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Ludwig Boltzmann Institut
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The HTA Core Model® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model® does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model

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Abstract

Introduction

The epidermal growth factor receptor (EGFR), a transmembrane receptor with tyrosine kinase activity, regulates cellular proliferation. In a subset of non-small cell lung cancers (NSCLC), gatekeeper mutations in the EGFR kinase domain induce constitutive activation of the receptor causing uncontrolled cell growth. Osimertinib, an irreversible third-generation EGFR tyrosine kinase inhibitor (EGFR-TKI), prevents cell cycle progression by selectively targeting both EGFR-TKI-sensitizing mutations and EGFRT790 resistance mutations, while sparing wild-type EGFR function.

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer. Quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for randomized controlled trials. Furthermore, the magnitude of clinically meaningful benefit that can be expected from osimertinib was evaluated based on, both the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology.

Results of the FLAURA trial

In the phase III, FLAURA study 556 patients with untreated advanced EGFR-mutated NSCLC were randomised 1:1 to osimertinib or standard of care (SoC) until disease progression or unacceptable toxicity. Compared with SoC EGFR-TKIs, osimertinib increased investigator-assessed median progression-free survival (PFS) by 8.7 months, and lowered the risk of disease progression or death by 54%. The PFS benefit was consistent across subgroups regardless of Asian or non-Asian race, Ex19del or L858R EGFR subtype, and presence or absence of central nervous system (CNS) metastases. Overall survival (OS) data were immature at interim analysis; however, 83% of osimertinib patients and 71% of SoC patients achieved 18-month survival. Grade ≥3 AEs were less common in the osimertinib group compared to SoC (34% versus 45%); however, decreased appetite (3%), pneumonia (2%), diarrhoea (2%), and prolonged QTc (2%) were most common. Cardiac and lung effects occurred more frequently in the osimertinib group than in the SoC group (10% and 4% versus 5% and 2%, respectively); notably cardiac failure (4%), prolonged QTc interval (10%), and interstitial lung disease (4%).

Conclusion

Overall, FLAURA is the first phase III, randomized, double-blind, comparative trial to demonstrate that osimertinib substantially increases PFS and lowers the risk of disease progression compared to first-generation EGFR-TKI as initial therapy for EGFR-mutated advanced NSCLC. The PFS benefit was consistent across subgroups regardless of race, EGFR subtype, and presence of CNS metastases. OS and quality of life data are needed to confirm patients achieve a clinically relevant benefit over time despite favourable tolerability. Currently, the optimal therapeutic sequencing of different generations of EGFR-TKI remains unknown. Further analyses are necessary to fully characterize the resistance mechanisms to osimertinib for targeting by fourth-generation inhibitors. A new class of inhibitors, designed to target a triple mutation thought to confer resistance to fourth-generation EGFR-TKIs, is also under development.

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1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is osimertinib?
A0022	Who manufactures osimertinib?
A0007	What is the target population in this assessment?
A0020	For which indications has osimertinib received marketing authorisation?
Health problem and current use	
A0002	What is NSCLC?
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A0023	How many people belong to the target population?
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Clinical effectiveness	
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D0005	How does osimertinib affect symptoms and findings (severity, frequency) of NSCLC?
D0006	How does osimertinib affect progression (or recurrence) of NSCLC?
D0011	What is the effect of osimertinib on patients' body functions?
D0012	What is the effect of osimertinib on generic health-related quality of life?
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Safety	
C0008	How safe is osimertinib in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying osimertinib?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of osimertinib?
A0021	What is the reimbursement status of osimertinib?

2 Drug description

Generic/Brand name/ATC code:

Osimertinib/Tagrisso®/AZD9291

B0001: What is osimertinib?

third-generation EGFR-TKI

The epidermal growth factor receptor (EGFR), a transmembrane receptor with tyrosine kinase activity, regulates cellular proliferation. In a subset of non-small cell lung cancers (NSCLC), gatekeeper mutations in the EGFR kinase domain induce constitutive activation of the receptor resulting in uncontrolled cell growth. Osimertinib, an irreversible third-generation EGFR tyrosine kinase inhibitor (EGFR-TKI), prevents cell cycle progression by selectively targeting both EGFR-TKI-sensitizing mutations and EGFRT790M resistance mutations, while sparing wild-type EGFR function.

80 mg orally once daily

Osimertinib is administered as an 80 mg oral tablet taken once daily, with or without food, until disease progression or unacceptable toxicity. Patients who have difficulty swallowing may disperse the tablet in two ounces of non-carbonated water [2].

monitor cardiac and keratitis risks; reduce/ interrupt/ discontinue for safety/ tolerability

Patients with congenital or drug-induced long heart rate-corrected QT (QTc) interval, congestive heart failure, or electrolyte abnormalities should undergo periodic electrocardiogram (ECG) and electrolyte monitoring. Baseline and periodic cardiac monitoring, including left ventricular ejection fraction (LVEF) assessment, is required for patients with cardiac risk factors. Patients with symptoms of keratitis should be referred to an ophthalmologist. Dose interruption, reduction (40 mg), or discontinuation may be necessary in patients that develop interstitial lung disease (ILD) or pneumonitis, prolonged QTc interval, symptomatic congestive heart failure (CHF), or intolerance due to adverse events (AEs). Patients should avoid concomitant use of strong CYP3A inducers; if this is not possible, they should have their osimertinib dose increased to 160 mg when using strong CYP3A4 inducers [2].

A0022: Who manufactures osimertinib?

AstraZeneca

3 Indication

A0007: What is the target population in this assessment?

previously untreated EGFRm-positive advanced NSCLC

Osimertinib is indicated as initial therapy for patients with previously untreated epidermal growth factor mutation-positive (EGFRm) advanced non-small cell lung cancer (NSCLC) [3].

4 Current regulatory status

A0020: For which indications has osimertinib received marketing authorisation?

In November 2015, the US Food and Drug Administration (FDA) granted accelerated approval of osimertinib for EGFR-TKI-pre-treated advanced EGFRT790M-positive NSCLC along with the companion diagnostic test (Cobas® EGFR Mutation Test v2, Roche Molecular Systems) used to detect tumour EGFRT790M. Initial approval was based on the objective response rate (ORR) reported in two phase II, single-arm, open-label, clinical trials, AURA and AURA2 [4-7]. In September 2016, the Cobas® EGFR Mutation Test v2 received a label extension for use with plasma samples. In March 2017, osimertinib was granted full approval based on the results of the confirmatory phase III AURA3 trial [5, 8].

FDA: licensed for EGFR-TKI-pre-treated advanced EGFRT790M-positive NSCLC in November 2015

In December 2017, the FDA granted priority review to a supplemental new drug application (sNDA) for the use of osimertinib as first-line treatment for patients with advanced NSCLC whose tumours have EGFR exon 19 deletions (Ex19del) or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. In April 2018, osimertinib received approval for this indication based on results of the phase III FLAURA trial [3, 9].

FDA: licensed first-line for advanced EGFR-mutated NSCLC in April 2018

Based on results of the AURA and AURA2 trials, osimertinib received conditional marketing authorisation by the European Medicines Agency (EMA) in February 2016, for EGFRT790M-positive NSCLC, irrespective of previous EGFR-TKI treatment, as determined by a validated diagnostic test on a tumour sample or blood-based circulating tumour DNA (ctDNA) [5]. Full marketing authorisation was issued for this indication in April 2017, following results of the AURA3 trial [10]. In November 2017, the EMA accepted a variation to the marketing authorization application (MAA) for osimertinib as first-line treatment for EGFR-mutated NSCLC [11]. While osimertinib is not approved in Europe for the first-line setting, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation of osimertinib in April 2018 [12].

EMA: MAA for first-line treatment of EGFR-mutated NSCLC in November 2017; CHMP adopted a positive opinion in April 2018

5 Burden of disease

A0002: What is NSCLC?

NSCLC is the most common epithelial lung cancer and accounts for approximately 80–85% of all lung cancers. Adenocarcinoma, the most frequent histological type, has a survival rate of approximately 4–6% at five years [13-15]. EGFR-mutated tumours are typically characterized by air bronchogram, pleural retraction, small lesion size, and the absence of fibrosis [16]. Somatic EGFR mutations are found in up to 40% of Asian patients and 10–15% of Caucasian patients with lung adenocarcinoma [17, 18].

NSCLC accounts for 80–85% of all lung cancers; EGFR-mutations in 15–20% of adenocarcinomas

85–90% of EGFR mutations are Ex19del and L858R; confers sensitivity to TKIs

EGFRT790M confers acquired resistance to first-line EGFR-TKIs

EGFR mutations cluster in the region encoding the adenosine triphosphate-binding pocket of the kinase domain, exons 18 to 21, inducing constitutive activation of the receptor. Approximately 85–90% of all EGFR mutations are due to the in-frame exon 19 deletion (Ex19del) (45%) and the exon 21 point mutation (L858R) (40–45%), that substitutes arginine for leucine at position 858 [5, 16]. Commonly referred to as sensitizing mutations, they confer sensitivity to TKIs. While activating EGFR mutations in NSCLC are predictive of progression-free survival (PFS) and tumour response, EGFR-TKI-treated patients inevitably develop resistance and disease progression [16, 19]. Approximately 50–60% of known acquired resistance to first-line EGFR-TKIs is due to the EGFRT790M mutation, where threonine is substituted with methionine at position 790 in exon 20, impairing the binding of first-generation TKIs to the ATP-kinase binding pocket. Osimertinib, a third generation EGFR-TKI, was developed specifically to target the EGFRT790M [20]. Unlike first-generation EGFR-TKIs that reversibly inhibit EGFR, irreversible third-generation osimertinib has an acrylamide Michael acceptor that covalently bonds the EGFR C797 residue and circumvents the sterically hindered T70M substitution, allowing enhanced drug-kinase complex formation [5, 16].

A0004: What is the natural course of NSCLC?

staged I-IV by invasiveness

metastasizes to bone, liver, brain, lymph nodes

Lung cancer typically arises when epithelial cells lining the bronchial tubes undergo aberrant cell growth. To facilitate treatment, lung cancer is staged from I through IV based on tumour size, and presence or absence of lymph node involvement and metastases (TNM). Stage I lung cancer is <3 cm and localized to one lobe; stage II has spread to other parts of the lung or lymph nodes; stage III may be large or spread to lymph nodes between the lungs; and stage IV has metastasized to the adjacent bones, lung, brain, liver or any other organ.

A0006: What are the consequences of NSCLC for the society?

52–58% present with advanced cancer; relapse and metastasize

activating EGFR mutations confer favourable prognosis

Lung cancer is the second most commonly diagnosed cancer. While the implementation of smoking cessation programs and multidisciplinary treatments have reduced the incidence and mortality, 52–58% of lung cancer patients present with advanced-stage disease when curative treatment is no longer feasible. While demographic analyses suggest that adenocarcinoma histology, female gender, older age, non-smoking status, and Asian ethnicity are associated with better outcomes, they are surrogate markers for the presence of activating EGFR mutations (exon 19 deletion, L858R point mutation in exon 21) that are strong predictors of EGFR-TKI-responsiveness and prognosis [16, 21, 22].

A0023: How many people belong to the target population?

4,860 Austrians were diagnosed with NSCLC in 2015

EGFR-mutated NSCLC incidence in Europe: 10–15%

Lung cancer is the leading cause of cancer-related death in men and the second in women worldwide. The age standardized incidence rate for the European Standard Population was 57.9 per 100,000 persons per year in 2015. In Austria, 2,956 men and 1,904 women were diagnosed with lung cancer. It was the second most common cancer in men and women (12% of all cancers) [23]. Approximately 6.5% of people will be diagnosed with lung cancer during their lifetime and approximately one-third of patients with NSCLC have a stage III presentation. Assuming this, about 1,620 patients in Austria

(2015) had stage III NSCLC at the time of diagnosis. EGFR-mutated NSCLC accounts for approximately 10–15% of NSCLC patients in Europe, 30–40% in Asia, and 7–8% in North America [13]; and is diagnosed at a median age of 64 years (range 26-93) [3, 22].

A0005: What are the symptoms and the burden of disease or health condition?

NSCLC symptoms: cough, chest pain, weight loss, shortness of breath

Many lung cancers are not symptomatic until they have spread. Symptoms of NSCLC include incessant cough, bloody sputum, chest pain, wheezing or hoarseness, weight loss or loss of appetite, shortness of breath, fatigue, and recurrent bronchitis or pneumonia. Lung cancer may metastasize to bone, brain, liver or lymph nodes causing pain, headaches, improper balance, seizures, jaundice or lumps near the body's surface [14].

A0003: What are the known risk factors for NSCLC?

risk factors: non-smokers, female gender, Asian ethnicity, increasing age

Overall, the risk of lung cancer increases with age, tobacco use, radiation exposure, air pollution, and occupational exposure to asbestos, arsenic, chromium beryllium, nickel, second-hand smoking and other agents. The risk of developing lung cancer is typically tenfold higher in smokers compared to lifetime non-smokers [14]. However, the proportion of EGFR-mutated lung cancer is 32–64% in never smokers versus 6–33% in smokers; 22–60% in women versus 8–37% in men; 30–40% in Asians versus 10–15% in Caucasians; and 66% in those >50 years versus 57.8% in patients <50 years [13, 22].

A0024: How is NSCLC currently diagnosed according to published guidelines and in practice?

diagnosis: x-ray, CT and biopsy

While some lung cancers may be found through screening, most are identified when they become symptomatic. Following a clinical history and physical exam, a chest x-ray may be done to identify any abnormal areas in the lungs. A computed tomography (CT) scan may show the size, shape and location of any lung tumours or enlarged lymph nodes, and guide a needle biopsy if a suspected area is identified. Lung cancer is diagnosed by examining cells derived through biopsy, cytology or sputum sampling for the presence of cancer cells.

activating EGFR mutation status: PCR-based assessment of tissue or blood samples

Several polymerase chain reaction (PCR)-based platforms are available to assess tumours for the presence of activating EGFR mutations [20, 24]. Mutation analysis is typically performed on tissue samples from biopsy; however, circulating tumour cells (CTC) are collected non-invasively through liquid biopsy when tissue samples are inadequate. Circulating tumour DNA (ctDNA) analysis is a validated method of liquid biopsy that identifies tumour fragments within plasma. Strategies developed to enhance the sensitivity of ctDNA analysis include the amplified refractory mutation system (ARMS), digital PCR, PCR clamping, denaturing high performance liquid chromatography (DHPLC) and next generation sequencing (NGS). Commercially available kits such as the Roche Cobas® EGFR mutation tests (v1 and v2) and the QIAGEN therascreen EGFR Rotor-Gene Q PCR kit use ARMS to detect up to 1–5% of mutant DNA on a background of wild-type DNA. Digital droplet PCR (ddPCR) and Beads, Emulsions, Amplification and Magnetics (Beads) further increase the sensitivity of detection of mutant DNA to a threshold of 0.01–0.03% using a combination of digital PCR and flow cytometry. Cancer Personalized Profiling by deep Sequencing (CAPP-Seq), a NGS-based method, detected ctDNA in 100% of stage II-IV NSCLC patients and 50% of stage I patients with 96% specificity for the mutant allele to a threshold of 0.02% [20].

companion diagnostic: detects mutant DNA versus wild-type at 5% sensitivity

6 Current treatment

A0025: How is NSCLC currently managed according to published guidelines and in practice?

treatment by stage: surgery, radiation therapy, chemotherapy

Depending on the tumour stage, histology, and the patients' overall health, surgery, radiation therapy and/or platinum-based chemotherapy may be used alone or in combination to treat NSCLC. Treatment per NSCLC stages involves the following options [25]:

- Stage I and II NSCLC patients typically undergo surgery to remove the cancer. Stage II patients and a subset of patients with stage Ib tumours may benefit from postoperative adjuvant chemotherapy.
- Patients with stage I or II cancers that are not surgical candidates, due to co-morbidities or limited lung function, may undergo local radiation therapy.
- Stage III NSCLC patients are highly heterogeneous and may undergo a combination of treatment modalities including chemotherapy and radiation and/or surgery depending on the extent and localization of disease.
- Patients with stage IV disease are treated with systemic therapy or a symptom-based palliative approach.

stage III NSCLC

In appropriately selected patients, chemotherapy, molecularly targeted therapy, and/or immunotherapy may be used to treat stage III NSCLC [24]:

- While the optimal chemotherapy regimen for use with concurrent radiotherapy is not known, cisplatin plus etoposide, carboplatin, or vi-

norelbine and placlitaxel are commonly used. The combination of pemetrexed and cisplatin has also emerged as an option for stage III patients with non-squamous histology.

- The standard dose fractionation regimen of radiotherapy with chemotherapy for stage III NSCLC is 60 Gy in 30 daily fractions. Intensity modulated radiation therapy is preferred over 3D radiotherapy due to the reduced risk for pneumonitis.
- Patients with ALK translocations benefit from crizotinib, ceritinib, alectinib, lorlatinib or brigatinib therapy. First-line therapy for ROS1-translocated NSCLC is crizotinib; cabozantinib, ceritinib or lorlatinib may be effective for crizotinib-resistant cancers. First-line therapy for stage IV patients with BRAF V600E is combination dabrafenib plus trametinib.

targeted therapies

- Pembrolizumab, nivolumab, and atezolizumab block PD-L1 on T-lymphocytes and are used as second-line therapies for advanced NSCLC. Durvalumab is the first FDA-approved treatment for stage III unresectable NSCLC, but it is not yet approved in Europe [26].
- NSCLC patient with genetic alterations in EGFR may benefit from TKIs such as first generation erlotinib or gefitinib, or second-generation afatinib. Third generation TKI osimertinib also targets the EGFRT790M mutation associated with acquired resistance to EGFR-TKIs. However, osimertinib is not approved in Europe for the first-line setting, but the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation of osimertinib [12].

7 Evidence

A literature search was conducted on 05 April 2018 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “osimertinib”, “tagrisso”, “l01xe35”, “non small cell lung cancer”, “NSCLC”, “first line”, “untreated”, and “initial”. The manufacturer was also contacted and submitted a reference and a supplemental appendix that had already been identified by systematic literature search [3, 27]. A manual search identified five FDA approval documents [2, 9, 26, 28, 29], three EMA marketing authorization application notifications [10-12], six clinical guidance documents [14, 16, 21, 22, 24, 25], three clinical articles [7, 30, 31], two statistical documents [15, 25], and two cost editorials [32, 33]. Ongoing trials information was found on www.clinicaltrials.gov.

systematic literature search in 5 databases: 165 hits

manual search: 21 additional references

Overall, 185 references were identified. Included in this reported are:

overall: 186 references included: 4 studies

- FLAURA [3, 27]
- AURA3, phase III [8]
- AURA2, phase II [7]
- AURA, phase I/II [6, 30, 31]

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [34]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 5 of the Appendix.

applicability of study results

The external validity of the included trials was assessed using the EUnetHTA guideline on applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals, considering the following elements: population, intervention, comparator, outcomes and setting (Table 4) [35].

magnitude of clinically meaningful benefit assessed based on ESMO-MCBS

To evaluate the magnitude of "clinically meaningful benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used [36]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [37]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.

7.1 Quality assurance

internal and external review

This report has been reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

- How do you rate the overall quality of the report?
- Are the therapy options in the current treatment section used in clinical practice and are the presented standard therapies correct?
- Is the data regarding prevalence, incidence, amount of eligible patients correct?
- Are the investigated studies correctly analysed and presented (data extraction was double-checked by a second scientist)?
- Was the existing evidence from the present studies correctly interpreted?
- Does the current evidence support the final conclusion?
- Were all important points mentioned in the report?

quality assurance method

The LBI-HTA considers the external assessment by scientific experts from different disciplines a method of quality assurance of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

7.2 Clinical efficacy and safety – phase III studies

FLAURA: osimertinib versus SoC as initial therapy for advanced EGFR-mutated NSCLC

FLAURA (NCT02296125) is a multicentre, double-blind, randomised, controlled phase III study involving 556 patient with previously untreated, EGFR mutation-positive advanced NSCLC [3]. The study was designed to evaluate the safety and efficacy of osimertinib compared to standard of care (SoC) EGFR-TKIs gefitinib or erlotinib as initial treatment for locally advanced or metastatic EGFR-mutated NSCLC. Efficacy analyses were based on all randomly assigned patients comprising the intent-to-treat (ITT) population. Safety analyses involved all patients who received at least one dose of the study drug; all randomly assigned patients received at least one dose of the trial treatment.

ITT (n = 556): stratified by EGFR mutation status (EXdel19 or L858R) and race (Asian or non-Asian)

Eligible patients were 18 years or older, with untreated locally advanced or metastatic NSCLC, and a locally or centrally confirmed EGFR EX19del or L858R mutation alone or co-occurring with other EGFR mutations (Cobas® EGFR Mutation Test or investigational assay at an accredited laboratory). Patients with CNS metastases whose condition was neurologically stable were eligible. Any previous definitive treatment or glucocorticoid therapy must have been completed at least two weeks prior to trial entry. Patients were excluded if they had concurrent active malignancy, symptomatic brain metastases, spinal cord compression, uncontrolled systemic or gastrointestinal diseases, increased risk of QTc prolongation, arrhythmia or interstitial lung disease, concurrent cytochrome P450 inducers or prior systemic or EGFR-TKI treatment for advanced NSCLC. Study participants were stratified by EGFR tumour status (EXdel19 or L858R) and race (Asian or non-Asian).

80 mg osimertinib versus 250 mg gefitinib or 150 mg erlotinib orally, once daily

median treatment exposure: 16.2 months of osimertinib versus 11.5 months of SoC

Patients were randomised 1:1 to receive osimertinib (80 mg orally, once daily; n = 279) or SoC EGFR-TKI (250 mg gefitinib; n = 183 or 150 mg erlotinib; n = 94 orally, once daily) until disease progression, unacceptable toxicity or patient withdrawal. Dose interruptions, reductions and treatment beyond progression were allowed based on investigator-assessed continued clinical benefit. A protocol amendment allowed SoC patients to cross over to open-label osimertinib after confirmation of disease progression by blinded independent central review (BICR) and post-progression documented T790M-positive status as determined by local or central plasma or tissue testing. The median duration of total treatment exposure was 16.2 months (range 0.1–27.4) for patients receiving osimertinib and 11.5 months (range 0.0–26.2) for those receiving SoC.

death/progression at data cut-off: osimertinib: 49% SoC recipients: 74%

cross over: 48 SoC switched to osimertinib post-progression

At data cut-off, an event of Response Evaluation Criteria in Solid Tumours (RECIST)-defined progression or death had occurred in 136 (49%) of osimertinib patients and 206 (74%) of SoC patients. Approximately 67% of osimertinib recipients and 70% of SoC recipients continued treatment beyond RECIST-defined progression, while 82 (29% of osimertinib and 129 [47%] of SoC) patients started subsequent therapy. Of these, 55 SoC patients received osimertinib (48 on cross over and seven as second-line therapy outside of the trial). The median duration of follow-up for PFS was 15.0 (range 0.0–25.1) and 9.7 months (range 0.0–26.1) for the osimertinib and SoC groups, respectively.

primary endpoint: investigator-assessed PFS
secondary endpoints: OS, ORR, DOR, DCR, DTOR, and safety

The primary endpoint of investigator-assessed duration of PFS was evaluated from randomisation to RECIST-defined progression or death. Secondary endpoints reported in the article include the overall survival (OS; time from randomisation until all-cause death), objective response rate (ORR; percentage of patients with measurable disease with at least one partial [PR] or complete response [CR]), duration of response (DOR; time from response until progression or death), disease control rate (DCR; percentage of patients with a best overall response of CR, PR or stable disease [SD] ≥6 weeks before progression), depth of response (DTOR; change in target-lesion size from baseline), and safety. Other endpoints not reported in the current analysis include patient reported outcomes (PRO; Cancer Therapy Satisfaction Questionnaire), health related quality of life (HRQoL; EORTC QLQ-C30), disease-related symptoms (HRQoL; EORTC QLQ-LC13), and pharmacokinetics. Tumours were assessed according to RECIST version 1.1 at baseline, every six weeks for 18 months, then every 12 weeks until disease progression. Adverse events (AEs) were graded for severity according to the National Cancer Institute Common Terminology Criteria version (CTCAE) version 4.0.

PROs, HRQoL, symptoms, pharmacokinetics were not reported in this analysis

ITT: median age 64 years, 62% Asian, 21% CNS metastases, 63% had EX19del mutations, 37% had L858R mutations in EGFR

The ITT population (n = 556) had a median age of 64 years (range 26–93), 63% were female, 62% were Asian, 64% were never smokers, 21% had central nervous system (CNS) metastases, 63% harboured EX19 del mutations and 37% had L858R mutations in EGFR at randomisation. Detailed patient characteristics including inclusion- and exclusion criteria can be found in Table 5 and study quality is described in Table 6 of the appendix, respectively. Clinical efficacy data are presented in Table 1 and AEs are listed in Table 2.

7.2.1 Clinical efficacy

D0001: What is the expected beneficial effect of osimertinib on mortality?

OS results were immature; 83% of osimertinib patients and 71% of SoC patients reached 18-month survival

The median OS could not be calculated for either treatment group; survival data were immature at the time of data analysis. Approximately 89% (95% confidence interval [CI] 85–92%, n = 248) of the osimertinib group and 82% (95% CI 77–86%, n = 227) of the SoC group reached 12-month survival. At 18 months, 83% (95% CI 78–87%, n = 232) of osimertinib patients and 71% (95% CI 65–76%, n = 197) of SoC patients achieved survival. At interim analysis of OS, a total of 141 patients had died, 58 (21%) of osimertinib recipients and 83 (30%) of SoC recipients (HR for death 0.63, 95% CI 0.45–0.88; p = 0.007).

D0006: How does osimertinib affect progression (or recurrence) of NSCLC?

median investigator-assessed PFS:
osimertinib: 18.9 months
SoC: 10.2 months

The primary endpoint of median investigator-assessed PFS was 18.9 months (95% CI 15.2–21.4) in osimertinib patients versus 10.2 months (95% CI 9.6–11.1) in SoC patients. The median duration of follow-up for PFS was 15.0 months (range 0.0–25.1) and 9.7 (range 0.0–26.1) for the osimertinib and SoC groups, respectively. Compared with SoC, osimertinib increased PFS as determined by BICR (HR for disease progression or death 0.45, 95% CI 0.36–0.57; p < 0.001).

The PFS benefit of osimertinib over SoC was demonstrated across all predefined subgroups; a PFS benefit was observed regardless of race (n = 347 Asians, HR 0.55, 95% CI 0.42–0.72 versus n = 209 non-Asians, HR 0.34, 95% CI 0.23–0.48) and osimertinib demonstrated a PFS benefit over SoC regardless of EGFR mutation type (n = 349 EX19del, HR 0.43, 95% CI 0.32–0.56 versus n = 207 L858R, HR 0.51, 95% CI 0.36–0.71). Consistent PFS benefit was also observed in the presence or absence of known or treated CNS metastases at trial entry (n = 116 CNS metastases, HR 0.47, 95% CI 0.30–0.74 versus n = 440 no CNS metastases HR 0.46, 95% CI 0.36–0.59) and irrespective of the status of known or treated CNS metastases at trial entry; CNS progression was observed in 17 patients (6%) in the osimertinib group and 42 (15%) in the SoC group.

consistent PFS benefit: across race, EGFR mutation type and presence/absence of CNS metastases

D0005: How does osimertinib affect symptoms and findings (severity, frequency) of NSCLC?

The investigator-assessed ORR in the ITT population was 80% (95% CI 75–85) in the osimertinib group and 76% (95% CI 70–81) in the SoC group recipients (odds ratio [OR] 1.27, 95% CI 0.85–1.90; p = 0.24). Patients without CNS metastases at trial entry derived similar clinical benefit from osimertinib than those without (n = 116 CNS metastases, OR 0.5, 95% CI 0.2–1.3; p = 0.16 versus n = 440 no CNS metastases, OR 1.6, 95% CI 1.0–2.5; p = 0.04). The percentage of patients with the best overall response, or DCR, was 97% (95% CI 94–99) in the osimertinib group versus 92% (95% CI 89–95) in the SoC group (OR 2.78, 95% CI 1.25–6.78; p = 0.01). The median best percentage change in target lesion size, or DTOR, was -54.7% (range -100.0–61.9) in osimertinib recipients versus -48.5% (range -100.0–54.1) in SoC recipients.

ORR ITT:
osimertinib: 80%
SoC: 76%

The median TTR was 6.1 weeks (95% CI 6.0–6.1) in the osimertinib group and 6.1 weeks (95% CI not estimable) the SoC group. Among responders, disease progression or death occurred in 106 of 223 (48%) of osimertinib recipients and 158 of 210 (75%) of SoC recipients at the time of data analysis. The median DOR was 17.2 months (95% CI 13.8–22.0) in osimertinib patients and 8.5 months (95% CI 7.3–9.8) in SoC patients. Patients with CNS metastases had a median DOR of 13.8 months (95% CI 10.8–20.2) in the osimertinib group versus 8.3 months (95% CI 5.5–9.6) in the SoC group.

median DOR:
osimertinib: 17.8 months
SoC: 8.5 months

D0011: What is the effect of osimertinib on patients'body functions?

Osimertinib may cause ILD, pneumonitis, prolonged QT interval, cardiomyopathy, keratitis and embryo-foetal toxicity [2]. Changes in QTc interval were reported in 29 (10%) of osimertinib patients and 13 (5%) of SoC patients. Cardiac failure was reported in 12 (4%) of patients in the osimertinib group and 6 (2%) of patients in the SoC group. Most AEs, ten of 12 osimertinib patients versus five of six SoC patients, were a result of decreased left ventricular ejection fraction (LVEF) [27]. ILD and pneumonitis were reported in six (2%) and five (2%) osimertinib patients and 4 (1%) and 2 (1%) of SoC patients, respectively [27]. Keratitis was reported in 0.7% of 1142 patients treated with osimertinib in clinical trials [2]. Osimertinib may cause infertility and foetal harm based on its mechanism of action.

ILD, pneumonitis, prolonged QTc interval, cardiomyopathy, keratitis, infertility and foetal toxicity

D0012: What is the effect of osimertinib on generic health-related quality of life?

generic health-related QoL: no evidence

No evidence was reported regarding the effect of osimertinib on generic health-related QoL.

D0013: What is the effect of osimertinib on disease-specific quality of life?

disease-specific QoL: no evidence

No evidence was reported regarding the effect of osimertinib on disease-specific QoL.

Table 1: Efficacy results of FLAURA [3, 27]

Descriptive statistics and estimate variability	Treatment group	Osimertinib	SoC EGFR-TKI
	Number of subjects	279	277
	Progression or death at data cut-off, n (%)	136 (49)	206 (74)
	BICR-assessed median PFS, m (95% CI) Investigator-assessed median PFS, m (95% CI) Median DOFU for PFS, m (95% CI) PFS, n, m (95% CI), with CNS metastases PFS, n, m (95% CI) without CNS metastases PFS, n, m (95% CI), with exon 19 deletion PFS, n, m (95% CI), with L858R mutation	17.7 (15.1–21.4) 18.9 (15.2–21.4) 15.0 (0.0–25.1) n=53; 15.2 (12.1–21.4) n= 226; 19.1 (15.2–23.5) n= 175; 21.4 (16.5–24.3) n=104; 14.4 (11.1–18.9)	9.7 (8.5–11.0) 10.2 (9.6–11.1) 9.7 (0.0–26.1) n=63; 9.6 (7.0–12.4) n= 214;10.9 (9.6–12.3) n=174; 11.0 (9.7–12.6) n=103; 9.5 (8.1–11.0)
	Investigator-assessed ORR, % (95% CI) ORR, n, % (95% CI) with CNS metastases ORR, n, % (95% CI) without CNS metastases	80 (75–85) n=53; 76 (62–86) n=226; 81 (75–86)	76 (70–81) n=63; 88 (75–93) n=214; 73 (66–79)
	DCR, % (95% CI)	97 (94–99)	92 (89–95)
	DTOR, % (range)	-54.7 (-100–61.9)	-48.5 (-100–54.1)
	Response, n (%) CR PR SD ≥6 weeks Progression Death NE	 7 (3) 216 (77) 47 (17) 3 (1) 0 (0) 6 (2)	 4 (1) 206 (74) 46 (17) 14 (5) 5 (2) 7 (3)
	Investigator-assessed median DOR, m (95% CI) Range DOR, n, m (range), with CNS metastases DOR, n, m (range), without CNS metastases DOR continued response at 12 m, n, (95% CI) DOR continued response at 18 m, n, (95% CI) DOR continued response at 24 m, n, (95% CI)	17.2 (13.8–22.0) 0.0–23.8 n=40; 13,8 (10.8-20.2) n=183; 17.6 (13.8-23.0) 64 (58–70) 49 (41–56) NE (NE–NE)	8.5 (7.3–9.8) 0.0–24.9 n=54; 8.3 (5.5-9.6) n=156; 9.6 (8.1-11.2) 37 (31–44) 19 (13–26) 5 (1–16)
	Median TTR Weeks median (95% CI) ≤6 weeks after first dose, n/N (%) ≤12 weeks after first dose, n/N (%) ≤18 weeks after first dose, n/N (%)	 6.1 (6.0–6.1) 154/223 (69) 193/223 (87) 199/223 (89)	 6.1 (NE–NE) 148/210 (70) 180/210 (86) 196/210 (93)
	Median OS, m (95% CI) Survival at 6 m, %, (95% CI) Survival at 12 m, %, (95% CI) Survival at 18 m, %, (95% CI)	NE (NE–NE) 98 (96–99) 89 (85–92) 83 (78–87)	NE (NE–NE) 93 (90–96) 82 (77–86) 71 (65–76)
	Death n (%)	58 (21)	83 (30)
	QoL	NA	NA

Effect estimate per comparison	*Comparison groups*		Osimertinib versus SoC EGFR-TKI
	Investigator-assessed PFS (primary endpoint)	HR	0.46
		95% CI	0.37–0.57
		Log-rank test p-value	<0.001
	BICR-assessed PFS (primary endpoint)	HR	0.45
		95% CI	0.36–0.57
		Log-rank test p-value	<0.001
	Investigator-assessed PFS (subgroup analysis)	HR Asians (n=347) versus non-Asians (n=209)	0.55 versus 0.34
		95% CI	0.42–0.72 versus 0.23-0.48
		Log-rank test p-value	<0.001
	Investigator-assessed PFS (subgroup analysis)	HR with CNS metastases (n=116) versus without (n=440)	0.47 versus 0.46
		95% CI	0.30–0.74 versus 0.36–0.59
		Log-rank test p-value	<0.001
	Investigator-assessed PFS (subgroup analysis)	HR EX19del (n=349) versus L858R (n=207) mutation	0.43 versus 0.51
		95% CI	0.32–0.56 versus 0.36–0.71
		Log-rank test p-value	<0.001
	ORR, all patients	OR	1.27
		95% CI	0.85–1.90
		Log-rank test p-value	0.24
	ORR (subgroup analysis)	OR with CNS metastases versus without	0.5 versus 1.6
		95% CI	0.2–1.3 versus 1.0–2.5
		Log-rank test p-value	0.16 and 0.04
	DCR, all patients	OR	2.78
		95% CI	1.25–6.78
		Log-rank test p-value	0.01
	Death, all patients	HR	0.63
		95% CI	0.45–0.88
		Log-rank test p-value	0.007

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CNS = central nervous system; CR = complete response; DCR = disease-control rate; DOR = duration of response; DOFU = duration of follow-up; DTOR = depth of response; EGFR = epidermal growth factor receptor; m = months; n = number; N = total number; NA = not available; NE = not evaluable; NR = not reached; OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life; PR = partial response; SD = stable disease; TTR = time to response

7.2.2 Safety

C0008: How safe is osimertinib in relation to the comparator(s)?

common treatment-related AEs: rash, diarrhoea, dry skin, paronchia, stomatitis, decreased appetite, pruritus, AST and ALT elevation

The most frequent investigator-assessed AEs reported in the osimertinib group of the safety population (n = 279) were rash, diarrhoea, dry skin, paronchia, stomatitis, decreased appetite, pruritus, AST and ALT elevation [27]. Grade ≥3 AEs were observed in 95 (34%) of osimertinib patients and 125 (45%) of SoC patients [3]. The most common AEs of grade ≥3 severity in the osimertinib group were decreased appetite (3%), pneumonia (2%), diarrhoea (2%) and prolonged QTc (2%) [27].

cardiac AEs: osimertinib: 10% SoC: 5%

prolonged QTc: osimertinib: 10% SoC: 4%

ILD: osimertinib: 4% SoC: 2%

Cardiac effects were reported in a higher percentage of osimertinib patients than SoC patients (10% versus 5%, respectively). Cardiac AEs were predominantly of grade 1 (4%) or 2 (4%) for osimertinib recipients versus 3% and 1% for SoC recipients [3]. Cardiac failure was reported in 12 (4%) patients of the osimertinib group and six (2%) of the SoC group. A decrease in LVEF occurred in ten of 12 osimertinib patients and five of six SoC patients. Prolonged QTc interval was reported in 28 (10%) patients of the osimertinib group and in eleven 11 (4%) patients of the SoC group; one SoC patient experienced arrhythmia. AEs of ILD were observed in eleven (4%) patients of the osimertinib group and in six (2%) patients of the SoC group. In the osimertinib group, seven of eleven patients recovered while the remaining four patients were recovering [3]. No fatal cases of torsades des pointes, prolonged QT interval, ILD, or pneumonitis occurred in either treatment group [3].

AE-related death: osimertinib: 2% SoC: 4%

Serious adverse events (SAEs) were reported in 60 (22%) of the osimertinib group patients and in 70 (25%) patients of the SoC group. One osimertinib recipient had a SAE of prolonged QTc interval. SAEs of ILD occurred in six patients in the osimertinib group and four patients in the SoC group. Six (2%) of osimertinib patients experienced a fatal AE involving pneumonia, respiratory tract infection, cerebral infarction, myocardial infarction, pulmonary embolism and intestinal ischemia while ten (4%) of SoC patients died due to sepsis (n = 2), pneumonia (n = 1), endocarditis (n = 1), cognitive disorder and pneumonia (n = 1), peripheral-artery occlusion (n = 1), dyspnoea (n = 1), haemoptysis (n = 1), diarrhoea (n = 1) and death not otherwise specified (n = 1).

C0002: Are the harms related to dosage or frequency of applying osimertinib?

discontinued due to AE: osimertinib: 13% SoC: 18%

Osimertinib was associated with fewer AEs resulting in permanent discontinuation than SoC [37 patients (13%) versus 49 (18%), respectively].

interruption or dose reduction: QT polongation, decreased appetite, diarrhoea, pneumonia, and skin disorders

The frequency of AE-related dose interruption (25% for osimertinib versus 24% for SoC) and reduction (4% versus 5%, respectively) were similar between groups. The most frequently reported AEs leading to dose interruption in osimertinib recipients were QT prolongation (n = 8), decreased appetite (n = 7), diarrhoea (n = 7) and pneumonia (n = 5). QT prolongation (n = 5) and skin disorders (n = 10) were the leading causes of dose reductions in osimertinib patients [27].

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of osimertinib?

Osimertinib should be withheld in patients who present with worsening respiratory symptoms indicative of ILD. Clinical trials did not enrol patients with baseline QTc >470 msec. Patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those taking medications that prolong the QTc interval should undergo periodic EGC and electrolyte monitoring. Cardiac monitoring and LVEF assessment should be conducted in patients with cardiac risk factors and those who develop cardiac symptoms during treatment. Patients who develop symptoms of keratitis should be referred to an ophthalmologist. Osimertinib may cause foetal harm; females are advised to use effective contraception during treatment and for six weeks after the final dose. Males with female partners are advised to use effective contraception for four months following their final dose. The safety and effectiveness of osimertinib have not been established in paediatric patients. No dose adjustment is recommended for patients with renal or hepatic impairment [2].

susceptibles: monitor those with respiratory symptoms, long QTc, cardiac risk factors, keratitis

osimertinib may cause infertility and foetal harm

Table 2: Most frequent adverse events of FLAURA [3]

Adverse Event (according to CTCAE version 4.0)	**Osimertinib** (n = 279)			**SoC EGFR-TKI** (n = 277)		
≥15% in either Arm	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	273 (98)	83 (30)	6 (2)	271 (98)	103 (37)	11 (4)
Rash or acne	161 (58)	3 (1)	0 (0)	216 (78)	19 (7)	0 (0)
Diarrhoea	161 (58)	6 (2)	0 (0)	151 (57)	6 (2)	0 (0)
Dry skin	100 (36)	1 (<1)	0 (0)	100 (36)	3 (1)	0 (0)
Paronychia	97 (35)	1 (<1)	0 (0)	91 (33)	2 (1)	0 (0)
Stomatitis	80 (29)	1 (<1)	1 (<1)	56 (20)	1 (<1)	0 (0)
Decreased appetite	56 (20)	7 (3)	0 (0)	52 (19)	5 (2)	0 (0)
Pruritus	48 (17)	1 (<1)	0 (0)	43 (16)	0 (0)	0 (0)
Cough	46 (16)	0 (0)	0 (0)	42 (15)	1 (<1)	0 (0)
Constipation	42 (15)	0 (0)	0 (0)	35 (13)	0 (0)	0 (0)
Nausea	39 (14)	0 (0)	0 (0)	52 (19)	0 (0)	0 (0)
Fatigue	38 (14)	2(1)	0 (0)	33 (12)	2 (1)	0 (0)
Dyspnoea	35 (13)	1 (<1)	0 (0)	20 (7)	3 (1)	0 (0)
Anaemia	34 (12)	3 (1)	0 (0)	25 (9)	3(1)	0 (0)
Headache	33 (12)	1 (<1)	0 (0)	19 (7)	0 (0)	0 (0)
Vomiting	31 (11)	0 (0)	0 (0)	29 (10)	4 (1)	0 (0)
Upper RTI	28 (10)	0 (0)	0 (0)	18 (6)	0 (0)	0 (0)
Pyrexia	28 (10)	0 (0)	0 (0)	11 (4)	1 (<1)	0 (0)
Prolonged QT interval on ECG	28 (10)	5 (2)	1 (<1)	11 (4)	2 (1)	0 (0)
AST elevation	26 (9)	2 (1)	0 (0)	68 (25)	12 (4)	0 (0)
Alopecia	20 (7)	0 (0)	0 (0)	35 (13)	0 (0)	0 (0)
ALT elevation	18 (6)	1 (<1)	0 (0)	75 (27)	21 (8)	4 (1)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = common terminology for cancer adverse events; ECG = electrocardiogram; RTI = respiratory tract infection; SoC = standard of care

7.3 Clinical effectiveness and safety – further studies

AURA3: osimertinib versus platinum-based chemotherapy for EGFRT790M-mutated advanced NSCLC with progression following EGFR-TKI therapy

AURA3 (NCT02151981) is an ongoing multicentre, randomised, open-label, comparative, phase III study to evaluate osimertinib versus SoC platinum-based chemotherapy in 419 patients with locally advanced or metastatic NSCLC, who harbour a T790M and have progressed on previous EGFR-TKIs [8]. Patients were stratified by Asian or non-Asian race, and randomly assigned 2:1 to receive either oral osimertinib (80 mg once daily) or intravenous pemetrexed (500 mg/m^2 of body-surface area) plus either carboplatin (target area under the curve, 5 [AUC5]) or cisplatin (75 mg/m^2) every three weeks for up to six cycles; maintenance pemetrexed was allowed. Patients were treated until disease progression, unacceptable toxicity or patient withdrawal. Both cross-over to osimertinib following progression and treatment beyond RECIST-defined progression were allowed based on investigator-assessed continued clinical benefit. The primary endpoint was investigator-assessed PFS; secondary endpoints included investigator-assessed ORR, DOR, DCR, tumour shrinkage, OS, PROs and safety. Tumours were assessed according to RECIST version 1.1 at baseline, every six weeks until disease progression up to 19 months. AEs were graded according to the CTCAE version 4.0.

median investigator-assessed PFS: 10.1 months for osimertinib versus 4.4 months for chemotherapy

median ORR: 71% for osimertinib versus 31% chemotherapy

DOR: 9.7 months for osimertinib versus 4.1 months for chemotherapy

OS: data immature

At a median follow-up of 8.3 months, osimertinib patients demonstrated a longer median PFS than chemotherapy patients (10.1 months versus 4.4 months; HR 0.30, 95% CI 0.23–0.41; $p < 0.001$). At 12 months, approximately 44% (95% CI 37–51) of osimertinib patients and 10% (95% CI 5–17) of chemotherapy patients were still progression-free. The PFS benefit of osimertinib over chemotherapy was observed across all predefined subgroups, including patients with CNS metastases (median PFS 8.5 months versus 4.2 months; HR 0.32, 95% CI 0.21–0.40; $p < 0.5$); EGFR Ex19del mutation (HR 0.34, 95% CI 0.24–0.46; $p < 0.5$); EGFR L858R mutation (HR 0.46, 95% CI 0.30–0.71; $p < 0.5$); Asian patients (HR 0.32, 95% CI 0.24–0.44; $p < 0.5$); and non-Asian patients (HR 0.48, 95% CI 0.32–0.75; $p < 0.5$). Median PFS among EGFR T790M-positive patients was 8.2 months for osimertinib recipients versus 4.2 months for chemotherapy recipients (HR 0.42, 95% CI 0.29–0.61; $p < 0.5$). Osimertinib treatment was associated with better ORR compared to chemotherapy (71% [95% CI 65–76] versus 31% [95% CI 24–40]; OR 5.43, 95% CI 3.47–8.48; $p < 0.001$). The ORR benefit of osimertinib over chemotherapy was reported on both tumour and plasma analyses (89 of 116 patients [77%] versus 22 of 56 patients [39%]; OR 4.96, 95% CI 2.49–10.15; $p < 0.001$). The median DOR was 9.7 months (95% CI 8.3–11.6) for osimertinib versus 4.1 months (95% CI 3.0–5.6) for chemotherapy. While OS data were not mature, 31 (13%) of osimertinib patients and 26 (19%) of chemotherapy patients had died at interim analysis.

AEs: diarrhoea, rash, dry skin, and paronychia

The proportion of patients with grade ≥3 AEs was lower with osimertinib (23%) than with platinum chemotherapy (47%). In the osimertinib group, the most commonly reported AEs were diarrhoea (41%), rash (34%), dry skin (23%) and paronychia (22%). ILD-like AEs and prolonged QT interval were reported in ten (4%) and ten (4%) of osimertinib recipients and one (1%) and one (1%) of chemotherapy patients, respectively. Osimertinib lead to fewer permanent discontinuations than chemotherapy (19 [7%] versus 14 [10%] of patients, respectively). Fatal AEs were reported in four patients in

the osimertinib group as a result of respiratory failure (n = 2), pneumonitis (n = 1), and ischemic stroke (n = 1).

AURA2: efficacy and safety of osimertinib for EGFRT790M-mutated advanced NSCLC with progression following EGFR-TKI therapy

AURA2 (NCT02094261) is a multicentre, open-label, single-arm phase II study to assess the safety and efficacy of osimertinib in 210 EGFR T790M-positive advanced NSCLC patients with progression following previous EGFR-TKI therapy [7]. Patients received oral osimertinib (80 mg once daily) and could continue beyond RECIST-defined progression based on investigator-assessed continued clinical benefit. The primary endpoint was BICR-assessed ORR; secondary endpoints included PFS, DOR, DCR, tumour shrinkage, OS, QoL, QTcF interval change after multiple dosing, pharmacokinetics and safety. Tumours were assessed according to RECIST version 1.1 at baseline, every six weeks until disease progression up to 11 months. Adverse events (AEs) were graded according to the CTCAE version 4.0.

BICR-assessed ORR at 13 months: 70%

DCR: 92%

median DOR: 11.4 months

median PFS: 9.9 months

OS: data not mature

symptoms: 75% were stable or improved

At a median follow-up of 13.0 months, 140 (70%, 95% CI 64–77) of 199 evaluable patients achieved an objective response by BICR; CR was confirmed in six (3%) of patients and PR was observed in 134 (67%) of patients. The ORR was consistent across subgroups, including patients with CNS metastases. The DCR was 182 of 199 patients (92%, 95% CI 87–95). The median DOR was 11.4 months (95% CI 9.0–not estimable), and 48% (95% CI 39–57) maintained response at 12 months. Tumour shrinkage was observed in 186 of 198 (94%) patients. The mean best percentage change in target lesion size from baseline was -52%. The median BIRC-assessed PFS was 9.9 months (95% CI 8.5–12.3); and PFS at 12 months was 44%. The PFS benefit of osimertinib was consistent across subgroups, including presence or absence of CNS metastases, Asian or non-Asian race, EGFR T790M co-occurring with EX19del versus L848R. At interim analysis, 44 (21%) of patients had died and OS data was not mature. Approximately 75% of patients on treatment improved or remained stable in their symptoms of lung cancer (QLQ-LC13; n = 85) and in the functioning domains of the QLQ-C30 (n = 90).

common treatment-related grade ≥3 AEs: prolonged QTc, neutropenia, and thrombocytopenia

The most common grade ≥3 adverse events were pulmonary embolism (3%), prolonged QTc (2%), decreased neutrophil count (2%), anaemia (1%), dyspnoea (1%), hyponatraemia (1%) increased ALT (1%) and thrombocytopenia (1%). Approximately 5% of patients discontinued osimertinib due to AEs. Serious AEs were reported in 52 (25%) of patients, 11 (5%) of which investigators assessed as treatment-related. Seven deaths resulted from AEs involving pneumonia (n = 2), pneumonia aspiration (n = 1), rectal haemorrhage (n = 1), dyspnoea (n = 1), failure to thrive (n = 1), and ILD (n = 1). Investigators assessed the ILD as the only treatment-related fatality.

AURA: safety, efficacy and tolerability of osimertinib for EGFRT790M-mutated advanced NSCLC with resistance to EGFR-TKIs

dose-escalation cohort: no defined maximum tolerated dose

AURA (NCT01802632) is a multicentre, open-label, phase I/II study to assess the safety, efficacy and tolerability of osimertinib in 253 patients with advanced EGFR-mutated NSCLC in whom resistance to treatment with EGFR-TKIs had developed [6]. The study included 31 patients in dose-escalation cohorts and 222 patients in five dose-expansion cohorts. Patients in the dose-escalation cohorts received a single dose of osimertinib followed by a pharmacokinetic evaluation period; after seven days they received the same dose daily for the remainder of the study. The first dose tested was 20 mg daily each subsequent dose cohort represented a 100% increase from the previous dose. If clinical activity was observed in an escalation cohort, a dose-expansion cohort was initiated where daily continuous dosing commenced with pharmacokinetic assessments. At data cut-off, enrolment into additional cohorts, including patients that had not received prior treatment, and phase II extension were ongoing [30].

ORR: 51%

median PFS: 9.6 months EGFRT790M-positive versus 2.8 months EGFRT790M-negative

AEs: diarrhoea, rash, decreased appetite

dosage: 80 mg daily

In the dose-escalation cohort where patients received osimertinib (dose range 20–240 mg per dose, once daily), no dose-limiting toxicities occurred at any dose level and the maximum tolerated dose could not be defined. In the expansion cohorts, all patients underwent tumour assessment for EGFRT790M status and 138 (62%) were positive for this mutation. A confirmed objective response was found in 123 (51%; 95% CI 45–58) of the 239 evaluable patients; 85% showed durable response of ≥6 months. Among 127 patients with centrally confirmed EGFR T790M, the response rate was 61% (95% CI 52–70) while the response rate among 61 patients without EGFR T790M mutations was 21% (CI 12–24). The median PFS was 9.6 months (95% CI 8.3–not estimable) in EGFR T790M-positive patients and 2.8 months (95% CI 2.1–4.3) in EGFR T790M-negative patients. The most frequent AEs were diarrhoea (47%), rash (40%), nausea and decreased appetite (21%); of these, diarrhoea and rash were assessed as dose dependent. Treatment-related serious AEs were observed in 6% of patients involving ILD leading to discontinuation of treatment. Based on clinical activity and safety data, the 80 mg once daily dose was selected for further investigation.

AURA pooled phase II: confirms AURA phase I findings

Preliminary results from the extension cohort of AURA were presented in a pre-planned pooled analysis with the phase II AURA2 study including 411 EGFR T790M-positive patients. In AURA phase I, investigator-assessed ORR was 71% (95% CI 57–82), median DOR was 9.6 months (95% CI 7.7–15.6) and median PFS was 9.7 months (95% CI 8.3–13.6). In the AURA pooled phase II, ORR was 66% (95% CI 61–71), median DOR was 12.5 months (95% CI 11.1–not estimable), and median PFS was 11.0 months (95% CI 9.6–12.4). The AURA pooled phase II results confirmed the findings of AURA phase I [31].

8 Estimated costs

A0021: What is the reimbursement status of osimertinib?

€ 6,132.50 per month, additional cost for molecular testing

16 months of osimertinib treatment: ~ € 98,120.00

In Austria, osimertinib is available as 80 mg, oval tablets in 30-tablet bottles. One bottle of 30 osimertinib (Tagrisso®) tablets (80 mg) is available for € 6,132.50 (ex-factory price) [33]. At the recommended dose of 80 mg per day, a median duration of treatment exposure of 16 months of osimertinib treatment would cost approximately € 98,120.00. Since osimertinib is indicated for EGFR-mutated NSCLC with an incidence of 10–15% in Europe and 4,860 Austrians are diagnosed with NSCLC, osimertinib would cost between € 35,764,740.00–53,647,110.00 annually with an additional cost of approximately £ 189.05 (~ € 165.00) per Cobas® EGFR Mutation Test v2 [32].

9 Ongoing research

60 registered studies

Several studies are ongoing to investigate osimertinib as monotherapy or in combination with other targeted therapies or immunotherapies to treat various stages of NSCLC. In May 2018, searches of www.clinicaltrials.gov and www.clinicaltrialsregister.eu using the search terms "osimertinib" and "non-small cell lung cancer" yielded 60 other registered studies (five phase III, twenty phase II, nine phase I/II, sixteen phase I, and ten observational, feasibility or real-world treatment studies). Most studies were industry-sponsored or conducted in collaboration with industry.

5 phase III studies

Selected recently completed and ongoing phase III studies evaluating osimertinib in patients with advanced EGFR-mutated NSCLC previously treated with EGFR-TKIs as third-line therapy, in combination with durvalumab (MEDI4736) (CAURAL), following tumour resection with or without adjuvant chemotherapy (ADAURA), for the treatment of brain metastases (APOLLO), and in a real world setting (ASTRIS):

- **NCT02959749:** is a phase II/III, randomised, open-label, interventional trial to compare the efficacy and toxicity of osimertinib or docetaxel-bevacizumab as third-line therapy in patients with locally advanced or metastatic EGFR T790M-mutaed NSCLC. Estimated study completion date is December 2017.
- **NCT02454933:** CAURAL is a phase III, multicentre, randomised, open-label study to assess the safety and efficacy of osimertinib in combination with the anti-PD-L1 monoclonal antibody durvalumab (MEDI4736) versus osimertinib monotherapy in patients with locally advanced or metastatic EGFR T790M-positive NSCLC who have received prior EGFR-TKI therapy. Estimated study completion date is March 2018.
- **NCT02474355:** ASTRIS is a phase III, multicentre, real world treatment study to determine the efficacy and safety of osimertinib in a real world setting in adults with advanced EGFR T790M-positive NSCLC who have received prior EGFR-TKI therapy. The study will close in participating countries following national reimbursement or within 18 months after the last patient enrolment in the event national reimbursement is not granted following a reasonable time after market license approval. Estimated study completion date is April 2019.
- **NCT02972333:** APOLLO is a phase III, multicentre, single-arm, open-label study to investigate the safety and efficacy of osimertinib in brain metastases from patients with EGFR T790M-positive NSCLC who have received prior EGFR-TKI therapy. Estimated study completion date is December 2019.
- **NCT02511106:** ADAURA plus is a phase III, multicentre, randomised, double-blind, placebo-controlled trial to evaluate the safety and efficacy of osimertinib versus placebo in patients with EGFR-mutated stage IB-IIIA NSCLC following complete tumour resection with or without adjuvant chemotherapy. Estimated study completion date is November 2021.

In addition, osimertinib is currently under investigation as a combination therapeutic with targeted agents. The TATTON trial (NCT02143466) will evaluate osimertinib in combination with the anti-PD-L1 monoclonal antibody durvalumab, or with MET inhibitor, AZD6094, or with MEK1/2 inhibitor, selumetinib, (AZD6244, ARRY-142886) in patients with advanced EGFR-mutated NSCLC. However, CAURAL and phase I TATTON were suspended when patients taking combination osimertinib with durvalumab experienced an increase in ILD [38]. Other combinations with anti-angiogenic agents or anti-EGFR monoclonal antibodies such as ramucirumab or necitumumab are under investigation (NCT02789345). A phase Ib trial is ongoing to evaluate the safety and tolerability of osimertinib and navitoxclax (ABT-263), a BCL-2 inhibitor that enhances the apoptotic response in late resistant t790M cells and sensitivity to EGFR inhibition [5].

10 Discussion

FDA: licensed as first-line for advanced EGFR-mutated NSCLC

EMA: MAA submitted for EGFRT790M-positive NSCLC irrespective of previous EGFR-TKI therapy; CHMP adopted a positive opinion in April 2018

In November 2015, the FDA granted accelerated approval of osimertinib for EGFR-TKI-pre-treated advanced EGFRT790M-positive NSCLC along with a companion diagnostic test, Cobas® EGFR Mutation Test v2.. Osimertinib received full approval in March 2017 when phase II results from AURA [6, 30, 31] and AURA2 [7] were confirmed in the phase III AURA3 trial [8]. Following the phase III FLAURA trial in April 2018 [3], osimertinib was approved as first-line treatment for advanced NSCLC with EGFR Ex19del or L858R substitution mutations as detected by an FDA-approved test [9]. In April 2017, osimertinib received marketing authorisation by the EMA for the treatment of EGFRT790M-positive NSCLC, irrespective EGFR-TKI pre-treatment, as determined by a validated tumour sample or blood-based ctDNA [10]. While osimertinib is not approved in Europe for the first-line setting, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation of osimertinib in April 2018 [12].

FLAURA: osimertinib increased median PFS, and reduced risk of progression or death; consistent PFS benefit across subgroups

immature OS

First-line FDA-approval of osimertinib was based on the interim results of FLAURA, a randomised, double-blind, controlled trial comparing the safety and efficacy of osimertinib (80 mg once daily) versus SoC EGFR-TKIs, gefitinib or erlotinib (250 mg and 150 mg once daily, respectively), in 556 untreated patients with advanced EGFR-mutated NSCLC [3]. Compared with SoC EGFR-TKIs, osimertinib increased median PFS by 8.7 months, and lowered the risk of disease progression or death by 54%. The PFS benefit was consistent across subgroups regardless of Asian or non-Asian race, Ex19del or L858R EGFR subtype, and presence or absence of CNS metastases. While the ORR was similar between osimertinib and SoC groups (80% versus 76%, respectively), osimertinib conferred a longer DOR than SoC (17.2 months versus 8.5 months). OS data was immature at interim analysis; however, 83% of osimertinib patients and 71% of SoC patients achieved 18-month survival.

The most frequently reported AEs in osimertinib patients were rash, diarrhoea, dry skin, paronchia, stomatitis, decreased appetite, pruritis, AST and ALT elevation. Grade ≥3 AEs were less common in the osimertinib group compared to SoC (34% versus 45%); however, decreased appetite (3%), pneumonia (2%), diarrhoea (2%), and prolonged QTc (2%) were most common. Cardiac and lung effects occurred more frequently in osimertinib recipients than SoC recipients (10% and 4% versus 5% and 2%, respectively); notably cardiac failure (4%), prolonged QTc interval (10%), and ILD (4%). Fatal AEs occurred in six osimertinib patients due to pneumonia, respiratory tract infection, cerebral infarction, myocardial infarction, pulmonary embolism and intestinal ischemia. While the frequency of AE-related dose interruption and reduction were similar between groups (25% and 4% versus 24% and 5%, respectively), fewer osimertinib patients discontinued due to AEs (13% versus 18%). QT prolongation, decreased appetite, diarrhoea, and pneumonia were the most common causes of osimertinib dose interruption.

cardiac and lung effects: cardiac failure, prolonged QTc, ILD

6 deaths: pneumonia, respiratory infection, cerebral infarction, myocardial infarction, pulmonary embolism and intestinal ischemia

Results of the FLAURA study hold some limitations. Follow-up is insufficient to evaluate OS and long-term safety, and no evidence was reported regarding the effect of osimertinib on generic or disease specific QoL. Mature OS data and QoL measures are needed to ensure patients achieve a clinically relevant benefit over time despite favourable tolerability. In addition, NSCLC patients with brain metastases typically have a worse prognosis than those without; although early-generation EGFR-TKIs demonstrate better CNS efficacy than chemotherapy, many patients progress. While the frequency of CNS progression at interim analysis was less than that observed in the SoC EGFR-TKI group, some cases of asymptomatic progression may have been undetected as only patients with brain metastases were routinely scanned. The ARCHER 1050 trial recently showed a superior median PFS with dacomitinib over gefitinib in patients with previously untreated EGFR-mutated advanced NSCLC but patients with brain metastases were excluded from the study.

FLAURA limitations: lack of irreversible comparator, OS and QoL data, and undetected brain metastases

The overall generalizability of FLAURA results are fairly good in that the study population demonstrated demographic and clinical characteristics representative of the global population of patients with EGFR-mutated advanced NSCLC. However, afatinib, now available for EGFR mutation-positive NSCLC, received FDA-approval as first-line treatment for NSCLC patients whose tumours have non-resistant EGFR mutations as detected by an FDA-approved test, including L861Q, G719X and S768I in January 2018 [39]. Approval was based on pooled analysis of phase II LUX-Lung 2, and phase III LUX-Lung 3 and LUX-Lung 6 trials demonstrating the activity of afatinib in non-resistant mutations based on ORR, DOR, DCR, PFS and OS. Afatinib was initially approved in 2013 for NSCLC with EGFR Ex19del or L858R mutations as detected by an FDA-approved test. Therefore, the second-generation irreversible EGFR-TKI, afatinib may have been a suitable comparator for irreversible osimertinib compared to first-generation reversible gefitinib and erlotinib. However, afatinib irreversibly inhibits wild-type EGFR expressed in skin and the gastrointestinal tract causing dose-limiting rash and diarrhoea, so it is unlikely that patients would tolerate doses sufficient to overcome T790M-mediated resistance [4].

generalizability: lack of irreversible EGFR-TKI comparator; afatinib indicated as first-line

FLAURA is a phase III trial with some methodological limitations. There is no risk of bias in the generation of randomisation sequence or allocation concealment. Patients were randomly assigned 1:1 to osimertinib or SoC using an interactive voice/web-based response system [40]. Patients, physicians and outcome assessors were blinded as patients received active osimer-

low risk of bias: randomised, double-blind, comparator-matched, industry funded, cross over

tinib plus comparator-matching placebo or active comparator plus osimertinib-matching placebo. Active and placebo tablets were identical and presented in the same packaging to ensure blinding. Selective outcome reporting is unlikely as all outcomes were reported as specified in the clinical protocol. The risk of bias may be increased by industry involvement in funding, study design, data collection, analysis and interpretation as well as due to cross over (48 patients switched to osimertinib).

ESMO-MCBS: grade 3; no meaningful clinical benefit

Given the non-curative treatment setting of osimertinib and the statistically significant primary endpoint PFS, we applied Form 2b of the ESMO-MCBS in order to assess whether osimertinib satisfies the criteria for a "meaningful clinical benefit" (score 4 or 5). Both the original as well as the adapted version of the MCBS were applied. The application of the ESMO-MCBS to the FLAURA study resulted in a grade 3 in both the original and the adapted version of the ESMO-MCBS, respectively. Therefore, osimertinib leads to no "meaningful clinical benefit" with the original scale or with the adapted framework.

resistance mechanisms: acquired EGFR mutations, MET and HER2 amplification, constitutive ERK activation, and small cell transformation; not fully characterized

Mechanisms of resistance to osimertinib have already been identified in patients with T790M-positive NSCLC after EGFR-TKI therapy, including acquired EGFR mutations C797S, L844V, and L718Q, MET and HER2 amplification, constitutive ERK activation, and small-cell transformation [5]. However, mechanisms of resistance to first-line osimertinib therapy remain to be fully characterized. No cases of acquired T790M mutation were observed in the nine patients with previously untreated EGFR-mutated NSCLC who received osimertinib in phase I of the AURA trial. Molecular analysis of tissue-based and post-progression plasma samples from FLAURA study participants may allow greater insight into the mechanisms of resistance [3].

consistent efficacy and safety results with former studies

The clinical efficacy and safety data from FLAURA are consistent with data from previous studies showing osimertinib holds high specificity for T790M mutation-positive advanced NSCLC and improves PFS, ORR and DOR with acceptable tolerability [3, 6-8, 30, 31]. Osimertinib was evaluated as initial EGFR-TKI therapy in FLAURA, while AURA3, AURA2 and AURA evaluated osimertinib in patients with EGFR-mutated NSCLC who had progressed following prior EGFR-TKI therapy. OS data was immature across the trials. The PFS and ORR benefits of conferred by osimertinib were consistent across subgroups regardless of race, EGFR subtype, or the presence of CNS metastases across trials. In the AURA study, 60 patients received osimertinib as first-line therapy; the PFS and ORR benefits afforded by osimertinib were the basis for conducting FLAURA. Common AEs reported in patients taking osimertinib include diarrhoea, rash, dry skin, paronchia, ILD and prolonged QT interval [3, 6-8]. Of the 52 serious AEs and seven deaths reported in AURA2, 11 and one fatality due to ILD were investigator assessed as treatment-related, respectively. Osimertinib lead to fewer permanent discontinuations compared to SoC EGFR-TKI or chemotherapy [3, 8].

Several studies are underway to investigate osimertinib as monotherapy or in combination with other targeted therapies or immunotherapies to treat various stages of EGFR-mutated NSCLC. Ongoing phase III studies are evaluating osimertinib in as third-line therapy, following tumour resection with or without adjuvant chemotherapy (ADAURA), for the treatment of brain metastases (APOLLO), and in a real world setting (ASTRIS). TATTON will evaluate osimertinib in combination with durvalumab, MET inhibitor AZD6094, or selumetinib in patients with advanced EGFR-mutated NSCLC. However, CAURAL and phase I TATTON were suspended when patients taking combination osimertinib with durvalumab experienced an increase in ILD [38]. Other approaches involve combinations with antiangiogentic agents or anti-EGFR monoclonal antibodies such as ramucirumab or necitumumab. A phase Ib trial is investigating osimertinib in combination with navitoclax following resistance to prior EGFR-TKI therapy. The BOOSTER trial is investigating combination osimertinib and bevacizumab for patients with acquired T790M mutation. Other third generation TKIs in clinical development for NSCLC include olmutinib, nazartinib, mavelertinib, avitinib, and lazertinib [20]. Trials involving third-generation EGFR-TKIs rociletinib and naquotinib as treatment for EGFR-mutated advance NSCLC were discontinued due to lack of efficacy versus first-generation TKIs [20]. Direct comparison trials would be needed to evaluate osimertinib versus second-generation afatinib and other third-generation EGFR-TKIs. The resistance mechanisms to osimertinib need to be fully characterized for targeting by fourth-generation inhibitors. A new class of inhibitors, designed to target triple mutations thought to confer resistance to fourth-generation EGFR-TKIs, is also under development [20].

several ongoing studies evaluating osimertinib as monotherapy or in combination with targeted therapies or immunotherapies

resistance mechanisms to osimertinib are not fully characterized

fourth-generation inhibitors target triple mutations

The cost of osimertinib, at the recommended dose of 80 mg per day, is € 6,132.50 per month [33]. A median duration of treatment exposure of 16 months of osimertinib treatment would cost approximately € 98,120.00. Since osimertinib is indicated for EGFR-mutated NSCLC with an incidence of 10–15% in Europe, osimertinib would cost between € 35,764,740.00–53,647,110.00 annually with an additional cost of approximately £ 189.05 (~ € 165.00) per Cobas® EGFR Mutation Test v2 [32]. At the monthly average wholesale price of € 6,132.50 per 80 mg tablet, osimertinib is more costly than other FDA-approved EGFR-TKIs, including afatinib (40 mg) at € 2,176.13, gefitinib (250 mg) at € 2,300.00, and erlotinib (150 mg) at € 1,809.77. While the National Institute for Health and Care Excellence (NICE) and the pan Canadian Oncology Drug Review Expert Review (pCODR) Committee recommended reimbursement for osimertinib for the treatment of EGFR-mutated NSCLC following prior TKI therapy, cost-effectiveness analyses should be performed following maturation of the OS data [4].

€ 6,132.50 per month; € 98,120.00 per 16 months of treatment

osimertinib more costly than other FDA-approved EGFR-TKIs

Overall, FLAURA is the first phase III, randomized, double-blind, comparative trial to demonstrate that osimertinib substantially increases PFS and lowers the risk of disease progression compared to first-generation EGFR-TKI as initial therapy for EGFR-mutated advanced NSCLC. The PFS benefit was consistent across subgroups regardless of race, EGFR subtype, and presence of CNS metastases. OS and QoL data are needed to confirm patients achieve a clinically relevant benefit over time despite favourable tolerability. Currently, the optimal therapeutic sequencing of different generations of EGFR-TKI remains unknown. However osimertinib holds efficacy for brain metastases that represent a significant clinical problem in patients treated with first and second generation EGFR-TKIs. Further analyses are necessary to fully characterize the resistance mechanisms to osimertinib for

FLAURA: phase III RCT demonstrates benefit in PFS, as initial therapy for EGFR-mutated NSCLC

optimal therapeutic sequencing of different generations of EGFR-TKI remains unknown

targeting by fourth-generation inhibitors. A new class of inhibitors, designed to target a triple mutation thought to confer resistance to fourth-generation EGFR-TKIs, is also under development.

Table 3: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS [36]

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	MG standard treatment	Efficacy				Safety		AJ	FM
							MG months	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
Adapted ESMO-MCBS	osimertinib	NSCLC	NC	PFS	2b	>6 months	+8.7	0.46 0.37–0.57	HR ≤0.65 AND Gain ≥3 months	3	-9% grade 3–4 AEs, -5% discontinuation	-	-	**3**
Original ESMO-MCBS	osimertinib	NSCLC	NC	PFS	2b	>6 months	+8.7	0.46 0.37–0.57	HR ≤0.65 AND Gain ≥3 months	3	-	-	-	**3**

Abbreviations: AJ = Adjustments; CI = confidence interval; FM = final adjusted magnitude of clinical benefit grade; HR = hazard ratio, m = months; MG = median gain; NSCLC = non-small cell lung cancer; PE = primary endpoint; PFS = progression-free survival; PM = preliminary magnitude of clinical benefit grade; QoL = quality of life

DISCLAIMER

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

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12 Appendix

Table 4: Administration and dosing of osimertinib or standard of care TKI [2, 3, 28, 29]

	Osimertinib	SoC TKI (gefitinib or erlotinib)
Administration mode	Orally, once/day with or without food; patients with difficulty swallowing may disperse tablet in 2 ounces of un-carbonated water [2]	Gefitinib orally once/day with or without food; patients with difficulty swallowing may immerse tablet in 4–8 ounces of water [28]; erlotinib orally on an empty stomach [29]
Description of packaging	80 mg beige, oval, tablets marked "AZ 80" on one side, supplied in bottles of 30 tablets; 40 mg round tablets are also available in bottles of 30 [2]	Gefitinib: 250 mg brown film-coated tablets, debossed "IRESSA 250," supplied in bottles of 30 tablets [28] Erlotinib: 150 mg white film-coated tablets, printed "T150," supplied in bottles of 30 tablets [29]
Total volume contained in packaging for sale	30-tablet bottle of 80 mg dose contains 30 tablets (80 mg/tablet, 80 mg/day); 30-tablet bottle of 40 mg dose pack contains 30 tablets (40 mg/tablet, 40 mg/day) under specific circumstances [2, 3]	30-tablet bottle of 250 mg gefitinib contains 30 tablets (250 mg/tablet, 250 mg/day) [28] 30-tablet bottle of erlotinib contains 30 tablets (150 mg/tablet, 150 mg/day) [29]
Dosing	80 mg/day; discontinue in patients with ILD/pneumonitis, prolonged QTc interval, symptomatic CHF or LVD ≥4 weeks; withhold if AEs of grade ≥3 or QTc interval ≥500 msec on 2 separate ECGs; if baseline QTc is ≥481 msec, resume at 40 mg. If AEs improve to grade 0-2 within 3 weeks, resume at 80 mg or 40 mg daily [2].	250 mg/day of gefitinib or 150 mg/day of erlotinib may be reduced to 10 mg/day. Discontinue gefitinib or erlotinib in patients with ILD, severe hepatic impairment, ulcerative keratitis, or GI perforation. Withhold gefitinib for grade ≥2 ALT and/or AST elevations, ocular disorders, grade ≥3 diarrhoea, or skin disorders [28, 29].
Median treatment duration	Until DP or unacceptable toxicity or as long as there is clinical benefit; median DTTE was 16.2 months (range 0.1–27.4) [3]	Until DP or unacceptable toxicity; median DTTE was 11.5 months (range 0-26.2) for SoC TKI [3]
Contraindications	None [2]	None [28, 29]
Drug interactions	Increase to 160 mg/day in patients receiving strong CYP3A inducers or avoid them [2].	Increase gefitinib to 500 mg/day with CYP3A4 inducers, avoid PPIs, monitor INR with warfarin [28]. Erlotinib concentrations increase with CYP3A4 inhibitors, decrease with CYP3A4 or CYP1A2 inducers; and drugs that alter pH alter absorption [29].

Abbreviations: AE = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CHF = congestive heart failure; DDTE = duration of total treatment exposure; DP = disease progression; ECG = electrocardiogram; GI = gastrointestinal; ILD = interstitial lung disease; INR = international normalized ratio; LVD = left ventricular dysfunction; PPI = proton pump inhibitor; QTc = QT interval corrected for heart rate

Table 5: Characteristics of the FLAURA trial

Title: Osimertinib in untreated EGFR-mutated advanced NSCLC (FLAURA) [3, 27]			
Study identifier	NCT02296125, EudraCT2014-002694-11, D5160C00007, U1111-1160-2242, FLAURA		
Design	International (29 countries), multicentre (132 sites), randomized, double-blind, comparative, phase III		
	Duration of main phase:	December 2014-March 2016 screened 994 patients; 556 patients randomized 1:1 to receive osimertinib (n=279) or SoC EGFR-TKI (n=277) Data cut-off: June 12, 2017; 136 (49%) osimertinib patients and 206 (74%) SoC EGFR-TKI patients experienced progression or death Median duration of follow-up for PFS: 15.0 months (range 0–25.1) and 9.7 months (range 0–26.1) for osimertinib and SoC groups, respectively	
	Duration of Run-in phase:	Not applicable	
	Duration of Extension phase:	After data cut-off, 141 (56%) osimertinib and 64 (23%) SoC EGFR-TKI patients continued receiving trial treatment; 55 (43%) of SoC EGFR-TKI patients received osimertinib (48 on crossover, 7 outside of the trial as second line treatment)	
Hypothesis	Superiority The study was designed to assess the safety and efficacy of osimertinib in patients with previously untreated EGFRm-positive advanced NSCLC compared to SoC EGFR-TKIs, gefitinib or erlotinib.		
Funding	AstraZeneca		
Treatments groups	Osimertinib *(n= 279 efficacy; n=279 safety; n=141 ongoing at data cut-off; n=82 treatment post-discontinuation of osimertinib)*	80 mg orally once daily, with or without food + placebo SoC EGFR-TKI until disease progression or unacceptable toxicity	
	SoC EGFR TKI *(n= 279 efficacy; n=277 safety; n=64 ongoing at data cut-off; n=99 treatment post-discontinuation of SoC EGFR-TKI; n=48 cross-over to osimertinib of which 30 were ongoing at data cut-off)* Gefitinib (n=183) Erlotinib (n=94)	SoC EGFR-TKI taken until disease progression or unacceptable toxicity 250 mg orally once daily + placebo osimertinib 150 mg orally once daily + placebo osimertinib	
	Notes	Treated beyond disease progression if patients continued to derive investigator-assessed clinical benefit Protocol amendment allowed SoC EGFR-TKI patients to cross over to open-label osimertinib after BICR-assessed progression and local or centrally confirmed T790M mutation.	
Endpoints and definitions	Progression-free survival Primary endpoint	PFS	Time from randomization until progression (RECIST v1.1) or all-cause death, regardless of withdrawal or therapy prior to progression (approximately 11.5 months)
	Objective response rate Secondary endpoint	ORR	The number (%) of patients with measurable disease with at least 1 visit response of CR or PR (approximately 11.5 months)
	Progression-free survival in T790M-positive or T790M–negative patients Secondary endpoint	PFS	Time from randomization until progression (RECIST v1.1) or all-cause death, regardless of withdrawal or therapy prior to progression (approximately 11.5 months)
	Overall survival Secondary endpoint	OS	Time from randomization until all-cause death (approximately 29 months)
	PRO by therapy satisfaction CTSQ-16 Questionnaire Secondary endpoint	CTSQ-16	Questionnaire assesses satisfaction with and preference for chemo, hormonal, and biological therapies in either oral and/or IV form (approximately 2 months)
	Pharmacokinetics Secondary endpoint	PK	Pharmacokinetics exposure parameters derived from plasma concentrations (approximately 9 months)
	PRO of disease-related symptoms and HRQoL Secondary endpoint	EORTC QLQ-C30	30-item questionnaire measuring general cancer symptoms and function (approximately 20 months)
	Duration of response Secondary endpoint	DOR	Time from first response until progression or death (approximately 11.5 months)
	Disease Control Rate Secondary endpoint	DCR	Percentage of patients with a best overall response of CR, PR, or SD (approximately 11.5 months)

<table>
<tr><td rowspan="3">Endpoints and definitions
(continuation)</td><td>Depth of response
Secondary endpoint</td><td>DTOR</td><td colspan="3">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 to baseline (approximately 11.5 months)</td></tr>
<tr><td>HRQoL by EORTC QLQ-LC13
Secondary endpoint</td><td>EORTC QLQ-LC13</td><td colspan="3">Questionnaire measuring lung cancer symptoms and side effects from conventional chemo-and radiotherapy (approximately 20 months)</td></tr>
<tr><td>Adverse events
Secondary endpoint</td><td>AEs</td><td colspan="3">AEs graded by CTCAE version 4.0 (expected average 13 months)</td></tr>
<tr><td>Database lock</td><td colspan="5">Last update posted February 2018</td></tr>
<tr><td colspan="6">Results and Analysis</td></tr>
<tr><td>Analysis description</td><td colspan="5">Primary Analysis
ITT: Primary endpoint was investigator-assessed PFS (RECIST version 1.1). A sensitivity analysis of PFS was performed on the basis of data from BICR of RECIST assessments for all the patients.
Efficacy analyses, based on the full analysis set, included all randomly assigned patients. Safety analyses consisted of all patients who received at least one dose of study drug.
A log-rank test, stratified by race (Asian versus non-Asian) and mutation type (Ex19 del versus L858R), was used to compare PFS between treatment groups, Breslow approach to handle tied events. Data for patients without progression or death at the time of analysis were censored at the time of the last RECIST assessment.
Approximately 359 events of progression or death in a total of 530 randomly assigned patients would provide 90% power to detect a hazard ratio of 0.71 at a two-sided alpha level of 5%.</td></tr>
<tr><td rowspan="3">Analysis population</td><td>Inclusion</td><td colspan="4">✪ Adults (aged ≥18 years) with pathologically confirmed LA or metastatic NSCLC not amenable to curative surgery or radiotherapy
✪ Local or central confirmation of the EGFR exon 19 deletion (EX19 del) or p.Leu858Arg (L858R) EGFR mutation, alone or co-occurring with other EGFR mutations
✪ Patients with CNS metastases whose condition was neurologically stable were eligible
✪ Any previous definitive treatment or glucocorticoid therapy had to be completed at least 2 weeks before initiation of the trial treatment</td></tr>
<tr><td>Exclusion</td><td colspan="4">✪ Prior treatment with EGFR-TKIs or any systemic anti-cancer therapy for LA or metastatic NSCLC
✪ Radiotherapy to ≥30% of bone marrow or with a wide field of radiation, or major surgery within 4 weeks of the first dose of study drug
✪ Medications or supplements that induce cytochrome P450 (CYP) 3A4, an alternative anti-cancer treatment, or an investigational drug within 5 half-lives of the compound or any of its related material
✪ Concurrent and/or other active malignancy that requires treatment within 2 years of first dose of study drug
✪ Spinal cord compression symptomatic and unstable brain metastases, except those who have completed definitive therapy, are not on steroids, have stable neurologic status for at least 2 weeks after completing definitive therapy and steroids
✪ Severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses; or active infection including hepatitis B, hepatitis C and HIV
✪ Refractory nausea and vomiting, chronic gastrointestinal disease, inability to swallow the formulated product, or previous significant bowel resection that precludes adequate absorption of osimertinib
✪ Cardiac criteria involving: mean resting corrected QTc >470 msec; abnormalities in rhythm, conduction or morphology of resting ECG; or factors that increase QTc prolongation or risk of arrhythmic events or unexplained sudden death <40 years of age in first-degree relatives or concomitant medication that prolongs the QT interval
✪ History of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment or clinically active ILD</td></tr>
<tr><td>Characteristics</td><td>Osimertinib
(n = 279)</td><td>Standard EGFR-TKI
(n = 277)</td><td>Total
(n =5 56)</td></tr>
</table>

Analysis population *(continuation)*	Median age (range), years	64 (26–85)	64 (35–93)	64 (26–93)
	Male, n (%)	101 (36)	105 (38)	206 (37)
	Race, n (%) Caucasian Asian Other	 101 (36) 174 (62) 4 (1)	 100 (36) 173 (62) 4 (1)	 201 (36) 347 (62) 8 (1)
	Smoking status, n (%) Never Current Former	 182 (65) 8 (3) 89 (32)	 175 (63) 9 (3) 93 (34)	 357 (64) 17 (3) 182 (33)
	WHO Performance Status, n (%) 0 1 Missing data	 112 (40) 167 (60) 0	 116 (42) 160 (58) 1 (<1)	 228 (41) 327 (59) 1 (<1)
	Histologic type, n (%) Adenocarcinoma Other	 275 (99) 4 (1)	 272 (98) 5 (2)	 547 (98) 9 (2)
	Overall disease classification, n (%) Metastatic Locally advanced Missing data	 264 (95) 14 (5) 1 (<1)	 262 (95) 15 (5) 0	 526 (95) 29 (5) 1 (<1)
	Metastases, n (%) Visceral metastases CNS metastases	 94 (34) 53 (19)	 103 (37) 63 (23)	 197 (35) 116 (21)
	EGFR mutation type at randomization, n (%) Exon 19 deletion L858R	 175 (63) 104 (37)	 174 (63) 103 (37)	 349 (63) 207 (37)
	EGFR mutation type by central test, n (%) Exon 19 deletion L858R No mutation detected, invalid test, or no or inadequate sample	 158 (57) 97 (35) 24 (9)	 155 (56) 90 (32) 32 (12)	 313 (56) 187 (34) 56 (10)
	EGFR-TKI comparator, n (%) Gefitinib Erlotinib	 NA NA	 183 (66) 94 (34)	 183 (66) 94 (34)
Applicability of evidence				
Population	FLAURA was conducted in untreated patients with advanced NSCLC whose tumours harbour a local or centrally confirmed EGFR EX19del or L858R mutation. Alone or co-occurring with other EGFR mutations. Patients with stable CNS metastases were also eligible. The study population had a median age of 64 years, 63% were female, 62% were Asian, 64% were never smokers, 21% had CNS metastases, 63% and 37% harboured EX19del and L858R mutations, respectively. Study demographics and clinical characteristics are representative of the global population with EGFR-mutated advanced NSCLC.			
Intervention	The dosage and administration of osimertinib used in FLAURA is consistent with the recommended dosage and administration and that determined in the dose-defining AURA study [6, 9]. Dose interruptions, reductions, and treatment beyond progression were allowed based on investigator-assessed continued clinical benefit. SoC patients were allowed to cross over to osimertinib following confirmation of BICR-assessed progression and post-progression documented T790M-positive status.			
Comparators	While first-generation reversible gefitinib and erlotinib were used as comparators, second-generation irreversible afatinib is currently available and may have formed a suitable comparison. However, afatinib irreversibly binds wild-type EGFR also, causing dose-limiting rash and diarrhoea.			
Outcomes	While osimertinib improves PFS, ORR, DOR compared to SoC EGFR-TKI in FLAURA, OS data were not mature and QoL was not reported in this analysis. Some cases of CNS progression may have gone undetected as only patients with brain metastases were routinely scanned.			
Setting	FLAURA was a multinational study conducted in 29 countries, approximately 62% of patients were Asian, 36% were Caucasian, and 1% were of other race.			

Abbreviations: AEs = adverse events; BICR = blinded independent central review; CR = complete response; CTCA = Common Terminology Criteria for Adverse Events; CTSQ = Cancer Therapy Satisfaction Questionnaire; DCR = disease control rate; DOR = duration of response; DTOR = depth of response; ECG = electrocardiogram; EGFR = Epidermal Growth Factor Receptor; EGFRm = EGFR sensitising mutation; HRQoL = health-related quality of life; HIV = human immunodeficiency virus; ILD = interstitial lung disease; IV = intravenous; LA = locally advanced; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO = patient reported outcomes; QTc = corrected QT interval; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; SoC = standard of care; TKI = tyrosine kinase inhibitor; WHO = World Health Organization

Table 6: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [34, 40]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: randomised 1:1 to osimertinib SoC gefitinib or erlotinib using the IVRS/IWRS system. The actual EGFR-TKI was selected at a site/country level according to the country's marketing authorisation prior to the site initiation. Patients stratified at randomisation based on EGFR mutation (Ex19del or L858R) and race (Asian or non-Asian).		yes
Adequate allocation concealment: The IVRS/IWRS assigns the bottles of study material to be dispensed to each patient.		yes
Blinding:	**Patient:** patients received active osimertinib plus comparator-matching placebo or active comparator plus osimertinib-matching placebo. Active and placebo tablets are identical and presented in the same packaging to ensure blinding.	yes
	Treating physician: The IVRS/IWRS assigns the bottles of study material to be dispensed to each patient. Patients received active osimertinib plus comparator-matching placebo or active comparator plus osimertinib-matching placebo. Active and placebo tablets are identical and present in the same packaging to ensure blinding.	yes
	Outcome assessor: centralised randomisation and allocation; sensitivity analysis was planned to assess PFS by pre-defined subgroups	yes
Selective outcome reporting unlikely: primary endpoints include investigator-assessed PFS, OS, ORR, DOR, DCR, DTOR and safety. Other endpoints not included in this analysis include mature OS, QoL, pharmacokinetics as per protocol.		yes
No other aspects which increase the risk of bias: industry funded the study, assisted with study design, collected, analysed and interpreted the data; all authors reviewed the manuscript and had full access to study data, cross-over		no
Risk of bias – study level		low-risk

Abbreviations: DCR = disease control rate; DOR = duration of response; DTOR = depth of treatment response; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; IVRS/IWRS = interactive web response system; interactive web response system; OS = overall survival; PFS = progression-free survival; QoL = quality of life; SoC = standard of care