistically significant difference in the hazard ratio for PFS and OS by CNS metastatic status was observed in FLAURA2, with a greater benefit for those with CNS metastases. In response to EAG clarification question B10 the company provided results for participants with CNS metastases (but not those without). |
| Special considerations including | None highlighted in the NICE scope. | None reported in the CS | NA | NA |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| issues related to equity or equality | | | | |
| Other considerations | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. | NA | NA | NA |

# 3 CLINICAL EFFECTIVENESS

The clinical effectiveness critique focuses on the following key questions:

- Is there evidence of clinical effectiveness?
- Are estimates that feed into the economic model reliable and appropriate to the scope?
- Have the most appropriate estimates been selected to feed into the economic model?

## 3.1 Overview of evidence reported in company submission

Table 4 provides an overview of the outcomes reported in the company submission, the data sources used, if and how the outcome informed the economic model, whether the outcome is within the NICE scope, and whether the outcome is recommended by the EMA.[13] The EAG's critique focuses on determining whether these estimates can be considered reliable and whether they were the most appropriate estimates to select. Each source of data is considered in turn.

**Table 4: Overview of clinical evidence included in the company submission**

| Key outcomes | Source of data | Included in company model | Recommended by EMA[13] |
|---|---|---|---|
| Progression-free survival (PFS) | Company trial[14] | Yes | Yes |
| Overall survival (OS) | Company trial[14] | Yes | Yes |
| Time to treatment discontinuation (TTD) | Company trial[14] (outcome not pre-specified) | Yes | No |
| Adverse events (AEs) | (i) Company trial[14]<br>(ii) OPAL study[15] (not included in the model) | Yes | Yes |
| Health-related quality of life (HRQoL) | Company trial[14] | Yes | Yes (but no specific instrument recommended)[16] |
| Objective response rate (ORR) | Company trial[14] | No | Yes |
| Duration of response (DOR) | Company trial[14] | No | Yes |

## 3.2 Critique of the company trial

The evidence for all outcomes reported in the company submission comes from the FLAURA2 trial (NCT04035486). Documentation for FLAURA2, including the study protocol and journal publications, was submitted to the EAG as part of the CS and is considered in the critique of the trial, below (sections 3.2.1 to 3.2.4).

Additional adverse event data were provided in Appendix F of the CS from the company's OPAL trial.[15] This trial was not identified through the company's systematic literature review (SLR) as it was a non-randomised study. In response to EAG clarification question A6, the company noted that OPAL is an AstraZeneca sponsored trial which was provided with the CS to share further safety data to support decision making. In the CS, the OPAL trial is only briefly mentioned in section B.2.10.2 "additional studies", but no data are reported, and the reader is signposted to the appendix. Outcome data from OPAL are not included in the company's economic model, however the OPAL study is briefly considered in section 3.2.4.4.1 of the EAG report.

### 3.2.1 Study design and Risk of Bias assessment

Section B.2.3 of the CS summarises the design and methodology of the FLAURA2 trial. FLAURA2 is a phase III, international, multi-centre, open-label, randomised trial and is ongoing (estimated completion June 2026).[17] A total of 557 patients with epidermal growth factor receptor (EGFR) mutation (Ex19del and/or L858R) positive locally advanced/metastatic NSCLC, and who were previously untreated for advanced disease, were randomised (using a 1:1 ratio) to receive osimertinib plus pemetrexed and cisplatin or carboplatin (n=279), or to receive osimertinib monotherapy (n=278). The multicentre study included 151 sites in 21 countries across Europe, Africa, Asia-Pacific, North America, and South America. The FLAURA2 trial only included five sites in the UK, in which 23 patients were enrolled. The EAG considers the FLAURA2 study design to be appropriate.

FLAURA2 was conducted in two parts: a safety run-in period, and an open-label, phase III, randomised period. The CS reports results from the randomised period, with the primary statistical analysis conducted at data cut off on 03 April 2023. A second interim analysis is reported in the CS for an 'ad hoc' data cut off on 08 January 2024 for overall survival (OS) only. Further detail is provided in section 3.2.4.1 of the EAG report.

In line with EMA recommendations[13] efforts were taken by FLAURA2 trial investigators to limit potential bias related to the open-label nature of the trial. A quality assessment of the FLAURA2 trial was provided in Table 14 (CS, p.51) and Appendix D of the CS. The company's quality assessment of FLAURA2 did not highlight any concerns. Study quality was assessed at the trial-level, using an adapted version of the tool from Centre for Reviews and Dissemination (CRD) guidance for systematic reviews.[18, 19] Although this meets NICE requirements, the approach is somewhat outdated and more robust tools exist that specifically focus on risk of bias and facilitate assessment at the outcome-level.[20]

The EAG has conducted a more detailed risk of bias assessment at the outcome-level, using the Risk of Bias 2 tool (RoB2).[20] The EAG's full RoB2 assessment is reported in Appendix APPENDICES9.1 and is summarised in

Table 5. The FLAURA2 outcomes assessed by the EAG are those included in the CS economic model:

- progression-free survival (PFS),
- overall survival (OS),
- time to treatment discontinuation (TTD),
- adverse events (AEs) and
- health-related quality of life (HRQoL).

Full outcome definitions and measurement processes are outlined in the CS in section B.2.3. PFS was the FLAURA2 primary outcome, defined as the time from randomisation until the date of objective disease progression, or death. Objective disease progression was measured by trial investigators using the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1[21] and was also assessed by a blinded independent central review (BICR). OS was reported as a key secondary efficacy outcome and defined as the time from randomisation until death due to any cause. TTD was not a pre-specified outcome in the trial, but was derived from FLAURA2 data, by the company, for the purpose of the CS. AEs reported in the CS were defined as those having occurred after the first dose of treatment and within 28 days of the last dose of treatment, but prior to or on the start date of subsequent anti-cancer treatment. In FLAURA2, HRQoL was measured by the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30 and EORTC QLQ-LC13). In the CS, the EQ-5D-5L is described as an "exploratory endpoint". However, as the EQ-5D-5L data is used in the CS economic model (mapped to EuroQol-5 dimensions-3 level (EQ-5D-3L)), the EAG's assessment of RoB focuses on EQ-5D-5L only for HRQoL.

The EAG assessed OS, PFS and AEs, based on the published trial report by Planchard 2023 (including the related appendix and trial protocol) and the CS.[1, 2, 11, 14] For assessment of HRQoL (EQ-5D-5L), the EAG referred to the FLAURA2 protocol for information about data collection and analysis, and to the CS for results (Table 28), as EQ-5D-5L results were not located in a published trial report. As TTD was not a pre-specified trial outcome and was calculated by the company for the economic model, the EAG also referred to the CS for the assessment of this outcome.

**Table 5: Risk of bias in the FLAURA2 trial, assessed at the outcome level using RoB 2**

| RoB 2 domain | Outcome | | | | |
|---|---|---|---|---|---|
| | **OS** | **PFS** | **TTD** | **AE** | **HRQoL (EQ-5D-5L)** |
| Randomization process | Low | Low | Low | Low | Low |
| Deviations from intended interventions | Some concerns | Some concerns | Low | Some concerns | Some concerns |
| Missing outcome data | Low | Low | High | Low | Some concerns |
| Measurement of the outcome | Low | Low | Some concerns | Some concerns | Some concerns |
| Selection of the reported result | Low | Low | Some concerns | Low | Low |
| **Overall** | Some concerns | Some concerns | High | Some concerns | Some concerns |

OS = overall survival. PFS = progression-free survival. TTD = time to treatment discontinuation. AE = adverse events. HRQoL = health-related quality of life.

#### *3.2.1.1 EAG's Risk of Bias assessment using RoB 2*

The EAG judged results for OS and PFS to be at some concerns of risk of bias. This was due to a lack of clarity regarding use of subsequent treatments after the discontinuation of study treatments and whether subsequent treatment use is reported for participants at pre- or post-progression. The EAG also notes an imbalance in type/ class of the subsequent treatments used across the treatment groups (CS, Table 12). Patients in the osimertinib monotherapy group were more likely to receive subsequent anti-cancer treatments than patients in the osimertinib plus chemotherapy group. For example, osimertinib monotherapy patients were almost twice as likely to receive osimertinib as second line therapy (20.8%, 19/91) compared to osimertinib plus chemotherapy (10.5%, 6/57). It is not clear from the CS whether osimertinib was continued as a monotherapy or given in combination with another anti-cancer therapy. Although allocation to subsequent treatment was not a protocol deviation, this potential for bias is recorded in the "*bias due to deviations from the intended interventions*" domain of the EAG's RoB2 assessment. PFS was investigator-assessed, and the open label design of the trial may have the potential to influence subsequent treatment choice. However, the EAG considers the open-label design as unlikely to have biased the results for PFS in FLAURA2, as a sensitivity analysis based on data by BICR provided results consistent with investigator assessment.

There were some concerns of risk of bias for AEs. AEs were analysed using a per-protocol analysis of only those who had received ≥1 dose of treatment. However, only one person from the intervention group was analysed in the control group (they were randomised to osimertinib plus chemotherapy, but only received osimertinib and therefore were included in the osimertinib monotherapy group) and only 6 people received no treatment overall

(balanced across groups: 3 intervention; 3 control). The measurement of AEs could have been influenced by knowledge of the outcome, though the EAG considers this to be unlikely, so the EAG is content with the measurement of adverse events within FLAURA2.

HRQoL (EQ-5D-5L) was also judged at some concerns of risk of bias due to missing data and the potential for measurement of the outcome to have been influenced by the open-label trial design. Concerns regarding subsequent treatment were also identified. The EAG considers that although the baseline HRQoL values appear imbalanced this is unlikely to be due to bias due in the randomisation process. However, this imbalance may introduce bias in the comparison of HRQoL across arms if the baseline values are not adjusted for in analyses. HRQoL estimates may be biased upwards in the osimertinib plus chemotherapy group due to a larger proportion of missing data in that group (which is likely to be linked to people feeling in poorer health and therefore not completing EQ-5D questionnaires). See section 4.2.7 for further discussion of the implications of this for the economic model.

TTD was judged to be at high risk of bias due to no information reported in the CS about missing data. There were also some concerns of risk of bias in the measurement of the outcome and selection of the reported result, because TTD was not a pre-specified outcome and there was a lack of detail provided in the CS about outcome measurement for TTD.

### 3.2.2 Population

The eligibility criteria for FLAURA2 are reported in the CS in Table 6.[1] Patients were included in FLAURA2 if they were aged 18 years or older (20 years or older in Japan), had EGFR mutation positive NSCLC (Ex19del or L858R, alone or in combination with other EGFR mutations) and were previously untreated for advanced disease. Eligible participants had a baseline WHO performance status (WHO PS) of 0 to 1 and one or more lesions (not previously irradiated). Lesions needed to be accurately measured at baseline with computed tomography (CT) or magnetic resonance imaging (MRI) and be ≥10mm in the longest diameter and suitable for accurate repeated measurements. Participants were also required to have a life expectancy >12 weeks at day one (of treatment). The EAG's clinical advisors considered these criteria appropriate for the decision problem.

Baseline demographic characteristics were balanced across treatment groups and the EAG has no concerns about the comparability of the groups within the study. The FLAURA2 trial only included five sites in the UK, in which 23 patients were enrolled. Results are not reported for the UK only subgroup. A recent paper by Molife *et al.* reports 'real world' data on epidermal growth factor receptor mutation (EGFRm) advanced NSCLC from the Adelphi NSCLC Disease Specific Programme (DSP)™ survey.[3] The Adelphi NSCLC DSP is a multinational, cross-sectional, survey of physicians and their patients conducted to describe current clinical practice and disease management. Molife *et al.* report data from 2857 patients collected at the end of 2020, of which 279 were UK patients. The data from the UK sample from Molife *et al.* are reported alongside the baseline data from FLAURA2, in Table

6: Comparison of baseline characteristics between FLAURA2 and the UK cohort from Molife *et al.* (2023)Table 6 for comparison.
The EAG notes differences in patient characteristics between FLAURA2 and UK patients in the Adelphi NSCLC DSP. For example, the median age of participants across all patients in FLAURA2 was 61 years (26 to 85 years), which was younger than the mean age of 65.6 (SD 10.0) reported in Molife.[3] The EAG's clinical advisors considered FLAURA2 demographics to be broadly representative of patients seen in UK clinical practice. However, they noted that the proportion of FLAURA2 participants from an Asian background and those with baseline CNS metastases was higher than typically seen in UK clinical practice. The company's UK clinical advisory board also noted that the proportion of participants with baseline CNS metastases in FLAURA2 was higher than seen in UK practice (p.11, Advisory board meeting report provided to EAG). The implications of this are considered in section 3.2.4.2 of the EAG report.

### 3.2.3 Interventions

A summary of study treatments is provided in the CS in Table 7 (p.35).[1] Further details of the treatments and dosing instructions are provided in Appendix 6 of the FLAURA2 trial publication by Planchard *et al.*, 2023.[14] Patients in the intervention group received osimertinib (80mg tablet once daily) plus pemetrexed (500mg mg/$m^2$), and cisplatin (75mg mg/$m^2$) or carboplatin (a pharmacologically guided dose, defined as an area under the concentration-time curve of 5mg per millilitre per minute), administered intravenously on day 1 of 21 day cycles for four cycles. This was followed by osimertinib 80mg once daily plus pemetrexed (500mg mg/$m^2$) maintenance, every three weeks. Patients in the osimertinib monotherapy group received osimertinib at a dose of 80mg once daily. Osimertinib plus chemotherapy has not received UK marketing authorisation. However, the dose used in FLAURA2 matches NICE Guidance for osimertinib monotherapy (TA654). The regimen of chemotherapy (cisplatin or carboplatin) was selected by the investigator prior to randomisation. EAG clinical experts noted that cisplatin had a higher toxicity profile than carboplatin but did not consider choice of chemotherapy to be critical to efficacy. EAG clinical experts noted that carboplatin would be their preferred choice due to the lower toxicity and reduced administration time ('chair time').

In both groups, study treatments were given until disease progression (defined by Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1)), occurrence of unacceptable toxicity, consent withdrawal, or until another discontinuation criterion was met. Dose modifications were permitted when clinically appropriate. Dose reduction of chemotherapy was prioritised above osimertinib dose modification, to manage toxicities whilst maintaining the dose intensity of osimertinib. A maximum of two dose reductions were allowed for each chemotherapy agent and a third resulted in the discontinuation of that agent. For osimertinib, one dose reduction was permitted, and it was discontinued following a second dose reduction caused by toxicity. Dose modifications are outlined in the CS (Table 7).[1] EAG clinical experts agreed this reflected their clinical practice.

## Table 6: Comparison of baseline characteristics between FLAURA2 and the UK cohort from Molife *et al.* (2023)

| Baseline characteristics | FLAURA2 Total (N=557) | Molife (2023) Total Overall (N=2857) | Molife (2023) Total UK (N=279) |
|---|---|---|---|
| Age (years) | Median 61.0 (26, 85) | Mean 65.6 (SD 10.6) | Mean 65.6 (SD 10.0) |
| Sex, n (%) | | | |
| Female | 342 (61.4) | 1611 (56.0) | 166 (60) |
| Race, n (%) | | | |
| Asian | 355 (63.7) | 730 (26) | 23 (8) |
| White | 157 (28.2) | 1755 (61) | 211 (76) |
| American Indian or Alaskan Native | 17 (3.1) | NR | NR |
| Black or African | 5 (0.9) | NR | NR |
| African American | NR | 83 (3) | 0 |
| Hispanic-Latino | NR | 59 (2) | 7 (3) |
| Other | 23 (4.1) | 260 (9) | 38 (14) |
| BMI (kg/m$^2$)[†] | | | |
| Mean (SD) | [redacted] | NR | NR |
| Smoking status, n (%) | | | |
| Never | 369 (66.2) | 1513 (53) | 138 (50) |
| Smoker | 188 (33.8) | 1293 (45) | 137 (49) |
| Tumour stage at initial diagnosis, n (%) | | | |
| Stage I | NR | 53 (2) | 2 (1) |
| Stage II | NR | 98 (3) | 3 (1) |
| Stage IIA | NR | 88 (3) | 1 (<1) |
| Stage IIIB | [redacted] | 250 (9) | 5 (2) |
| Stage IIIC | [redacted] | 170 (6) | 3 (1) |
| Stage IVA | [redacted] | 807 (28) | 62 (22) |
| Stage IVB | [redacted] | 1368 (48) | 202 (72) |
| Histology type, n (%) | | | |
| Adenocarcinoma | 550 (98.7) | 2553 (89) | 271 (97) |
| Adenosquamous carcinoma | 2 (0.4) | NR | NR |
| Squamous cell carcinoma | NR | 189 (7) | 6 (2) |
| Large cell carcinoma | NR | 93 (9) | 1 (1) |
| Other | 5 (0.9) | 13 (1) | 1 (1) |
| Don't know | NR | 9 (0) | 0 |

Note: FLAURA2 data reproduced from the CS Table 8. BMI = body mass index; NR = not reported. Smoking information is reported in Molife (2023) as "smoking history: Yes or No" – for the purposes of this table, conflated "yes" to be "smoker" and "no" to be "never".

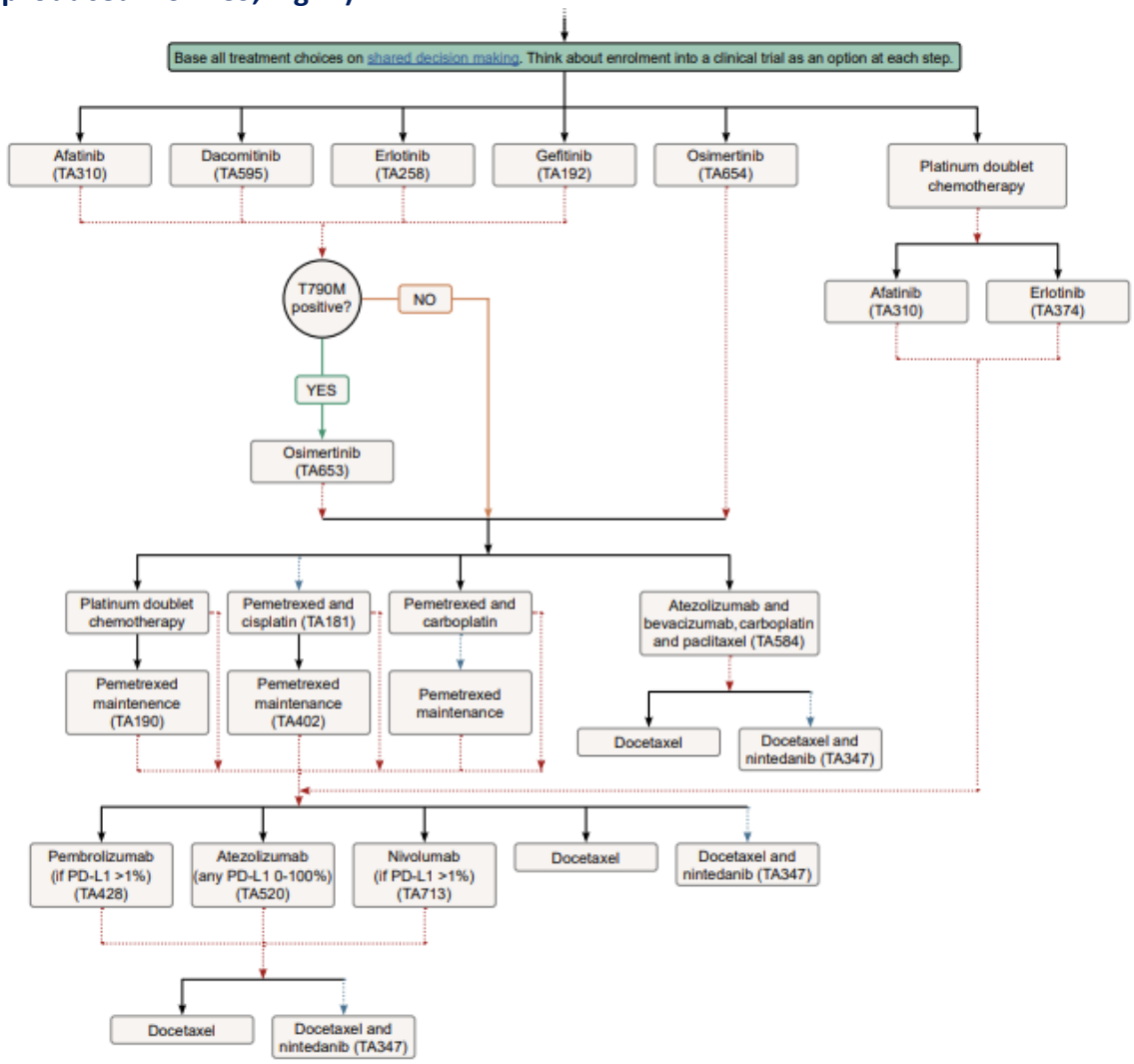
Investigators were permitted to prescribe pre-treatment and concomitant treatments, as recommended by the approved label for the chemotherapy agents (CS, section B.2.3.3.5). Pre-treatment for chemotherapy had to be completed before beginning in the osimertinib plus chemotherapy treatment group. Permitted medications included pre-medication for anti-diarrhoea, nausea and vomiting (in the osimertinib plus chemotherapy group), calcium folinate/folinic acid for pemetrexed overdose, and leukocyte-depleted blood transfusions and concomitant corticosteroid/bisphosphonates/RANK-ligand inhibitors for bone metastases. Palliative local therapy was permitted for patients in survival follow-up or with no evidence of clinical progression. Vaccines were given as appropriate, and investigators could prescribe additional concomitant medications to support patient safety and wellbeing. EAG clinical experts noted that the prescription of pre-treatment and concomitant treatments in FLAURA-2 was appropriate and is in line with NHS practice. Non-permitted medications are summarised in the CS (section B.2.3.3.5) and included other anti-cancer therapies, investigational agents, and non-palliative radiotherapy.
[redacted] Neither the CS nor trial reports state whether patients received any non-permitted medications.

### *3.2.3.1 Subsequent treatment after discontinuation of investigational products*

The EAG has noted that reporting of participant numbers receiving any subsequent anti-cancer therapy differs across tables and reports provided by the company, "due to [redacted] or because [redacted] (Detail provided in footnote, Table 30 of Clinical Study Report [CSR]).[22] This impacted [redacted]. The proportions reported by the EAG for discontinuation of all investigational products (study treatments) below are from CS, Table 12, supplemented by Table 17 of the CSR. However, the EAG notes that a third table reporting post-treatment therapies (Table 14.1.13.2b, CSR Appendix, Full Analysis Set [FAS]), does not agree with either source.[22] The EAG has not been able to identify an explanation for the difference. However, the EAG considers that the impact on effect estimates is likely to be small.

At the April 2023 data cut, 123 participants in the osimertinib plus chemotherapy arm and 151 in the osimertinib monotherapy arm had discontinued all study treatments (CS, Table 12).
[redacted]participants [redacted] discontinued all study treatments due to disease progression (Safety Analysis Set [SAS], CSR Fig.2, and Table 14.1.1.1b of CSR Appendix). Upon discontinuation of all study treatments (for any reason), FLAURA2 participants were treated according to the country-specific standard of care and therefore subsequent treatments were not randomly allocated.

**Figure 1: NICE-recommended options for the systemic treatment of EGFRm NSCLC. (Reproduced from CS, Fig. 1)**




Of those who discontinued study treatments, the proportion receiving any subsequent anti-cancer therapy differed between the arms, with 46.3% (57/123) in the osimertinib plus chemotherapy arm and 60.3% (91/151) of those in the osimertinib monotherapy arm receiving any subsequent anti-cancer therapy (Table 12, CS [FAS]). CSR Table 17 reports that [redacted] and [redacted] received a [redacted] anti-cancer therapy. This suggests that, whilst osimertinib plus chemotherapy increases time progression free, after disease progression patients are less likely to be suitable for subsequent anti-cancer treatment. The EAG's clinical advisors agreed this is in line with expectations.

[redacted] The EAG notes that

[redacted] of the CSR. However, Appendix 16 did not form part of the company's evidence submission for the present technology appraisal.

Table 12 of the CS also reports type/ class of treatment received at any subsequent line. The most common subsequent treatment was cytotoxic chemotherapy. 72% (41/57) of patients who discontinued and received a subsequent treatment in the osimertinib plus chemotherapy arm and 89% (81/91) of patients who discontinued and received a subsequent treatment in the osimertinib monotherapy arm. A more detailed breakdown of 2L and 3L (third-line) anti-cancer treatments is reported in Table 17 of the CSR. [redacted] There are differences between the subsequent treatments received, with a [redacted] proportion of patients receiving chemotherapy at 2L if they had osimertinib monotherapy at 1L. The EAG notes the NHS treatment pathway would not include further treatment with EGFRm TKIs after osimertinib, and monoclonal antibody treatments would be an option at 3L rather than 2L (see Figure 1)

Continuation of study treatments beyond disease progression was allowed if the FLAURA2 investigator felt the patient had a continued clinical benefit.[14]. However, this was counted as a continuation of first-line therapy and not as a subsequent treatment in the CS. The EAG is not clear if Table 12 of the CS includes participants continuing on 1L treatments or only those at 2L and beyond.

The EAG's clinical experts stated that pemetrexed would not be used subsequently in clinical practice for patients who have osimertinib plus chemotherapy at 1L, and this agrees with the company's clinical advice. Of the 37 participants receiving subsequent chemotherapy in the osimertinib plus chemotherapy arm, the EAG notes that seven received pemetrexed at 2L. There are therefore some differences in the subsequent treatments received in FLAURA2 from those that would be received in the NHS, and these [redacted]. The results for overall survival may therefore not fully reflect UK clinical practice.

### 3.2.4 Trial Results

Results from two data cut off points were presented in the CS. Data for PFS, OS, TTD, HRQoL, and AEs are presented from the 'primary analysis' conducted at data cut off on 03 April 2023. The primary analysis of PFS was planned to take place when approximately 278

PFS events and at least 16 months of follow-up after the last subject in had occurred in the 556 randomised patients (~50% maturity). In the trial protocol, it was stated that hypothesis testing for overall survival would only be conducted at the time of primary analysis if the progression-free survival analysis was statistically significant. As this was the case, overall survival was also analysed at this time point.

Further OS data are presented from a 'second interim analysis' conducted at data cut off on 08 January 2024. PFS data were not reported at this data cut off point – the EAG requested it from the company in the clarification letter (clarification question A1), but the company stated it was not available. The 08 January 2024 OS analysis was described as an ad-hoc analysis of OS only, as part of the [redacted] and it is not outlined in the trial protocol. The company reported in the CS and trial protocol that a final OS analysis will be conducted when the data are ~60% mature (when approximately 334 deaths, across the two treatment groups, have occurred). It is reported in the CS that this is [redacted]

#### *3.2.4.1 Efficacy results*

##### 3.2.4.1.1 Primary analysis: data cut off 03 April 2023

Results for PFS by investigator assessment and by BICR (data cut off 03 April 2023) are presented in Table 15 and Table 16 of the CS, respectively. Disease progression according to investigator assessment or death occurred in 120 patients (43%) in the osimertinib plus chemotherapy group and in 166 (60%) in the osimertinib monotherapy group (51.3% data maturity). Median PFS follow-up was 19.5 months in the osimertinib plus chemotherapy group and 16.5 months in the osimertinib monotherapy group. Therefore, investigator-assessed PFS was longer in the osimertinib plus chemotherapy group than the osimertinib monotherapy group (hazard ratio (HR) 0.62, 95% CI 0.49 - 0.79, p<0.001; median PFS 25.5 months vs 16.7 months). PFS assessment by BICR was consistent with investigator assessment (HR 0.62, 95% CI 0.48 - 0.80). Given the similarity of results from investigator assessed and BICR, the EAG is content that the results are not sensitive to lack of blinding of assessor. As stated in the CS, the proportional hazards assumption does not hold at the data cut off 03 April 2023. As such, HRs are not constant over time (CS, Fig. 24) and should be interpreted accordingly.

OS data (data cut off 03 April 2023) is reported on page 59, and Table 19 of the CS. OS data were immature (26.8% maturity). There were 71 deaths (25.4%) in the osimertinib plus chemotherapy group and 78 deaths (28.1%) in the osimertinib monotherapy group (HR 0.90, 95% CI 0.65-1.24). The EAG notes that the proportional hazards assumption also does not hold for OS at this data cut off (CS, Fig. 17).

TTD was a post-hoc analysis conducted for the purpose of inclusion in the economic model in the CS. Neither absolute nor relative effect summaries for TTD from FLAURA2 are reported in the clinical effectiveness section of the CS.

#### 3.2.4.1.2 Second interim analysis: 08 January 2024

As noted, only OS data is provided at the data cut off 08 January 2024 (Table 18, CS). OS data at this timepoint remained immature (41%). Death had occurred in 100/279 (35.8%) patients in the osimertinib plus chemotherapy group and in 126/278 (45%) in the monotherapy group (HR 0.75, 95% CI 0.57 - 0.97). The EAG notes that the proportional hazards assumption also does not hold for OS at this data cut off (CS, Fig. 17).

### *3.2.4.2 Subgroup analyses*

Subgroup analyses are outlined in section B.2.7 of the CS with full results in Appendix E of the CS. Prespecified subgroup analyses were conducted for ethnicity, age, sex, smoking history, central nervous system (CNS) metastases status at study entry, and EGFRm type (Ex19del or L858R). At the data cut off 03 April 2023, a PFS benefit was found across all subgroups analysed for the osimertinib plus chemotherapy group compared to the osimertinib monotherapy group. In an additional analysis, the CS reports that no evidence of a quantitative interaction was identified (p=0.1608) and thus the company reported consistency of treatment benefit across all subgroups. However, the EAG notes that subgroup analyses typically have low power to detect a statistical difference in treatment effect. Furthermore, the violation of the proportional hazards' assumption means that differences between subgroups may be masked when comparing hazard ratios. Visual inspection of Figure 12 in the CS suggests that the benefit of osimertinib plus chemotherapy is less clear for those without baseline CNS metastases, WHO PS=0 and for non-Chinese Asian patients.

Subgroup data for OS is not reported in the CS for the main data cut (03 April 2023). At the second data cut of 08 January 2024, the CS reports that an OS benefit was found across most subgroups in favour of osimertinib plus chemotherapy. However, visual inspection of CS Fig. 13 indicates there is evidence of a differential treatment effect by 'race', with strong evidence of a benefit for Chinese-Asian participants (HR 0.49, 95% CIs 0.27, 0.91) but no evidence of an effect for non-Chinese Asian patients (HR 1.04, 95% CIs 0.70, 1.54). Although the EAG agrees with the CS that subgroup analyses typically have low power, it is noted that the treatment benefit is also less clear for those ≥65 years of age, WHO PS=0 and those who had no CNS metastases at baseline. As noted above, the violation of the proportional hazards assumption for OS means that comparing HRs may not fully reflect differences between subgroups.

The EAG clinicians noted that although CNS metastases are more common in NSCLC patients with Ex19del or L858R EGFR mutations, the proportion of FLAURA2 participants with CNS metastases was considered to be higher than typically observed in UK practice. As the subgroup analyses suggest there may be a greater treatment benefit of osimertinib plus chemotherapy for participants with baseline CNS metastases than for those without CNS metastases, it is possible that the overall benefit in UK clinical practice may be lower than that demonstrated in the FLAURA2 trial. The company's UK advisory group also noted the [redacted]

[redacted]. In clarification question B10, the EAG asked the company to provide cost-effectiveness results for FLAURA2 participants with and without CNS metastases at baseline. In response, the company provided an additional analysis for the CNS metastases group only and noted that the proportional hazards assumption was violated for both OS and PFS analyses. See sections 4.2.4.1 and 4.2.6.4 for further discussion and section 5.2.1. for results.

#### *3.2.4.3 Health Related Quality of Life (HRQoL)*

Details of the HRQoL assessment (data cut off 03 April 2023) were reported in section B.2.6.1.3 of the CS. HRQoL was assessed with the EORTC QLQ-C30 (core 30-item questionnaire designed to assess HRQoL in all cancer patients) and the EORTC QLQ-LC13 (a 13-item additional supplement to the EORTC QLQ-C30, for use with lung cancer patients). Baseline scores were balanced between treatment arms for EORTC QLQ-C30 and EORTC QLQ-LC13. The CS states that baseline scores indicate participants were generally mildly symptomatic as would be expected, given the good WHO PS at baseline. A non-clinically meaningful improvement in global health status and physical functioning was observed in both treatment arms, however a mixed picture was observed for specific items. For example, a non-clinically meaningful worsening in appetite loss was observed in the osimertinib plus chemotherapy arm only, but clinically meaningful improvements in cough and non-clinically meaningful improvements in dyspnoea and chest pain were observed in both treatment arms. EORTC QLQ-C30 and EORTC QLQ-LC13 data from FLAURA2 did not directly inform the company's economic model.

In the CS, HRQoL was also assessed by the EQ-5D-5L as an "exploratory endpoint". Responses to the EQ-5D-5L questionnaire were mapped onto the utility values for the EQ-5D-3L tool using the Hernandez-Alava model,[4] as per the NICE position statement of October 2019.[5] The EAG agrees that this is the most appropriate mapping model to value EQ-5D-5L responses. These data for the PFS period were included in the economic model. The EAG considers these measures appropriate to capture HRQoL but raises concerns with face-validity and bias of the estimates provided using the statistical methodology. This issue is further discussed in EAG report section 4.2.7.1.4.

[redacted]EQ-5D-5L assessments took place during the treatment period at cycle 1 day 1, day 22, day 43 (±1 day), and every 6 weeks (±3 days) from day 64, and also at treatment discontinuation, progression follow-up and survival follow-up (FLAURA2 trial protocol, Table 2).[14] EQ-5D-5L data outlined in the CS (Table 28) indicate that baseline EQ-5D-5L mean scores were imbalanced, with a higher score in the osimertinib plus chemotherapy group. The EAG also notes that participant's EQ-5D-5L scores in the osimertinib monotherapy group improved markedly more in the pre-progression period than those in the osimertinib plus chemotherapy group. In the osimertinib plus chemotherapy group, EQ-5D-5L had a mean score of [redacted] (SD [redacted]) at baseline, [redacted] (SD [redacted]) at pre-progression and [redacted] (SD [redacted]) at post-progression. In the osimertinib monotherapy group, EQ-5D-5L had a mean score [redacted] (SD [redacted]) at baseline, [redacted] (SD [redacted]) at pre-progression and [redacted] (SD [redacted]) at post-progression. The EAG is concerned with this imbalance at baseline and differential

improvement pre-progression. The implications are considered further in sections 4.2.7.1.2 and 4.2.7.1.3 of the EAG report.

Table 28 in the CS reported the number of EQ-5D-5L observations in each treatment group at baseline, pre-progression and post-progression. In the osimertinib plus chemotherapy group (n=279 randomised): there were 248 observations in 248 patients at baseline, 3,526 observations in 267 patients at pre-progression, and 247 observations in 70 patients at post-progression. In the osimertinib monotherapy group (n=278 randomised): there were 252 observations in 252 patients at baseline, 3286 observations in 268 patients at pre-progression, and 365 observations in 124 patients at post-progression. There are more observations in the osimertinib plus chemotherapy group, however patients in this group spent longer in the PFS period, and therefore are expected to have a higher number of observations.

Table 14.2.10.8.1b in the FLAURA2 CSR appendix (provided by the company) reports compliance with EQ-5D-5L by visit, with regard to the number of expected forms, received forms and compliance rate per treatment group. Missing data is slightly higher in the osimertinib plus chemotherapy group, particularly at the beginning of the trial whilst patients are still undergoing chemotherapy and are likely to have felt more unwell. In the later stages of the trial, missing data is equivalent between the groups. However, as Table14.2.10.8.1b does not report the data by progression status it is not possible to make inferences about the rate of missing data for the patients in the progression-free vs progressed groups. The EAG therefore has concerns about missing HRQoL data and further discussion is provided in section 4.2.7.1.1 of the EAG report.

#### *3.2.4.4 Safety analyses*

An overview of AEs is provided in Table 30 in the CS. The EAG's clinical advisors confirmed that the key potential AEs had been captured in the company's results. Analysis of AEs was conducted as part of the primary analysis (data cut off 03 April 2023). This was based on the SAS, which consisted of 551 patients who had received treatment – three patients (1.08%) in the osimertinib plus chemotherapy group and three patients (1.08%) in the osimertinib monotherapy group did not receive treatment. The analysis included AEs that occurred after the first dose of treatment and within 28 days of the last dose of treatment, or until the data cut-off date. The duration of exposure to study treatment in the SAS ranged from 0.1 months to 33.8 months. Median total exposure was 21.09 months and total median exposure was higher in the osimertinib plus chemotherapy group (22.31 months) than the osimertinib monotherapy group (19.32 months).

AEs causally related to treatment were more common in the osimertinib plus chemotherapy group (97.5%) than the osimertinib monotherapy group (87.6%), as were Grade ≥3 AEs (63.8 vs 27.3%), AEs resulting in dose modifications (71.7 vs 20.4%), SAEs (37.7 vs 19.3%), and AEs resulting in discontinuation of any study drug (47.8 vs 6.2%). AEs with outcome of death were also higher in the osimertinib plus chemotherapy group (6.5%) than the osimertinib monotherapy group (2.9%). Life-threatening AEs with maximum severity of Common

Terminology Criteria for Adverse Events (CTCAE) Grade 4 were also higher in the osimertinib plus chemotherapy group (8%) than the osimertinib monotherapy group (1.1%).

The economic model includes AEs that were grade 3 or above only and that were observed in at least 2% of one of the trial arms. All AE data in the company's model comes from the FLAURA2 trial. These data are presented in Table 33 of the CS. In the osimertinib plus chemotherapy group, the following CTCAE grade ≥3 AEs were reported by ≥2% of patients: anaemia, neutropenia, thrombocytopenia, febrile neutropenia, leukopenia, neutrophil count decreased, platelet count decreased, white blood cell count decreased, ejection fraction decreased. Pneumonia, diarrhoea, pulmonary embolism, decreased appetite, fatigue. In the osimertinib monotherapy arm, no individual CTCAE grade ≥3 AEs were reported by ≥2% of patients.

The CS (Table 31) reported that AEs that occurred more frequently (>10% difference) in the osimertinib plus chemotherapy group compared to the osimertinib monotherapy group were mainly chemotherapy-related adverse drug reactions, including: anaemia, nausea, neutropenia, decreased appetite, vomiting, constipation, fatigue, neutrophil count decreased, thrombocytopenia, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, platelet count decreased, and oedema peripheral. In summary, the EAG notes that there were substantially more AEs (especially grade ≥3 AEs) in the osimertinib plus chemotherapy group compared to osimertinib monotherapy, which is well tolerated.

#### 3.2.4.4.1 OPAL study: adverse events

As noted in section 3.2 of the EAG report, additional adverse event data were submitted in Appendix F of the CS. These data were from the company's OPAL study.[15] This study was not identified through the company's systematic literature review and no data were presented in the main text of the CS. The EAG is content that OPAL does not contribute to the CS economic model, and it does not add useful data beyond that contributed by the FLAURA2 trial. Therefore, a full critique of the OPAL trial is not included in the EAG report, however a brief comparison of the AEs reported in OPAL (and provided Appendix F of the CS) with the AEs in FLAURA2 is provided below.

The OPAL trial was a non-randomised phase 2 trial, in which sixty-seven patients were enrolled to one of the following treatment groups at the discretion of the investigator: osimertinib plus cisplatin and pemetrexed (n=34) or osimertinib plus carboplatin and pemetrexed (n=33). The OPAL trial assessed safety, objective response rate, complete response rate, disease control rate, and progression-free survival. In the total OPAL sample (n=67; received osimertinib plus chemotherapy), the most commonly reported all grade adverse events were: anaemia (95.5%), aspartate aminotransferase increased (83.6%), platelet count decreased (88.1%), neutrophil count decreased (76.1%), creatinine increased (71.6%). In comparison, in the osimertinib plus chemotherapy arm of the FLAURA2 trial

(n=276), the most commonly occurring AEs were anaemia (46.4%), diarrhoea (43.5%), and nausea (43.1%) (CS, Table 31).

The most common grade ≥3 AEs were similar between the OPAL and FLAURA2 trials. In the OPAL trial, the most common grade ≥3 AEs were neutrophil count decreased (44.8%), anaemia (22.4%), and platelet count decreased (20.9%). In the osimertinib plus chemotherapy arm of the FLAURA2 trial, the most common grade ≥3 AEs were anaemia (19.9%), neutropenia (13.4%), and neutrophil count decreased (11.2%). In the CS, the company noted that these AEs in FLAURA2 are known adverse drug reactions which are expected with chemotherapy treatment. EAG clinical advice confirmed this is accurate.

## 3.3 Critique of the systematic review of clinical effectiveness

The CS reports a systematic literature review (SLR) of clinical effectiveness which resulted in the identification of one study (FLAURA2) in six reports. The EAG critiqued the SLR using the ROBIS tool [23] and judged the review to be at an overall low risk of bias. A full summary of the ROBIS assessment and critique is provided in Appendix 9.2.

The protocol for the SLR initially reflected the NICE scope in its inclusion of multiple comparators. However, the company submission positions osimertinib monotherapy as the current standard of care for NSCLC patients in the UK. The scope of the SLR was revised accordingly, to include only randomised controlled trials (RCTs) of osimertinib plus chemotherapy compared to osimertinib monotherapy. Consequently, no network meta-analysis or indirect comparisons were reported in the CS. The EAG agrees that osimertinib monotherapy is the appropriate comparator and have no concerns with the revised eligibility criteria for the SLR or absence of indirect comparisons. However, the EAG notes that had all comparators from the NICE scope been considered, an indirect comparison would have been feasible using the company's FLAURA study,[9] which compared osimertinib monotherapy with either gefitinib or erlotinib. FLAURA underpinned the CS for TA654.[8] As FLAURA and FLAURA2 were sponsored by the same company, it is reasonable to assume that individual participant data would also have been available for the indirect comparison.

## 3.4 Conclusions of the clinical effectiveness section

With the exception of choice of comparator, the company's submitted evidence is in line with the original scope. The EAG agrees with the company that osimertinib monotherapy is the appropriate comparator, as it is the current standard of care for patients in England, who are receiving first line treatment for locally advanced or metastatic NSCLC. Although an indirect comparison would have been feasible using data from the company's earlier FLAURA study (osimertinib monotherapy vs. gefitinib or erlotinib) the EAG notes that, according to the CS, the UK market share for erlotinib is [redacted] and is [redacted] for gefitinib. The generalisability of such an indirect comparison to clinical practice in the NHS is therefore unclear.

The estimates of clinical effectiveness come from the company's FLAURA2 RCT. The EAG notes that data for OS are immature at both the April 03 2023 and January 08 2024 data cut offs. Based on the data cut of April 03 2023, there is evidence that osimertinib plus chemotherapy improves PFS compared to osimertinib monotherapy. However, Grade 4 AEs were higher for the osimertinib plus chemotherapy group than for the osimertinib monotherapy group. The EAG has concerns about the face validity of the HRQoL findings. Using the RoB 2 tool to assess bias at the outcome level, the EAG considers there to be some concerns of bias for OS, PFS, AEs and HRQoL (EQ-5D-5L) and for TTD to be at high risk of bias. This assessment is due to concerns regarding missing data and measurement of the outcomes and a lack of reporting clarity around subsequent line therapies. The EAG is also concerned about the generalisability of FLAURA2 outcomes to the NHS in England, given differences in patient demographics and uncertainties regarding the proportion of patients who received second and third line therapies in FLAURA2 (pre- and post-progression) and whether these treatments are routinely available on NHS.

# 4 COST EFFECTIVENESS

## 4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review to identify previous cost-effectiveness analyses. The EAG appraised the SLR using the ROBIS tool.[23] With additional information provided by the company in response to clarification questions, the EAG finds the review of cost-effectiveness evidence to be at low risk of bias overall. A completed ROBIS assessment is provided in Appendix 9.2.2 and 9.2.3.

The company identified three previous NICE TAs for patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations relevant to this appraisal (TA654, TA595 and TA411),[8, 24, 25], although TA411 restricted to squamous NSCLC. TA654 is the most relevant previous model as it is the appraisal of osimertinib monotherapy for this population, which is the comparator in the present appraisal. None of the previous models included osimertinib in combination with chemotherapy ('osimertinib plus chemotherapy'). The EAG therefore agrees that a de novo model was necessary, and it is appropriate that the company used the previous models to identify model structure and input parameters.

## 4.2 Summary and critique of the company's submitted economic evaluation by the EAG

### 4.2.1 NICE reference case checklist

Table 7 below summarises the EAG's comments on the CS, in relation to the NICE reference case.

**Table 7: NICE reference case checklist**

| Element of health technology assessment | Reference case | EAG comment on company's submission |
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|---|---|---|
| Perspective on outcomes | All direct health effects, whether for patients or, when relevant, carers | The model considered health effects relevant to patients, consistent with NICE reference case . |
| Perspective on costs | NHS and PSS | The EAG notes that PSS costs were not included in the model. These costs may have been relevant, particularly if more patients in the osimertinib plus chemotherapy group require a higher usage of personal social services in the community. The EAG however agrees that the PSS costs would not have been cost drivers and does not have concerns about the exclusion of PSS costs in this appraisal. |
| Type of economic evaluation | Cost–utility analysis with fully incremental analysis | No concerns, consistent with NICE reference case. |
| Time horizon | Long enough to reflect all important differences in costs or outcomes between the technologies being compared | The company used a 20 year time horizon. The EAG considers this to be sufficiently long for this patient population |
| Synthesis of evidence on health effects | Based on systematic review | Health effects were based on a single trial (FLAURA2) identified in a systematic review. PFS, and OS are estimated from flexible survival modelling extrapolated beyond the trial follow-up period. |
| Measuring and valuing health effects | Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults. | Health effects in the model are expressed in QALYs.<br><br>The source of QALYs is the EQ-5D-5L (FLAURA2 trial) for the progression free health-state and EQ-5D-3L (Labbe 2014 study) for the progressed disease health-state. |
| Source of data for measurement of health-related quality of life | Reported directly by patients and/or carers | EQ-5D-5L questionnaires were completed by patients in the FLAURA2 trial at frequent intervals (6-weekly after initial |

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| | | period) for the PFS health state; and the literature for the PD health state.<br><br>Responses to the EQ-5D-5L questionnaires were valued using the EQ-5D-3L value set for the UK population using the Hernandez-Alava mapping algorithm, as per NICE position statement.[5]<br><br>The EAG is concerned about the lack of face validity of the HRQoL estimates for patients in the FLAURA2 trial (e.g. 0.828 in the pre-progression period, compared with UK population norm of 0.799 for ages 55-64), and that the company pooled estimates for intervention and control groups (see section 4.2.7.1.4). An alternative source of patient data is the FLAURA trial,[9] used to inform TA654 for osimertinib monotherapy.<br><br>Utility data for the PD health state was informed by EQ-5D-3L utilities from a Canadian cohort study.[7] Although this is a departure from the NICE preferred reference case, the EAG agrees with the company that the PD utilities reported directly from the patients in the FLAURA2 trial produced estimates that may be too high. The EAG suggests using estimates as per TA654, based on patients from the FLAURA trial.[9] |
| Source of preference data for valuation of changes in health-related quality of life | Representative sample of the UK population | Utility data for treatment differences in utilities for the PFS health state is informed by |

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| | | the FLAURA2 trial population (n=557 of which 23 are UK patients). The population is on average 61 years of age, whereas the UK population may be closer to 65.6 years (see section 3.2.2).<br><br>Utility data for the PD health state is informed by a Canadian population (n=475, of which n=183 are EGFR mutated, median age=64 years).<br><br>The EAG agrees that both populations are broadly similar to the UK population, but notes the FLAURA2 trial population may be younger than the advanced NSCLC population with EGFR mutations.[3]<br><br>For the PFS health state, responses to the EQ-5D-5L questionnaires were valued using the EQ-5D-3L value set for the UK population using the Hernandez-Alava mapping algorithm, as per NICE position statement. Although the EAG agrees this is the most appropriate method to value responses to the EQ-5D-5L data, it does not agree that these estimates have face validity (see concerns raised in section 4.2.7.1.4).<br><br>The company applied disutilities for adverse events from a range of sources which have been used in previous TAs. The company did not use the utilities by group using the FLAURA2 trial data. The EAG |

| | | |
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| | | prefers to estimate utilities per group instead of applying disutilities for discrete adverse events (see section 4.2.7.2.1).<br><br>The source of preference data for the PD health state is the UK population value set for the EQ-5D-5L applied to the Canadian cohort in the Labbe 2014 study. The EAG notes these may be too low, and prefers using values from TA654 (see section 4.2.7.2.1). |
| Equity considerations | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | The company did not raise any equity considerations. |
| Evidence on resource use and costs | Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS | Resource use estimates were primarily sourced from Brown *et al.* (2013), with some adaptations. This is an old study and may not reflect current NHS practise. The use of second and third line treatments are based on the FLAURA2 trial supplemented with expert opinion. FLAURA2 is an international study with only 23 patients in the UK, so may not reflect the distribution of subsequent treatments used in the NHS. PSS costs were not included.<br><br>Resources were valued using up-to-date NHS payment scheme costs and PSSRU estimates. The EAG suggests using the NHS national collection of costs (reference costs) as these are more likely to portray the true opportunity cost of using these resources. |

| | | |
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| Discounting | The same annual rate for both costs and health effects (currently 3.5%) | As per NICE reference case. |

PSS, personal social services; PSSRU, personalised social services research unit; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.

### 4.2.2 Model structure

The company used a 3-state partitioned survival model with states: progression free, progressed disease, and death. Patients may move from progression free to death or progressed disease, and from progressed disease to death. The EAG considers this to be an appropriate model structure to effectively model the cost-effectiveness of NSCLC patients and in keeping with the previous models in the disease area, including those from TA654, TA595 and TA411.[8, 24, 25] The model uses a 30-day cycle length, which the EAG considered suitable and in line with previous models.

Overall and progression-free survival curves were extrapolated from clinical trial data to model the cohort of patients over their modelled lifetime. The model assumes that patients who have progressed disease may switch treatment to subsequent 2L and 3L treatments, to reflect treatments in UK clinical practice. The impact of subsequent treatments on overall survival (OS) is not explicitly modelled, as overall survival is taken directly from the FLAURA2 study. Whilst this approach is common in partitioned survival models, it does assume that the impact of subsequent treatments used in the model would be the same as those used in the trial (discussed further in section 4.2.8.1). The cost of subsequent treatments is included in the total costs of the intervention and the comparator. The EAG considers this approach appropriate but is concerned that the subsequent treatments modelled may not reflect current UK clinical practice (see section 4.2.8.1).

In addition to costs and utilities assigned to each health state, patients in the model may experience adverse events, which incur costs for their management and disutilities. The EAG considers this approach to modelling adverse events appropriate but is concerned that multiple adverse events were not included. The EAG notes it may also be more appropriate to model treatment differences in utilities directly, using HRQoL data from FLAURA2 (see sections 4.2.7.1.2 and 4.2.8.6).

### 4.2.3 Perspective, time horizon and discounting

The company took a UK NHS and PSS perspective in line with the NICE reference case. The model used a time horizon of 20 years which is in line with previous appraisals. A scenario analysis with a 10 year time horizon was provided, which shows a small increase to the ICER. The EAG agrees that 20 years is a sufficiently long time-horizon for patients with EGFRm NSCLC. In the base-case a 3.5% discount rate was used for both benefits and costs with a scenario using 1.5%. The EAG considers the 3.5% discount rate appropriate for this appraisal.

### 4.2.4 Population

The company modelled a population with previously untreated locally advanced/metastatic EGFR mutation-positive (Ex19del or L858R) NSCLC. The NICE scope restricted to advanced EGFRm NSCLC, however, EAG clinical advisors indicated they would use osimertinib in a locally advanced/metastatic EGFRm population, and would want to be able to use the osimertinib plus chemotherapy in that population also. This is in line with the inclusion criteria for the FLAURA2 trial. As noted in Table 3 of the EAG report, the EAG is satisfied that including locally advanced EGFRm NSCLC is appropriate and that the focus on patients with the most common EGFR mutations (Ex19del or L858R) is also appropriate. The EAG also heard that not all patients who would receive osimertinib first line would be considered eligible for osimertinib plus chemotherapy which would only be appropriate for those fit enough to tolerate the toxicity of the chemotherapy.

The company's base-case uses a model population assumed to be representative of previously untreated locally advanced/metastatic EGFRm NSCLC patients in the UK, which was based on the patient demographics in the FLAURA2 trial, with a median age of 61 years, with 61% of patients being female and a mean BMI of 24.38kg/$m^2$ (see section 3.2.2). As FLAURA2 is an international trial with only 23 patients from the UK, patient demographics of those enrolled in the trial may not be representative of the UK population. As discussed in section 3.2.2, a recent study of EGFRm advanced NSCLC patients included 279 UK patients with an average age of 65.6 years (SD=10.0) and a proportion of 60% females.[3] This suggests the proportion of females in FLAURA2 is likely well matched to the UK EGFRm NSCLC population, however, the average population age may be higher than the median age enrolled in FLAURA2.

Age is incorporated in the model as determining general population mortality and utility as the cohort ages. Treatment effects do not depend on age. It is unclear whether the treatment effects observed in the FLAURA2 trial would be maintained for a population that is approximately 5 years older, which would require adequately powered subgroup analyses by age group. The EAG prefers to use an average age of 65.6 years in their base-case to better reflect general population mortality and utility as the cohort ages, however notes the uncertainty as to the impact of age on treatment effects.

#### *4.2.4.1 Subgroups*

The subgroup results from the FLAURA2 trial showed some trends but no statistically significant differences between subgroups, although analyses lacked statistical power. (EAG report section 3.2.4.2, and CS Figs. 12 and 13) There is some indication that osimertinib plus chemotherapy may have a greater benefit for both PFS and OS in patients with baseline CNS metastases compared to those without. The EAG heard from their clinical advisors that this is a subgroup where they would like to use osimertinib plus chemotherapy. Whilst the EAG acknowledges that there is insufficient evidence of a subgroup effect, we requested subgroup analyses modelling those with and without CNS metastases separately. The company conducted an analysis for the CNS metastases subgroup in their response to the

EAG's clarification questions (EAG clarification question B10) but did not provide the results for the subgroup without baseline CNS metastases. Using the company's base-case settings for the CNS metastases subgroup osimertinib plus chemotherapy had a deterministic ICER of £18,834.80 (Table 14, company's response to clarification question B10), compared with £27,280.04 for the full population. This suggests that the ICER would be > £30,000 in the subgroup without CNS metastases.

### 4.2.5 Interventions and comparators

The company modelled the cost-effectiveness of osimertinib plus chemotherapy compared to osimertinib monotherapy. No other comparators were considered. The NICE scope included dacomitinib, afatinib, erlotinib, and gefitinib as potential comparators, however the company convened an advisory board of nine clinicians who unanimously stated that osimertinib would be used at 1L in this patient population. The EAG's clinical advisors agreed with this view and told us that the other comparators would only be used for patients with other rare EGFR mutations, and those with a WHO PS greater than 2 who are unfit for osimertinib, and so not covered by the company's decision population. The EAG therefore agrees that the choice of comparator is appropriate.

The company assumed that, for those receiving platinum based chemotherapy, 50% of patients would receive cisplatin and 50% would receive carboplatin. However, the EAG heard from their clinical advisors that carboplatin is used instead of cisplatin because it takes less time in hospital to administer and toxicity is lower, with less nausea and side effects than cisplatin. The EAG's preference, and base-case, assumes that 100% of patients on osimertinib plus chemotherapy receive carboplatin.

Assumed subsequent treatments are discussed in section 4.2.8.2 of the EAG report.

### 4.2.6 Treatment effectiveness and extrapolation

For time-to-event outcomes the company fitted seven different parametric survival curves to each treatment arm: exponential, gamma, generalised gamma, Gompertz, loglogistic, lognormal, Weibull, and for overall survival spline models with up to 3 knots were also fitted. Model selection was based upon assessment of the proportional hazards assumption, model comparison criterion (Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC)), visual inspection of fit to Kaplan-Meier curves, "complexity of trial hazard" (inspection of empirical hazard plots), and clinical plausibility of extrapolations. The EAG considers the approach taken to model fitting and selection appropriate and extensive, although there remains uncertainty in the extrapolations which is discussed below.

#### *4.2.6.1 Overall Survival (OS)*

The company found that the proportional hazards assumption did not hold for OS. Of the parametric models fitted the Gompertz distribution gave the lowest AIC and BIC for both osimertinib plus chemotherapy and osimertinib monotherapy, although a similar model fit was achieved with the Weibull distribution for osimertinib monotherapy (CS, Tables 36-37).

However, the company argued that based on visual inspection (CS, Fig. 19) and clinical expert opinion, the long-term survival predictions from the Gompertz model were too pessimistic. The opinion of the company's clinical experts varied in which parametric curve they found most plausible (which included gamma and Weibull) but felt that no curve achieved both satisfactory fit to the trial data and plausible extrapolations. The company therefore explored various flexible spline models, with different numbers of internal knots and with the spline defined on either the hazard, normal (which the EAG assumes to be the log cumulative hazard used by Royston and Parmar 2002,[26]) or odds scale. The best fitting spline models for osimertinib plus chemotherapy were those with 2-knots, whereas the best fitting spline modes for osimertinib monotherapy were the 1-knot models. The company selected the 2-knot spline on a normal scale for both treatments in their base-case based on this giving the best spline fit to the osimertinib plus chemotherapy arm and giving a potentially conservative estimate of survival in the long-term in line with feedback from their clinical advisors. The company provided scenario analyses using (i) the 2-knot spline on the odds scale, (ii) using the Weibull for the osimertinib plus chemotherapy arm, (iii) using the gamma model for the osimertinib monotherapy arm.

The EAG agrees that the proportional hazards assumption does not hold for OS, as can be seen from the crossing survival curves and non-parallel and crossing lines in the log-cumulative hazard plots (CS, Figs. 6 and 17), and so it is appropriate to fit separate curves for each arm.[27] The EAG's clinical experts advised that patients with EGFR mutations respond poorly to 2L and 3L treatments, and they would expect 10 year survival to be very low. In the FLAURA Randomised Control Trial (RCT), which compares osimertinib monotherapy with other EGFR tyrosine kinase inhibitors (TKIs), the final data-cut gives a median overall survival of 38.6 months (95% CI 34.5–41.8) and shows that by 4 years OS for osimertinib monotherapy is approximately 38% and only slightly higher than that for other EGFR tyrosine kinase inhibitors (TKIs) (Fig. 1 of Ramalingham *et al.* 2020).[28] The patient population for FLAURA is similar to FLAURA2, with the exception that there is a higher proportion of patients with CNS metastases in FLAURA2.[9] The EAG notes that the 3-year OS for osimertinib monotherapy from FLAURA2 is slightly lower than that for FLAURA (which could be due to the higher proportion of patients with CNS metastases in FLAURA2), and so it is expected that 4-year OS would also be slightly lower than 38%. A recent retrospective cohort analysis of national registry data in the Netherlands on patients diagnosed with stage IV NSCLC with del19 or L858R (exon 21) treated with other EGFR TKIs found that five-year survival rates were 12% (95% CI 10%–15%), although this was around 20% for those with the del19 mutation.[29] Although the 5-year OS is likely to be higher for osimertinib compared with other EGFR TKIs, given that the OS curves for osimertinib and other EGFR TKIs move closer together by 4-years in FLAURA, we might not expect this to be a large difference, suggesting that a 5-year OS for osimertinib monotherapy of around 20% might be plausible.

Based on the company's selected TTD curves (see section 4.2.6.3) they predict for both arms that all patients have stopped osimertinib by 8 years, and so the EAG would expect that the OS curves would have begun to converge by that time.

The best fitting model on the basis of AIC and BIC across all parametric and spline models that were fitted is the Gompertz for both osimertinib plus chemotherapy and osimertinib monotherapy, and this also gives the best visual fit to the data (CS, Tables 36-39). The 4-year OS estimate from the Gompertz for osimertinib monotherapy is approximately 30%, which is lower than that seen in FLAURA, and so the EAG agrees this may be an underestimate. The 5-year OS estimate from the Gompertz is for osimertinib monotherapy is approximately 12.5%, which is similar to that found for other EGFR TKIs from the Netherlands registry study, which the EAG would expect to be lower than for osimertinib monotherapy. The OS curves from the Gompertz have converged and are close to 0% by 84 months, which is earlier than would be expected based on the TTD extrapolations assumed by the company. The EAG therefore agrees that the long-term extrapolations for osimertinib monotherapy from the Gompertz may be pessimistic but have provided a scenario using the Gompertz distribution for both osimertinib plus chemotherapy and osimertinib monotherapy as a conservative estimate of cost-effectiveness.

The Weibull gave a similar fit to the Gompertz for osimertinib monotherapy, and an adequate fit for osimertinib plus chemotherapy, and was preferred by one of the company's clinical experts. The 4-year OS estimates for osimertinib monotherapy from the fitted Weibull model are approx. 37.5% (CS, Fig. 19), which is similar to OS from FLAURA (which has better survival that the FLAURA2 study population), and the 5-year OS estimate is just over 25%, which is plausibly higher than the estimates from the Netherlands registry study. The OS curves for the Weibull have begun to converge by 10 years, although the curves are still separated at this point (CS, Fig. 19). The company has provided a scenario using the Weibull for osimertinib plus chemotherapy, but the Weibull gives a better fit to the osimertinib monotherapy arm. The EAG has provided a scenario using the Weibull for both osimertinib plus chemotherapy and osimertinib monotherapy.

The gamma distribution was preferred by two of the company's clinical experts, although it does not appear to give a good visual fit to the Kaplan-Meier data (CS, Fig. 19), and the EAG considers the OS estimates at 4 and 5 years are likely to be too high. The EAG has provided a scenario using the Gamma distribution for both treatments.

The EAG agrees with the company that it is necessary to fit the flexible spline models to both fit well to the data from FLAURA2 and give plausible extrapolations. Regardless of the scale on which the spline models are fitted, a consistent finding is that the 1-knot models fit best to osimertinib monotherapy and the 2-knot models fit best to osimertinib plus chemotherapy. The EAG therefore prefers to use a 1-knot model for osimertinib monotherapy and a 2-knot model for osimertinib plus chemotherapy. The company could not fit the 1-spline model on the normal scale, and so the EAG explored spline models on the hazards scale and odds scale (EAG report, Figure 2 and Figure 3). The EAG considers the most plausible model to be that on the odds scale, which gives OS for osimertinib monotherapy (1-knot spline) of approximately 35% at 4 years (which is slightly lower than in

FLAURA to account for lower survival on FLAURA2), 25% at 5 years (which is higher than the Netherlands registry study to account for the benefit of osimertinib over other EGFR TKIs), and a small proportion of around 5% at 10 years (within the range given by the company's clinical advisors, but still higher than the EAG's clinical advisors felt was realistic). This model shows the OS curves converging (1-knot for monotherapy and 2-knot for osimertinib plus chemotherapy), but still slightly separated at 10 years (Figure 3). This is the EAG's preferred model for its base-case, however the EAG also provides a scenario using the 1-knot model on the hazards scale for osimertinib monotherapy and a 2-knot model on the hazards scale for osimertinib plus chemotherapy, which gives 10-year OS predictions more in line with the view of the EAG's clinical advisors (Figure 2).

**Figure 2: Kaplan Meier OS curves and extrapolations (spline-based models on hazards scale): osimertinib plus chemotherapy and osimertinib monotherapy (CS, Fig. 20)**

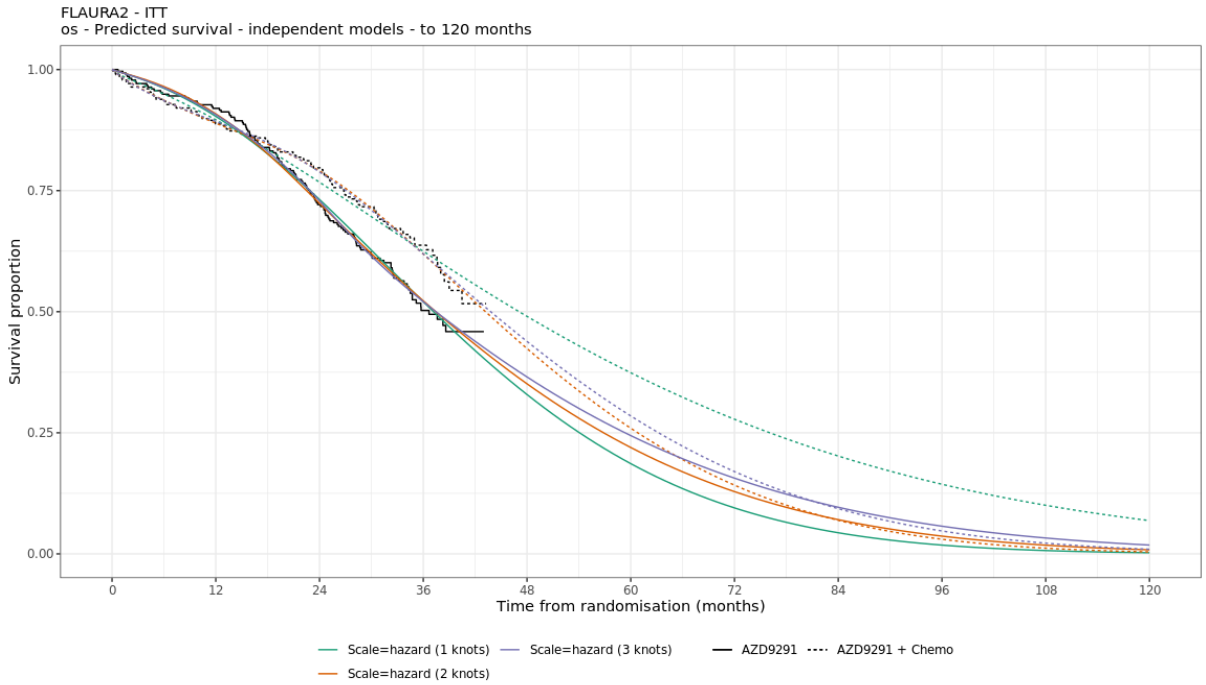
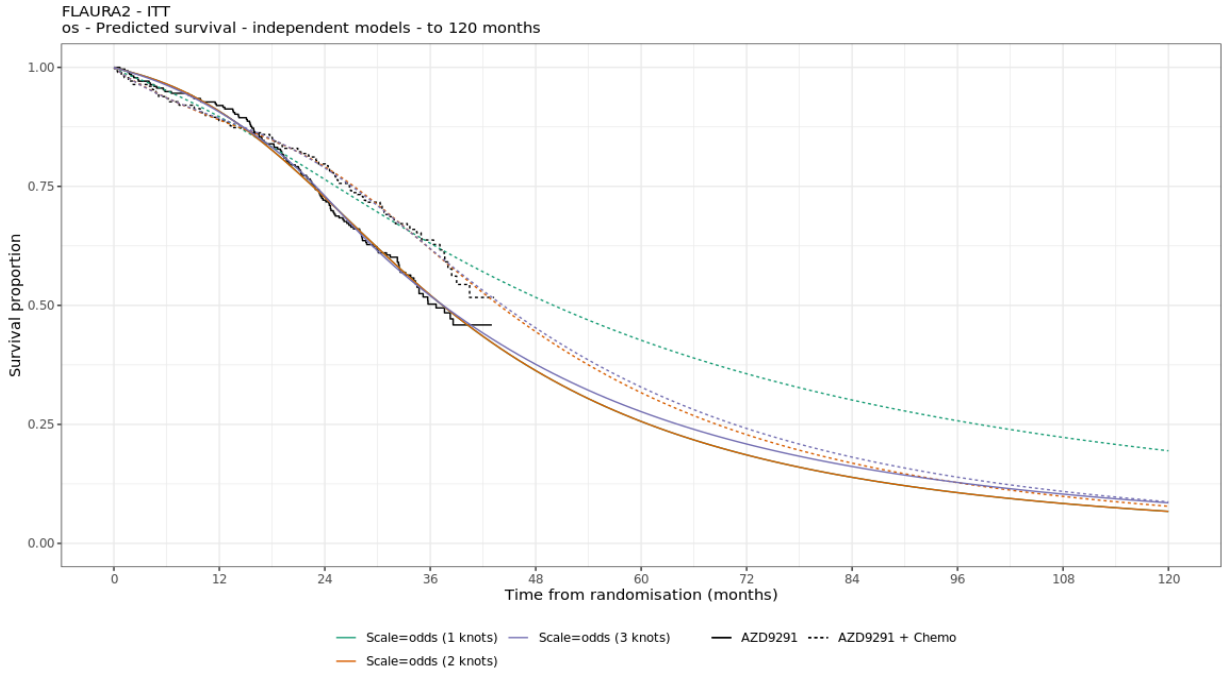


**Figure 3: Kaplan Meier OS curves and extrapolations (spline-based models on odds scale): osimertinib plus chemotherapy and osimertinib monotherapy (CS, Fig. 22)**




#### *4.2.6.2 Progression Free Survival (PFS)*

The company found that the proportional hazards assumption was violated for PFS, and therefore fitted parametric curves separately to each arm. The EAG agrees that the proportional hazards assumption does not hold for PFS, based on the crossing lines in the log-cumulative hazards curves (CS, Fig. 24).

The best fitting parametric curves for osimertinib plus chemotherapy were the Gompertz, generalised gamma, and Weibull, which gave similar model fit for both AIC and BIC. The company noted that all give a good visual fit, but some of their clinical experts felt the extrapolations from the Gompertz and generalised gamma curves were too pessimistic and that the Weibull curve was more plausible. The best fitting parametric curves for osimertinib monotherapy were the log-logistic, gamma, and Weibull, which gave similar model fit for both AIC and BIC. The company noted that all curves give a reasonable fit to the Kaplan-Meier data, but the company's experts felt that the log-logistic gave implausibly optimistic extrapolations. Based on model fit, visual inspection, and expert opinion, the company chose the Weibull distribution for both treatments in their base-case but provide scenarios using the Gompertz for osimertinib plus chemotherapy as a conservative estimate, and using the Gamma as a plausible model for osimertinib monotherapy.

For osimertinib plus chemotherapy the EAG's clinical advisors felt that the extrapolations (EAG Figure 4, and CS Fig. 26) would be most likely to lie between the Gompertz and generalised gamma (which may be too low), and the Weibull extrapolations may be too high as ultimately all patients will become resistant to TKIs. The truth may therefore lie somewhere in between. For osimertinib monotherapy the EAG's clinical advisors agreed

that the log-logistic gave extrapolations that were too high, and that the extrapolations from the Gompertz, Weibull or gamma were more plausible (EAG Figure 5, and CS Fig. 27). The EAG is content that the Weibull is an appropriate choice for osimertinib monotherapy, but for osimertinib plus chemotherapy a PFS curve that lies between the Weibull and Gompertz may be more plausible. The EAG retains the Weibull for both treatments in its base-case but notes that the company's deterministic scenario analyses show that the ICER increases when the Gompertz is used instead of the Weibull for osimertinib plus chemotherapy for PFS. The ICER is therefore likely slightly underestimated by using the Weibull distribution.

**Figure 4: FLAURA2 PFS KM and extrapolations for osimertinib plus chemotherapy (CS, Fig. 26)**

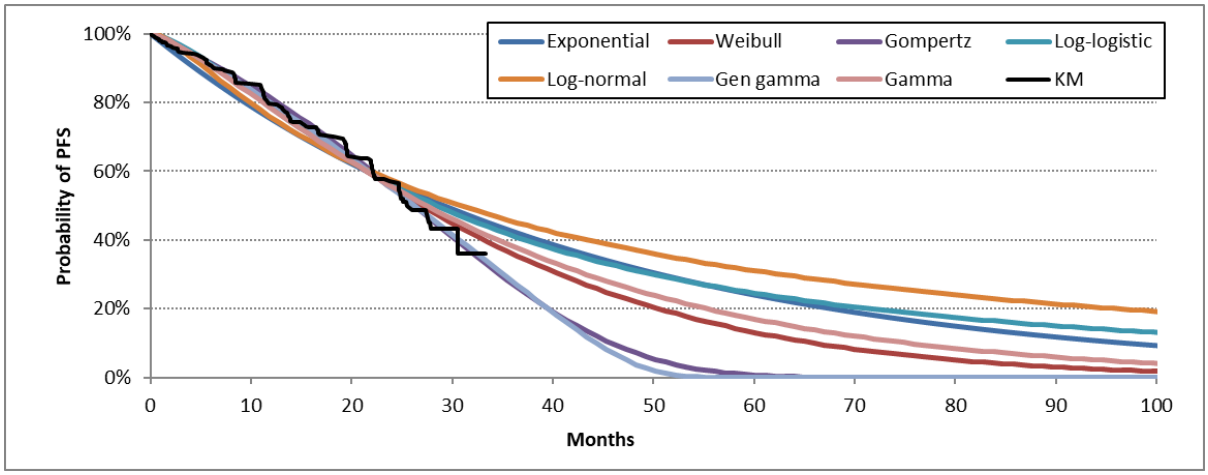
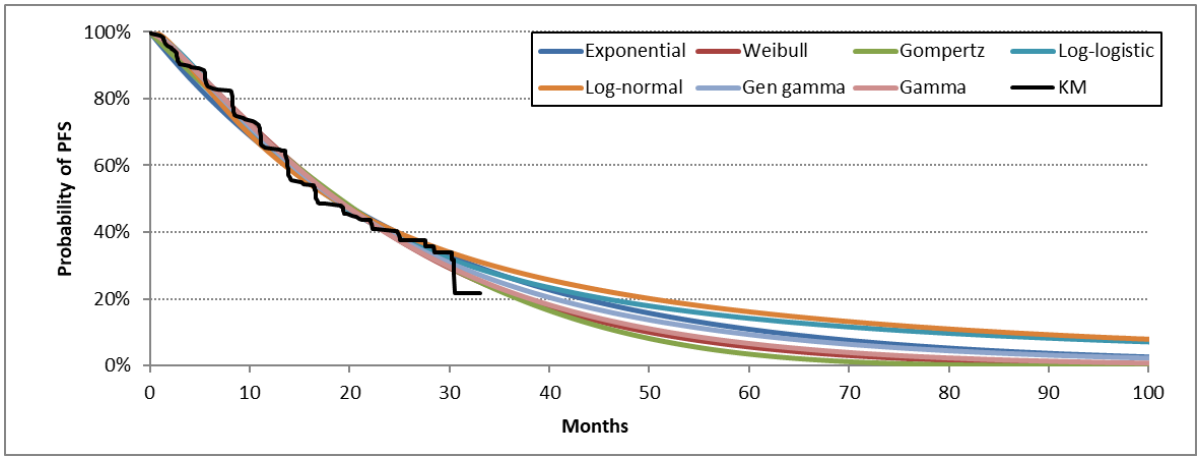



**Figure 5: FLAURA2 PFS KM and extrapolations for osimertinib monotherapy (CS, Fig. 27)**



#### *4.2.6.3 Time to treatment discontinuation (TTD)*

The company modelled time to treatment discontinuation based on model fit and visual inspection of data from the FLAURA2 trial, and this is modelled separately for each of the components of the osimertinib plus chemotherapy combination. The EAG heard from their clinical experts that they would reduce or stop the chemotherapy components first. The EAG therefore agrees with the company's approach to modelling TTD separately for each component.

For the osimertinib component of osimertinib plus chemotherapy the company found that most parametric models gave a similar model fit (except log-normal and log-logistic), with Gompertz having the lowest AIC (and second lowest BIC). The company chose the Gompertz for their base-case and presented a scenario using the generalised gamma. The EAG considered all curves except the Gompertz and generalised gamma to be implausible as their extrapolations (CS, Fig. 28) lay about the curve chosen for PFS (Weibull curve in CS, Fig. 26). The EAG felt the Gompertz was the most plausible choice, as it gave the best match to the curve chosen for PFS, which would be expected if osimertinib is likely to be continued until disease progression in the majority of cases. The EAG is therefore content with the company's choice of curve for TTD for the osimertinib component of osimertinib plus chemotherapy.

For osimertinib monotherapy the company found that all models gave a good fit to the data, with the log-logistic, gamma, and Weibull models having the best fit on AIC and BIC. The company preferred the gamma distribution because the extrapolation for the log-logistic was considered implausibly high, and conducted a scenario analysis using the Weibull. With the exception of the Gompertz, the EAG viewed all of the extrapolations (CS, Fig. 29) as implausible because they gave estimates that lie well above the PFS curve used in the model (Weibull curve in CS, Fig. 27). Although the EAG heard that some patients may continue osimertinib after progression if progression is only at a single site or only by a small amount, and they are still obtaining clinical benefit from osimertinib, there would be other patients for whom osimertinib would stop at progression. The EAG therefore felt that the TTD curve should not be substantially above the PFS curve. The Gompertz didn't give the best fit on the AIC and BIC, but the model fit statistics are adequate (CS, Table 45), the visual fit appears to be good, the extrapolations are plausible compared with the curve used for PFS, and it is the same parametric model used for TTD for the osimertinib component of osimertinib plus chemotherapy. The EAG therefore uses the Gompertz for osimertinib monotherapy TTD in its base-case.

For the pemetrexed component of osimertinib plus chemotherapy the company found that the log-normal, generalised gamma, and log-logistic gave the best fit to the data, but the extrapolations were implausible (CS, Fig. 30). The company selected the exponential because it gave the lowest proportion still on pemetrexed after 5 years. The EAG agrees that the exponential gives more plausible extrapolations but note that it does not fit the earlier part of the curve well, overestimating the proportion of patients on pemetrexed up to

around 18 months, and then underestimating the proportion on pemetrexed after that. The EAG has used the exponential in its base-case, but note that a more flexible model would be required to both fit the data from FLAURA2 and give plausible extrapolations.

The company did not constrain TTD to be less than PFS in their base-case because they argue that patients may continue to take treatments for a bit longer after disease progression. They state that they conducted a scenario analysis where they do impose this constraint, but results are not presented in their report. The EAG has provided the results of this assumption as a scenario analysis, although as mentioned above this may underestimate TTS because some patients will continue osimertinib after progression.

#### *4.2.6.4 Extrapolations for CNS metastases subgroup*

In their response to EAG clarification question B10, the company provided detailed survival modelling for the baseline CNS metastases subgroup for use in a subgroup specific model. The same process was followed to model and extrapolate OS, PFS, and TTD as for the full population.

For OS, the company found that all parametric and spline models give similar statistical fit, and so they relied on visual fit and expert opinion to select the OS curves. The company preferred the 2-knot splines on the normal scale for both OS curves. The choice of curves relied on expert opinion that there would be 10% of patients alive at 10 years on osimertinib plus chemotherapy compared with 2% on osimertinib monotherapy. The EAG considers this extrapolation to be highly uncertain, and so run a scenario for the CNS metastases subgroup using the 2-knot spline on the hazard scale which gives less optimistic long-term survival estimates.

For PFS, most of the models gave a reasonable statistical fit for both curves. The company selected the Weibull based on visual fit and expert opinion. The EAG notes the uncertainty in the choice of model for extrapolation due to small numbers at risk at the end of the curves (see Figs. 11-12 of company response to clarification question B10), and although not shown on the company's figure, difference in extrapolations between models. The EAG provides a scenario using the Gompertz model for both curves, based on this giving the best statistical fit for the osimertinib plus chemotherapy curve, and an adequate fit for the osimertinib monotherapy curve especially towards the end of the curve.

The company assumed a Gamma distribution for TTD for osimertinib in osimertinib monotherapy, and Gompertz and Exponential models for TTD of the osimertinib and pemetrexed components respectively in osimertinib plus chemotherapy. The EAG agrees that these choices are reasonable.

### 4.2.7 Health related quality of life

The model requires data on utilities for the health states of PFS and PD.

#### *4.2.7.1 Utilities for the PFS health state*

The utilities for the PFS state are informed by the FLAURA2 trial. Completeness of EQ-5D-5L data and frequency is discussed in section 3.2.4.3 of the EAG report. Patients in the osimertinib plus chemotherapy group had lower completion rates than patients in the osimertinib monotherapy group, particularly in the first 16 weeks of the trial, presumably when many patients would still be on chemotherapy. More patients on the osimertinib plus chemotherapy group were classified as "unknown status", whereby it was not possible to discern whether they had progressed or not progressed in their disease. These patients did not enter the statistical analysis of HRQoL estimates.

Responses to the EQ-5D-5L were mapped onto the UK preference tariffs for the UK population for EQ-5D-3L using the Hernandez-Alava model,[4] as per NICE position statement of October 2019, to derive utilities.[5]

Utility data were analysed using a linear mix model, referred in the CS as a mixed model for repeated measures (MMRM). In the primary analysis, data were truncated at progression and analysed by period, i.e., all observations for patients in the pre-progression period were analysed separately from observations in the post-progression period. Patients classified as "unknowns" were dropped from the analysis.

Baseline utility values for the FLAURA2 trial data were [redacted] for the osimertinib plus chemotherapy group, and [redacted] for the osimertinib monotherapy group. The company claimed there were no clinically meaningful differences between the two groups at the pre-progression state and reported similar values per group in the EQ-5D-VAS score. The company therefore analysed the data jointly for both groups (not adjusted for treatment allocation group when estimating utilities) using the MMRM model. This returned a utility mean value for the PFS health state of [redacted] (SE [redacted]).

##### 4.2.7.1.1 Bias due to missing data and statistical analysis of utility data in the PFS health state

The PFS health state utility in the company's model was informed by responses to the EQ-5D-5L questionnaires for patients in the FLAURA2 trial in the pre-progression period. Missing EQ-5D-5L data is discussed in section 3.2.4.3 in the report. Although the EAG agrees with the company that completion rates were high and similar for many time points, it was always lower for the osimertinib plus chemotherapy group, and particularly lower in the first 16 weeks of the trial, when patients are more likely to be going through chemotherapy and report lower utility scores. This is likely to bias the utility estimates for PFS differentially across treatment groups, in favour of osimertinib plus chemotherapy.

HRQoL data were analysed by progression status (pre- and post-progression). For patients where it was not possible to ascertain whether they had progressed or not, they were classified as "unknown status" and were not included in the statistical MMRM analysis by progression status. In CS Table 28, more patients in the osimertinib plus chemotherapy group were classified as "unknown status" ([redacted] vs [redacted] in the osimertinib monotherapy group), and these unknowns reported a lower utility score than the PFS utility and a lower score for the intervention group. This again suggests the PFS utility estimated may be overestimated

since the "unknowns" are excluded, and also that this may be the case more for the osimertinib plus chemotherapy group, which may mask difference between interventions.

The EAG disagrees that the MMRM model specified is the most appropriate model to deal with the bias arising from missing utility data. Data are not missing completely at random, as EQ-5D-5L missingness depends on variables such as group allocation, progression status, and HRQoL itself. Using a linear mixed model to adjust for missingness would be appropriate if the model adjusted for variables that predict missingness. That is not the case in this CS, particularly when the estimates are pooled per arm. Not including all predictors of missing data, introduces bias in the estimation of utilities using the linear mixed model approach.

#### 4.2.7.1.2 Differential in utility between groups

The CS argues that the HRQoL between groups in the FLAURA2 trial is similar between groups in the pre-progression period, and patients report similar EQ-5D-VAS scores in the pre-progression period, but it neglects that at baseline patients in the intervention group report a higher quality of life.

Although not statistically significant, patients in the osimertinib plus chemotherapy group of the FLAURA trial report a [redacted] utility score at baseline ([redacted]) compared with patients in the osimertinib monotherapy group ([redacted]). Furthermore, utility estimates reported for the FLAURA2 trial by group and progression status (CS, Table 28) show a bigger [redacted] from baseline in utility for patients in the osimertinib monotherapy group ([redacted]), compared with the osimertinib chemotherapy group ([redacted]). This means that there is [redacted] between the two groups,[30] with the osimertinib plus chemotherapy group having an estimated [redacted] in utility compared with the osimertinib monotherapy group.

The EAG therefore suggests applying [redacted] in the PFS health state for the osimertinib plus chemotherapy group, informed by the FLAURA2 trial. This means applying a utility [redacted] of 0.06 to the chemotherapy group. The EAG notes that the true [redacted] from chemotherapy is likely to be [redacted] than the [redacted] estimated, given the issue with more missing data and "unknown status" patients in the intervention group discussed above. To avoid double-counting, the EAG removes the disutilities from adverse events during the PFS period, as differences in these will be captured in the estimated utility differences from FLAURA2.

#### 4.2.7.1.3 Disutilities from adverse events unlikely to portray the utility differences between treatments in the PFS health state

The company acknowledged that patients in the intervention group would incur disutilities arising from adverse events of chemotherapy. These disutility values are informed by the literature by Brown *et al*.,[10] as used in previous TAs (TA655, TA713, TA595, TA374, and TA654) and are included for each adverse event in the beginning of the first model cycle.

The disutilities are applied to an estimated number of days within the first cycle, informed by expert opinion and previous TAs.

Clinical advice to the EAG suggested that chemotherapy has longer lasting effects, throughout the whole chemotherapy period and potentially beyond, which means that patients treated with chemotherapy in the PFS health state would, on average, have [redacted] mean quality of life estimates throughout the PFS period compared with patients in the control group. This opinion is substantiated by utility estimates in the literature.[31] The EAG believes that the disutilities for adverse events applied in the company's model may be too short lived. In the EAG's base-case, we suggest applying [redacted] to the osimertinib plus chemotherapy to the PFS health state, derived from the difference in utility [redacted] from baseline for patients in the FLAURA2 trial (as described in section 4.2.7.1.2). These utility [redacted] take into account the adverse events and side effects experienced by patients in both groups. As such, in the EAG's base-case, disutilities from adverse events were set to zero to avoid double counting.

#### 4.2.7.1.4 Lack of face validity of utility values derived from the FLAURA2 trial

The EAG agrees that, in the absence of EQ-5D-3L data, responses to the 5L questionnaire can be used and mapped onto EQ-5D-3L values using the Hernandez-Alava mapping model,[4] as recommended by NICE position statement. These have, however, produced values that appear too [redacted] and lack face validity. The EQ-5D-3L population norm for UK population aged 55-64 years (mean age of patients in FLAURA trial is 61 years) is [redacted]; for the UK population aged 65-74 (mean age of NSCLC patients in 65.6 years[3]) the norm is 0.779.[6] It is therefore unlikely that patients with advance NSCLC with EFGR mutations undergoing treatment would have a quality-of-life score [redacted] than the average UK population.

In clarification question B5, the EAG asked the company to comment on the face validity of the values for the PFS health state. The company agreed that the mapped EQ-5D-5L utilities result in an upward lift of the utility values compared with the direct EQ-5D-3L utilities [32] and cites Nafees (2017), where the utilities in PFS are as high as 0.84.[33]

The EAG notes other studies where utilities were reported for the NSCLC population. Nafees 2008[34] reports a utility score of 0.673 for patients responding to therapy and 0.653 for patients in stable disease. Labbe (2017)[7], the same study used by the company to inform the utility value for the PD health state, reported utilities of patients with stable advanced disease between 0.72 (stable on chemotherapy) and 0.77 (stable on "most appropriate treatment"). Galetta *et al.* (2014), [31] an Italian study reporting utilities with UK tariffs, reported baseline utilities for NSCLC patients (regardless of EFGR status) in a trial of two chemotherapy treatments of 0.661 and 0.71, and decreasing after chemotherapy. Pickard *et al*.,[30] reports a utility score for patients who underwent chemotherapy of 0.72. A previous TA (TA654) of osimertinib monotherapy reported PFS scores around 0.794.[8]

The EAG therefore believes that the PFS utility values derived from patients' responses to the EQ-5D-5L on the FLAURA2 trial are [redacted] for the following reasons:

1. Missing data in the EQ-5D-5L questionnaires may be overvaluing the PFS utility estimates, and the MMRM is not adequately specified to address bias due to missingness, as discussed above.
2. The mapping model may be deriving higher utilities than what is expected. As the company noted in clarification questions, the Hernandez-Alava mapping model may be deriving higher than expected utilities.

#### *4.2.7.2 Utilities for the PD health state*

Using the FLAURA2 trial data for patients in the PD health state, and the same MMRM statistical model described above, the PD health state utility varies between [redacted] and [redacted] depending group and on model specification used (supplementary information provided in CS "AstraZeneca data on file FLAURA2 EQ5D MMRM 2024"). The company considered these utility values [redacted] than expected and not appropriate due to high levels of missing data observed in the later follow-up time points. The company instead used a value from the literature of 0.64,[7] a Canadian cohort study from 2017 for the NSCLC population reporting utilities using the UK tariffs, also used in previous TA653[35] and similar to values used in two other TAs (TA309/TA402 and TA347).[36-38]

##### 4.2.7.2.1 The value of PD utility may be too low

Using the MMRM model and methodology applied to estimate the PFS utility from the FLAURA2 trial data, the company estimated that the PD utility value is [redacted]. The company argued that this value is too [redacted] due to missing data and most observations happening at the start of progression. The EAG agrees with the company's reasons for stating that this value is too [redacted]. The EAG also considers that the concerns regarding missing data, MMRM and mapping outlined in section 4.2.7.1.4 for PFS, also apply to the PD utility value.

The company instead preferred to use a PD utility value of 0.64 derived from Labbe *et al.*,[7] a 2017 Canadian study in the NSCLC population (n=475, of which n=183 are in the EGFRm population) and used in a previous CS for TA654. The EAG believes this value is, potentially, too low. The PD utility estimated from mapping to EQ-5D-3L values from the EORTC-QLQ-C30 questionnaires in the FLAURA trial[9] for TA654 was 0.704, and the value ultimately preferred by the committee for TA654 was 0.678.

The [redacted] in utility from PFS to PD estimated from utilities derived using mapped scores in the FLAURA trial is [redacted] (Table 5, in company's response to EAG clarification questions).[9] The company's MMRM model suggest a [redacted] from PFS to PD health states of [redacted] (Table 3, company's response to EAG clarification questions). The EAG agrees this may be an underestimation, but the [redacted] of [redacted], from [redacted] for PFS to 0.64 for PD, used in the company base-case is likely to [redacted] the [redacted], which is [redacted] differences between these health states reported for other TAs for the same population, such as TA654.

The EAG has used in their base-case the utility value of 0.678, as per TA654, and provides a scenario using the PD utility value of 0.64.

#### *4.2.7.3 Additional information on utility data provided after clarification questions*

Given that there is a difference in utility scores at baseline between groups, the EAG requested more clarity in the specification of the MMRM model, estimation of utilities by treatment group, and adjustment for baseline utility. After clarification questions, the company provided information on the model-specification, and confirmed that the model did not adjust for baseline utility. The company also provided the results for pre- and post-progression adjusted for baseline utility, which did not change substantially (for PFS these were [redacted] from [redacted]), but again these were estimated jointly for both groups and not by group, as requested by the EAG.

In clarification question B5, the EAG requested additional utility data by mapping from disease-specific questionnaires in the FLAURA2 trial using mapping models described in the Oxford database of mapping model.[39] These were not made available as the company considered these a departure from NICE methods and not appropriate for decision-making. The EAG also requested the utility values used in TA654 which were derived from the previous FLAURA trial EORTC-QLQ-C30 questionnaires mapped onto EQ-5D-3L utilities using a mapping algorithm. These were provided by the company and were 0.794 for the PFS health state and 0.701 for the PD health state.

The EAG requested the company to use different methods to deal with missing data such as multiple imputation with chained equations, to address uncertainty in the estimates due to missingness. The company argued that completion rate was high and consistent between treatment groups, and that the MMRM adequately addressed missing data, and therefore these alternative estimates were not provided. The EAG agrees that the completion rate was relatively high, but not consistent between groups at key time points, particularly when they were most likely to differ, and that the MMRM model does not adequately addresses the mechanisms of missing data, as described in section 4.2.7.1.1.

### 4.2.8 Resources and costs

#### *4.2.8.1 First line treatments costs*

The list prices of osimertinib, carboplatin, cisplatin, and pemetrexed are reported in Table 2 of the CS (and as per the BNF)[40].

The average cost of a course of osimertinib calculated by the company was [redacted] at the list price using the median treatment duration from FLAURA2. Osimertinib monotherapy is currently available under a commercial access agreement, [redacted]

For all other treatments, the company sourced dosing information from the MHRA label for each treatment and the drug acquisition costs were sourced from the electronic market information tool (eMIT).[41]. Commercial agreements are in place for atezolizumab and

bevacizumab which are component of ABCP (Atezolizumab + bevacizumab + carboplatin + paclitaxel), a subsequent treatment in the company's model. Details of these commercial agreements and results from applying the confidential prices to key analyses from the CS and EAG cost-effectiveness analyses (EAG report, Section 5) can be found in the confidential appendix to this report.

The company assumed that for those receiving platinum-based chemotherapy 50% of patients would receive cisplatin and 50% would receive carboplatin. Clinical advisors to the EAG suggested that carboplatin is used instead of cisplatin because it takes less time in hospital to administer and toxicity is lower, with less nausea and side effects than cisplatin. The EAG therefore prefers to assume in its base-case that 100% of patients on the osimertinib plus chemotherapy group receive carboplatin.

Treatment duration is based on TTD data from FLAURA2 for osimertinib and pemetrexed, which the EAG critiques in section 4.2.6.3. Relative dose intensity (RDI) was applied to cost calculations for osimertinib and pemetrexed, informed by the average RDI from the FLAURA2 trial in the company's base-case, with a scenario analysis assuming 100% RDI. As RDI data for cisplatin and carboplatin were not available from FLAURA2, the company applied a 100% RDI in the cost calculations for cisplatin and carboplatin. RDI for platinum-based chemotherapy has been modelled in previous TAs, including TA683 (pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer) which modelled a median RDI of 96.4% for chemotherapy from the KEYNOTE-189 clinical trial.[42] The EAG prefers to use the RDI used in TA683 in their base-case, rather than assume that the RDI is 100%. Vial wastage for IV treatments was not included in the company's base-case, in line with assumption in TA654, but the company provided a scenario analysis with treatment wastage included. Clinical advisors to the EAG agreed that wastage would be minimal, and so the EAG considers it reasonable to assume no wastage.

Treatment administration costs were applied to oral and IV administration in the company base-case. Orally administered treatments, such as osimertinib, were assigned an administration cost based on an approximate 12-minute dispensing time of a band 6 pharmacist. Administration costs for pemetrexed, which is administered by intravenous infusion, were based on the frequency of administration from the label's dosing schedule and applied costs from the NHS payment schedule for the delivery of complex chemotherapy. As cisplatin and carboplatin are assumed to be administered at the same time as pemetrexed no further administration costs are applied. The company used the same method to calculate the administration costs for the IV administered subsequent treatments. The EAG considers the company's assumptions with regards to the administration to be sensible and the sources for administration unit costs to be relevant and up to date.

#### *4.2.8.2 Subsequent treatment costs*

After a patient discontinues 1L treatment, the costs of 2L and 3L treatments are modelled. Treatment costs are applied based on the time spent on subsequent treatments estimated from RCTs that included those treatments, and the proportions of patients that receive each subsequent treatment estimated from FLAURA2 and expert opinion. The EAG agrees with the sources used to estimate treatment duration for subsequent treatment, however, has some concerns with the assumptions made on the proportion of patients on each subsequent treatment.

As noted in section 3.2.3.1, the proportions of patients receiving subsequent anticancer treatments after discontinuing 1L treatment in FLAURA2 was higher ([redacted]) for those receiving osimertinib monotherapy at 1L compared with osimertinib plus chemotherapy ([redacted]). Of those discontinuing 1L treatment the distribution of 2L treatments was based on the FLAURA2 trial but adjusted to match expert clinical opinion that (i) a proportion of patients would receive atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP), which wasn't observed in the FLAURA2 trial; and (ii) that patients receiving osimertinib plus chemotherapy at 1L would not receive pemetrexed at later lines. Based on expert opinion 15% of 2L treatments were assumed by the company to be ABCP, and the other proportions were adjusted to match the proportions receiving 2L treatments in FLAURA2 by reducing the proportion of patients on pemetrexed and docetaxel. For those that had osimertinib plus chemotherapy at 1L, none received pemetrexed at 2L, and for those who had osimertinib monotherapy at 1L equal proportions were removed from pemetrexed and docetaxel at 2L. The resulting assumed distribution is shown in Table 8, reported as the proportion of all patients discontinuing 1L treatment (with the normalised proportions for those having subsequent 2L treatments shown in square brackets below for comparison).

**Table 8: Distribution of patients across 2L treatments for those discontinuing 1L treatment in company base-case (CS, Table 54), with normalised proportions of those accessing 2L treatments displayed below in []'s**

| From ↓To → | PDC | Pemetrexed | Docetaxel | ABCP |
|---|---|---|---|---|
| Osimertinib + chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; PDC, platinum doublet chemotherapy.

The EAG's clinical experts agreed that pemetrexed would not be used at later lines following osimertinib plus chemotherapy at 1L, however they would not expect there to be other differences in how patients are treated at 2L. They also advised that only a small proportion of patients would be fit enough for ABCP after 1L treatment, and the numbers on ABCP would be low. To explore the impact of this we ran a scenario using the percentages reported in FLAURA2 (CSR, Table 17), where no patients receive ABCP, and we move the [redacted] receiving pemetrexed after osimertinib plus chemotherapy at 1L to platinum doublet chemotherapy (PDC) ([redacted]) and docetaxel ([redacted]), which achieves a balance of the normalised

proportion for PDC across treatments. The resulting distribution is shown in Table 9. Because the subsequent treatments only effect costs in the model, this effectively models the situation where there is no difference in the proportions of those discontinuing 1L treatments who go onto receive ABCP across treatment arms.

**Table 9: Distribution of patients across 2L treatments for those discontinuing 1L treatment assumed in EAG Scenario 1a and base-case, with normalised proportions of those accessing 2L treatments displayed below in []'s**

| From ↓To → | PDC | Pemetrexed | Docetaxel | ABCP |
|---|---|---|---|---|
| Osimertinib + chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; PDC, platinum doublet chemotherapy

Data from SACT suggest that the proportion accessing 2L ABCP may be less than 10%. We therefore ran a further scenario (Scenario 1b) where we assume 10% of patients that discontinue osimertinib monotherapy at 1L receive ABCP at 2L. Based on the proportions receiving 2L therapy from FLAURA this corresponds to a normalised proportion of 11% receiving ABCP in those having osimertinib at 1L and accessing 2L treatment. Assuming that the proportions receiving ABCP out of those receiving 2L treatment does not differ between arms gives a normalised proportion of 11% receiving ABCP in those having osimertinib plus chemotherapy at 1L and accessing 2L treatment (Table 10). The EAG assumes no patients access ABCP at 2L (Scenario 1a) in its base-case but acknowledge that this is likely an underestimate, and the reality is likely to lie between Scenarios 1a and 1b.

**Table 10: Distribution of patients across 2L treatments for those discontinuing 1L treatment assumed in EAG Scenario 1b, with normalised proportions of those accessing 2L treatments displayed below in []'s**

| From ↓To → | PDC | Pemetrexed | Docetaxel | ABCP |
|---|---|---|---|---|
| Osimertinib + chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; PDC, platinum doublet chemotherapy.

The company based the distribution of patients receiving different 3L treatments directly on data from the FLAURA2 trial (see CS, Table 55), which the EAG considers reasonable.

Note that whilst the company modelled the costs of subsequent treatments, OS is based on the results of FLAURA2, where patients received a range of subsequent treatments that may not be representative of NHS practice (see discussion in section 3.2.3.1).

#### *4.2.8.3 Resource use*

The company incorporated resource use from a study on lung cancer resource use by Brown *et al*.,[10] which they updated based on advice from their clinical experts. Although this study has been widely used as a source for resource use estimates in previous TAs in the disease area, the cost estimations were made over a decade ago when there were fewer treatment options available and different standards of care for NSCLC patients in the UK. It is therefore unclear to what extent these resource use estimates are still representative of current standard of care. The EAG did not identify any more recent UK resource use studies in the disease area, and so sought advice from our clinical advisors on the plausibility of the company's resource use assumptions. The EAG's clinical advisors suggested that, on average:

- patients would be seen monthly whilst on treatment, and every three months when not on treatment, although some appointments may be by telephone
- patients would receive two MRI scans per year unless a patient is known to have brain metastases in which case they would have four MRI scans per year
- patients would have four CT scans per year unless they stop treatment altogether
- Patients would have two ECGs per year whilst on osimertinib, but none otherwise.
- The 3.69 average number of A&E visits per year assumed by the company for progressed disease were higher than might be seen in practice, they suggested on average 2 visits, and that there may be some A&E visits for those on chemotherapy in the progression-free health-state

The table below summarizes the resource use estimates suggested by the company and the EAG's clinical advisors for the PFS and PD health cases.

**Table 11: Estimated resource use per annum in the company, and in EAG base-case**

| | Progression-free health state | | Progressed disease health state | |
|---|---|---|---|---|
| **Resource type** | **Company base-case** | **EAG assumption** | **Company base-case** | **EAG assumption** |
| Outpatient visits | 9.61 | 12.175 | 7.91 | 9.5 |
| MRI scans | 2.00 | 2 (or 4 for those with CNS metastases) | 2.00 | 2 (or 4 for those with CNS metastases) |
| CT scans (chest) | 0.62 | 2 | 0.24 | 2 |
| CT scans (other) | 0.36 | 2 | 0.42 | 2 |
| ECG | 1.04 | 2 | 0.88 | 0 |
| Clinical nurse specialist | 12 hours contact time | 12 hours contact time | 12 hours contact time | 12 hours contact time |
| A&E visits | 0 | 0 | 3.96 consultations | 2 |

#### *4.2.8.4 Resource use for patients with brain metastases*

The company assumed that the resource use costs for patients with CNS metastases are higher by a factor of 1.2, based on a study by Kong *et al*. 2021[43] on NSCLC patients in the US. The EAG agrees that resource use costs will be higher for those with CNS metastases, but it is unclear whether the additional costs from US claims databases would reflect the costs incurred in the UK. The EAG's clinical advisors suggested that the main difference resource use for patients with CNS metastases would be an increased number of MRI scans from two a year to four a year. The EAG ran a scenario where this is the only increase in resource use costs for patients with CNS metastases (Table 11) and use this in the EAG's base-case. The company assumed that the proportion of patients with CNS metastases is the same as that seen in FLAURA2, which the EAG considers reasonable.

#### *4.2.8.5 Valuing resource use*

In the company's base-case, outpatient visits, MRI scans, CT scans, ECG, A&E visits and clinical nurse specialist resource use were valued using tariffs reported in the NHS payment scheme 2023/25.[44] Unit costs were multiplied by the resource use estimates described in section 4.2.8.3 above. The cost of a nurse specialist was taken from unit costs from health and social care (PSSRU)[45] assuming a band 6 hospital-based nurse.

The EAG considers that the NHS Collection of Costs Data reporting NHS reference costs[46] better portray the true opportunity cost of the use of resource on the NHS. Therefore, at clarification questions, the EAG suggested that the unit costs were sourced from the NHS national collection of costs. The company provided new unit costs using the EAG's suggested source but has made some assumptions that the EAG disagrees with, for example, using outpatient procedure costs to value outpatient follow-up visits (clinical advisors to the EAG suggest these should be clinical oncology or medical oncology specialist visits), and direct access reference costs for imaging. Direct access costs are typically applied when patients are referred for imagining from primary care, but not when they are already being followed-up in secondary care. The EAG has therefore re-valued resource use applying more plausible unit costs. Table 12 below presents the unit costs in the company's base-case and the EAG's unit costs.

**Table 12: Unit costs and sources used in the CS, and in the EAG's base-case**

| Cost item | Company's base- case unit cost | Source in CS | EAG's base-case unit cost | Source |
|---|---|---|---|---|
| Outpatient visit | £141 | NHS Payment Scheme 2023/25:WF01A, Non-Admitted Face-to-Face Attendance, First, Clinical oncology | £164 | NHS National Collection of Costs 2021/22: Clinical oncology- Non-Admitted Face-to-Face Attendance, Follow-up |
| MRI | £150 | NHS Payment Scheme 2023/25: RD01A & RD02A, Magnetic Resonance | £240 | NHS National Collection of Costs 2021/22: Imagining: Outpatient. RDO2A 19 years and over Magnetic |

| Cost item | Company's base- case unit cost | Source in CS | EAG's base-case unit cost | Source |
|---|---|---|---|---|
| | | Imaging Scan of One Area, without Contrast/ with Post-Contrast, 19 years and over | | Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over |
| CT scan (chest) | £91 | NHS Payment Scheme 2023/25: RD21A, Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over | £119 | NHS National Collection of Costs 2021/22: Imagining: Outpatient. RD21A, Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over |
| CT scan (other) | £93 | NHS Payment Scheme 2023/25: RD22Z, Computerised Tomography Scan of One Area, with Pre- and Post-Contrast | £182 | NHS National Collection of Costs 2021/22: Imagining: Outpatient. RD22Z, Computerised Tomography Scan of One Area, with Pre- and Post-Contrast |
| ECG | £135 | NHS Payment Scheme 2023/25:EY51Z, Electrocardiogram Monitoring or Stress Testing (outpatient) | £301 | NHS National Collection of Costs 2021/22: Outpatient procedures, Clinical Oncology. EY51Z, Electrocardiogram Monitoring or Stress Testing |
| A&E | £275 | NHS Payment Scheme 2023/25: VB01Z:VB09Z, Emergency Medicine, Type 1 and 2 Departments | £158 | NHS National Collection of Costs 2021/22: 180, Emergency Medicine Service, Consultant led<br>Same as suggested by company after clarification questions |
| Clinical nurse specialist | £52 | PSSRU 2023: Cost per working hour band 6 hospital-based nurse | £119 | NHS National Collection of Costs 2021/22: N10AF, Specialist Nursing, Cancer Related, Adult, Face to face<br>Same as suggested by company after clarification questions |

#### *4.2.8.6 Resource use and costs for management of adverse events*

The company's model includes the cost of treating adverse events in the model with a one-off pay-off in the first cycle, reflecting the proportions of patients having each adverse event type and the average duration of the adverse event (CS, Tables 48, 29 & 65). The model assumes that patients only incur a single adverse event of each type and it is treated only once and in the short-term. Clinical advice to the EAG suggested that treatment for toxicities associated with chemotherapy would be expected to continue whilst patients are on chemotherapy. As such, it is possible that the rate of occurrence of adverse events, particularly for the osimertinib plus chemotherapy group is under-estimated, as are their associated costs.[46] The company's model includes only grade 3 adverse events which were observed in at least 2% of patients (6 patients) in a trial group. The EAG believes that all grade 3 and above adverse events should be included in the model, regardless of how rare they are, as some very rare adverse events may be costly to treat. The EAG acknowledges, however, that given the very long list of AEs reported for patients, particularly those

receiving chemotherapy, it would be computationally difficult and time-consuming to include all rare AEs, and these are unlikely to have a large impact on the ICER.

Cost sources for AE treatment unit costs were taken from the NHS payment scheme. After clarification questions from the EAG, the company provided unit costs from the NHS national collection of costs, replicated in Table 13 below. Costs were included for the treatment of decreased neutrophil count, decreased white blood cell count and leukopenia.

Clinical advice to the EAG suggested that not all adverse events would be treated with hospital admissions, but a few rare events may require longer than short stay admission. The EAG considers the unit costs applied by the company after clarification questions broadly appropriate.

**Table 13: Unit costs and sources used in the company's response to clarification questions for adverse events**

| Adverse event | Company's Unit cost provided in response to EAG's clarification questions | Source[46] |
|---|---|---|
| Diarrhoea | £589 | Calculated, weighted average- FD10A-M Non-Malignant Gastrointestinal Tract Disorders with/without (single/multiple) Interventions, Non-elective short stay. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022. |
| Fatigue | £770 | Calculated, weighted average- SA01G-SA01K Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia – non-elective short stay (Weighted Average); Non-elective short stay. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022. |
| Anaemia | £770 | Assumed same as fatigue |
| Decreased appetite | £876 | Calculated (weighted average), FD04A-E, Nutritional disorders with/without interventions, all CC scores, Non-elective short stay. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022. |
| Pneumonia | £669 | Calculated- DZ11K-N, P-V Lobar, atypical or viral pneumonia with/without single/multiple interventions – non-elective long stay (Weighted Average). NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022. |
| Neutropenia | £543 | Calculated, weighted average- SA08G, SA08H, SA08J. Other haematological or splenic disorders, with CC score 0-6+, non-elective short stay. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022. |
| Neutrophil count decreased | £543 | Assumed same as neutropenia |
| Platelet count decreased | £676 | Calculated, weighted average- SA09G, SA09H, SA09J-L, Other red blood cell disorders with CC score 0-14+. NHS |

| Adverse event | Company's Unit cost provided in response to EAG's clarification questions | Source[46] |
|---|---|---|
| | | (2022). National schedule of reference costs: the main schedule 2021 to 2022. |
| Thrombocytopenia | £699 | Calculated, weighted average SA12G-K Thrombocytopenia with CC Score 0-8+, non-elective short stay. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022. |
| Febrile neutropenia | £2,975 | Calculated, inflated from 2007/2008 to 2021/2022 (2286*334.5/257). Morgan *et al*. 2007 (DSU report), inflated using Pay & Price Index |
| White blood cell count decreased | £543 | Assumed same as neutropenia |
| Ejection fraction decreased | £666 | Calculated, weighted average, EB03A-E, Heart failure or shock, with CC score 0-14+, non-elective short stay. NHS (2022). National schedule of reference costs: the main schedule 2021 to 2022. |
| Leukopenia | £543 | Assumed same as neutropenia |
| Pulmonary embolism | £773 | Calculated, weighted average, DZ09J-Q, Pulmonary Embolus with/without intervention, Non-elective spell. National schedule of reference costs: the main schedule 2021 to 2022. |

# 5 COST EFFECTIVENESS RESULTS

## 5.1 Company's cost effectiveness results

The company reported cost-effectiveness results for osimertinib with pemetrexed and platinum-based chemotherapy (osimertinib plus chemotherapy) compared with osimertinib monotherapy. The company's base-case includes a [redacted] discount for osimertinib in the osimertinib plus chemotherapy group and a discount of [redacted] for osimertinib in the osimertinib monotherapy group and eMIT prices for other treatments. For the results using confidential prices for all treatments please see the EAG report's confidential appendix.

The company reported their deterministic results in Table 14, which gives an ICER of £27,280. The company also provided results of a probabilistic sensitivity analysis (PSA) with 1,000 iterations reported in Table 15, which results in a slightly higher ICER of £28,318. However, the EAG found that 1,000 iterations were insufficient for stable results. The EAG explores convergence of the probabilistic model in section 5.1.1 below.

### Table 14: Company deterministic base-case results (CS, Table 68)

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|---|
| Osimertinib + Chemotherapy | [redacted] | [redacted] | [redacted] | - | - | - | - |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £27,280 |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

### Table 15: Company base-case probabilistic results after 1,000 iterations run (CS, Table 70)

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|---|
| Osimertinib + Chemotherapy | [redacted] | [redacted] | [redacted] | - | - | - | - |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £28,318 |

### Table 16: Company base-case probabilistic results after 50,000 iterations run

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|---|
| Osimertinib + Chemotherapy | [redacted] | [redacted] | [redacted] | | | | |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £30,113 |

### 5.1.1 Convergence in the company's probabilistic model

The benefit of a PSA over a deterministic analysis is that it can account for the non-linearity of the relationship between model inputs and outputs and captures the uncertainty in the input parameters. A model's PSA should demonstrate convergence to prevent stochastic variation from biasing the model outputs.

**The company ran 1,000 iterations of the PSA in their base-case and provided graphs of the convergence in incremental costs and incremental QALYs (**Error! Not a valid bookmark self-reference.**). Repeat runs of the company's model by the EAG found significant variation in the results of the ICER due to a lack of convergence in the model's incremental QALYs by 1,000 iterations. Additional runs of the company base-case PSA confirmed the substantial Monte Carlo error after 1,000 iterations, with 3 of the 5 runs of the company's base-case by the EAG producing ICERs above £30,000 per QALY (**
**Figure 7). The sensitivity of the ICER to the number of iterations is due to the small number of incremental QALYs between groups. The EAG ran the company's base-case probabilistic analysis with 50,000 iterations which resulted in a higher ICER of £30,113 (Table 16 and Figure 8) compared with ICER £28,318 in the company's model run (Table 15 and**
Figure 7).

**Figure 6: Convergence of ICER of company reported base-case (provided by the company in the corrected company model after clarification questions) (Full range)**

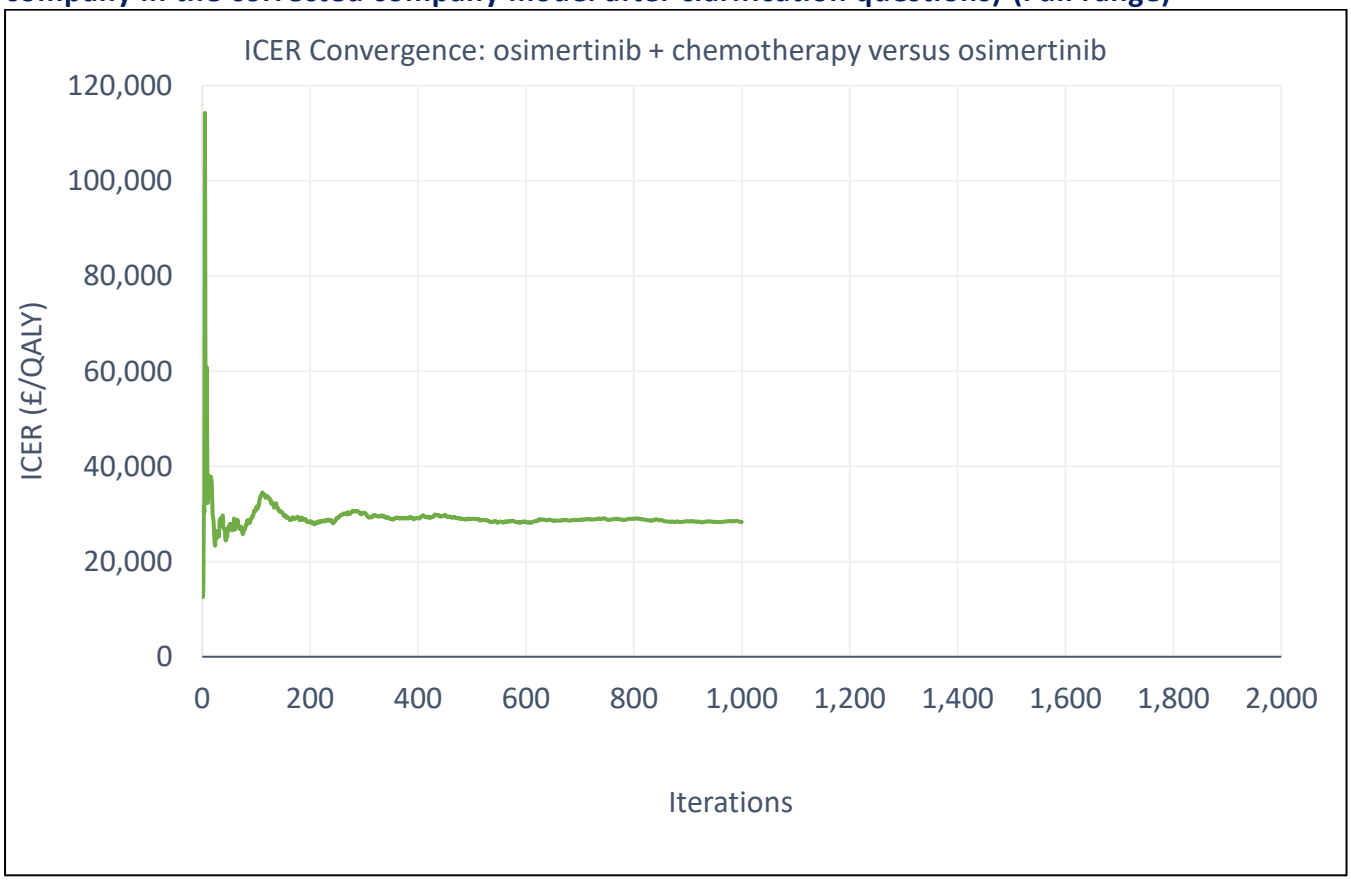


**Figure 7: Between chains comparison of ICER by number of iterations from repeated runs of company base-case up to 1,000 iterations each – Company run results taken from the corrected company model after clarification questions**

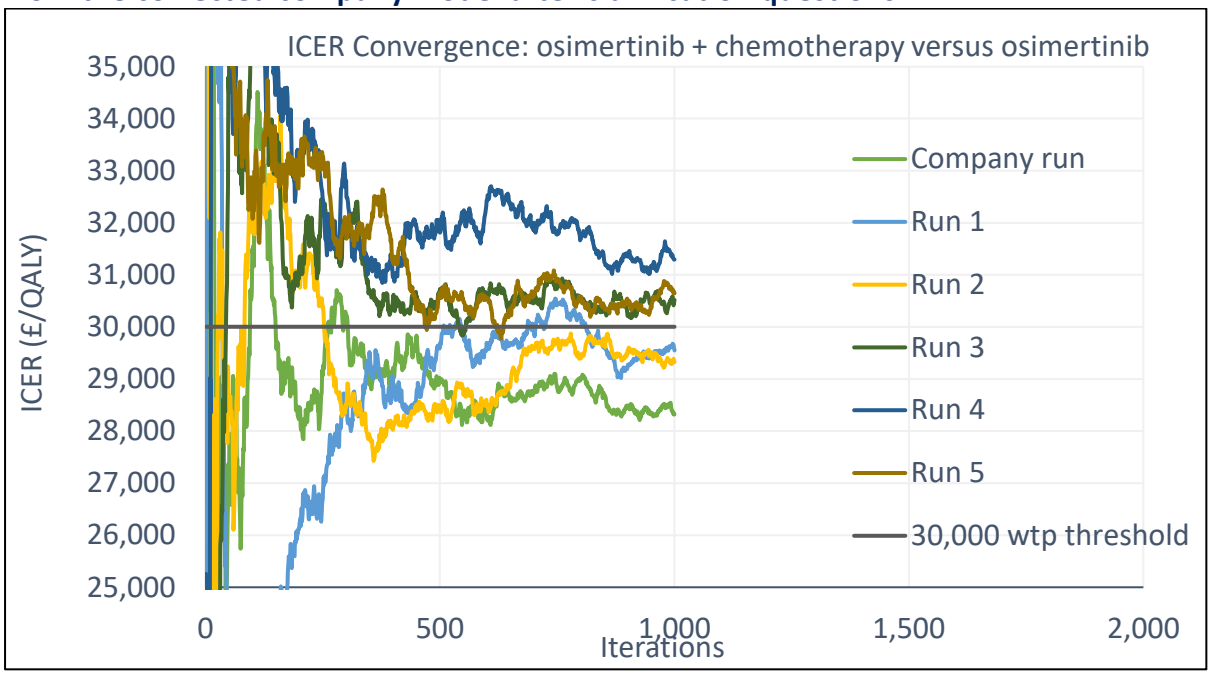
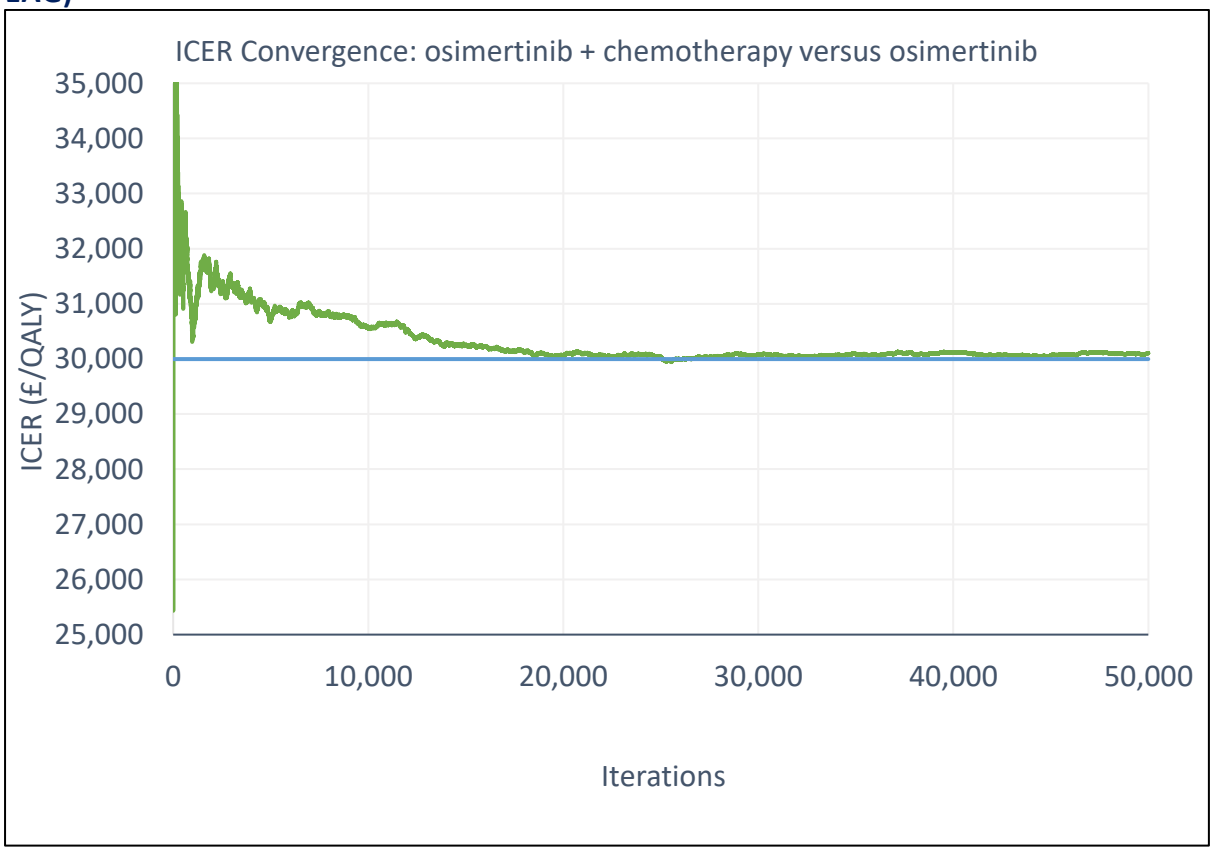



**Figure 8: Convergence of the ICER at 50,000 iterations (company's base-case run by EAG)**



## 5.2 Company's sensitivity analyses

The company's deterministic sensitivity analyses are reported in the below tornado plots (**Error! Reference source not found.**). Cost-effectiveness outcomes were most sensitive to the following parameters: utilities for the PFS and PD health-states, treatment durations, proportions of patients on subsequent treatments, patient characteristics and the discount rate. The parameter to which the ICER was most sensitive was the utility for the progression-free health state.

Table 17 reports the company's 14 one-way scenario analyses. These included adjusting the time horizon, the inclusion of the cost of treatment wastage, adjusting the discount rate, alternative utility inputs, alternative treatment cost scenarios and applying different extrapolations of the overall survival and progression-free survival curves. The scenarios chosen depict uncertainty in a high number of parameters and model assumptions that affect the ICER. Scenarios which increased the ICER included: reducing the time horizon to 10 years, including wastage in the treatment cost calculations, using the utilities from FLAURA2 for both PF and PD states, and using 100% relative dose intensity in all treatment cost calculations. Scenarios which lowed the ICER included: lowering the discount rate for costs and QALYs to 1.5% and changing progression-free survival assessment to BICR. The scenarios reported that explored alternative extrapolations of survival and TTD curves reported higher ICERs than the company base-case for: osimertinib mono PFS gamma distribution, osimertinib + chemo PFS Gompertz distribution, both arms OS 2-spline odds, and osimertinib mono time-to-treatment discontinuation Weibull distribution.

**Figure 9: Tornado diagram reporting the results of the company's deterministic sensitivity analysis (CS, Fig. 33)**

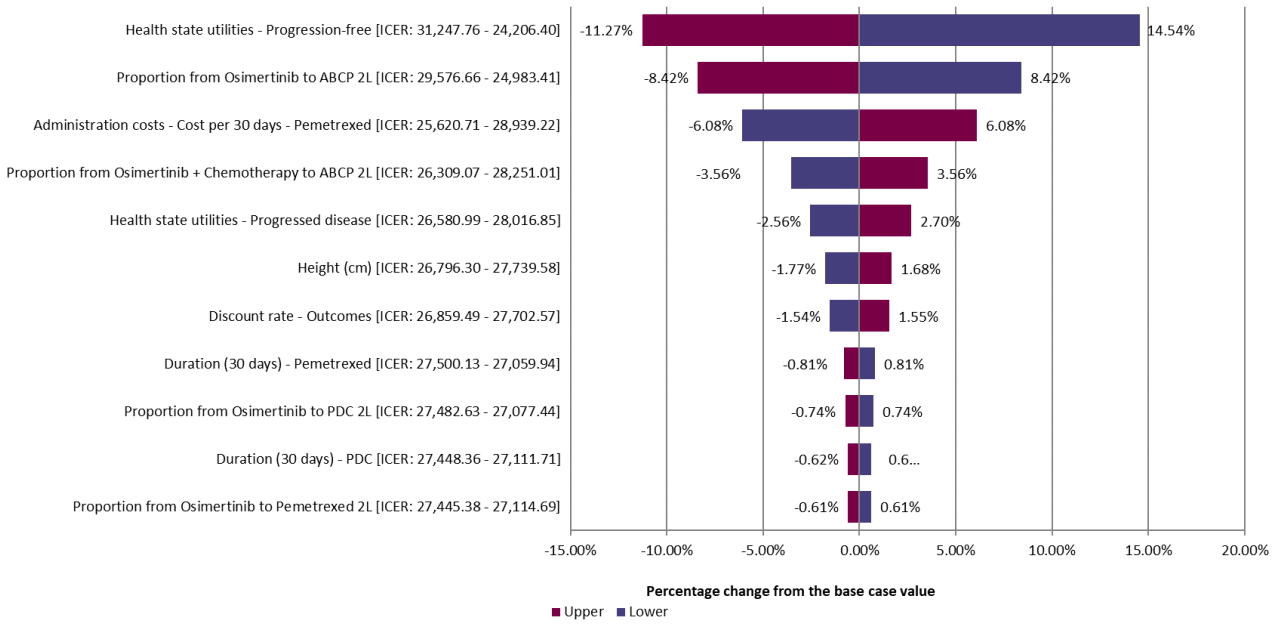


**Table 17: Results of the company's scenario analysis (CS, Table 73)**

| Scenario | Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| 1. Time horizon of 10 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £29,722 | 8.9% |
| 2. Inclusion of the cost of wastage | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,986 | 20.9% |
| 3. Discount rate of 1.5% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £25,571 | -6.3% |
| 4. Utility source - FLAURA2 (PFS & PD) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £28,897 | 5.9% |
| 5. Progression-free survival extrapolation – Gamma (osimertinib) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £27,911 | 2.3% |
| 6. Progression-free survival extrapolation – Gompertz (osimertinib + chemotherapy) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £34,885 | 27.9% |
| 7. Overall survival extrapolation – 2 spline odds (both arms) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,292 | 18.4% |
| 8. Overall survival extrapolation – Weibull (both arms) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £14,605 | -46.5% |

| Scenario | Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| 9. Overall survival extrapolation – Gamma (both arms) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £14,560 | -46.5% |
| 10. TTD survival (osimertinib + chemotherapy (osimertinib)) extrapolation – Gen gamma | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £15,009 | -45.0% |
| 11. TTD survival (osimertinib) extrapolation - Weibull | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £31,500 | 15.5% |
| 12. Progression-free survival source - BICR | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £22,995 | -15.7% |
| 13. Removal of administration cost of chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £10,687 | -60.8% |
| 14. Relative dose intensity - 100% for all treatments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £33,891 | 24.2% |

### 5.2.1 CNS metastases subgroup results

In clarification question B10, the EAG requested subgroup analysis for patients with and without CNS metastases. The company provided results from a deterministic analysis for the subgroup of patients with CNS metastases only (Table 18). It was not possible to run the PSA samples from the model provided by the company.

**Table 18: Company deterministic results for CNS metastases subgroup (Table 14, company's response to EAG's clarification questions)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|---|
| Osimertinib + Chemotherapy | [redacted] | [redacted] | - | - | - |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] | £18,835 |

## 5.3 Model validation and face validity check

The CS lacks details of their model validation and face validity check.

The EAG applied a validation check based on the TECH-VER framework developed by Büyükkaramikli *et al*. (2019).[47] This included checking the model results adhered to 'Black-box tests' and where potential errors were identified in the black-box tests underwent the 'White-box tests' of the TECH-VER framework. This involves checking the detailed model calculations that are being inspected, running through the related code or by scrutinizing the formulae in the relevant ranges in a spreadsheet, cell by cell. In addition to these formal checks, further white-box tests were completed by the EAG where anomalies were identified when navigating the model to understand the model calculations. In the above tests the EAG found the model well modelled and with few errors, however there were two key issues identified:

1. As discussed in section 5.1.1, the PSA takes a large number of runs for results to converge. The results reported in the CS have insufficient samples for convergence (and give a lower ICER than obtained from longer model runs).

2. The EAG identified an error in the formulae for the 2-knot spline on the odds scale for OS in the osimertinib plus chemotherapy group. The formulae in the CS model incorrectly gives the 1-knot odds spline, rather than the 2-knot odds spline. The company does not provide results for this model, and so it does not affect their reported results. The EAG corrected the spill formula in column U of sheet 'Extrapolations Data' so that cell U4 reads:

   =(spline("odds",2,'Clinical_data (PSM + TTD)'!AE$7:AE$10,'Clinical_data (PSM + TTD)'!AE$12:AE$15,'Clinical_data (PSM + TTD)'!AE$17,$B$4:$B$249))

Correcting cell U4 automatically corrects the other cells in column U. The EAG uses the corrected formulae in its scenarios and base-case.

# 6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

## 6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG performed one-way scenario analyses to explore the main drivers of cost-effectiveness and the uncertainties around the economic model. We describe the scenarios below and report the results in section 6.2. All scenarios were based on the executable model submitted by the company after clarification questions "ID6328 osimertinib company economic model - clarification response 240624LI [CON].xlsm" with the correction for the 2-knot spline on the odds scale for OS in the osimertinib plus chemotherapy group made as described in section 5.3.

### 6.1.1 Exploring alternative distribution of 2L treatments after discontinuing 1L

In scenario 1, the EAG explores alternative assumptions about the distribution of 2L treatments after discontinuing 1L treatment (see section 4.2.8.2). Cells in the range F40:T41 in the "Cost_SubTx" sheet of the company's Excel model were adjusted:

- Scenario 1a uses the distribution of 2L treatments as set out in Table 9.
- Scenario 1b uses the distribution of 2L treatments as set out in Table 10.

### 6.1.2 Exploring different assumptions of chemotherapy treatments in the intervention group

Scenario 2 explores the effect of 100% of patients on the osimertinib plus chemotherapy receiving carboplatin only, compared with 50% carboplatin and 50% cisplatin in company's base-case (see section 4.2.8.1). Cells F39:F40 in the Settings sheet of the company's Excel model were adjusted.

### 6.1.3 Exploring the effect of population age in the model

Scenario 3 explores the model population starting, on average, at 65.6 years of age (see section 4.2.4). Cell F25 in the Settings sheet of the company's Excel model was adjusted.

### 6.1.4 Alternative assumptions for overall survival (OS)

In scenario 4, the EAG explores alternative assumptions for extrapolating OS. The scenarios include:

- Scenario 4a using the Gompertz for OS for both treatments
- Scenario 4b using the Weibull for OS for both treatments
- Scenario 4c using the Gamma for OS for both treatments
- Scenario 4d using 1-knot model on odds scale for osimertinib monotherapy and 2-knot model on odds scale for osimertinib plus chemotherapy for OS
- Scenario 4e using 1-knot model on hazards scale for osimertinib monotherapy and 2-knot model on hazards scale for osimertinib plus chemotherapy for OS

Cells L83-M83 and AA83-AC83 were adjusted for osimertinib plus chemotherapy OS and osimertinib OS respectively in sheet "Survival (PSM)" in the company's Excel model.

### 6.1.5 Using Gompertz curve for TTD on the osimertinib monotherapy group

Scenario 5a explores using the Gompertz curve for TTD on the osimertinib monotherapy group (see section 4.2.6.1). Cells AA17-AC17 were adjusted in the "Survival (TTD)" sheet in the company's Excel model.

Scenario 5b uses the company's base-case curves but constrains TTD not to be greater than PFS. Cell E70 was adjusted in the "Setting" sheet in the company's Excel model.

### 6.1.6 Assuming a relative dose intensity of 96.4% for carboplatin and cisplatin

In scenario 6, the EAG assumes RDI 96.4% for carboplatin and cisplatin, as discussed in section 4.2.8.1. Cells O16:O17 were adjusted in the "Costs Tx" sheet in the company's Excel model.

### 6.1.7 Varying resource use and updating unit costs

In scenario 7, the EAG explores the impact of different resource use in UK clinical practice, including for patients with brain metastases (as informed by the EAG's clinical advisors), and updated the source of unit costs. These were discussed in sections 4.2.8.3, 4.2.8.5, and 4.2.8.6. Table 11 and Table 12 describe the EAG's units of resource use and costs.

Resource use was edited in the company's 'Costs_DM' sheet. The EAG resource use estimates were adjusted to a 30 day estimate and included in cells G13:19 for the progression-free health state and cells G33:G39 in the progressed disease health state. The EAG's preferred unit costs for disease management were also input in the 'Costs_DM' sheet in cells L13:L19 for the progression-free health state and L33:L39 for the progressed disease health state.

### 6.1.8 Exploring different sources of utilities for the PFS and PD health states

In scenario 8, the EAG explores different assumptions for health state utilities.

- Scenario 8a assume a disutility [redacted] in the PFS health state for the osimertinib plus chemotherapy group and set disutilities for AEs to zero, keep PFS and PD utilities from the company base-case (see sections 4.2.7.1.2 and 4.2.7.1.3)
- Scenario 8b assume a disutility [redacted] in the PFS health state for the osimertinib plus chemotherapy group and set disutilities for AEs to zero, 0.794 for PFS, keep PD as 0.64 as company's base-case (see section 4.2.7.1.1, 4.2.7.1.2 and 4.2.7.1.4)
- Scenario 8c assume a disutility [redacted] in the PFS health state for the osimertinib plus chemotherapy group and set disutilities for AEs to zero, 0.794 for PFS and assume 0.678 for PD, as per TA654 (see section 4.2.7.2.1)

- Scenario 8d assume a disutility [redacted] in the PFS health state for the osimertinib plus chemotherapy group and set disutilities for AEs to zero, 0.77 for PFS and keep the company's PD value of 0.64 (see section 4.2.7.1.4)
- Scenario 8e assume a disutility [redacted] in the PFS health state for the osimertinib plus chemotherapy group and set disutilities for AEs to zero, 0.794 for progression-free state and keep the company's PD value of 0.64 (see section 4.2.7.1.2)
- Scenario 8f vary health-state utilities to 0.794 for PFS and assume 0.678 for PD, as per TA654, keeping disutilities for adverse events as per company's base-case and not apply a disutility to the intervention group in PFS (see section 4.2.7.1.2)

To adjust the disutility in the PFS health state for the osimertinib plus chemotherapy group, we adjusted Cell AY10 in the "Flow" sheet to the assumed disutility and set Cells H24:H41 in the "Utilities" sheet to 0 to avoid double-counting disutilities. Cells AY13:AY258 were all edited to distribute the disutility over the relevant time cycles, apply the disutility to only those in the progression-free health state, and apply the discount rate for QALYs.

To adjust the utilities for the PFS and PD health-states we adjusted cells G16:G17 in the "Utilities" sheet in the company's Excel model.

### 6.1.9 Subgroup analyses for patients with CNS metastases

In scenario 9, the EAG explores subgroup analyses for those with CNS metastases.

- Scenario 9a analysis for the CNS subgroup using the 2-knot spline on the hazard scale for OS (see section 5.3)
- Scenario 9b analysis for the CNS subgroup using the Gompertz for PFS (see section 4.2.6.2)

The CNS subgroup is specified in the company's Excel model in cells E16:F16 in the "Settings" sheet. The choice of survival models is made by adjusting cells L17:M17; L83:M83; AA17:AC17; AA83:AC83 in the "Survival (PSM)" sheet.

## 6.2 Impact on the ICER of the EAG's additional clinical and economic analyses

Table 19 reports the results of the EAG's one-way scenario analyses. The assumptions to which the ICER is most sensitive are the proportions of patients receiving 2L treatments, assumptions around the extrapolation of OS curves and extrapolation of TTD for osimertinib monotherapy, and utilities, particularly in the PFS state and applying the utility differences from FLAURA2 to the osimertinib plus chemotherapy group instead of applying AE disutilities.

**Table 19: Results of the EAG's scenario analysis (deterministic results)**

| Scenario | Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| Company base-case | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £27,280 | - |
| Scenario 1a: alternative assumptions about the distribution of 2L treatments from Table 9 (No ABCP at 2L) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £40,029 | +47% |
| Scenario 1b: alternative assumptions about the distribution of 2L treatments from Table 10 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £30,530 | +12% |
| Scenario 2: 100% of patients on the osimertinib plus chemotherapy receive carboplatin | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £27,388 | 0% |
| Scenario 3: where average age of 65.6y | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £27,325 | 0% |
| Scenario 4a: Gompertz for OS for both treatments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £30,474 | +12% |

| Scenario | Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| Scenario 4b: Weibull for OS for both treatments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £14,605 | -46% |
| Scenario 4c: Gamma for OS for both treatments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £14,560 | -47% |
| Scenario 4d: 1-knot model on odds scale for osimertinib monotherapy and 2-knot model on odds scale for osimertinib plus chemotherapy for OS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,291 | +18% |
| Scenario 4e: 1-knot model on hazards scale for osimertinib monotherapy and 2-knot model on hazards scale for osimertinib plus chemotherapy for OS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £34,616 | +27% |
| Scenario 5a: Gompertz for TTD of osimertinib monotherapy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £40,348 | +48% |

| Scenario | Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| Scenario 5b: TTD bounded to not exceed PFS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £46,780 | +71% |
| Scenario 6: RDI 96.4% for carboplatin and cisplatin | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £27,262 | 0% |
| Scenario 7: EAG's resource use assumptions (Table 11) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £31,268 | +14% |
| Scenario 8a: disutility of [redacted] for chemotherapy group | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £30,339 | +11% |
| Scenario 8b: disutility of [redacted] for chemotherapy group, PFS utility of 0.794; PD utility 0.64 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,227 | +20% |
| Scenario 8c: disutility of [redacted] for chemotherapy group, PFS utility of 0.794; PD utility 0.678 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,833 | +20% |
| Scenario 8d: disutility of [redacted] for | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £33,692 | +24% |

| Scenario | Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| chemotherapy group, PFS utility of 0.77; PD utility 0.64 | | | | | | | | |
| Scenario 8e: disutility of [redacted] for chemotherapy group, PFS utility of 0.794; PD utility 0.64 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £29,422 | +8% |
| Scenario 8f: PFS utility of 0.794; PD utility 0.678 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £29,280 | +7% |
| Scenario 9a: CNS metastases subgroup with 2-knot spline on hazard scale for OS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £22,801 | -16% |
| Scenario 9b: CNS metastases subgroup with Gompertz for PFS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £20,766 | -24% |

## 6.3 EAG's preferred assumptions

Given the exploratory analysis performed in section 6.2, the EAG's preferred assumptions and their cumulative impact on the ICER are listed below.

- Alternative assumptions about the distribution of 2L treatments after discontinuing 1L treatment (see section 4.2.8.2) as set out in Table 9 (EAG Scenario 1a)
- 100% of patients on the osimertinib plus chemotherapy receive carboplatin, compared to 50% in company's base-case (EAG Scenario 2)
- Average age of 65.6 years, compared to 61y in company's base-case (EAG Scenario 3)
- 1-knot model on odds scale for osimertinib monotherapy group and 2-knot model on odds scale for osimertinib plus chemotherapy group for OS (EAG Scenario 4d)
- Gompertz for TTD of osimertinib monotherapy (EAG Scenario 5)
- RDI 96.4% for carboplatin and cisplatin (EAG Scenario 6)
- EAG's resource use assumptions (Table 11) with alternative unit costs (EAG Scenario 7)
- Disutility [redacted] in the PFS health state for the osimertinib plus chemotherapy group and AEs to zero, 0.794 for PFS, and 0.678 for PD (EAG Scenario 8c)

In Table 20 the EAG's preferred assumptions are incrementally added to show the overall effect on the deterministic ICER. The probabilistic results for the EAG's base-case based on 50,000 samples are presented in Table 21.

In both analyses, QALYs and costs are higher for the osimertinib plus chemotherapy group. In the EAG's deterministic base-case, the ICER is an incremental £88,444 per QALY gained (a 224% increase from the company's base-case), and the probabilistic ICER is an incremental 84,177 per QALY gained, a 209% increase from the company's base-case.

The cost-effectiveness acceptability curve for the EAG's base-case is presented in Figure 10. Under the EAG's assumptions, if the NHS is willing to pay £20,000 per incremental QALY, there is a 7.5% probability that osimertinib plus chemotherapy is cost-effective compared with osimertinib monotherapy. When willing to pay £30,000 per incremental QALY there is 13.8% chance of cost-effectiveness. The probability of osimertinib plus chemotherapy is low throughout the range of willingness to pay thresholds, and only rises above 50% when willing to pay above £80,000 per incremental QALY.

The EAG also ran the deterministic analysis for the subgroup with CNS metastases using the assumptions of the EAG's base-case. The ICER (Table 22) is £32,162 per incremental QALY gained. This is a 71% increase compared with the deterministic results of the CNS subgroup analysis reported by the company in response to EAG's clarification questions of £18,835, and an 18% increase from the company's base-case ICER.

**Table 20: EAG preferred assumptions added incrementally and EAG base-case (deterministic results)**

| EAG Assumption Number | Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| 0 | Company base-case | | | | | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £27,280 | - |
| 0+1a | + EAG assumptions about the distribution of 2L treatments | | | | | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £40,029 | +47% |
| 0+1a+2 | + 100% of patients on the osimertinib plus chemotherapy receive carboplatin | | | | | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £40,142 | +47% |
| 0+1a+2+3 | + average age of 65.6y | | | | | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £40,208 | +47% |
| 0+1a+2+3+4d | +1-knot model on odds scale for osimertinib monotherapy and 2-knot model on odds scale for osimertinib plus chemotherapy for OS | | | | | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £48,162 | +77% |
| 0+1a+2+3+4d+5a | + Gompertz for TTD of osimertinib monotherapy | | | | | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £64,282 | +136% |
| 0+1a+2+3+4d+5a+6 | + RDI 96.4% for carboplatin / cisplatin | | | | | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £64,253 | +136% |
| 0+1a+2+3+4d+5a+6+7 | + EAG's resource use assumptions (Table 11) | | | | | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £68,826 | 152% |

| EAG Assumption Number | Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| 0+1a+2+3+4d+5a+6+7 +8c = EAG BaseCase | + PFS utility of 0.794; PD utility 0.678, and disutility of -0.06 PFS on osimertinib plus chemotherapy (instead of including AE disutilities) | | | | | | | |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £88,444 | 224% |

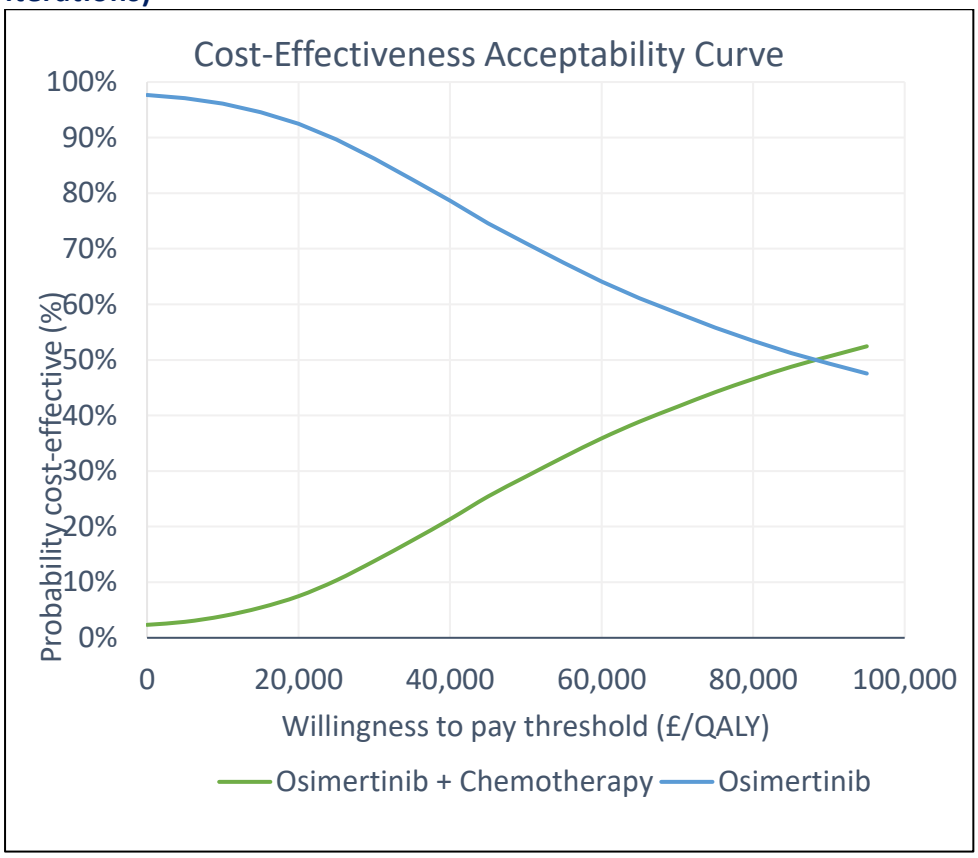
**Table 21: EAG base-case probabilistic results after 50,000 iterations run**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER incremental (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| Osimertinib + Chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £84,177 | 209% |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - | - |

**Table 22: Deterministic results of the CNS subgroup analysis with the EAG's base-case assumptions applied**

| EAG Assumption Number | Osimertinib + chemotherapy | | Osimertinib monotherapy | | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | Change from base-case ICER (%) |
|---|---|---|---|---|---|---|---|---|
| | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | | | | |
| EAG base-case assumptions applied to the CNS subgroup analysis | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,162 | +18% |

**Figure 10: Cost-effectiveness acceptability curve for EAG base-case (50,000 PSA iterations)**




## 6.4 Conclusions of the cost effectiveness section

The company have submitted a cost-effectiveness model that addresses the decision problem defined in the final scope. The model structure is a partitioned survival model, largely aligned with prior NICE TAs in advanced NSCLC, including for osimertinib monotherapy (TA654). The model is largely informed by FLAURA2, a large trial in the advanced NSCLC population with EGFR mutations Ex19del and L858R. Effectiveness results from the trial inform rates of OS, PFS, PD, and TTD in the model.

The model results are sensitive to assumptions around the extrapolation of OS and TTD. The ICER increased when using the EAG's preferred assumptions, however, there remains uncertainty around the most appropriate assumptions for extrapolation (Key Issues 5 and 6).

Utilities for the PFS health state were informed by responses to the EQ-5D-5L questionnaires at 6-weekly follow-up points by patients in the trial. In the absence of a direct valuation of the EQ-5D-5L health states, the company used the Hernandez-Alava mapping model to the EQ-5D-3L utilities,[4] as per NICE position statement.[5] This yielded utility values without face validity, with patients with advanced NSCLC receiving treatment (including chemotherapy) achieving higher utility scores than the general UK population for

the same age group. This was likely due to bias introduced by missing data, mainly in the intervention group, and the mapping model yielding higher than expected utilities. An additional assumption by the company is that patients in the intervention and control groups have similar utility scores in the PFS health state. Disutility for adverse events in the chemotherapy group were modelled in the short-term, whereas clinical advisors to the EAG suggested these would be prolonged for longer. The PD utility was obtained from the literature and likely to be too low. As such, the EAG suggested alternative values for PFS and PD utilities, informed by utilities used in previous TA for osimertinib monotherapy in the same population (TA654),[8] and the application of [redacted] in utility in PFS period for patients in the osimertinib plus chemotherapy group (see key issues 4, 7, and 8).

The incremental costs are very sensitive to assumptions on the subsequent treatments used by patients at 2L (Key Issue 10). This is partly because a [redacted] proportion of patients received 2L treatment for the osimertinib monotherapy group, and so there are [redacted] subsequent treatment costs associated with osimertinib monotherapy. There is uncertainty around the proportions who will receive ABCP at 2L and how this differs when osimertinib is used with or without chemotherapy. The EAG's base-case assumes no patients receive ABCP at 2L, when in fact a small proportion may receive ABCP at 2L. However, the EAG's incremental base-case results also represent the scenario where the same proportions of those who discontinue 1L treatments receive ABCP for osimertinib monotherapy and osimertinib plus chemotherapy. However, the EAG acknowledges that their base-case may give overestimate the ICER.

Resource use to treat patients at follow-up and during adverse events was informed by a study in the literature from 2013 updated using the company's clinical experts' advice.[10] Clinical advisors to the EAG suggested that the level of resource use suggested was no longer indicative of current clinical practice and suggested alternative units of resource use, reducing this cost. The EAG also applied NHS national schedule of reference costs, with specialities informed by the EAG's clinical advisors, to value the resources. Reducing and re-valuing resource use had a large impact by reducing the costs for the osimertinib monotherapy group by more than in the osimertinib plus chemotherapy group which increased the ICER.

Whilst there is uncertainty around the cost-effectiveness of osimertinib plus chemotherapy for the full population in the scope, the ICER was substantially lower in the CNS metastases subgroup at £32,162 per QALY gained, although the results for this subgroup may lack statistical power.

The main drivers of the ICERs are the assumptions around the extrapolation curves used for OS, extrapolation for the TTD for osimertinib monotherapy, subsequent treatments used at 2L, follow-up resource use, and utilities, particularly differences in utilities between treatments in the PFS health state.

# 7 SEVERITY AND INNOVATION

The CS states the severity modifier was not applicable for this submission.

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# 9 APPENDICES

## 9.1 Appendix 1: Risk of BIAS

### 9.1.1 FLAURA2 risk of bias assessment, using RoB2 tool, for assignment to intervention

| Domain | Signalling question | OS | PFS | TTD | AE | HRQoL (EQ- 5D-5L) | Comments |
|---|---|---|---|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | Y | Y | Y | Y | Random assignment using central randomisation and blinding of the sponsor/ global study team during randomisation period. Treatment assigned using IVRS/IWRS. |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | Y | Y | Y | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | N | N | N | N | N | EQ-5D-5L values did differ between groups at baseline (higher in the osimertinib plus chemotherapy group mean 0.79 (SD 0.18) compared to osimertinib monotherapy group mean 0.75 (0.24) at baseline. However, this is unlikely to suggest a problem with the randomisation process. Other outcomes did not have baseline differences to suggest issues with randomisation. |
| | **Risk of bias judgement** | **Low** | **Low** | **Low** | **Low** | **Low** | **No concerns regarding the randomisation process** |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | Y | Y | Y | Y | Y | Open-label trial in which participants were aware of assigned intervention. |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | Y | Y | Y | Y | Y | Open-label trial in which personnel at study sites were aware of assigned intervention. |
| | 2.3. If Y/PY/NI to 2.1/2.2: Were there deviations from the intended interventions that arose because of the trial context? | PY | PY | PN | PN | PY | There is the potential for the result for PFS, OS and HRQoL to be biased given the absence of detail on the use of subsequent treatments across arms, though we acknowledge this is not a protocol deviation. The use of subsequent treatments was not balanced between groups. |
| | 2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | PY | PY | NA | NA | PY | |

| Domain | Signalling question | OS | PFS | TTD | AE | HRQoL (EQ- 5D-5L) | Comments |
|---|---|---|---|---|---|---|---|
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | PY | PY | NA | NA | PY | |
| | 2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention? | Y | Y | Y | N | Y | Per-protocol analysis (in people who had received >1 treatment dose) for safety outcomes. Other outcomes used intention-to-treat analysis. |
| | 2.7. If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised? | NA | NA | NA | N | NA | For AEs: Only one person from the intervention group was analysed in the control group and only 6 people received no treatment overall (balanced across groups: 3 intervention; 3 control). |
| | **Risk of bias judgement** | **Some concerns** | **Some concerns** | **Low** | **Some concerns** | **Some concerns** | **Some concerns for OS, PFS, AE, HRQoL because there is the potential for the effect to be biased given unclear information regarding use of subsequent treatments between groups. There appears to be an imbalance in type/class of subsequent treatments between the two arms. Additional concerns for AEs due to the use of per-protocol analysis.** |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | Y | Y | NI | Y | N | No participants were highlighted as being lost to follow-up in the full analysis set for efficacy data. Unclear if there is missing data for TTD. In the safety analysis set, no participants listed as lost to follow-up - 6 did not receive treatment and were not included in safety analysis set (276/279 received osimertinib-chemo group, 275/278 received osimertinib monotherapy).<br><br>Table 14.2.10.8.1b in the appendix to the CSR provided by the company reports the compliance with EQ-5D-5L by visit and provides the number of expected forms, received forms and compliance rate per treatment group. The table shows that missing data is slightly higher in the osimertinib plus chemotherapy group and this is particularly the case at the beginning of the trial whilst patients are still undergoing chemotherapy and are likely to have felt more unwell. |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | NA | PN | NA | N | |

| Domain | Signalling question | OS | PFS | TTD | AE | HRQoL (EQ- 5D-5L) | Comments |
|---|---|---|---|---|---|---|---|
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | NA | NI | NA | Y | |
| | 3.4. If Y/PY/Ni to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | NA | NI | NA | Y | Low HRQoL is likely to have impacted completion of HRQoL measures. |
| | **Risk of bias judgement** | **Low** | **Low** | **High** | **Low** | **Some concerns** | **Some concerns for HRQoL outcome due to missing data and high risk of bias for TTD due to a lack of information on missing data.** |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | N | N | NI | N | N | No details provided about the measurement of TTD (not a pre-specified outcome in the trial). Measurement of the other outcomes was appropriate. |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | PN | PN | NI | PN | PN | No details provided about the measurement of TTD – it is possible that the point at which "treatment discontinuation" was recorded could have been different between groups, but details are not reported to be able to judge this. Measurement of the outcome was unlikely to differ between groups for the other outcomes. |
| | 4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants? | Y | Y | Y | Y | Y | Outcome assessors were aware of the intervention received by study participants (though they did do a sensitivity analysis of PFS based on data assessed by blinded independent central review as well). |
| | 4.4. If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | N | PN | PY | PY | PY | OS: objective outcome. PFS: although open-label, PFS probably not affected because measured with RECIST v1.1 by investigators and sensitivity analysis based on data by BICR provided results consistent with investigator assessment. AEs, TTD and HRQoL could be affected by knowledge of intervention received, but seems unlikely. |
| | 4.5.: If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of the intervention received? | NA | NA | PN | PN | PN | |
| | **Risk of bias judgement** | **Low** | **Low** | **Some concerns** | **Some concerns** | **Some concerns** | **Some concerns for AE/ HRQoL outcome due to potential for knowledge of intervention received influencing outcome measurement; no concerns for other outcomes due to either being objective or having used BICR which generated consistent results** |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded | Y | Y | N | Y | Y | TTD was not a pre-specified outcome and it is not listed in the trial protocol. Other outcome data were analysed in line with a pre-specified statistical analysis plan, finalised 19 March 2019. |

| Domain | Signalling question | OS | PFS | TTD | AE | HRQoL (EQ- 5D-5L) | Comments |
|---|---|---|---|---|---|---|---|
| | outcome data were available for analysis? | | | | | | |
| | 5.2 Is the numerical result being assessed likely to have been selected on the basis of the results from: multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | PN | PN | PN | PN | PN | |
| | 5.3 Is the numerical result being assessed likely to have been selected on the basis of the results from: multiple eligible analyses of the data? | PN | PN | NI | PN | PN | |
| | **Risk of bias judgement** | **Low** | **Low** | **Some concerns** | **Low** | **Low** | **Some concerns regarding bias in the selection of the reported result for TTD because it was not a pre-specified trial outcome. No concerns for other outcomes.** |
| **Overall bias** | **Risk of bias judgement** | **Some concerns** | **Some concerns** | **High** | **Some concerns** | **Some concerns** | |

### 9.1.2 FLAURA2 risk of bias assessment, using RoB2 tool, for adhering to intervention

| **RoB2 assessments using adhering to intervention (the 'per-protocol' effect)** | | | |
|---|---|---|---|
| **Bias due to deviations from intended interventions** | 2.1 Were participants aware of their assigned intervention during the trial? | Y | Open label trial, in which participants and study personnel were aware of treatment assignment. |
| | 2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | Y | |
| | 2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes? | Y | At the start of the trial, 6 people did not receive treatment (unclear which groups these were from); these were excluded from the safety analysis. 30 patients in the intervention group did not complete study treatment due to adverse events, compared to 17 in the control group. |

| | | | |
|---|---|---|---|
| | 2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention? | N | Safety analysis was based on all those who received at least one dose of the intervention. |
| | **Risk of bias judgement** | **Some concerns** | |
| **Overall bias** | **Risk of bias judgement** | **Some concerns** | Overall risk of bias was some concerns due to some non-adherence to the assigned intervention and analysis based on all those who received at least one dose of study drug. |

For the safety analysis, it is more relevant to consider adherence to the intervention (the “per-protocol” effect). Domain 2 (Bias due to deviations from intended interventions) was therefore assessed separately for the effect of adhering to the intervention for the safety analysis

## 9.2 Appendix 2: ROBIS

### 9.2.1 ROBIS: systematic review of clinical effect[23]

| **DOMAIN 1: STUDY ELIGIBILITY CRITERIA** | |
|---|---|
| 1. Did the review adhere to pre-defined objectives and eligibility criteria? | Y |
| 2. Were the eligibility criteria appropriate for the scope? | Y |
| 3. Were eligibility criteria unambiguous? | Y |
| 4. Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | Y |
| 5. Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | Y |
| **Risk of bias judgement:** | Low |

**Rationale:**

- Whilst not initially provided, the review protocol does broadly align with the plan for review.
- The EAG noted that the NICE scope includes a broader range of comparators. The systematic review does not align with the NICE scope and the subsequent analysis is – if only conceptually – incomplete.
- The inclusion criteria align with the NICE scope. However, inclusion criteria – as set out in Doc B appendices - do not appear to have been followed as it relates to studies included in the review. The EAG questioned this in the clarification stage. Below the EAG clarification question and company response are copied for context:

  ***EAG clarification question:***
  *A4. The criteria for including interventions and comparators in the systematic review align with the decision problem as specified in the NICE scope, but are inconsistent with the decision problem as subsequently framed in the company submission (please see Clarification Table 1 below at end of document). Please can you clarify the reasons for this discrepancy? As the systematic review should underpin the selection of evidence presented in the company submission, please can you explain why the systematic review includes a broader range of comparators (aligning with the NICE scope) but that the evidence presented in the company submission focuses on a narrower comparison of osimertinib with pemetrexed and platinum-based chemotherapy versus osimertinib?*

  ***Company Response:***
  *The clinical systematic literature review (SLR) was initially conducted using broad inclusion criteria to assure that it sufficiently captured treatments available globally for the treatment of metastatic or locally advanced NSCLC and relevant data. After publication of the NICE scope final scope, the gathering of UK clinical insight, and the consideration of current clinical guidelines such as ESMO, the company concluded that osimertinib monotherapy was the only relevant comparator for the osimertinib plus chemotherapy regimen.[48],[49]*

- The SLR was limited in study identification to first line or EGFR type. Whilst this aligns with the scope, it could cause eligible studies which do not report treatment line to be missed. The searches were limited to English language. It would have been preferable to limit language of publication at study selection to ensure eligible non-English studies were identified even if not included.

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| **DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES** |
|---|

| | |
|---|---|
| 1. Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | Y |
| 2. Were methods additional to database searching used to identify relevant reports? | Y |
| 3. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | PY |
| 4. Were restrictions based on date, publication format, or language appropriate? | PY |
| 5. Were efforts made to minimize error in selection of studies? | PN |
| **Risk of bias judgement:** | **Low** |

**Rationale:**

- Searches were made of appropriate databases using suitable search terms.
- Searches were limited by treatment line OR EGFR mutation terms, which is undesirable, but does not appear to have omitted eligible studies. The search is also limited to English language and human only populations. Again, this is undesirable (best practice is to remove non-English language or animal studies at screening) but this does not appear to have impacted retrieval.
- Studies where the inclusion was unclear were excluded – it is unclear why study authors were not contacted to clarify inclusion/exclusion.

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| **DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL** | |
|---|---|
| 1. Were efforts made to minimize error in data collection? | Y |
| 2. Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | Y |
| 3. Were all relevant study results collected for use in the synthesis? | Y |
| 4. Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | Y |
| 5. Were efforts made to minimise error in risk of bias assessment? | Y |
| **Risk of bias judgement:** | Low |

**Rationale:**

- Data extraction criteria and methods of extraction were not provided within the original CS but were provided after clarification questions. The EAG were content with the explanation provided and revised the original ROBIS judgement of NI (no information) to Y (yes).
- Eligible studies as defined by the NICE scope appear to be missing. The EAG expressed concern about the completeness of studies included in questions for clarification.
- RoB was undertaken using a tool suggested by the NICE handbook. The EAG consider the RoB2 tool to be more appropriate as it appraises the risk of bias at the outcome level, thus highlighting any potential concerns for data in the decision model.

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| **DOMAIN 4: SYNTHESIS AND FINDINGS** | |
|---|---|
| 1. Did the synthesis include all studies that it should? | Y |

| | | |
|---|---|---|
| 2. | Were all pre-defined analyses reported or departures explained? | Y |
| 3. | Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | PY |
| 4. | Was between-study variation (heterogeneity) minimal or addressed in the synthesis? | N/A |
| 5. | Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | N/A |
| 6. | Were biases in primary studies minimal or addressed in the synthesis? | N/A |
| | **Risk of bias judgement:** | Low |

**Rationale:**
The company use a tighter inclusion criterion than specified by NICE in the final scope, resulting in the identification of only study and therefore precluding the possibility to undertake a network analysis or indirect treatment comparison.

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

### 9.2.2 ROBIS: systematic review of economic evaluations

| DOMAIN 1: STUDY ELIGIBILITY CRITERIA | |
|---|---|
| 1. Did the review adhere to pre-defined objectives and eligibility criteria? | Y |
| 2. Were the eligibility criteria appropriate for the scope? | Y |
| 3. Were eligibility criteria unambiguous? | Y |
| 4. Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | Y |
| 5. Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | Y |
| **Risk of bias judgement:** | Low |
| **Rationale for concern:** 1. Whilst not initially provided, the review protocol does broadly align with the plan for review. | |

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES | |
|---|---|
| 1. Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | Y |
| 2. Were methods additional to database searching used to identify relevant reports? | Y |
| 3. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | Y |
| 4. Were restrictions based on date, publication format, or language appropriate? | Y |
| 5. Were efforts made to minimize error in selection of studies? | Y |
| **Risk of bias judgement:** | **Low** |
| **Rationale for concern:** • searches were made of appropriate databases using suitable search terms. | |

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL | |
|---|---|
| 1. Were efforts made to minimize error in data collection? | Y |
| 2. Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | Y |
| 3. Were all relevant study results collected for use in the synthesis? | Y |
| 4. Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | Y |
| 5. Were efforts made to minimise error in risk of bias assessment? | Y |
| **Risk of bias judgement:** | Low |
| **Rationale for concern:** The company did not provide detail on the methods, tools, or process used to extract and appraise studies in the original CS. In clarification, the company provided the full-detail of the methods and tool used (Drummond Checklist). The EAG accepts that the review is of reasonable quality. | |

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| DOMAIN 4: SYNTHESIS AND FINDINGS | |
|---|---|
| 1. Did the synthesis include all studies that it should? | PY |
| 2. Were all pre-defined analyses reported or departures explained? | Y |
| 3. Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | Y |
| 4. Was between-study variation (heterogeneity) minimal or addressed in the synthesis? | N/A |
| 5. Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | Y |
| 6. Were biases in primary studies minimal or addressed in the synthesis? | N/A |
| **Risk of bias judgement:** | Low |
| **Justification for judgement**<br>Synthesis was appropriate given the aim of the review. | |

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

### 9.2.3 ROBIS assessment: company systematic review of HRQoL

| DOMAIN 1: STUDY ELIGIBILITY CRITERIA | |
|---|---|
| 1. Did the review adhere to pre-defined objectives and eligibility criteria? | PY |
| 2. Were the eligibility criteria appropriate for the scope? | Y |
| 3. Were eligibility criteria unambiguous? | Y |
| 4. Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | Y |
| 5. Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | Y |
| **Risk of bias judgement:** | Low |
| **Rationale for concern:** 1. Whilst not initially provided, the review protocol does broadly align with the plan for review. | |

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES | |
|---|---|
| 1. Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | Y |
| 2. Were methods additional to database searching used to identify relevant reports? | Y |
| 3. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | Y |
| 4. Were restrictions based on date, publication format, or language appropriate? | Y |
| 5. Were efforts made to minimize error in selection of studies? | Y |
| **Risk of bias judgement:** | **Low** |
| **Rationale for concern:** • searches were made of appropriate databases using suitable search terms. | |

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL | |
|---|---|
| 1. Were efforts made to minimize error in data collection? | Y |
| 2. Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | Y |
| 3. Were all relevant study results collected for use in the synthesis? | Y |
| 4. Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | Y |
| 5. Were efforts made to minimise error in risk of bias assessment? | Y |
| **Risk of bias judgement:** | Low |
| **Rationale for concern:** The company did not provide detail on the methods, tools, or process used to extract and appraise studies in the original CS. In clarification, the company provided the full-detail of the methods and tool used (Drummond Checklist). The EAG accepts that the review is of reasonable quality. | |

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

| DOMAIN 4: SYNTHESIS AND FINDINGS | |
|---|---|
| 1. Did the synthesis include all studies that it should? | N |
| 2. Were all pre-defined analyses reported or departures explained? | Y |
| 3. Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | Y |
| 4. Was between-study variation (heterogeneity) minimal or addressed in the synthesis? | N/A |
| 5. Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | Y |
| 6. Were biases in primary studies minimal or addressed in the synthesis? | N/A |
| **Risk of bias judgement:** | **HIGH** |

**Justification for judgement**

1. We are concerned that the OPAL study was not identified in the searches. Whilst we appreciate it is non-randomised, it is still a P2 trial and the searches and review should have accounted for this.

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

**Response to factual accuracy check and confidential information check**

# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

07/08/2024

[Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.]

**Issue 1 Number of annual A&E visits in the progressed disease state**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| • Page 69<br>The number of A&E visits reported does not reflect the actual model input, page 69: The EAG report states “The 17.16 average number of A&E visits per year assumed by the company for progressed disease were higher than might be seen in practice, they suggested on average 2 visits, and that there may be some A&E visits for those on chemotherapy in the progression-free health-state. ” This is also reported Table 11.<br>This value of 17.16 was a typo in the original company submission and was corrected in the company’s clarification question response. | The 17.16 annual A&E consultations should be corrected to 3.96 annual A&E consultations. | The number of A&E visits reported does not reflect the model input. | Thank you for spotting this. The EAG has corrected the text and table as requested. |

**Issue 2 Generalisability of findings to the NHS in England, considering currently available 2L and 3L treatments and patient demographics**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| • Page 21<br><br>The EAG comments state: "The company assume that patients will receive Atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP) at 2L, and that the proportions will be higher for osimertinib monotherapy. The EAG heard that ABCP is not often used for this patient group."<br><br>We believe that the current wording is misleading, as it omits evidence relating to ABCP usage in UK clinical practice. | The company request that the EAG expand on their statement, due to conflicting evidence, and amend the sentence as follows:<br><br>The EAG heard that ABCP is not often used for this patient group. However, ABCPs are licensed and reimbursed in this population (TA584), the clinicians consulted by the company as part of this appraisal said that ABCPs were omitted from the subsequent treatments. | This assumption does not accurately reflect NHS clinical practice based on licensing, reimbursement or clinical opinion submitted by the company. | The EAG did acknowledge the company's clinical advice on this issue in the main text (section 4.2.8.2) but have now edited p.21 to clarify this in the summary of Key Issue 10, and highlighted the uncertainty around ABCP use. We have reworded to:<br><br>"The company assumes that patients will receive Atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP) at 2L, and that the proportions will be higher for osimertinib monotherapy, based on expert opinion from the company's clinical advisors. The EAG however heard that only a small proportion of this patient group would be fit enough for ABCP at 2L. Also, the only differences in subsequent treatments expected between osimertinib plus chemotherapy and osimertinib monotherapy would be that pemetrexed would not be used at later lines following osimertinib plus chemotherapy at 1L. The EAG acknowledges that there is uncertainty around the proportion of patients receiving ABCP treatments at 2L, and incremental costs are sensitive to the assumed subsequent treatments at 2L." |

| | | | |
|---|---|---|---|
| | | | We further amended the rest of the key issue 10 table to later read:<br><br>"The EAG has presented scenarios with different distributions of subsequent treatments at 2L. In those that receive 2L treatment, Scenario 1a assumes 0% receive ABCP, and Scenario 1b assumes approximately 11% receive ABCP (compared with 15% for the company base-case)."<br><br>And later<br><br>" The deterministic ICER under the EAG's Scenario 1a is £40,029 and under Scenario 1b is £30,530, in comparison with £27,280 in the company's base-case."<br><br>The EAG has also clarified wording describing Scenario 1b in section 4.2.8.2 on p.68, and in the 1st column of Table 19.<br><br>Finally, the EAG has added an explanation of the choice of base-case and uncertainty around this in section 4.2.8.2 on p. 68:<br><br>"(...) We therefore ran a further scenario (Scenario 1b) where we assume 10% of patients that discontinue osimertinib monotherapy at 1L receive ABCP at 2L. Based on the proportions receiving 2L therapy from FLAURA this corresponds to a normalised proportion of 11% receiving ABCP in those having osimertinib at 1L and accessing 2L treatment. Assuming following osimertinib monotherapy at 1L, and that the |

| | | | |
|---|---|---|---|
| | | | proportions receiving ABCP out of those receiving 2L treatment does not differ between arms gives a normalised proportion of 11% receiving ABCP in those having osimertinib plus chemotherapy at 1L and accessing 2L treatment (Table 10). The EAG assumes no patients access ABCP at 2L (Scenario 1a) in its base-case but acknowledge that this is likely an underestimate, and the reality is likely to lie between Scenarios 1a and 1b.” |

**Issue 3 Model convergence**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| • Page 75<br>The convergence of the ICER in the PSA was evaluated by visually inspecting the ICER convergence plot within the Excel model. The company have re-run the model and after 200 simulations, fluctuations around the mean probabilistic ICER were approximately within £1,000-£2,000 per QALY, therefore it was considered convergence had occurred from this simulation onwards. The convergence plot in the EAG report suggests that the number of model runs required for the ICER to stabilise is much higher, this does not reflect the model. | The company propose that the convergence plot from the company submission is used, as this is pulled directly from the model, and the EAG convergence plot is discarded. | When re-running the model, convergence is observed after the 200th simulation. The plot in the EAG report does not reflect the current model and may therefore be incorrect. | Figure 6 in the report is a copy of the convergence results provided by the company after the corrected version of the model was provided in response to EAG's B7 clarification question. This is not a figure resulting from the EAG running the company's model, but a figure provided by the company.<br>The EAG's report has a different formatting scheme which changed the colour of the figure and the aspect ratio when copying, which may have caused confusion to the company.<br>The EAG has now elongated the aspect ratio to include the same axis markings which show the 200$^{th}$ iteration. The EAG further clarifies the figure title:<br>"Figure 6: Conversion of ICER of company reported (provided by company in the company model after clarification questions)" |

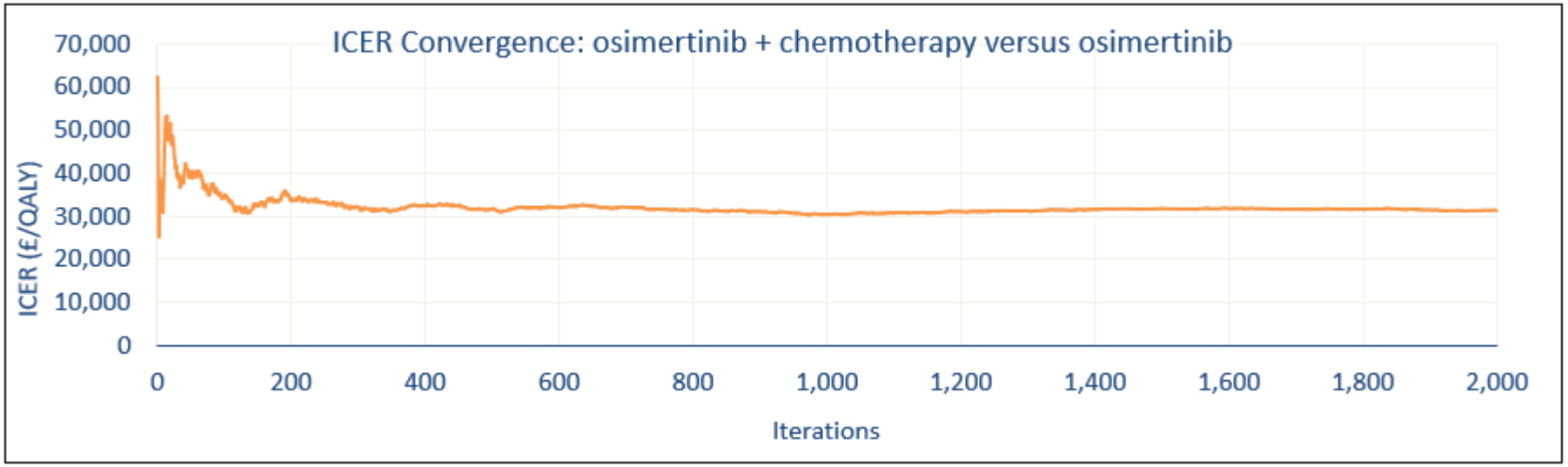


*Figure 1: ICER Convergence plot*

**Issue 4 Clarification of location of an error**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| • Page 22<br>The EAG states that they "identified an error in the formulae for the 2-knot spline on the odds scale for OS in the osimertinib plus chemotherapy group, which it corrected." | Please could the EAG clarify the location of this error. | The company are able to reproduce ICERs detailed within the EAG report using the current version of the model, therefore it is unclear what error was corrected by the EAG. | The EAG explains how to correct this error in section 5.3 of the EAG report. By changing the formula in cell U4 of 'Extrapolation data' to<br>'=(spline("odds",2,'Clinical_data (PSM + TTD)'!AE$7:AE$10,'Clinical_data (PSM + TTD)'!AE$12:AE$15,'Clinical_data (PSM + TTD)'!AE$17,$B$4:$B$249))'<br>the spill formula will update the formulas for the rest of column U.<br>Currently the formulae in column U are identical to the formulae for the 1-knot spline model on the odds scale in column T.<br>The company is able to reproduce the ICERs because in their base case the company does not use the 2-knot spline. However, the correction is required when the 2-knot spline is selected. |

| Location of incorrect marking | Description of incorrect marking | Amended marking |
|---|---|---|
| No incorrect marking identified | | |
| | | The EAG has taken the opportunity to correct typos throughout the report, mostly on subject-verb discordance. |

NICE National Institute for Health and Care Excellence

**Single Technology Appraisal**

# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

**Clinical expert statement**

## Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

# Part 1: Treating EGFR mutation-positive advanced non-small-cell lung cancer and current treatment options

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

| | |
|---|---|
| **1. Your name** | Dr Shobhit Baijal |
| **2. Name of organisation** | British Thoracic Oncology Group |
| **3. Job title or position** | Consultant Medical Oncologist |
| **4. Are you (please tick all that apply)** | ☒ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with EGFR mutation-positive advanced non-small-cell lung cancer?<br>☒ A specialist in the clinical evidence base for EGFR mutation-positive advanced non-small-cell lung cancer or technology?<br>☐ Other (please specify): |
| **5. Do you wish to agree with your nominating organisation's submission?**<br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☐ Yes, I agree with it<br>☐ No, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ Other (they did not submit one, I do not know if they submitted one etc.) |
| **6. If you wrote the organisation submission and/or do not have anything to add, tick here.**<br>(If you tick this box, the rest of this form will be deleted after submission) | ☐ Yes |
| **7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | n/a |

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| **8. What is the main aim of treatment for EGFR mutation-positive advanced non-small-cell lung cancer?**<br>(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability) | Prolong survival and maintain / improve quality of life |
| **9. What do you consider a clinically significant treatment response?**<br>(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount) | Clinically meaningful prolongation in efficacy outcomes compared with standard of care<br>(PFS / OS greater than 3 months) |
| **10. In your view, is there an unmet need for patients and healthcare professionals in EGFR mutation-positive advanced non-small-cell lung cancer?** | yes |
| **11. How is EGFR mutation-positive advanced non-small-cell lung cancer currently treated in the NHS?**<br>• Are any clinical guidelines used in the treatment of the condition, and if so, which?<br>• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)<br>• What impact would the technology have on the current pathway of care? | Treatment options are driven by what is reimbursed.<br>The accepted standard of care first line treatment is Osimeritnib |
| **12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?**<br>• How does healthcare resource use differ between the technology and current care? | The current technology will combine intravenous chemotherapy to the standard of care (oral drug) – which will have resource implications.<br>Treatment will need to be delivered in a chemotherapy day unit<br><br>It is unlikely investment will be needed to absorb the increased demand as the patient population is relatively rare |

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| • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)<br>• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) | |
| **13. Do you expect the technology to provide clinically meaningful benefits compared with current care?**<br>• Do you expect the technology to increase length of life more than current care?<br>• Do you expect the technology to increase health-related quality of life more than current care? | Yes I expect it to improve survival for this population<br><br>There is likely to be a trade off against increased toxicity for the technology |
| **14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | For patients with EGFR mutated advanced NSCLC |
| **15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?**<br>(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed) | There are greater considerations for toxicity management, but manageable by HCP's |
| **16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | Treatment would be discontinued on loss of clinical benefit or unmanageable toxicities |

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| **17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?**<br>• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care | n/a |
| **18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?**<br>• Is the technology a 'step-change' in the management of the condition?<br>• Does the use of the technology address any particular unmet need of the patient population? | Based on the trial efficacy outcomes – yes this is a step-change |
| **19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | This will need to be considered in treating patients with the combination as the chemotherapy component will add a toxicity burden |
| **20. Do the clinical trials on the technology reflect current UK clinical practice?**<br>• If not, how could the results be extrapolated to the UK setting?<br>• What, in your view, are the most important outcomes, and were they measured in the trials?<br>• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? | Yes<br><br>PFS data |

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| • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | |
| **21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | no |
| **22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [TA761]?** | no |
| **23. How do data on real-world experience compare with the trial data?** | n/a |
| **24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.<br>Please state if you think this evaluation could<br>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation | n/a |

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| • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population<br>• lead to recommendations that have an adverse impact on disabled people.<br>Please consider whether these issues are different from issues with current care and why.<br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme.<br>Find more general information about the Equality Act and equalities issues here. | |

## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The PFS benefit seen in the trial is clinically substantial and meaningful

This is a treatment option that should be available to our EGFR positive NSCLC patients

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

## Your privacy

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

## Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

## Information on completing this form

In part 1 we are asking you about living with EGFR mutation-positive advanced non-small-cell lung cancer or caring for a patient with EGFR mutation-positive advanced non-small-cell lung cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

### Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 6 September.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

**We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

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Patient expert statement

Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

# Part 1: Living with this condition or caring for a patient with EGFR mutation-positive advanced non-small-cell lung cancer

**Table 1 About you, EGFR mutation-positive advanced non-small-cell lung cancer, current treatments and equality**

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| **1. Your name** | [redacted] |
| **2. Are you (please tick all that apply)** | ☐ A patient with EGFR mutation-positive advanced non-small-cell lung cancer?<br>☐ A patient with experience of the treatment being evaluated?<br>☒ A carer of a patient with EGFR mutation-positive advanced non-small-cell lung cancer?<br>☐ A patient organisation employee or volunteer?<br>☐ Other (please specify): |
| **3. Name of your nominating organisation** | |
| **4. Has your nominating organisation provided a submission? (please tick all options that apply)** | ☐ No (please review all the questions and provide answers when possible)<br>☐ Yes, my nominating organisation has provided a submission<br>☐ I agree with it and **do not wish to** complete a patient expert statement<br>☐ Yes, I authored / was a contributor to my nominating organisations submission<br>☐ I agree with it and **do not wish to** complete this statement<br>☐ I agree with it and **will be** completing |

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| **5. How did you gather the information included in your statement? (please tick all that apply)** | ☒ I am drawing from personal experience<br>☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:<br>☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference<br>☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference<br>☐ I have not completed part 2 of the statement |
| **6. What is your experience of living with EGFR mutation-positive advanced non-small-cell lung cancer?**<br>**If you are a carer (for someone with EGFR mutation-positive advanced non-small-cell lung cancer) please share your experience of caring for them** | My wife was diagnosed with stage 4 non-small-cell lung cancer in early 2017 though she had been ill with increasingly high levels of back pain and persistent chest infections from around September 2016, around the time I had major heart surgery myself. She was registered disabled from corrective surgery to remove multiple tumours in her spine so mobility was a huge issue for her. As the disease advanced, the tumours metastasised to her brain and bones. But her main issue from the beginning was depression and anxiety which kicked in almost immediately after diagnosis. She increasingly suffered from crying, reclusiveness, agoraphobia, anxiety, loss of hope and inability to engage with the people who loved her. Our son also has a chronic health condition; unfortunately he was only 15 when she was diagnosed, and the impact of her suffering on him was, and still is, enormous. The diagnostic process was traumatic and is a useful background: I took her to our local casualty on a Saturday in January 2017 unable to walk, sit or lie without severe pain but even though we eventually found out her back was broken in several places we were discharged and told to arrange an appointment with her GP on the Monday. I refused to accept that and took her then to another hospital who admitted her straight away. After a week or so, they diagnosed spinal secondaries and she was transferred to a world renowned spinal unit in a different hospital, where a team of surgeons rebuilt her spine. She was discharged home- now disabled - after two and a half months in hospital. I believe our appalling experience in that A&E department had a detrimental and long lasting impact on her mental health and |

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| | quality of life, which indirectly affected what she got out of her treatments. We experienced both the best and the worst of the NHS on that long and difficult journey. She died in a hospice on Friday September 13, 2019 spending two and half months there.<br>Though I was working full-time, I was able to do that from home so I could attend to her needs. That included a wide variety of things such as lifting objects she couldn't pick up, helping her walk, washing, shopping, cooking, cleaning, taking our son to school, ordering and giving her medication, driving her to multiple appointments, advocating for her in and out of hospital, handling her state benefits, trying to help her psychologically, being in constant touch with our GP; traveling to the hospital or hospice when she was an impatient, loading her pill tray; the list goes on.<br>She was unable to walk upstairs to the bathroom, so with the help of a crowdfunding campaign I organised, we raised enough money to build a garden room with a shower, sink and toilet which was extremely helpful. Overall, caring for her was shattering and all-consuming, especially while trying also to look after our son. I suffered from the physical manifestations of anxiety - including dizziness, visual disturbance, eczema - as a result of what we were going through. Needless to say it was difficult to fulfil my obligations at work, but thankfully, my employers were incredibly understanding.<br>My wife was forced to give up work in the first three months after diagnosis. She was also forced to give up her passion for gardening - and we vacated our allotment early on in her illness.<br>In summary, my wife's overall quality of life was adversely affected by her difficulty in walking, severe pain in her back, constipation caused by morphine tablets, difficulty caring for herself, anxiety and depression and her dependence on me for many of her everyday needs. |

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| **7a. What do you think of the current treatments and care available for EGFR mutation-positive advanced non-small-cell lung cancer on the NHS?**<br>**7b. How do your views on these current treatments compare to those of other people that you may be aware of?** | I am only am only aware of the treatments my wife received and they are, in my view, a two-edged sword. On diagnosis, she was given a few months to live, but after spinal surgery and the targeted therapies of first gefitinib and then osimertinib, she lived for 2 years and 8 months after diagnosis; far longer than her doctors expected.<br>The ease by which the drugs were taken – merely a tablet every day- was extremely helpful and meant we did not need visit to hospital as often.<br>The gefitinib shrank her tumours, but stopped being effective after 18 months. The osimertinib was effective for perhaps 8 months. While the tumours were shrinking, she was able to self-care a little more – perhaps heating some soup, or washing herself. She was unable to use a bath but could use the shower in the garden room we had built. This became increasingly more difficult as the drugs started to fail and the tumours started to grow and spread. But she was never able to return to anything remotely like her previous life of going to work, gardening, going out with friends and so on.<br>As there is so little hope for people diagnosed with later stage NSCLC, the fact that there are drug treatments at all is incredibly important. I remember the elation we felt when we discovered that my wife was genetically compatible with the therapies she was given. However, these treatments should in my view be given alongside advocacy, counselling and psychological support, as well as honest and detailed information about management of side-effects and drug efficacy for this incredibly vulnerable group of patients. In my view, the terminally ill are the most vulnerable group of patients the NHS cares for. Their needs, especially their psychological needs, are so often left unmet.<br>It was clearly positive that she lived to see our son's sixteenth and seventeenth birthdays, and witnessed him getting into college to study science. Precious moments we will treasure. We managed to go away on holiday twice, though by the second holiday her agoraphobia and diarrhoea were so severe, so never left the cottage. |

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| **8. If there are disadvantages for patients of current NHS treatments for EGFR mutation-positive advanced non-small-cell lung cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these** | Though the drug therapies extended my wife's life expectancy, her quality of life was increasingly poor, though I suspect this was mostly as a result of her condition, not side-effects from the drugs. However, the side effects were sometimes difficult: severe diarrhoea at times being the worst, but loss of appetite too. Itching and a skin rash affected her but her precarious mental health meant she used the medication as an excuse to avoid sunlight and stay indoors. She seemed, for example, to fixate on various skincare products which she believed were unsafe to use while taking the medication, when I'm not sure there is much evidence for that. I often felt it might cheer her up if she had a small gin as she had enjoyed a 'drink' in happier times, though I was not able to convince her to do that, despite reassurances from her clinicians and I suspect that distorted concerns over the side effects of the drugs were a factor in this. Indeed, I sometimes found it difficult to be able to distinguish between genuine and perceived side-effects because her mental health was so precarious. She received little if no meaningful psychological care which might have made her final few years easier and perhaps derive more benefit from the medication.<br>Both the gefitinib and osimertinib were prescribed after hospital visits, entailing long waits at our hospital pharmacy, which were exhausting for both me and my wife. However, we discovered we could wait for the drugs to be dispensed at a Maggies centre nearby, a wonderfully welcoming place and so unlike anything we'd seen before in the health system.<br>It would be helpful for sick and terminally ill patients to be prioritised in pharmacies so they do not have to wait too long, or at least can wait in comfort. She found it easy to swallow the tablets, but was increasingly confused about when and which tablets to take. She took at least 30 pills day, so explanation and support on taking any medication is essential. |
| **9a. If there are advantages of osimertinib with pemetrexed and platinum-based chemotherapy over current treatments on the NHS please describe these.** | The reassurance that this combination will extend a patient's life by a significant period of time, compared to osimertinib alone, will clearly be important for many patients. If the tumours are held at bay for longer, then there will presumably be a |

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| **For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?**<br>**9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**<br>**9c. Does osimertinib with pemetrexed and platinum-based chemotherapy help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these** | positive impact on the ability for patients to care for themselves and to feel more independent - though I would be very surprised if patients would be able to do things like return to work, or carry out any physical activities such as gardening based on my experience. |
| **10. If there are disadvantages of osimertinib with pemetrexed and platinum-based chemotherapy over current treatments on the NHS please describe these.**<br>For example, are there any risks with osimertinib with pemetrexed and platinum-based chemotherapy? If you are concerned about any potential side effects you have heard about, please describe them and explain why | As the side effects of Osimertinib were already debilitating for my wife, it is clear from the supporting literature that the adjunctive chemotherapies would worsen an already difficult situation. Impact on appetite, constipation fatigue, vomiting, dry skin all seem to be significantly more difficult with this new regime, however, I note that diarrhoea seems to be only slightly more of an issue for patients. These side effects make it difficult to, for example, self-care, enjoy food, go out socially, or take part in enjoyable activities which in my experience increased my wife's reclusive and detached behaviour.<br>Osimertinib with pemetrexed and platinum-based chemotherapy would be likely to involve longer visits to hospital, potentially more frequently. I found the hospital visits incredibly tiring and draining as did my wife so this is also potentially a major drawback.<br>Though having this treatment combination as an option for patients is positive, it needs to be absolutely clear to patients that quality of life may not improve for everyone. It seems to me that this regime could be extremely debilitating for many patients so they would need to be given full information before deciding to go ahead. |

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| **11. Are there any groups of patients who might benefit more from osimertinib with pemetrexed and platinum-based chemotherapy or any who may benefit less? If so, please describe them and explain why**<br>Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments | Unable to answer this question |
| **12. Are there any potential equality issues that should be taken into account when considering EGFR mutation-positive advanced non-small-cell lung cancer and osimertinib with pemetrexed and platinum-based chemotherapy? Please explain if you think any groups of people with this condition are particularly disadvantage**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics<br><br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br>Find more general information about the Equality Act and equalities issues here. | Older people potentially, who have difficulty using public transport or driving to treatment. |
| **13. Are there any other issues that you would like the committee to consider?** | It was hard for me to ascertain if the data in the literature showed equal effects for men and women. Also, it would be useful to know what the effect of the combination was on the size of tumours, and the rate of metastasis over time. |

## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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