TAGRISSO®
(osimertinib)

1. NAME OF THE MEDICINAL PRODUCT

TAGRISSO 80 mg film-coated tablets

TAGRISSO 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 80 mg tablet contains a dose of 80 mg osimertinib (as mesylate).

Each 40 mg tablet contains a dose of 40 mg osimertinib (as mesylate).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

The TAGRISSO 80 mg tablet is a beige, 7.25 x 14.5 mm, oval, biconvex tablet, debossed with "AZ" and "80" on one side and plain on the reverse.

The TAGRISSO 40 mg tablet is a beige, 9 mm, round, biconvex tablet, debossed with "AZ" and "40" on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TAGRISSO (osimertinib) is indicated for:

- the adjuvant treatment after tumour resection in patients with non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.
- the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.
- the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy. (See Clinical efficacy and safety section)

4.2 Posology and method of administration

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

When considering the use of TAGRISSO, EGFR mutation status should be determined using a validated test method (see section 4.4) for:

- exon 19 deletions or exon 21 (L858R) substitution mutations (in tumour specimens for adjuvant treatment and tumour or plasma specimens for first-line treatment)
- T790M mutations (in tumour or plasma specimens following progression on or after EGFR TKI therapy).

Posology

The recommended dose of TAGRISSO is 80 mg osimertinib once a day.

Duration of treatment

Patients in the adjuvant setting should receive treatment until disease recurrence or unacceptable toxicity or up to a maximum of 3 years. Treatment duration for more than 3 years was not studied.

Patients with locally advanced or metastatic lung cancer should receive treatment until disease progression or unacceptable toxicity.

Missed dose

If a dose of TAGRISSO is missed, make up the dose unless the next dose is due within 12 hours.

TAGRISSO can be taken with or without food at the same time each day.

Dose adjustments

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of TAGRISSO should be reduced to 40 mg taken once daily. Dose reduction guidelines for adverse reactions toxicities are provided in Table 1.

Table 1 Recommended dose modifications for TAGRISSO

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary[b]	ILD/Pneumonitis	Permanently discontinue TAGRISSO
Cardiac[b]	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue TAGRISSO
Cutaneous[b]	Stevens-Johnson Syndrome and Toxic epidermal necrolysis	Permanently discontinue TAGRISSO
Blood and	Aplastic anaemia	Permanently discontinue

Target Organ	Adverse Reaction[a]	Dose Modification
lymphatic system[b]		TAGRISSO
Other	Grade 3 or higher adverse reaction	Withhold TAGRISSO for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of TAGRISSO for up to 3 weeks	TAGRISSO may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue TAGRISSO

[a] Note: The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

[b] Refer to Section 4.4 Special warnings and special precautions for use for further details.

Special patient populations

No dosage adjustment is required due to patient age, body weight, gender, ethnicity and smoking status (see section 5.2).

Paediatric and adolescents

The safety and efficacy of TAGRISSO in children or adolescents aged less than 18 years have not been established. No data are available.

Method of administration

This medicinal product is for oral use. The tablet should be swallowed whole with water. The tablet should not be crushed, split or chewed.

If the patient is unable to swallow the tablet, it may first be dispersed in 50 mL of non-carbonated water. The tablet should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional half a glass of water should be added to ensure that no residue remains and then immediately swallowed. No other liquids should be added.

If administration via nasogastric tube is required, the same process as above should be followed but using volumes of 15 mL for the initial dispersion and 15 mL for the residue rinses. The resulting 30 mL of liquid should be administered as per the naso-gastric tube manufacturer's instructions with appropriate water flushes. The dispersion and residues should be administered within 30 minutes of the addition of the tablets to water.

Elderly (>65 years)

Population pharmacokinetic (PK) analysis indicated that age did not have an impact on the exposure of osimertinib and hence, osimertinib can be used in adults without regard to age.

Hepatic impairment

Based on clinical studies, no dose adjustments are necessary in patients with mild hepatic impairment (Child Pugh A) or moderate hepatic impairment (Child Pugh B). Similarly based on population PK analysis, no dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin between 1.0 to 1.5x ULN and any AST) or moderate hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST). The appropriate dose of TAGRISSO has not been established in patients with severe hepatic impairment (see section 5.2).

Renal impairment

Based on clinical studies and population PK analysis, no dose adjustments are necessary in patients with mild, moderate, or severe renal impairment. The safety and efficacy of TAGRISSO has not been established in patients with end-stage renal disease [Creatinine clearance (CLcr) less than 15 mL/min, calculated by the Cockcroft and Gault equation], or on dialysis. Caution should be exercised when treating patients with severe and end-stage renal impairment (see section 5.2).

4.3 Contraindications

None.

4.4 Special warnings and special precautions for use

Assessment of EGFR mutation status

When considering the use of TAGRISSO as an adjuvant therapy after tumour resection in patients with NSCLC, EGFR mutation positive status (exon 19 deletions or exon 21 (L858R) substitution mutations) indicates treatment eligibility. A validated test should be performed in a clinical laboratory using tumour tissue DNA from diagnostic tumour biopsy specimen or tumour tissue taken during surgery.

When considering the use of TAGRISSO as a treatment for locally advanced or metastatic NSCLC, it is important that the EGFR mutation positive status is determined. A validated test should be performed in a clinical laboratory using either tumour tissue DNA or circulating tumour DNA (ctDNA) obtained from a plasma sample.

Only robust, reliable and sensitive test(s) with demonstrated utility for the determination of EGFR mutation status should be used.

Positive determination of EGFR mutation status (exon 19 deletions or exon 21 (L858R) substitution mutations for first-line treatment or T790M mutations following progression on or after EGFR TKI therapy) using either a tissue-based or plasma-based test indicates eligibility for treatment with TAGRISSO. However, if a plasma-based ctDNA test is used and the result is negative, it is advisable to follow-up with a tissue test wherever possible due to the potential for false negative results using a plasma-based test.

Interstitial lung disease (ILD)

Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) were reported in 3.8% and were fatal in 0.3% (n=5) of the 1479 patients who received TAGRISSO in ADAURA, FLAURA and AURA studies.

The incidence of ILD was 11.3% in patients of Japanese ethnicity, 1.6% in patients of non-Japanese Asian ethnicity and 2.5% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 2.8 months.

Withhold TAGRISSO and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms which may be indicative of ILD (e.g. dyspnoea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed.

Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

Case reports of erythema multiforme (EM) and toxic epidermal necrolysis (TEN) have been uncommonly reported, and Stevens-Johnson syndrome (SJS) have been rarely reported, in association with TAGRISSO treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM, SJS and TEN. If signs and symptoms suggestive of EM develop, close patient monitoring and drug interruption or discontinuation of TAGRISSO should be considered. If signs and symptoms suggestive of SJS or TEN appear, TAGRISSO should be interrupted. TAGRISSO should be discontinued immediately if SJS or TEN is diagnosed.

QTc interval prolongation

When possible, avoid use of TAGRISSO in patients with congenital long QT syndrome (see section 4.8). Consider periodic monitoring with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medications that are known to prolong the QTc interval. Withhold TAGRISSO in patients who develop a QTc interval greater than 500 msec on at least 2 separate ECGs until the QTc interval is less than 481 msec or recovery to baseline if the QTc interval is greater than or equal to 481 msec, then resume TAGRISSO at a reduced dose as described in Table 1. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation in combination with any of the following: Torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia.

Changes in cardiac contractility

Across clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases greater than or equal to 10 percentage points and a drop to less than 50% occurred in 3.2% (40/1233) of patients treated with TAGRISSO who had baseline and at least one follow-up LVEF assessment. In a placebo controlled trial (ADAURA), 1.6% (5/312) of patients treated with TAGRISSO and 1.5% (5/331) of patients treated with placebo experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%.

Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and TAGRISSO has not been established. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who

develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

Keratitis

Keratitis was reported in 0.7% (n=10) of the 1479 patients treated with TAGRISSO in the ADAURA, FLAURA and AURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist (see section 4.2).

Aplastic Anaemia

Rare reports of aplastic anaemia have been reported in association with TAGRISSO treatment. Some cases had a fatal outcome. Before initiating treatment, patients should be advised of signs and symptoms of aplastic anaemia including but not limited to persistent fever, bruising, bleeding, pallor. If signs and symptoms suggestive of aplastic anaemia develop, close patient monitoring and drug interruption or discontinuation of TAGRISSO should be considered. TAGRISSO should be discontinued in patients with confirmed aplastic anaemia.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Strong CYP3A4 inducers can decrease the exposure of osimertinib. Osimertinib may increase the exposure of breast cancer resistant protein (BCRP) and P-glycoprotein (P-gp) substrates.

Active substances that may increase osimertinib plasma concentrations

In vitro studies have demonstrated that the Phase I metabolism of osimertinib is predominantly via CYP3A4 and CYP3A5. In a clinical pharmacokinetic study in patients, TAGRISSO co-administered with 200 mg itraconazole twice daily (a strong CYP3A4 inhibitor) had no clinically significant effect on the exposure of osimertinib (area under the curve (AUC) increased by 24% (90% CI 15, 35) and C_{max} decreased -20% (90% CI -27, -13). Therefore, CYP3A4 inhibitors are not likely to affect the exposure of osimertinib.

Active substances that may decrease osimertinib plasma concentrations

In a clinical pharmacokinetic study in patients, the steady-state AUC of osimertinib was reduced, -78% (90% CI -81, -76), when co-administered with rifampicin (600 mg daily for 21 days). It is recommended that concomitant use of strong CYP3A inducers (e.g. Phenytoin, rifampicin, carbamazepine, St. John's Wort) with TAGRISSO should be avoided. If not possible, then increase TAGRISSO dose to 160 mg during the treatment with strong CYP3A inducer and resume at 80 mg, 3 weeks after discontinuation of the strong CYP3A inducer. Based on physiologically-based pharmacokinetic (PBPK) model simulations, no dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.

Effect of gastric acid reducing active substances on osimertinib

In a clinical pharmacokinetic study, co-administration of omeprazole did not result in clinically relevant changes in osimertinib exposures. Gastric pH modifying agents can be concomitantly used with TAGRISSO without any restrictions.

Active substances whose plasma concentrations may be altered by TAGRISSO

Based on *in vitro* studies, osimertinib is a competitive inhibitor of BCRP transporter.

In a clinical PK study, co-administration of TAGRISSO with rosuvastatin (sensitive BCRP substrate) increased the AUC and C_{max} of rosuvastatin by 35% (90% CI 15, 57) and 72% (90% CI 46, 103), respectively. Patients taking concomitant medications with disposition dependent upon BCRP and with narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving TAGRISSO.

In a clinical PK study, co-administration of TAGRISSO with simvastatin (sensitive CYP3A4 substrate) decreased the AUC and C_{max} of simvastatin, -9% (90% CI -23, 8) and -23% (90% CI -37, -6), respectively. These changes are small and not likely to be of clinical significance. Clinical PK interactions with CYP3A4 substrates are unlikely.

In a clinical PK study, co-administration of TAGRISSO with fexofenadine (PXR/P-gp substrate) increased the AUC and C_{max} of fexofenadine by 56% (90% CI 35, 79) and 76% (90% CI 49, 108) after a single dose and 27% (90% CI 11, 46) and 25% (90% CI 6, 48) at steady state, respectively. Patients taking concomitant medications with disposition dependent upon P-gp and with narrow therapeutic index (e.g. digoxin, dabigatran, aliskiren) should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving TAGRISSO (see section 5.2).

4.6 Pregnancy, lactation and fertility

Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving TAGRISSO. Patients should be advised to use effective contraception for the following periods after completion of treatment with TAGRISSO: at least 6 weeks for females and 4 months for males.

Pregnancy

There are no or limited amount of data from the use of TAGRISSO in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Based on its mechanism of action and preclinical data, TAGRISSO may cause foetal harm when administered to a pregnant woman. Administration of osimertinib to pregnant rats was associated with embryolethality, reduced foetal growth and neonatal death at exposures similar to what is expected in humans (see section 5.3). TAGRISSO is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether osimertinib or its metabolites are excreted in human milk. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death. There is insufficient information on the excretion of osimertinib or its metabolites in animal milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with TAGRISSO.

Fertility

There are no data on the effect of TAGRISSO on human fertility. Results from animal studies have shown that TAGRISSO has effects on male and female reproductive organs and could impair fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

TAGRISSO has no or no marked influence on the ability to drive and use machines.

4.8 Undesirable effects

Overall summary of the safety profile

Studies in EGFR mutation positive NSCLC patients

The data described below reflect exposure to TAGRISSO in 1479 patients with EGFR mutation positive NSCLC. These patients received TAGRISSO at a dose of 80 mg daily in three randomised Phase 3 studies (ADAURA, adjuvant; FLAURA, first-line; AURA3, second-line only), two single-arm Phase 2 studies (AURAex; AURA2, second-line or greater) and one Phase 1 study (AURA1, first-line or greater) (see section 5.1).

Most adverse reactions were Grade 1 or Grade 2 in severity. The most commonly reported adverse drug reactions (ADRs) were diarrhoea (47%), rash (45%), paronychia (33%), dry skin (32%), and stomatitis (24%). Grade 3 and Grade 4 adverse reactions with TAGRISSO were 9% and 0.1%, respectively. In patients treated with TAGRISSO 80 mg once daily, dose reductions due to adverse reactions occurred in 3.2% of the patients. Discontinuation due to adverse reactions was 4.6%.

Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from clinical studies. Patients with clinically important abnormalities in rhythm and conduction as measured by resting ECG (e.g. QTc interval greater than 470 ms) were excluded from these studies. Patients were evaluated for LVEF at screening and every 12 weeks thereafter.

Tabulated list of adverse reactions

Adverse reactions have been assigned to the frequency categories in Table 2 where possible based on the incidence of comparable adverse event reports in a pooled dataset from the 1479 EGFR mutation positive patients who received TAGRISSO at a dose of 80 mg daily in the ADAURA, FLAURA, AURA3, AURAex, AURA2 and AURA1 studies.

Adverse reactions are listed according to system organ class (SOC) in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented

in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the CIOMS III convention and is defined as: very common (≥1/10); common (>1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data).

Table 2 Adverse reactions reported in ADAURA, FLAURA and AURA studies[a]

MedDRA SOC	CIOMS descriptor/overall frequency (all CTCAE grades[b])	Frequency of CTCAE grade 3 or higher
MedDRA Preferred Term		
Blood and lymphatic system disorders		
Aplastic anaemia	Rare (0.07%)	0.07%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	Common (5%)	0%
Interstitial lung disease[c]	Common (3.8%)[d]	1.1%
Gastrointestinal disorders		
Diarrhoea	Very common (47%)	1.4%
Stomatitis[e]	Very common (24%)	0.5%
Eye disorders		
Keratitis[f]	Uncommon (0.7%)	0.1%
Skin and subcutaneous tissue disorders		
Rash[g]	Very common (45%)	0.7%
Paronychia[h]	Very common (33%)	0.4%
Dry skin[i]	Very common (32%)	0.1%
Pruritus[j]	Very common (17%)	0.1%
Alopecia	Common (4.6%)	0%
Urticaria	Common (1.9%)	0.1%
Palmar-plantar erythrodysaesthesia syndrome	Common (1.7%)	0%
Erythema multiforme[k]	Uncommon (0.3%)	0%
Toxic epidermal necrolysis[l]	Uncommon (0.2%)	
Cutaneous vasculitis[l]	Uncommon (0.2%)	
Stevens-Johnson syndrome[m]	Rare (0.02%)	
Investigations		
Blood creatine phosphokinase increased	Common (1.6%)	0.3%
QTc interval prolongation[n]	Uncommon (0.8%)	

MedDRA SOC	CIOMS descriptor/overall frequency (all CTCAE grades[b])	Frequency of CTCAE grade 3 or higher
MedDRA Preferred Term		
(Findings based on test results presented as CTCAE grade shifts)		
Leukocytes decreased[o]	Very common (65%)	1.2%
Lymphocytes decreased[o]	Very common (62%)	6%
Platelet count decreased[o]	Very common (53%)	1.2%
Neutrophils decreased[o]	Very common (33%)	3.2%
Blood creatinine increased[o]	Common (9%)	0%

[a] Data is pooled from ADAURA, FLAURA and AURA (AURA3, AURAex, AURA2 and AURA1) studies; only events for patients receiving at least one dose of TAGRISSO as their randomised treatment are summarised.

[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

[c] Includes: interstitial lung disease, pneumonitis, organising pneumonia.

[d] 5 CTCAE grade 5 events (fatal) were reported.

[e] Includes: mouth ulceration, stomatitis.

[f] Includes: corneal erosion, corneal epithelium defect, keratitis, punctate keratitis.

[g] Includes: acne, dermatitis, dermatitis acneiform, drug eruption, erythema, folliculitis, pustule, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin erosion.

[h] Includes: nail bed disorder, nail bed infection, nail bed inflammation, nail discolouration, nail disorder, nail dystrophy, nail infection, nail pigmentation, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.

[i] Includes: dry skin, eczema, skin fissures, xeroderma, xerosis.

[j] Includes: eyelid pruritis, pruritis, pruritis generalised.

[k] Five of the 1479 patients in the ADAURA, AURA and FLAURA studies reported erythema multiforme. Post-marketing reports of erythema multiforme have also been received, including 7 reports from a post-marketing surveillance study (N=3578).

[l] Estimated frequency. The upper limit of the 95% CI for the point estimate is 3/1479 (0.20%). No reports in clinical trials.

[m] One event reported in a post-marketing study, and the frequency has been derived from the ADAURA, FLAURA and AURA studies and the post-marketing study (N=5057).

[n] Represents the incidence of patients who had a QTcF prolongation >500msec.

[o] Represents the incidence of laboratory findings, not of reported adverse events.

Table 3 Adverse reactions reported in ADAURA[a] study

MedDRA SOC	TAGRISSO (N=337)		Placebo (N=343)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)[c]**	**Any Grade (%)**	**Grade 3 or higher (%)[c]**
MedDRA Preferred Term				
Respiratory, thoracic and mediastinal disorders				
Epistaxis	5.6	0	0.9	0
Interstitial lung disease[d]	3.0	0	0	0
Eye disorders				
Keratitis[e]	0.6	0	0.3	0
Gastrointestinal disorders				
Diarrhoea	46.3	2.4	19.8	0.3
Stomatitis[f]	28.2	1.8	6.4	0
Skin and subcutaneous tissue disorders				
Rash[g]	39.2	0.3	19.0	0
Paronychia[h]	36.5	0.9	3.8	0
Dry skin[i]	29.4	0.3	7.3	0
Pruritus[j]	19.3	0	8.7	0
Alopecia	5.6	0	2.0	0
Palmar-plantar erythrodysaesthesia syndrome	1.8	0	0	0
Urticaria	1.5	0	0.3	0.3

MedDRA SOC	TAGRISSO (N=337)		Placebo (N=343)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)[c]**	**Any Grade (%)**	**Grade 3 or higher (%)[c]**
MedDRA Preferred Term				
Investigations				
Blood creatine phosphokinase increased	3.3		0.9	
QTc interval prolongation[k]	0.6		0	
(Findings based on test results presented as CTCAE grade shifts)				
Leukocytes decreased[l]	54.0	0	25.4	0
Platelet count decreased[l]	47.2	0	6.6	0.3
Lymphocytes decreased[l]	43.8	2.2	14.4	0.9
Neutrophils decreased[l]	25.6	0.3	10.2	0.3
Blood creatinine increased[l]	9.8	0	4.5	0.3

In ADAURA, the median duration of study treatment was 22.5 months for patients in the TAGRISSO arm and 18.7 months for patients in the placebo arm.

[a] Only events for patients receiving at least one dose of TAGRISSO as their randomised treatment are summarised.

[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

[c] All events were Grade 3. There were no deaths.

[d] Includes: interstitial lung disease, pneumonitis.

[e] Includes: keratitis, punctate keratitis, corneal erosion, corneal epithelium defect.

[f] Includes: stomatitis, mouth ulceration.

[g] Includes: acne, dermatitis, dermatitis acneiform, drug eruption, erythema, folliculitis, pustule, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin erosion.

[h] Includes: nail bed disorder, nail bed infection, nail bed inflammation, nail discolouration, nail disorder, nail dystrophy, nail infection, nail pigmentation, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.

[i] Includes: dry skin, eczema, skin fissures, xeroderma, xerosis.

[j] Includes: eyelid pruritis, pruritis, pruritis generalised.

[k] Represents the incidence of patients who had a QTcF prolongation >500 msec.

[l] Represents the incidence of laboratory findings, not of reported adverse events.

Table 4 Adverse reactions reported in FLAURA[a] study

MedDRA SOC	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
NCI Grade[b]	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
MedDRA Preferred Term				
Respiratory, thoracic and mediastinal disorders				
Epistaxis	6.1	0	5.1	0
Interstitial lung disease[c]	3.9	1.1	2.2	1.4
Eye disorders				
Keratitis[d]	0.4	0	1.4	0
Gastrointestinal disorders				
Diarrhoea[e]	58	2.2	57	2.5
Stomatitis[f]	32	0.7	22	1.1
Skin and subcutaneous tissue disorders				
Rash[g]	58	1.1	78	6.9
Dry skin[h]	36	0.4	36	1.1
Paronychia[i]	35	0.4	33	0.7
Pruritus[j]	17	0.4	17	0
Alopecia	7.2	0	13	0
Urticaria	2.2	0.7	0.4	0
Palmar-plantar erythrodysaesthesia syndrome	1.4	0	2.5	0
Investigations				

MedDRA SOC	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
NCI Grade[b]	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
MedDRA Preferred Term				
QTc interval prolongation[k]	1.1		0.7	
Blood creatine phosphokinase increased	0.4		0.4	
(Findings based on test results presented as CTCAE grade shifts)				
Leukocytes decreased[l]	72	0.4	31	0.4
Lymphocytes decreased[l]	63	5.6	36	4.2
Platelet count decreased[l]	51	0.7	12	0.4
Neutrophils decreased[l]	41	3.0	10	0
Blood creatinine increased[l]	8.8	0	6.7	0.4

In FLAURA, the median duration of study treatment was 16.2 months for patients in the TAGRISSO arm and 11.5 months for patients in the EGFR TKI comparator arm.

[a] Only events for patients receiving at least one dose of TAGRISSO as their randomised treatment are summarised.

[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

[c] Includes: interstitial lung disease, pneumonitis.

[d] Includes: corneal erosion, corneal epithelium defect, keratitis, punctuate keratitis.

[e] 1 CTCAE grade 5 event (fatal) was reported in the EGFR TKI comparator arm.

[f] Includes: mouth ulceration, stomatitis.

[g] Includes: acne, dermatitis, dermatitis acneiform, drug eruption, erythema, folliculitis, pustule, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin erosion.

[h] Includes: dry skin, eczema, skin fissures, xeroderma, xerosis.

[i] Includes: nail bed disorder, nail bed infection, nail bed inflammation, nail discolouration, nail disorder, nail dystrophy, nail infection, nail pigmentation, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.

[j] Includes: eyelid pruritis, pruritis, pruritis generalised.

[k] Represents the incidence of patients who had a QTcF prolongation >500 msec.

[l] Represents the incidence of laboratory findings, not of reported adverse events.

Table 5 Adverse reactions reported in AURA3[a] study

MedDRA SOC	TAGRISSO overall frequency (N=279)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) overall frequency (N=136)	
NCI Grade[b]	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
MedDRA Preferred Term				
Respiratory, thoracic and mediastinal disorders				
Epistaxis	5.4	0	1.5	0
Interstitial lung disease[c,d]	3.6	0.4	0.7	0.7
Eye disorders				
Keratitis[e]	1.1	0	0.7	0
Gastrointestinal disorders				
Diarrhoea	41	1.1	11	1.5
Stomatitis[f]	19	0	15	1.5
Skin and subcutaneous tissue disorders				
Rash[g]	34	0.7	5.9	0
Dry skin[h]	23	0	4.4	0
Paronychia[i]	22	0	1.5	0
Pruritus[j]	13	0	5.1	0
Alopecia	3.6	0	2.9	0
Urticaria	2.5	0	1.5	0
Palmar-plantar erythrodysaesthesia syndrome	1.8	0	0.7	0
Investigations				
QTc interval prolongation[k]	1.4		0	
Blood creatine phosphokinase increased	0.7		0.7	
(Findings based on test results presented as CTCAE grade shifts)				

MedDRA SOC	TAGRISSO overall frequency (N=279)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) overall frequency (N=136)	
NCI Grade[b]	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
MedDRA Preferred Term				
Leukocytes decreased[l]	61	1.1	75	5.3
Platelet count decreased[l]	46	0.7	48	7.4
Neutrophils decreased[l]	27	2.2	49	12
Blood creatinine increase[l]	6.5	0	9.2	0

In AURA3, the median duration of study treatment was 8.1 months for patients in the TAGRISSO arm and 4.2 months for patients in the chemotherapy arm.

[a] Only events for patients receiving at least one dose of TAGRISSO are summarised.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[c] Includes: interstitial lung disease, pneumonitis.
[d] 1 CTCAE grade 5 event (fatal) was reported.
[e] Includes: corneal erosion, corneal epithelium defect, keratitis, punctuate keratitis.
[f] Includes: mouth ulceration, stomatitis.
[g] Includes: acne, dermatitis, dermatitis acneiform, erythema, folliculitis, pustule, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pustular.
[h] Includes: dry skin, eczema, skin fissures, xerosis.
[i] Includes: nail bed disorder, nail bed inflammation, nail bed tenderness, nail discolouration, nail disorder, nail dystrophy, nail infection, nail ridging, onychalgia, onychoclasis, onycholysis, onychomadesis, paronychia.
[j] Includes: eyelid pruritus, pruritus, pruritus generalised.
[k] Represents the incidence of patients who had a QTcF prolongation >500msec.
[l] Represents the incidence of laboratory findings, not of reported adverse events.

Safety findings in the single-arm Phase 2 AURAex and AURA2 studies were generally consistent with those observed in the AURA3 TAGRISSO arm. No additional or unexpected toxicity has been observed and adverse events have been aligned in type, severity and frequency.

Description of selected adverse reactions

Haematological events

Early reductions in the median laboratory counts of leukocytes, lymphocytes, neutrophils and platelets have been observed in patients treated with TAGRISSO, which stabilised over time and then remained above the lower limit of normal. Adverse events of leukopenia, lymphopenia, neutropenia and thrombocytopenia have been reported, most of which were mild or moderate in severity and did not lead to dose interruptions.

OTc prolongation

Of the 1479 patients in ADAURA, FLAURA and AURA studies treated with TAGRISSO 80 mg, 0.8% of patients (n=12) were found to have a QTc greater than 500 msec, and 3.1% of patients (n=46) had an increase from baseline QTc greater than 60 msec. A pharmacokinetic analysis with TAGRISSO predicted a concentration-dependent increase in QTc interval prolongation. No QTc-related arrhythmia events were reported in the ADAURA, FLAURA, or AURA studies (see section 4.4).

Special populations

Elderly

In ADAURA, FLAURA and AURA (N=1479), 43% of patients were 65 years of age and older, and 12% were 75 years of age and older. Compared with younger subjects (<65), more subjects ≥65 years old had reported adverse reactions that led to study drug dose modifications (interruptions or reductions) (14% versus 8%). The types of adverse reactions reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (11% versus 8%). No overall differences in efficacy were observed between these subjects and younger subjects.

4.9 Overdose

In TAGRISSO clinical trials a limited number of patients were treated with daily doses of up to 240 mg without dose limiting toxicities. In these studies, patients who were treated with TAGRISSO daily doses of 160 mg and 240 mg experienced an increase in the frequency and severity of a number of typical EGFR-induced AEs (primarily diarrhoea and skin rash) compared to the 80 mg dose.

There is no specific treatment in the event of TAGRISSO overdose. Physicians should follow general supportive measures and should treat symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

TAGRISSO is a Tyrosine Kinase Inhibitor (TKI). It is an oral potent and selective irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harboring sensitising mutations (EGFRm) and TKI-resistance mutation T790M.

In vitro studies have demonstrated that TAGRISSO has high potency and inhibitory activity against EGFR across a range of all clinically relevant EGFR sensitising mutant and T790M mutant non-small cell lung cancer (NSCLC) cell lines (apparent IC_{50}s from 6 nM to 54 nM against phospho-EGFR). This leads to inhibition of cell growth, while showing significantly less activity against EGFR in wild-type cell lines (apparent IC_{50}s 480 nM to 1.9 μM against phospho-EGFR). *In vivo* oral administration of TAGRISSO lead to tumour shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumour models.

Based on an analysis of dose-exposure response relationships over the dose range of 20 mg (0.25 times the recommended dose) to 240 mg (3 times the recommended dose), no apparent efficacy (Objective Response Rate (ORR), Duration of Response (DoR) and Progression-Free Survival (PFS)) relationship for osimertinib was identified. Over the same dose range, increased exposure led to increased probability of adverse reactions, specifically rash, diarrhoea and ILD.

Cardiac electrophysiology

The QTc interval prolongation potential of TAGRISSO was assessed in 210 patients who received osimertinib 80 mg daily in AURA2. Serial ECGs were collected following a single dose and at steady state to evaluate the effect of TAGRISSO on QTc intervals. A pharmacokinetic/pharmacodynamic analysis with TAGRISSO predicted a drug-related QTc interval prolongation at 80 mg of 14 msec with an upper bound of 16 msec (90% CI).

Clinical efficacy and safety

Adjuvant treatment of EGFR mutation positive NSCLC, with or without prior adjuvant chemotherapy – ADAURA

The efficacy and safety of TAGRISSO for the adjuvant treatment of patients with EGFR mutation-positive (exon 19 deletions or L858R substitution mutations) NSCLC who have had complete tumour resection with or without prior adjuvant chemotherapy was demonstrated in a randomised, double-blind, placebo-controlled study (ADAURA).

Patients with resectable tumours (except for stage IA), were required to have EGFR exon 19 deletions or exon 21 L858R substitution mutations identified by the cobas EGFR Mutation Test performed prospectively using biopsy or surgical specimen in a central laboratory. The study excluded patients with clinically important ECG abnormalities identified on resting ECG (e.g. QTc interval >470 ms), history of interstitial lung disease or prior treatment with neoadjuvant or adjuvant EGFR-TKIs.

Patients were randomised (1:1) to receive TAGRISSO 80 mg orally once daily or placebo following recovery from surgery and standard adjuvant chemotherapy. Patients not receiving adjuvant chemotherapy were randomised within 10 weeks and patients receiving adjuvant chemotherapy within 26 weeks following surgery. Randomisation was stratified by mutation type (exon 19 deletions or exon 21 L858R substitution mutations), ethnicity (Asian or non-Asian) and staging based on pTNM (IB or II or IIIA) according to AJCC 7th edition. Treatment was given for 3 years or until disease recurrence or unacceptable toxicity.

The primary efficacy outcome measure was disease-free survival (DFS) by investigator assessment for stage II-IIIA. Secondary endpoints included DFS for the overall population (stage IB-IIIA) and overall survival (OS) for stage II-IIIA and stage IB-IIIA.

A total of 682 patients were randomised to TAGRISSO (n=339) or to placebo (n=343). The median age was 63 years (range 30-86 years), 11% were ≥75 years of age; 70% were female, 64% were Asian and 72% were never smokers. Baseline WHO performance status was 0 (64%) or 1 (36%); 31% had stage IB, 34% II, and 35% IIIA. With regard to EGFR mutation

status, 55% were exon 19 deletions and 45% were exon 21 L858R substitution mutations; 9 patients (1%) also had a concurrent de novo T790M mutation. The majority (60%) of patients received adjuvant chemotherapy prior to randomisation (26% IB; 71% IIA; 73% IIB; 80% IIIA).

An analysis of DFS for both the stage II-IIIA population and the overall population (IB-IIIA) was conducted. ADAURA demonstrated a statistically significant and clinically meaningful reduction in the risk of disease recurrence or death for patients treated with TAGRISSO compared to patients treated with placebo. Patients with stage II-IIIA disease treated with TAGRISSO compared to placebo, achieved 83% reduction in the risk of disease recurrence or death (median not calculated (NC) and 19.6 months, respectively, HR=0.17, 99.06% CI: 0.11, 0.26; P<0.0001). The overall population (IB-IIIA) treated with TAGRISSO compared to placebo demonstrated 80% reduction in the risk of disease recurrence or death (median NC and 27.5 months, respectively, HR=0.20, 99.12% CI: 0.14, 0.30; P<0.0001).

In the overall population, there were 37 patients who had disease recurrence on TAGRISSO. The most commonly reported sites of recurrence were: lung (19 patients); lymph nodes (10 patients) and CNS (5 patients). There were 157 patients who had disease recurrence on placebo. The most commonly reported sites were: lung (61 patients); lymph nodes (48 patients) and CNS (34 patients).

Efficacy results from ADAURA by investigator assessment are summarised in Table 6 and 7, and the Kaplan-Meier curve for DFS in stage II-IIIA patients and in the overall population (IB-IIIA) is shown in Figure 1 and Figure 2, respectively. Overall survival (OS) data were not mature at the time of DFS analysis.

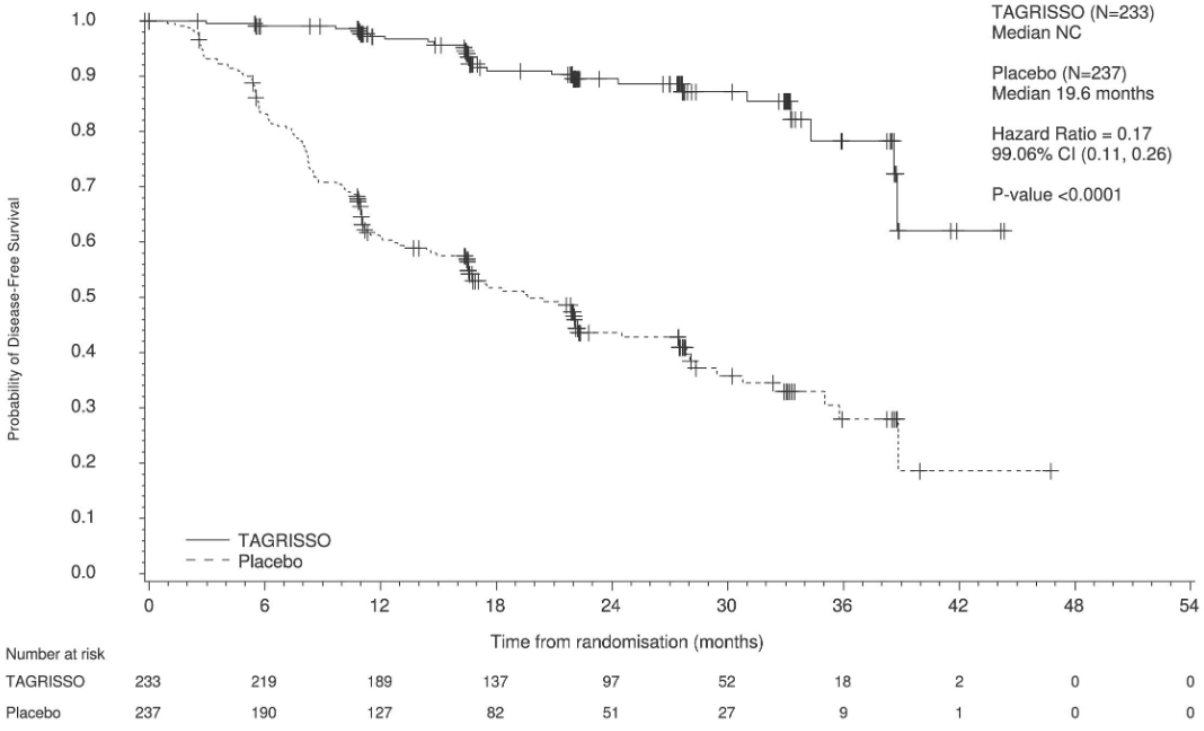
Table 6 Efficacy Results in Stage II-IIIA Patients by Investigator Assessment

Efficacy Parameter	**TAGRISSO (N=233)**	**Placebo (N=237)**
Disease Free Survival		
Number of events (%)	26 (11.2)	130 (54.9)
Recurrent disease (%)	26 (11.2)	129 (54.4)
Deaths (%)	0	1 (0.4)
Median, months (95% CI)	NC (38.8, NC)	19.6 (16.6, 24.5)
HR (99.06% CI); P-value[a]	0.17 (0.11, 0.26); P<0.0001	
DFS rate at 12 months (%) (95% CI)	97.2 (93.9, 98.7)	60.8 (54.1, 66.8)

Efficacy Parameter	TAGRISSO (N=233)	Placebo (N=237)
DFS rate at 24 months (%) (95% CI)	89.5 (84, 93.2)	43.6 (36.5, 50.6)
DFS rate at 36 months (%) (95% CI)[b]	78.3 (64.5, 87.3)	27.9 (18.9, 37.6)

HR=Hazard Ratio; CI=Confidence Interval; NC= Not Calculable
DFS results based on investigator assessment
A HR< 1 favours TAGRISSO
Median follow-up time for DFS was 22.1 months for patients receiving TAGRISSO and 14.9 months for patients receiving placebo.
[a] Adjusted for an interim analysis (33% maturity) a p-value < 0.0094 was required to achieve statistical significance.
[b] The number of patients at risk at 36 months was 18 patients in the osimertinib arm, and 9 patients in the placebo arm.

Figure 1 Kaplan-Meier curve of Disease-Free Survival (Stage II-IIIA Patients) by investigator assessment



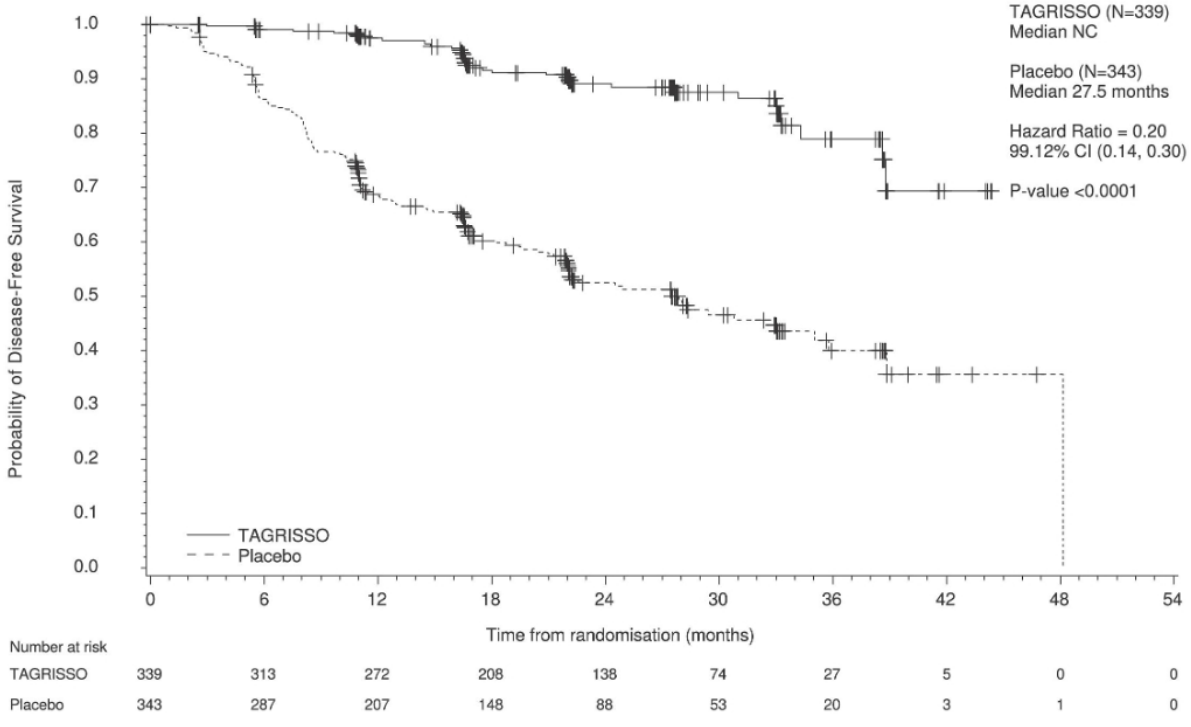
+ Censored patients.
The values at the base of the figure indicate number of subjects at risk.
NC = Not Calculable.

Table 7 Efficacy Results in Overall (IB-IIIA) Patients According by Investigator Assessment

Efficacy Parameter	**TAGRISSO (N=339)**	**Placebo (N=343)**
Disease Free Survival		
Number of events (%)	37 (10.9)	159 (46.4)
Recurrent disease (%)	37 (10.9)	157 (45.8)
Deaths (%)	0	2 (0.6)
Median, months (95% CI)	NC (NC, NC)	27.5 (22.0, 35.0)
HR (99.12% CI); P-value[a]	0.20 (0.14, 0.30); P<0.0001	
DFS rate at 12 months (%) (95% CI)	97.4 (94.9, 98.7)	68.5 (63.2, 73.2)
DFS rate at 24 months (%) (95% CI)	89.1 (84.5, 92.4)	52.4 (46.4, 58.1)
DFS rate at 36 months (%) (95% CI)[b]	78.9 (68.7, 86.1)	40.0 (32.1, 47.8)

HR=Hazard Ratio; CI=Confidence Interval; NC= Not Calculable
DFS results based on investigator assessment
A HR< 1 favours TAGRISSO
Median follow-up time for DFS was 22.1 months for patients receiving TAGRISSO and 16.6 months for patients receiving placebo.
[a] Adjusted for an interim analysis (29% maturity) a p-value < 0.0088 was required to achieve statistical significance.
[b] The number of patients at risk at 36 months was 27 patients in the osimertinib arm, and 20 patients in the placebo arm.

Figure 2 Kaplan-Meier curve of disease-free survival (overall population) by Investigator Assessment



+ Censored patients.
The values at the base of the figure indicate number of subjects at risk.
NC = Not Calculable.

The DFS benefit of TAGRISSO compared to placebo was consistent across all predefined subgroups analysed, including ethnicity, age, gender, and EGFR mutation type (Exon 19 deletions or L858R substitution mutations).

A clinically meaningful improvement in an exploratory analysis of CNS DFS (time to CNS recurrence or death) for patients on TAGRISSO compared to patients on placebo was observed with a HR of 0.18 (95% CI: 0.10, 0.33; P<0.0001) for the overall population, indicating a 82% reduction in the risk of CNS disease recurrence or death in the TAGRISSO arm compared to placebo.

Patient Reported Outcomes

HRQL, as measured by the Short Form (36) Health Survey version 2 (SF-36v2) questionnaire, was overall maintained in both arms, with more than 75% of stage II-IIIA patients in either arm not experiencing a clinically meaningful deterioration in the physical or mental component of the SF-36, or death. There was no difference between the arms in the time to deterioration (TTD) for the mental component of SF-36 or death (HR=0.90; 95% CI: 0.61, 1.33) ; median TTD of 39.0 months, 95% CI: NC, NC in the TAGRISSO arm and not reached in the placebo arm. A trend of shorter TTD for the physical component of SF-36 or death was observed in the TAGRISSO arm (HR=1.43, 95% CI: 0.96, 2.13) ; median TTD not reached in either arm.

Previously untreated EGFR mutation positive locally advanced or metastatic NSCLC – FLAURA

The efficacy and safety of TAGRISSO for the treatment of patients with EGFR mutation positive locally advanced or metastatic NSCLC, who had not received previous systemic treatment for advanced disease, was demonstrated in a randomised, double-blind, active-controlled study (FLAURA). Patient tumour tissue samples were required to have one of the two common EGFR mutations known to be associated with EGFR TKI sensitivity (Ex19del or L858R), as identified by local or central testing.

Patients were randomised 1:1 to receive either TAGRISSO (n=279, 80 mg orally once daily) or EGFR TKI comparator (n=277; gefitinib 250 mg orally once daily or erlotinib 150 mg orally once daily). Randomisation was stratified by EGFR mutation type (Ex19del or L858R) and ethnicity (Asian or non-Asian). Patients received study therapy until intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. For patients receiving EGFR TKI comparator, post-progression crossover to open-label TAGRISSO was permitted provided tumour samples tested positive for the T790M mutation.

The primary efficacy end-point was progression-free survival (PFS) as assessed by investigator. Additional efficacy end-points included overall survival (OS), objective response rate (ORR), duration of response (DoR), second PFS after start of first subsequent therapy (PFS2), time to first subsequent therapy or death (TFST) and time from randomisation to second progression on subsequent treatment or death (TSST) as assessed by investigator. CNS PFS, CNS ORR and CNS DoR as assessed by BICR, and patient reported outcomes (PRO) were also assessed.

The baseline demographic and disease characteristics of the overall study population were: median age 64 years (range 26-93 years), ≥75 years old (14%), female (63%), White (36%), Asian (62%), never smokers (64%). All patients had a World Health Organization (WHO) performance status of 0 or 1. Thirty-six percent (36%) of patients had metastatic bone disease and 35% of patients had extra-thoracic visceral metastases. Twenty one percent (21%) of patients had CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases).

TAGRISSO demonstrated a clinically meaningful and highly statistically significant improvement in PFS compared to EGFR TKI comparator (median 18.9 months and 10.2 months, respectively, HR=0.46, 95% CI: 0.37, 0.57; P<0.0001). Efficacy results from FLAURA by investigator assessment are summarised in Table 8, and the Kaplan-Meier curve for PFS is shown in Figure 3. The final analysis of overall survival (58% maturity) demonstrated a statistically significant improvement with an HR of 0.799 (95.05% CI: 0.641, 0.997; P = 0.0462) and a clinically meaningful longer median survival time in patients randomised to TAGRISSO compared to EGFR TKI comparator (Table 8 and Figure 4). A greater proportion of patients treated with TAGRISSO were alive at 12, 18, 24 and 36 months (89%, 81%, 74% and 54%, respectively) compared to patients treated with EGFR TKI comparator (83%, 71%, 59% and 44%, respectively).

Table 8 Efficacy results from FLAURA by investigator assessment

Efficacy Parameter	TAGRISSO (N=279)	EGFR TKI comparator (gefitinib or erlotinib) (N=277)
Progression-Free Survival		
Number of events (62% maturity)	136 (49)	206 (74)
Median, months (95% CI)	18.9 (15.2, 21.4)	10.2 (9.6, 11.1)
HR (95% CI); P-value	0.46 (0.37, 0.57); P<0.0001	
Overall Survival		
Number of deaths, (58% maturity)	155 (56)	166 (60)
Median OS in months (95% CI)	38.6 (34.5, 41.8)	31.8 (26.6, 36.0)
HR (95.05% CI); P-value	0.799 (0.641, 0.997); P=0.0462[†]	
Objective Response Rate[*1]		
Number of responses (n), Response Rate % (95% CI)	223 80 (75, 85)	210 76 (70, 81)
Odds ratio (95% CI); P-value	1.3 (0.9, 1.9); P=0.2421	
Duration of Response (DoR)[*]		
Median, Months (95% CI)	17.2 (13.8, 22.0)	8.5 (7.3, 9.8)
Second PFS after start of first subsequent therapy (PFS2)		
Number of patients with second progression (%)	73 (26)	106 (38)
Median PFS2, months (95% CI)	NC (23.7, NC)	20.0 (18.2, NC)
HR (95% CI); P-value	0.58 (0.44, 0.78); P=0.0004	
Time from randomisation to first subsequent treatment or death (TFST)		
Number of patients who had first subsequent treatment or died (%)	115 (41)	175 (63)
Median TFST, months (95% CI)	23.5 (22.0, NC)	13.8 (12.3, 15.7)
HR (95% CI); P-value	0.51 (0.40, 0.64); P<0.0001	
Time from randomisation to second subsequent treatment or death (TSST)		
Number of patients who had second subsequent treatment or died (%)	74 (27)	110 (40)
Median TSST, months (95% CI)	NC (NC, NC)	25.9 (20.0, NC)
HR (95% CI); P-value	0.60 (0.45, 0.80); P=0.0005	

HR=Hazard Ratio; CI=Confidence Interval, NC=Not Calculable
PFS, ORR, DoR and PFS2 results based on RECIST investigator assessment
[*]Based on unconfirmed response
Median follow-up time for PFS was 15.0 months for patients receiving TAGRISSO and 9.7 months for patients receiving EGFR TKI comparator.

Median survival follow-up time was 35.8 months for patients receiving TAGRISSO and 27.0 months for patients receiving EGFR TKI comparator.

PFS, ORR, DoR, PFS2, TFST and TSST results are from data cut-off 12 June 2017. OS results are from data cut-off 25 June 2019.

A HR< 1 favours TAGRISSO, an Odds ratio of >1 favours TAGRISSO

† Adjusted for an interim analysis (25% maturity) a p-value < 0.0495 was required to achieve statistical significance.

[1] ORR results by Blinded Independent Central Review (BICR) were consistent with those reported via investigator assessment; ORR by BICR assessment was 78% (95% CI: 73, 83) on TAGRISSO and 70% (95% CI: 65, 76) on EGFR TKI comparator.

Figure 3 Kaplan-Meier Curves of Progression-Free Survival as assessed by investigator in FLAURA

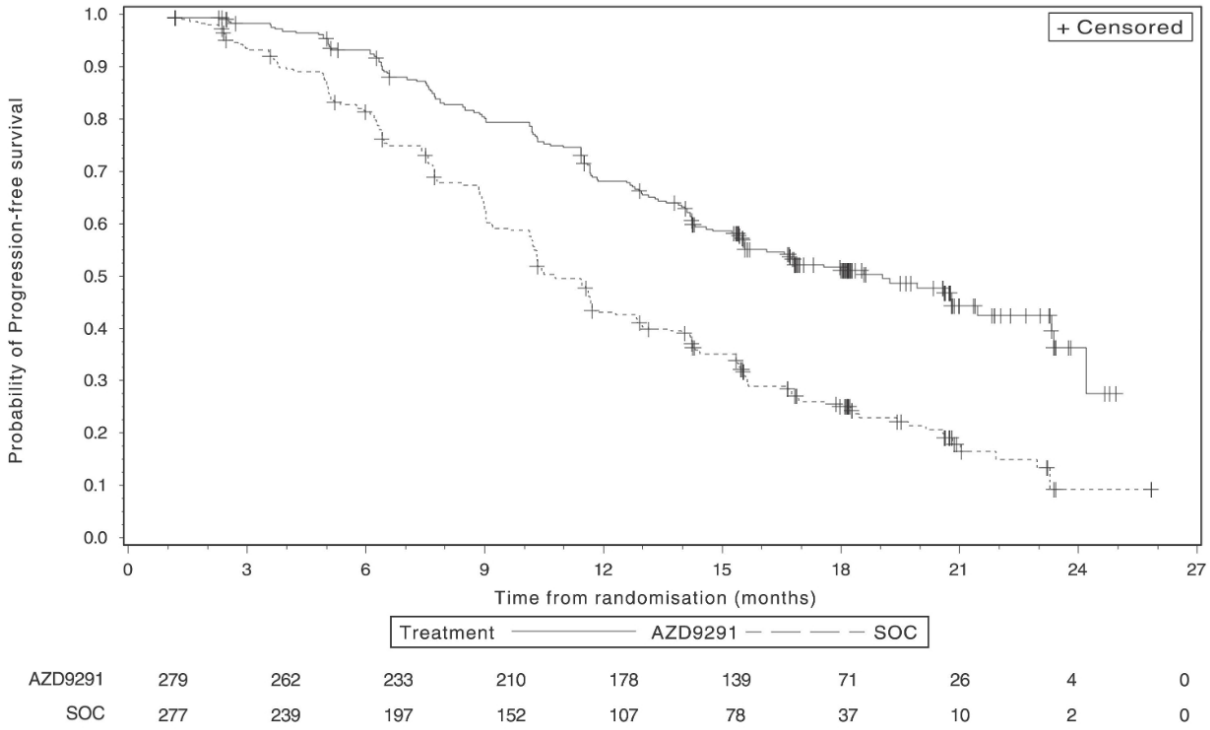
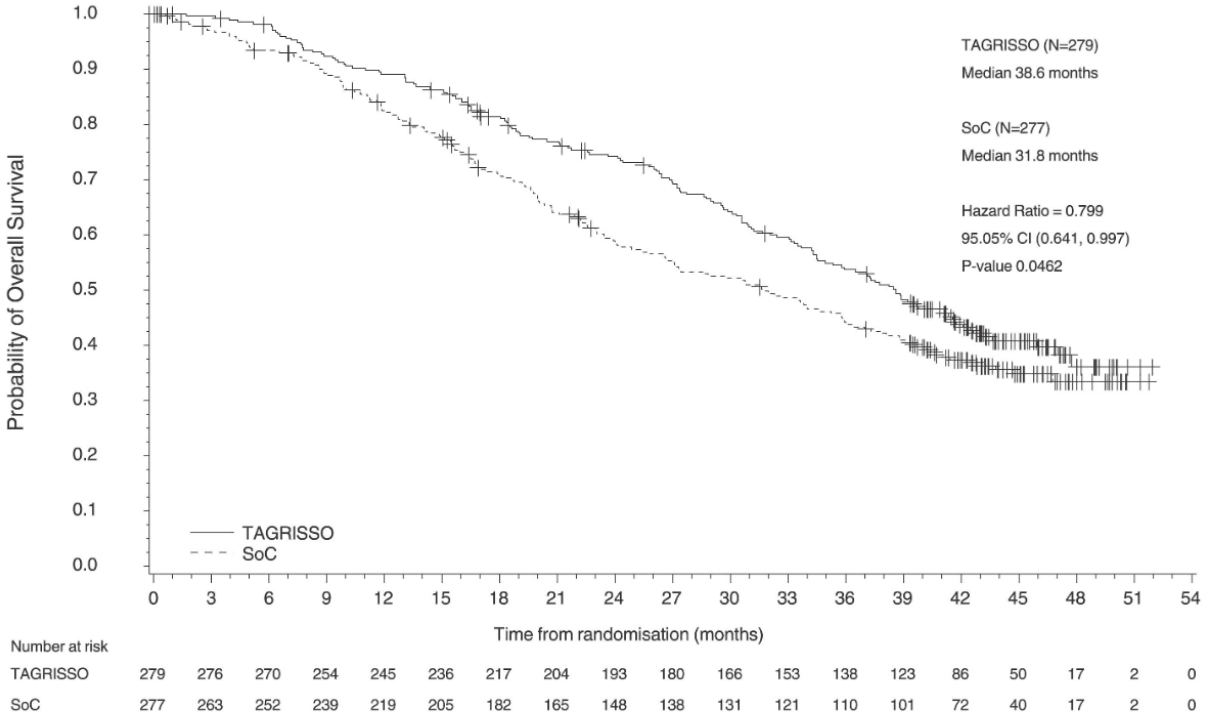


Figure 4 Kaplan-Meier Curves of Overall Survival in FLAURA



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The values at the base of the figure indicate number of subjects at risk.

The PFS benefit of TAGRISSO compared to EGFR TKI comparator was consistent across all predefined subgroups analysed, including ethnicity, age, gender, smoking history, CNS metastases status at study entry and EGFR mutation type (Exon 19 deletion or L858R).

Patients randomised to TAGRISSO as first-line treatment also had clinically meaningful improvements in PFS2, TFST and TSST compared to patients randomised to EGFR TKI comparator. The analysis of these post-progression end–points demonstrated that PFS benefit was largely preserved through subsequent lines of therapy.

In patients with locally advanced EGFRm NSCLC not amenable to curative surgery or radiotherapy, the objective response rate was 93% (95% CI 66, 100) for patients receiving TAGRISSO (n=14) and 60% (95% CI 32, 84) for patients receiving EGFR TKI comparator (n=15).

CNS metastases efficacy data in FLAURA study

Patients with CNS metastases not requiring steroids and with stable neurologic status for at least two weeks after completion of the definitive therapy and steroids were eligible to be randomised in the FLAURA study. Of 556 patients, 200 patients had available baseline brain scans. A BICR assessment of these scans resulted in a subgroup of 128/556 (23%) patients with CNS metastases and these data are summarised in Table 9. EGFR mutation type (Ex19del or L858R) and ethnicity (Asian or non-Asian) was generally balanced within this analysis between the treatment arms. CNS efficacy by RECIST v1.1 in FLAURA

demonstrated a statistically significant improvement in CNS PFS (HR=0.48, 95% CI 0.26, 0.86; P=0.014).

Table 9 CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in FLAURA

Efficacy Parameter	TAGRISSO N=61	EGFR TKI comparator (gefitinib or erlotinib) N=67
CNS Progression-Free Survival[1]		
Number of Events (%)	18 (30)	30 (45)
Median, Months (95% CI)	NC (16.5, NC)	13.9 (8.3, NC)
HR (95% CI); P-value	0.48 (0.26, 0.86); P=0.014	
CNS progression free and alive at 6 months (%) (95% CI)	87 (74, 94)	71 (57, 81)
CNS progression free and alive at 12 months (%) (95% CI)	77 (62, 86)	56 (42, 68)
CNS Objective Response Rate[1]		
CNS response rate % (n) (95% CI)	66 (40) (52, 77)	43 (29) (31, 56)
Odds ratio (95% CI); P-value	2.5 (1.2, 5.2); P=0.011	
CNS Duration of Response[1]		
Median, Months (95% CI)	NC (12, NC)	14 (7, 19)
Patients remaining in response at 6 months (%) (95% CI)	86 (70, 94)	76 (55, 89)
Patients remaining in response at 12 months (%) (95% CI)	65 (46, 79)	67 (43, 82)

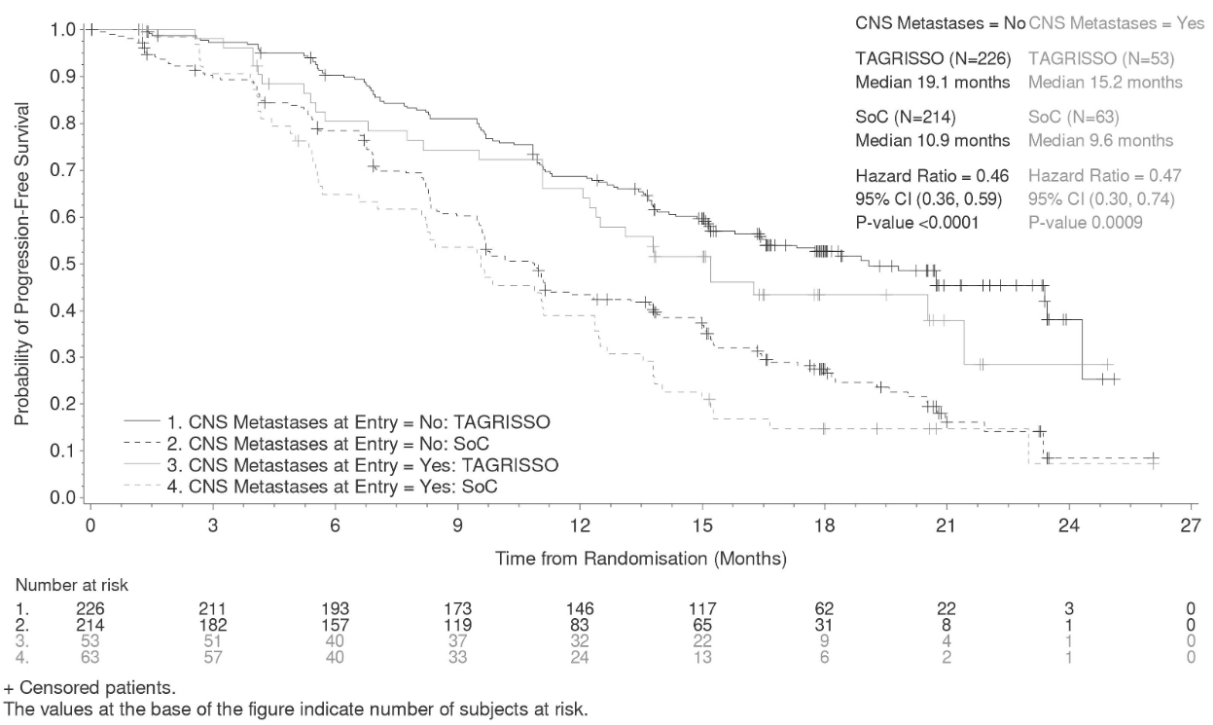
HR=Hazard Ratio; CI=Confidence Interval, NC=Not Calculable

A HR< 1 favours TAGRISSO, an Odds ratio of >1 favours TAGRISSO

[1] CNS PFS, ORR and DoR determined by RECIST v1.1 by CNS BICR (CNS measurable and non-measurable lesions at baseline by BICR) n=61 for TAGRISSO and n=67 for EGFR TKI comparator; responses are unconfirmed.

A pre-specified PFS subgroup based on CNS metastases status (identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases) at study entry was performed in FLAURA and is shown in Figure 5. Irrespective of CNS lesion status at study entry, patients in the TAGRISSO arm demonstrated an efficacy benefit over those in the EGFR TKI comparator arm.

Figure 5 Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in FLAURA



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The values at the base of the figure indicate number of subjects at risk.

Irrespective of CNS lesion status at study entry, based on investigator assessment, there were fewer patients with new CNS lesions in the TAGRISSO arm compared to the EGFR TKI comparator arm (TAGRISSO, 11/279 [3.9%] compared to EGFR TKI comparator, 34/277 [12.3%]). In the subset of patients without CNS lesions at baseline, there were a lower number of new CNS lesions in the TAGRISSO arm compared to the EGFR TKI comparator arm (7/226 [3.1%] vs. 15/214 [7.0%], respectively).

Patient Reported Outcomes (PRO)

Patient-reported symptoms and health-related quality of life (HRQL) were electronically collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). The LC13 was initially administered once a week for the first 6 weeks, then every 3 weeks before and after progression. The C30 was assessed every 6 weeks before and after progression. At baseline, no differences in patient reported symptoms, function or HRQL were observed between TAGRISSO and EGFR TKI comparator (gefitinib or erlotinib) arms. Compliance over the first 9 months was generally high (≥70%) and similar in both arms.

Key lung cancer symptoms analysis

Data collected from baseline up to month 9 showed similar improvements in TAGRISSO and EGFR TKI comparator groups for the five pre-specified primary PRO symptoms (cough, dyspnoea, chest pain, fatigue, and appetite loss) with improvement in cough reaching the established clinically relevant cutoff. Up to month 9 there were no clinically meaningful differences in patient-reported symptoms between TAGRISSO and EGFR TKI comparator groups (as assessed by a difference of ≥ 10 points). Data are presented in Table 10.

Table 10 Mixed Model Repeated Measures – Key lung cancer symptoms - mean change from baseline in TAGRISSO patients compared with EGFR TKI comparator (gefitinib or erlotinib)

	Cough		Dyspnoea		Chest Pain		Appetite loss		Fatigue	
Arms	TAGRISSO	gefitinib or erlotinib	TAGRISSO	gefitinib or erlotinib	TAGRISSO	gefitinib or erlotinib	TAGRISSO	gefitinib or erlotinib	TAGRISSO	gefitinib or erlotinib
N	248	252	248	252	248	252	252	247	252	247
Adj Mean	-10.97	-11.65	-4.04	-4.14	-6.62	-6.41	-6.15	-5.64	-5.48	-4.72
Estimated Difference (95%CI)	0.68 (-1.87, 3.24)		0.10 (-2.16, 2.35)		-0.21 (-2.51, 2.08)		-0.50 (-3.73, 2.73)		-0.77 (-3.59, 2.05)	

HRQL and physical functioning improvement analysis

Both groups reported similar improvements in most functioning domains and global health status/HRQL, indicating that patients overall health status improved. Up to month 9, there were no clinically meaningful differences between the TAGRISSO and EGFR TKI comparator groups in functioning or HRQL.

Pretreated T790M positive NSCLC patients – AURA3

The efficacy and safety of TAGRISSO for the treatment of patients with locally advanced or metastatic T790M NSCLC whose disease has progressed on or after EGFR TKI therapy, was demonstrated in a randomised, open label, active-controlled Phase 3 study (AURA3). All patients were required to have EGFR T790M mutation positive NSCLC identified by the cobas EGFR mutation test performed in a central laboratory prior to randomisation. The T790M mutation status was also assessed using ctDNA extracted from a plasma sample taken during screening. The primary efficacy outcome was progression-free survival (PFS) as assessed by investigator. Additional efficacy outcome measures included Objective Response Rate (ORR), Duration of Response (DoR), Disease Control Rate (DCR) and Overall Survival (OS) as assessed by investigator.

Patients were randomised in a 2:1 (TAGRISSO: platinum-based doublet chemotherapy) ratio to receive TAGRISSO (n=279) or platinum-based doublet chemotherapy (n=140). Randomisation was stratified by ethnicity (Asian and non-Asian). Patients in the TAGRISSO arm received TAGRISSO 80 mg orally once daily until intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Chemotherapy consisted of pemetrexed 500 mg/m^2 with carboplatin AUC5 or pemetrexed 500 mg/m^2 with cisplatin 75 mg/m^2 on day 1 of every 21 day cycle for up to 6 cycles. Patients whose disease had not progressed after four cycles of platinum-based chemotherapy could receive pemetrexed maintenance therapy (pemetrexed 500 mg/m^2 on day 1 of every 21 day cycle). Subjects on the chemotherapy arm who had objective radiological progression (by the investigator and confirmed by independent central imaging review) were given the opportunity to begin treatment with TAGRISSO.

The baseline demographic and disease characteristics of the overall study population were: median age 62 years, 15% of patients were ≥ 75 years old, female (64%), white (32%), Asian (65%). Sixty-eight percent (68%) of patients were never smokers, 100% of patients had a World Health Organization (WHO) performance status of 0 or 1. Fifty-four percent (54%) of patients had extra-thoracic visceral metastases, including 34% with CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases) and 23% with liver metastases. Forty-two percent (42%) of patients had metastatic bone disease.

AURA3 demonstrated a statistically significant improvement in PFS in the patients treated with TAGRISSO compared to chemotherapy. Efficacy results from AURA3 by investigator assessment are summarised in Table 11, and the Kaplan-Meier curve for PFS is shown in Figure 6. No statistically significant difference was observed between the treatment arms at the final OS analysis (conducted at 67% maturity), at which time 99 patients (71%) randomised to chemotherapy had crossed over to TAGRISSO treatment.

Table 11 Efficacy results from AURA3 by investigator assessment

Efficacy Parameter	TAGRISSO (N=279)	Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=140)
Progression-Free Survival		
Number of Events (% maturity)	140 (50)	110 (79)
Median, Months (95% CI)	10.1 (8.3, 12.3)	4.4 (4.2, 5.6)
HR (95% CI); P-value	0.30 (0.23, 0.41); P<0.001	
Overall Survival (OS)[1]		
Number of Deaths (% maturity)	188 (67.4)	93 (66.4)
Median OS, Months (95% CI)	26.8 (23.5, 31.5)	22.5 (20.2, 28.8)
HR (95% CI); P-value	0.87 (0.67, 1.13); P=0.277	
Objective Response Rate[2]		
Number of responses, Response Rate (95% CI)	197 71% (65, 76)	44 31% (24, 40)
Odds ratio (95% CI); P-value	5.4 (3.5, 8.5); P<0.001	
Duration of Response (DoR)[2]		
Median, Months (95% CI)	9.7 (8.3, 11.6)	4.1 (3.0, 5.6)
Disease Control Rate[3]		
Number of patients with disease control, Response rate (95% CI)	260 93% (90, 96)	104 74% (66, 81)
Odds ratio (95% CI); P-value	4.8 (2.6, 8.8); P<0.001	

HR=Hazard Ratio; CI=confidence interval; OS=Overall Survival
All efficacy results based on RECIST investigator assessment

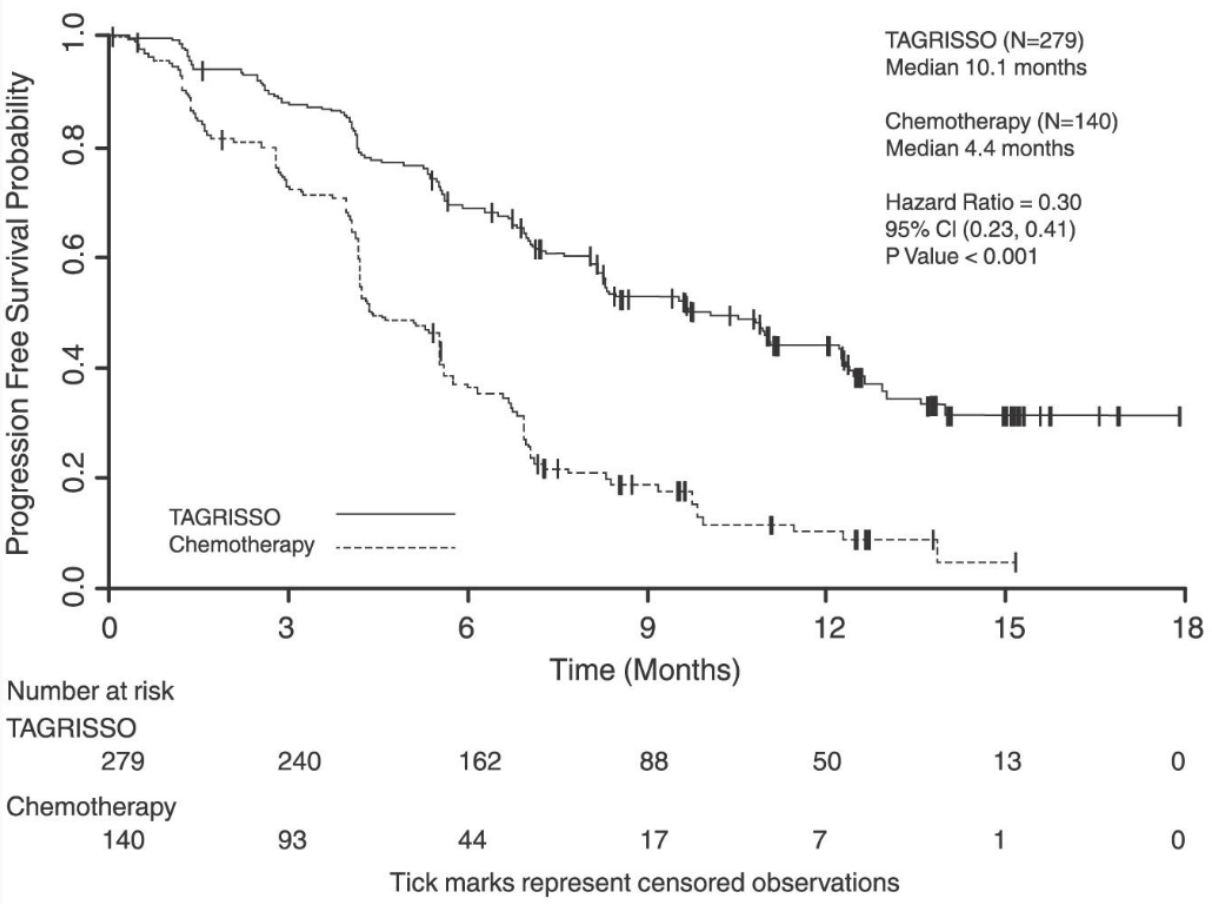
A HR< 1 favours TAGRISSO, an Odds ratio of >1 favours TAGRISSO

[1] The final analysis of OS was performed at 67% maturity. The CI for the HR has been adjusted for previous interim analyses. The OS analysis was not adjusted for the potentially confounding effects of crossover (99 [71%] patients on the chemotherapy arm received subsequent osimertinib treatment).

[2] ORR and DoR results by investigator assessment were consistent with those reported via Blinded Independent Central Review (BICR); ORR by BICR assessment was 64.9% [95% CI: 59.0, 70.5] on osimertinib and 34.3% [95% CI: 26.5, 42.8] on chemotherapy; DoR by BICR assessment was 11.2 months (95% CI: 8.3, NC) on osimertinib and 3.1 months (95% CI: 2.9, 4.3) on chemotherapy.

[3] Full analysis set

Figure 6 Kaplan-Meier Curves of Progression-Free Survival as assessed by investigator in AURA3



A sensitivity analysis of PFS was conducted by a Blinded Independent Central Review (BICR) and showed a median PFS of 11.0 months with TAGRISSO compared with 4.2 months with chemotherapy. This analysis demonstrated a consistent treatment effect (HR 0.28; 95% CI: 0.20, 0.38) with that observed by investigator assessment.

Clinically meaningful improvements in PFS with HRs less than 0.50 in favour of patients receiving TAGRISSO compared to those receiving chemotherapy were consistently observed in all predefined subgroups analysed, including ethnicity, age, gender, smoking history, CNS

metastases status at study entry, EGFR mutation (Exon 19 deletion and L858R), and duration of first-line therapy with an EGFR TKI.

CNS metastases efficacy data in AURA3 study

Patients with asymptomatic, stable brain metastases not requiring steroids for at least 4 weeks prior to the start of study treatment were eligible to be randomised in the study. A BICR assessment of CNS efficacy by RECIST v1.1 in the subgroup of 116/419 (28%) patients identified to have CNS metastases on a baseline brain scan are summarised in Table 12. CNS responses were observed irrespective of prior brain radiation status.

Table 12 CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in AURA3

Efficacy Parameter	TAGRISSO	Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin)
CNS Objective Response Rate[1]		
CNS response rate % (n/N) (95% CI)	70% (21/30) (51, 85)	31% (5/16) (11, 59)
Odds ratio (95% CI); P-value	5.1 (1.4, 21); P=0.015	
CNS Duration of Response[2]		
Median, Months (95% CI)	8.9 (4.3, NC)	5.7 (NC, NC)
CNS Disease control rate		
CNS disease control rate	87% (65/75) (77, 93)	68% (28/41) (52, 82)
Odds ratio (95% CI); P-value	3 (1.2, 7.9); P=0.021	
CNS Progression-free survival[3]	N=75	N=41
Number of Events (% maturity)	19 (25)	16 (39)
Median, Months (95% CI)	11.7 (10, NC)	5.6 (4.2, 9.7)
HR (95% CI); P value	0.32 (0.15, 0.69); P=0.004	

[1] CNS Objective Response Rate and Duration of Response determined by RECIST v1.1 by CNS BICR in the evaluable for response population (CNS measurable lesions at baseline by BICR) n=30 for TAGRISSO and n=16 for Chemotherapy

[2] Based on patients in the evaluable for response population with response only; DoR defined as the time from the date of first documented response (complete response or partial response, or stable disease ≥6 weeks)

[3] CNS Progression Free Survival determined by RECIST v1.1 by CNS BICR in the full analysis set population (CNS measurable and non-measurable lesions at baseline by BICR) n=75 for TAGRISSO and n=41 for Chemotherapy

NC=non-calculable

A HR< 1 favours TAGRISSO

A pre-specified PFS subgroup analysis based on CNS metastases status at study entry was performed in AURA3 and is shown in Figure 7 and Table 13.

Figure 7 Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in AURA3

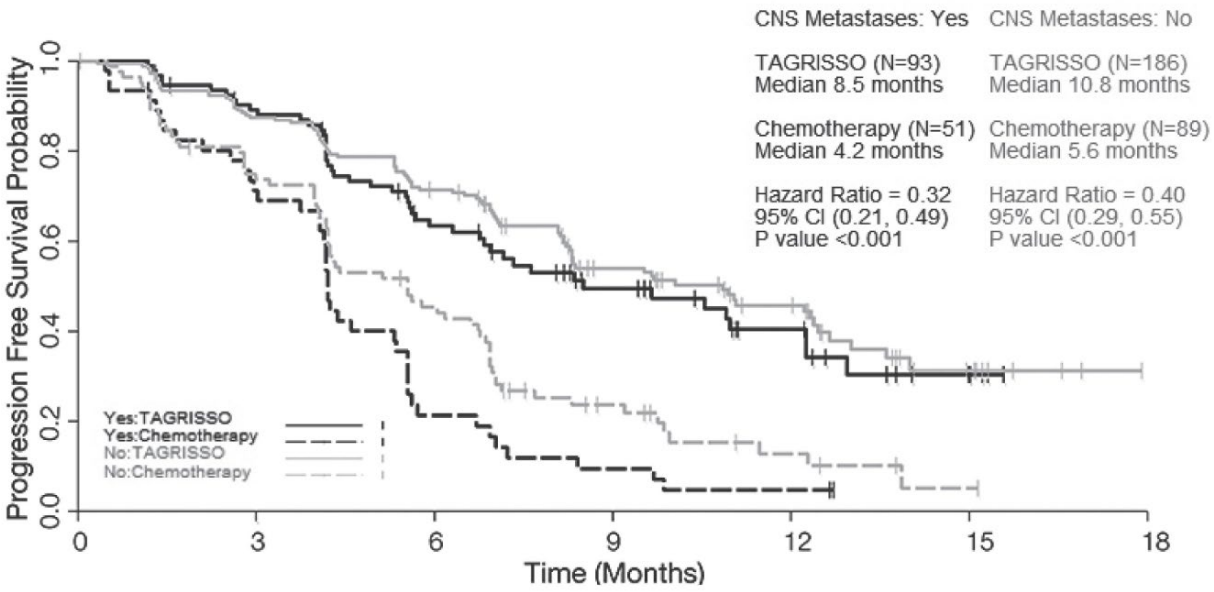


Table 13 PFS by CNS metastases at study entry based on investigator assessment (full analysis set) in AURA3

CNS metastases status	Yes		No	
	TAGRISSO N=93	**Chemotherapy N=51**	**TAGRISSO N=186**	**Chemotherapy N=89**
Number of events (maturity %)	48 (52)	42 (82)	92 (50)	68 (76)
Median, Months (95% CI)	8.5 (6.8, 12.3)	4.2 (4.1, 5.4)	10.8 (8.3, 12.5)	5.6 (4.2, 6.8)
HR (95% CI); P-value	0.32 (0.21, 0.49); P<0.001		0.40 (0.29, 0.55); P<0.001	

All efficacy results based on RECIST v1.1 investigator assessment
A HR< 1 favours TAGRISSO

AURA3 demonstrated an improvement in PFS for patients receiving TAGRISSO compared to those receiving chemotherapy irrespective of CNS metastases status at study entry.

TAGRISSO decreased the appearance of new CNS metastases (4.7%) as compared with chemotherapy (14.3%) according to RECIST v1.1 by investigator assessment.

Patient Reported Outcomes

Patient-reported symptoms and health-related quality of life (HRQL) were electronically collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). The LC13 was initially administered once a week for the first 6 weeks, then every 3 weeks before and after progression. The C30 was assessed every 6 weeks before and after progression.

Key lung cancer symptoms analysis

TAGRISSO improved patient-reported lung cancer symptoms compared to chemotherapy by demonstrating a statistically significant difference in mean change from baseline versus chemotherapy during the overall time period from randomisation until 6 months for 5 pre-specified primary PRO symptoms (appetite loss, cough, chest pain, dyspnoea, and fatigue) as shown in Table 14.

Table 14 Mixed Model Repeated Measures – Key lung cancer symptoms - mean change from baseline in TAGRISSO patients compared with chemotherapy

	Appetite Loss		**Cough**		**Chest Pain**		**Dyspnoea**		**Fatigue**	
Arms	TAGRISSO (279)	Chemo-therapy (140)	TAGRISSO (279)	Chemo-therapy (140)	TAGRISSO (279)	Chemo-therapy (140)	TAGRISSO (279)	Chemo-therapy (140)	TAGRISSO (279)	Chemo-therapy (140)
N	239	97	228	113	228	113	228	113	239	97
Adj Mean	-5.51	2.73	-12.22	-6.69	-5.15	0.22	-5.61	1.48	-5.68	4.71
Estimated Difference (95%CI)	-8.24 (-12.88, 3.60)		-5.53 (-8.89, -2.17)		-5.36 (-8.20, -2.53)		-7.09 (-9.86, -4.33)		-10.39 (-14.55, -6.23)	
P-value	P<0.001		P=0.001		P<0.001		P<0.001		P<0.001	

Adjusted mean and estimated differences obtained from a Mixed Model Repeated Measures (MMRM) analysis. The model included patient, treatment, visit, treatment-by-visit interaction, baseline symptom score, and baseline symptom score-by-visit interaction and used an unstructured covariance matrix.

HRQL and physical functioning improvement analysis

Patients on TAGRISSO had significantly greater chances of achieving a clinically meaningful improvement of greater than or equal to 10 points on the global health status and physical functioning of the EORTC-C30 questionnaire compared with chemotherapy during the study period Odds Ratio (OR) global health status: 2.11, (95% CI 1.24, 3.67, p=0.007); OR physical functioning 2.79 (95% CI 1.50, 5.46, p=0.002).

Pretreated T790M positive NSCLC patients - AURAex and AURA2

Two single-arm, open-label clinical studies, AURAex (Phase 2 Extension cohort, (n=201)) and AURA2 (n=210) were conducted in patients with EGFR T790M mutation positive lung cancer who have progressed on one or more prior systemic therapies, including an EGFR TKI. All patients were required to have EGFR T790M mutation positive NSCLC identified by an EGFR mutation test performed in a central laboratory prior to dosing. T790M mutation status was also assessed retrospectively using ctDNA extracted from a plasma sample taken during screening. All patients received TAGRISSO at a dose of 80 mg once daily. The primary

efficacy outcome measure of these two trials was objective response rate (ORR) according to RECIST v1.1 as evaluated by a Blinded Independent Central Review (BICR). Secondary efficacy outcome measures included Duration of Response (DoR) and Progression-Free Survival (PFS).

Baseline characteristics of the overall study population (AURAex and AURA2) were as follows: median age 63 years, 13% of patients were ≥75 years old, female (68%), White (36%), Asian (60%). Majority of the subjects (96.7%) recruited were of the adenocarcinoma subtype. All patients received at least one prior line of therapy. 31% (N=129) had received 1 prior line of therapy (EGFR-TKI treatment only, second-line, chemotherapy naïve), 69% (N=282) had received 2 or more prior lines. Seventy-two percent (72%) of patients were never smokers, 100% of patients had a World Health Organization (WHO) performance status of 0 or 1. Fifty-nine percent (59%) of patients had extra-thoracic visceral metastasis including 39% with CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery and/or prior radiotherapy to CNS metastases) and 29% with liver metastases. Forty-seven percent (47%) of patients had metastatic bone disease. The median duration of follow up for PFS was 12.6 months.

In the 411 pre-treated EGFR T790M mutation positive patients, the ORR by BICR in the evaluable for response population was 66% (95% CI: 61, 71). In patients with a confirmed response by BICR, the median DoR was 12.5 months (95% CI: 11.1, NE). The median PFS by BICR was 11.0 months 95% CI (9.6, 12.4).

Objective response rates by BICR above 50% were observed in all predefined subgroups analysed, including line of therapy, race, age and region. The ORR by BICR in AURAex was 62% (95% CI: 55, 68) and 70% (95% CI: 63, 77) in AURA2.

Among the patients in the evaluable for response population with objective responses, 85% (223/262) had documentation of response at the time of the first scan (6 weeks); 94% (247/262) had documentation of response at the time of the second scan (12 weeks).

CNS metastases efficacy data in Phase 2 studies (AURAex and AURA2)

A BICR assessment of CNS efficacy by RECIST v1.1 was performed in a subgroup of 50 (out of 411) patients identified to have measurable CNS metastases on a baseline brain scan. A CNS ORR of 54% (27/50 patients; 95% CI: 39.3, 68.2) was observed with 12% being complete responses.

5.2 Pharmacokinetic properties

Osimertinib pharmacokinetic parameters have been characterised in healthy subjects and NSCLC patients. Based on population pharmacokinetic analysis, osimertinib apparent plasma clearance is 14.3 L/h, apparent volume of distribution is 918 L and terminal half-life of approximately 44 hours. The AUC and C_{max} increased dose proportionally over 20 to 240 mg dose range. Administration of TAGRISSO once daily results in approximately 3-fold accumulation with steady-state exposures achieved by 15 days of dosing. At steady state, circulating plasma concentrations are typically maintained within a 1.6 fold range over the 24-hour dosing interval.

Absorption

Following oral administration of TAGRISSO, peak plasma concentrations of osimertinib was achieved with a median (min-max) t_{max} of 6 (3-24) hours, with several peaks observed over the first 24 hours in some patients. The absolute bioavailability of TAGRISSO is 70% (90% CI 67, 73). Based on a clinical pharmacokinetic study in patients at 80 mg, food does not alter osimertinib bioavailability to a clinically meaningful extent. (AUC increase 6% (90% CI -5, 19) and C_{max} decrease -7% (90% CI -19, 6)). In healthy volunteers administered an 80 mg tablet where gastric pH was elevated by dosing of omeprazole for 5 days, osimertinib exposure was not affected (AUC and C_{max} increase by 7% and 2%, respectively) with the 90% CI for exposure ratio contained within the 80-125% limit.

Distribution

Population estimated mean volume of distribution at steady state (V_{ss}/F) of osimertinib is 918 L indicating extensive distribution into tissue. *In vitro*, plasma protein binding of osimertinib is 94.7% (5.3% free). Osimertinib has also been demonstrated to bind covalently to rat and human plasma proteins, human serum albumin and rat and human hepatocytes.

Biotransformation

In vitro studies indicate that osimertinib is metabolised predominantly by CYP3A4, and CYP3A5. Based on *in vitro* studies, 2 pharmacologically active metabolites (AZ7550 and AZ5104) have subsequently been identified in the plasma of preclinical species and in humans after oral dosing with TAGRISSO; AZ7550 showed a similar pharmacological profile to TAGRISSO while AZ5104 showed greater potency across both mutant and wild-type EGFR. Both metabolites appeared slowly in plasma after administration of TAGRISSO to patients, with a median (min-max) t_{max} of 24 (4-72) and 24 (6-72) hours, respectively. In human plasma, parent osimertinib accounted for 0.8%, with the 2 metabolites contributing 0.08% and 0.07% of the total radioactivity with the majority of the radioactivity being covalently bound to plasma proteins. The geometric mean exposure of both AZ5104 and AZ7550, based on AUC, was approximately 10% each of the exposure of osimertinib at steady state.

The main metabolic pathway of osimertinib was oxidation and dealkylation. At least 12 components were observed in the pooled urine and faecal samples in humans with 5 components accounting for >1% of the dose of which unchanged osimertinib, AZ5104 and AZ7550, accounted for approximately 1.9, 6.6 and 2.7% of the dose while a cysteinyl adduct (M21), and an unknown metabolite (M25) accounted for 1.5% and 1.9% of the dose, respectively.

Based on *in vitro* studies, osimertinib is a competitive inhibitor of CYP 3A4/5 but not CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at clinically relevant concentrations. Based on *in vitro* studies, osimertinib is not an inhibitor of UGT1A1 and UGT2B7 at clinically relevant concentrations hepatically. Intestinal inhibition of UGT1A1 is possible but the clinical impact is unknown.

Elimination

Following a single oral dose of 20 mg, 67.8% of the dose was recovered in faeces (1.2% as parent) while 14.2% of the administered dose (0.8% as parent) was found in urine by 84 days of sample collection. Unchanged osimertinib accounted for approximately 2% of the elimination with 0.8% in urine and 1.2% in faeces.

Interactions with transport proteins

In vitro studies have shown that osimertinib is not a substrate of OATP1B1 and OATP1B3.

In vitro, osimertinib does not inhibit P-gp, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2K and OCT2 at clinically relevant concentrations.

Effects of osimertinib on P-gp and BCRP

Based on *in vitro* studies, osimertinib is a substrate of P-gp BCRP, but is unlikely to result in clinically relevant drug interactions with active substances by osimertinib at the clinical doses. Based on *in vitro* data, osimertinib is an inhibitor of BCRP (See section 4.5).

Special populations

In a population based PK analysis (n=1367), no clinically significant relationships were identified between predicted steady-state exposure (AUC_{ss}) and patient's age (range: 25 to 91 years), gender (65% female), ethnicity (including white, Asian, Japanese, Chinese and non-Asian-non-white patients), line of therapy and smoking status (n=34 current smokers, n=419 former smokers). Population PK analysis indicated that body weight was a significant covariate with a less than 20% change in osimertinib AUC_{ss} expected across a body weight range of 88 kg to 43 kg respectively (95% to 5% quantiles) when compared to the AUC_{ss} for the median body weight of 61 kg. Taking the extremes of body weight into consideration, from <43 kg to >88 kg, AZ5104 metabolite ratios ranged from 11.8% to 9.6% while for AZ7550 it ranged from 12.8% to 8.1%, respectively. Based on population PK analysis, serum albumin was identified as a significant covariate with a <30% change in osimertinib AUC_{ss} expected across the albumin range of 29 to 46 g/L respectively (95% to 5% quantiles) when compared to the AUC_{ss} for the median baseline albumin of 39 g/L. These exposure changes due to body weight or baseline albumin differences are not considered clinically relevant.

Hepatic impairment

Osimertinib is eliminated mainly via the liver. In a clinical trial, patients with mild hepatic impairment (Child Pugh A, n=7) or moderate hepatic impairment (Child Pugh B, n=5) had no increase in exposure compared to patients with normal hepatic function (n=10) after a single 80 mg dose of TAGRISSO. Based on population PK analysis, there was no relationship between markers of hepatic function (ALT, AST, bilirubin) and osimertinib exposure. The hepatic impairment marker serum albumin showed an effect on the PK of osimertinib. Clinical studies that were conducted excluded patients with AST or ALT >2.5x upper limit of normal (ULN), or if due to underlying malignancy, >5.0x ULN or with total bilirubin >1.5x ULN. Based on a pharmacokinetic analysis of 134 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin between 1.0 to 1.5x ULN and any AST), 8 patients with moderate hepatic impairment (total bilirubin between 1.5 times to 3.0 times ULN and any AST) and 1216 patients with normal hepatic function (total bilirubin less than or

equal to ULN and AST less than or equal to ULN), osimertinib exposures were similar. There are no data available on patients with severe hepatic impairment (see section 4.2).

Renal impairment

In a clinical trial, patients with severe renal impairment (CLcr 15 to less than 30 mL/min; n=7) compared to patients with normal renal function (CLcr greater than or equal to 90 mL/min; n=8) after a single 80 mg dose of TAGRISSO showed a 1.85-fold increase in AUC (90% CI: 0.94, 3.64) and a 1.19-fold increase in C_{max} (90% CI: 0.69, 2.07). Furthermore, based on a population PK analysis of 593 patients with mild renal impairment (CLcr 60 to less than 90 mL/min), 254 patients with moderate renal impairment (CLcr 30 to less than 60 mL/min), 5 patients with severe renal impairment (CLcr 15 to less than 30 mL/min) and 502 patients with normal renal function (greater than or equal to 90 mL/min), osimertinib exposures were similar. Patients with CLcr less than or equal to 10 mL/min were not included in the clinical trials.

Patients with brain metastases

In a microdose PET study in EGFR mutation positive NSCLC patients (n=4) with brain metastases, brain penetration and distribution of osimertinib was achieved at a median T_{max} of 22 min and a mean C_{max} of 1.5% injected dose reached the brain. This was similar to that observed in a healthy volunteers study (n=7; T_{max}: 11 min; C_{max}: 2.2% of injected dose reached the brain).

5.3 Preclinical safety data

Repeat dose toxicity

The main findings observed in repeat dose toxicity studies in rats and dogs comprised atrophic, inflammatory and/or degenerative changes affecting the epithelia of the eye (cornea), GI tract (including tongue), skin, and male and female reproductive tracts. These findings occurred at plasma concentrations that were below those seen in patients at the 80 mg therapeutic dose. The findings present following 1 month of dosing were largely reversible within 1 month of cessation of dosing.

Lens fibre degeneration was observed in the 104-week carcinogenicity rat study at exposures 0.2-times the AUC observed at the recommended clinical dose of 80 mg once daily and was consistent with the ophthalmoscopic observation of lens opacities which were first noted from week 52 and showed a gradual increase in incidence and severity with increased duration of dosing.

Carcinogenesis and mutagenesis

Osimertinib showed no carcinogenic potential when administered orally to Tg rasH2 transgenic mice for 26 weeks. An increased incidence of proliferative vascular lesions (angiomatous hyperplasia and haemangioma) in the mesenteric lymph node was observed in the rat 104-week carcinogenicity study at exposures 0.2-times the AUC observed at the recommended clinical dose of 80 mg once daily. Osimertinib did not cause genetic damage in in vitro and in vivo assays.

Reproductive toxicology

Based on studies in animals, male fertility may be impaired by treatment with TAGRISSO. Degenerative changes were present in the testes in rats and dogs exposed to osimertinib for ≥1 month and there was a reduction in male fertility in rats following exposure to osimertinib for 3 months. These findings were seen at clinically relevant plasma concentrations. Pathology findings in the testes seen following 1 month dosing were reversible in rats, however, a definitive statement on reversibility of these lesions in dogs cannot be made.

Based on studies in animals, female fertility may be impaired by treatment with TAGRISSO. In repeat dose toxicity studies, an increased incidence of anoestrus, corpora lutea degeneration in the ovaries and epithelial thinning in the uterus and vagina were seen in rats exposed to osimertinib for ≥1 month at clinically relevant plasma concentrations. Findings in the ovaries seen following 1 month dosing were reversible. In a female fertility study in rats, administration of osimertinib at 20 mg/kg/day (approximately equal to the recommended daily clinical dose of 80 mg) had no effects on oestrus cycling or the number of females becoming pregnant, but caused early embryonic deaths. These findings showed evidence of reversibility following a 1 month off-dose.

In a modified embryofoetal development study in the rat, osimertinib caused embryolethality when administered to pregnant rats prior to embryonic implantation. These effects were seen at a maternally tolerated dose of 20 mg/kg/day where exposure was equivalent to the human exposure at the recommended dose of 80 mg daily (based on total AUC). Exposure at doses of 20 mg/kg and above during organogenesis caused reduced foetal weights but no adverse effects on external or visceral foetal morphology. When osimertinib was administered to pregnant female rats throughout gestation and then through early lactation, there was demonstrable exposure to osimertinib and its metabolites in suckling pups plus a reduction in pup survival and poor pup growth (at doses of 20 mg/kg and above).

CNS distribution and *in vivo* intracranial tumour regression

In a rat study, a single oral dose of [^{14}C]-osimertinib was distributed to the intact brain with a maximum blood ratio of 2.2, with brain radioactivity levels being detectable out to 21 days. In an IV micro-dose PET study, [^{11}C] osimertinib penetrated the blood-brain barrier of the intact cynomolgus monkey brain (brain to blood AUC ratio of 2.62). Osimertinib was also distributed to the intact mouse brain (brain to plasma AUC ratio 1.8-2.8) following oral dosing.

These data are consistent with observations of anti-tumour activity of osimertinib in a pre-clinical mutant-EGFR intracranial brain mouse metastasis xenograft model (PC9; exon 19 del), osimertinib (25 mg/kg/day) demonstrated significant tumour regression that was sustained during the 60 day study period, and was associated with an increase in survival of the mice compared to control animals (78% survival after 8 weeks for osimertinib compared to 11% in control group).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The names of excipients may vary according to region.

Tablet core
Mannitol
Microcrystalline cellulose
Low-substituted hydroxypropyl cellulose
Sodium stearyl fumarate

Tablet coating
Polyvinyl alcohol
Titanium dioxide
Macrogol 3350
Talc
Yellow iron oxide
Red iron oxide
Black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Please refer to expiry date on the outer carton.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Perforated Al/Al blisters containing 10 tablets. Cartons of 30 tablets (3 blisters).

6.6 Instructions for use, handling and disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Product Owner

AstraZeneca AB
SE-151 85
Södertälje
Sweden

Date of revision of text

December 2022

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