1. NAME OF THE MEDICINAL PRODUCT

TAGRISSO 40 mg film-coated tablets

TAGRISSO 80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TAGRISSO 40 mg tablets

Each tablet contains osimertinib 40 mg (equivalent to 47.7mg of osimertinib mesylate)

TAGRISSO 80 mg tablets

Each tablet contains osimertinib 80 mg (equivalent to 95.4mg of osimertinib mesylate)

Excipient with known effect

This medicine contains 0.3 mg sodium per 40 mg tablet and 0.6 mg sodium per 80 mg tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

TAGRISSO 40 mg tablets:

Beige, 9mm, round, biconvex tablet, debossed with “AZ” and “40” on one side and plain on the reverse.

TAGRISSO 80 mg tablets

Beige, 7.25 x 14.5 mm, oval, biconvex tablet, debossed with “AZ” and “80” on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant Treatment of EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)

TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations.

First-line Treatment of EGFR Mutation-Positive Locally Advanced or Metastatic NSCLC

TAGRISSO in combination with pemetrexed and platinum-based chemotherapy is indicated for the first line treatment of adult patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations.

Locally Advanced, Unresectable (Stage III) EGFR Mutation-Positive NSCLC

TAGRISSO is indicated for the treatment of adult patients with locally advanced, unresectable (stage III) NSCLC whose disease has not progressed during or following concurrent or sequential platinum-based chemoradiation therapy and whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations.

Tagrisso as monotherapy is indicated for:

- the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.
- the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

4.2 Posology and method of administration

First-line Treatment of EGFR Mutation-Positive Locally Advanced or Metastatic NSCLC
Select patients for the first-line treatment of locally advanced or metastatic EGFR-positive NSCLC with TAGRISSO in combination with pemetrexed and platinum-based chemotherapy, based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens [see 5.1]. If these mutations are not detected in a plasma specimen, test tumor tissue if feasible.

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 in tumour or plasma specimens should be determined using a validated test method (see section 4.4).

Posology
The recommended dose is 80 mg osimertinib once a day until disease progression or unacceptable toxicity.

Locally Advanced, Unresectable (Stage III) EGFR Mutation-Positive NSCLC

Following platinum-based chemoradiation therapy, 80 mg tablet orally once daily with or without food, until disease progression or unacceptable toxicity.

Select patients with resectable tumors for the adjuvant treatment of NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor specimens
Treat patients in the adjuvant setting until disease recurrence, or unacceptable toxicity, or for up to 3 years. Treat patients with metastatic lung cancer until disease progression or unacceptable toxicity.

If a dose of TAGRISSO is missed, the dose should be made up 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 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 (Patients who have **not** received recent definitive platinum-based chemoradiation therapy) [see* 4.4 Special warnings and precautions for use*)*	ILD / Pneumonitis	Permanently discontinue TAGRISSO
*Pulmonary (Patients who **have** received recent definitive platinum-based chemoradiation therapy) [see Warnings and Precautions (*4.4*)]*	Grade 1 ILD / Pneumonitis	Withhold or continue TAGRISSO, as clinically indicated.
	Grade ≥2 ILD / Pneumonitis	Permanently discontinue TAGRISSO.
Cardiac	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 lymphatic system[b]	Aplastic anaemia	Permanently discontinue 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.

ECGs: Electrocardiograms; QTc: QT interval corrected for heart rate

Special populations

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

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 pharmacokinetic analysis, no dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin >1.0 to 1.5 times ULN and any AST) or moderate hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST). The safety and efficacy of this medicinal product has not been established in patients with severe hepatic impairment. Until additional data become available, use in patients with severe hepatic impairment is not recommended (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 this medicinal product 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).

Paediatric population

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 and it should not be crushed, split or chewed.

If the patient is unable to swallow the tablet, the tablet may first be dispersed in 50 mL of non-carbonated water. It 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

St. John's Wort should not be used together with TAGRISSO (see section 4.5).

4.4 Special warnings and precautions for use

Assessment of EGFR mutation status

When considering the use of TAGRISSO as adjuvant treatment after complete tumour resection in patients with NSCLC, EGFR mutation positive status (exon 19 deletions (Ex19del) or exon 21 L858R substitution mutations (L858R)) indicates treatment eligibility. A validated test should be performed in a clinical laboratory using tumour tissue DNA from biopsy or surgical specimen.

When considering the use of TAGRISSO in patients with locally advanced, unresectable NSCLC and whose disease has not progressed during or following platinum-based chemoradiation therapy, 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 a biopsy specimen.

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 using either tumour DNA derived from a tissue sample or circulating tumour DNA (ctDNA) obtained from a plasma sample.

Positive determination of EGFR mutation status (activating EGFR mutations for first-line treatment, exon 19 deletion or exon 21 (L858R) substitution mutations when TAGRISSO is given in combination with pemetrexed and platinum-based chemotherapy 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.

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

Interstitial lung disease (ILD)

Severe, life-threatening or fatal ILD or ILD-like adverse reactions (e.g. pneumonitis) have been observed in patients treated with TAGRISSO in clinical studies, including TAGRISSO following definitive platinum-based chemoradiation therapy. Most cases improved or resolved with interruption of treatment. Patients with a past 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 (see section 4.8).

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD. Treatment with this medicinal product should be interrupted pending investigation of these symptoms. If ILD is diagnosed, TAGRISSO should be discontinued and appropriate treatment initiated as necessary. Reintroduction of TAGRISSO should be considered only after careful consideration of the individual patient's benefits and risk.

Radiation pneumonitis

Radiation pneumonitis is usually observed for up to a year after patients receive radiation therapy to the lungs. For TAGRISSO dose modification guidance for radiation pneumonitis following definitive platinum-based chemoradiation therapy, refer to section 4.2.

Severe Cutaneous Adverse Reactions (SCARs)

Case reports of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with frequency categories of rare and not known, respectively, in association with TAGRISSO treatment. Before initiating treatment, patients should be advised of signs and symptoms of SJS and TEN. If signs and symptoms suggestive of SJS or TEN appear, TAGRISSO should be interrupted. TAGRISSO should be discontinued immediately if SJS or TEN are diagnosed.

QTc interval prolongation

QTc interval prolongation occurs in patients treated with TAGRISSO. QTc interval prolongation may lead to an increased risk for ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death.

No QTc related arrythmias were reported in ADAURA, LAURA, FLAURA, FLAURA2 or AURA studies (see section 4.8). Patients with clinically important abnormalities in rhythm and conduction as measured by resting electrocardiogram (ECG) (e.g. QTc interval greater than 470 msec) were excluded from these studies (see section 4.8).

When possible, the use of TAGRISSO in patients with congenital long QT syndrome should be avoided. Periodic monitoring with electrocardiograms (ECGs) and electrolytes should be considered in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products that are known to prolong the QTc interval. Treatment should be withheld 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. TAGRISSO should be permanently discontinued 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 studies, left ventricular ejection fraction (LVEF) decreases greater than or equal to 10 percentage points and a drop to less than 50% occurred in 4.2% (65/1577) of patients treated with TAGRISSO monotherapy who had baseline and at least one follow-up LVEF assessment. 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. In an adjuvant placebo-controlled study (ADAURA), 1.5% (5/325) 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%.In the LAURA study, following platinum-based chemoradiation therapy, 3.0% (4/135) of patients treated with TAGRISSO and no patients treated with placebo, who had both a baseline and post-baseline LVEF assessment, experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%. In the FLAURA2 study, 8.0% (21/262) of patients treated with TAGRISSO in combination with pemetrexed and platinum-based chemotherapy, who had baseline and at least one follow-up LVEF assessment, experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%.

Keratitis

Keratitis was reported in 0.6% (n=11) of the 1956 patients treated with TAGRISSO monotherapy in the ADAURA, FLAURA, FLAURA2, LAURA 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 Table 1).

Aplastic Anaemia

Rare cases of aplastic anaemia, including fatal events, have been reported in association with TAGRISSO treatment. Before initiating treatment, patients should be advised of signs and symptoms of aplastic anaemia including but not limited to persistent fever, bruising, bleeding, pallor, infection and fatigue. 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 (see section 4.2).

Age and body weight

Elderly patients (>65 years) or patients with low body weight (<50 kg) may be at increased risk of developing adverse events of Grade 3 or higher. Close monitoring is recommended in these patients (see section 4.8).

Hepatitis B Virus (HBV) reactivation

Hepatitis B virus reactivation can occur in patients treated with TAGRISSO, and in some cases, may result in fulminant hepatitis, hepatic failure, and death. Patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation while receiving TAGRISSO. In patients who develop reactivation of HBV while on TAGRISSO, treatment with TAGRISSO should be withheld and they should be managed according to local institutional guidelines.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

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, co-administration 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% and Cmax decreased by 20%). Therefore, CYP3A4 inhibitors are not likely to affect the exposure of osimertinib. Further catalyzing enzymes have not been identified.

Active substances that may decrease osimertinib plasma concentrations

In a clinical pharmacokinetic study in patients, the steady-state AUC of osimertinib was reduced by 78% when co-administered with rifampicin (600 mg daily for 21 days). Similarly, the exposure to metabolite AZ5104 decreased by 82% for the AUC and 78% for Cmax. It is recommended that concomitant use of strong CYP3A inducers (e.g. Phenytoin, rifampicin and carbamazepine) with TAGRISSO should be avoided. Moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil) may also decrease osimertinib exposure and should be used with caution, or avoided when possible. There are no clinical data available to recommend a dose adjustment of TAGRISSO. Concomitant use of St. John’s Wort is contraindicated (see section 4.3).

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 transporters.

In a clinical PK study, co-administration of TAGRISSO with rosuvastatin (sensitive BCRP substrate) increased the AUC and Cmax of rosuvastatin by 35% and 72%, respectively. Patients taking concomitant medicinal products with disposition dependent upon BCRP and with narrow therapeutic index should be closely monitored for signs of changed tolerability of the concomitant medication as a result of increased exposure whilst receiving TAGRISSO (see section 5.2).

In a clinical PK study, co-administration of TAGRISSO with simvastatin (sensitive CYP3A4 substrate) decreased the AUC and Cmax of simvastatin by 9% and 23% respectively. These changes are small and not likely to be of clinical significance. Clinical PK interactions with CYP3A4 substrates are unlikely. A risk for decreased exposure of hormonal contraceptives cannot be excluded.

In a clinical Pregnane X Receptor (PXR) interaction study, co-administration of TAGRISSO with fexofenadine (P-gp substrate) increased the AUC and Cmax 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 Fertility, pregnancy and lactation

Women of childbearing potential/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 this medicinal product: at least 2 months for females and 4 months for males. A risk for decreased exposure of hormonal contraceptives cannot be excluded.

Pregnancy

There are no or limited amount of data from the use of osimertinib in pregnant women. Studies in animals have shown reproductive toxicity (embryo lethality, reduced foetal growth, and neonatal death, see section 5.3). Based on its mechanism of action and preclinical data, osimertinib may cause foetal harm when administered to a pregnant woman. TAGRISSO should not be used during pregnancy unless the clinical condition of the woman requires treatment with osimertinib.

Breast-feeding

It is unknown whether osimertinib/metabolites are excreted in human milk. There is insufficient information on the excretion of osimertinib/metabolites in animal milk. However, osimertinib and its metabolites were detected in the suckling pups and there was poor pup growth and a reduction in pup survival (see section 5.3). 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 osimertinib 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 negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Studies in EGFR mutation-positive NSCLC patients

The safety of TAGRISSO as a monotherapy is based on pooled data from 1956 patients with EGFR mutation-positive non-small cell lung cancer. These patients received TAGRISSO at a dose of 80 mg daily in five randomised Phase 3 studies (ADAURA, adjuvant; FLAURA, and FLAURA2 (monotherapy arm) first line; LAURA (post platinum-based chemoradiation therapy) and AURA3, second line only), two Phase 2 single-arm studies (AURAex and AURA2, second line or later) and one Phase 1 study (AURA1, first-line or later) (see section 5.1). Most adverse reactions were Grade 1 or 2 in severity. The most commonly reported adverse drug reactions (ADRs) were diarrhoea (46%), rash (45%), paronychia (33%), dry skin (31%), and stomatitis (23%). Grade 3 and Grade 4 adverse reactions across the studies were 11% and 0.2%, respectively. In patients treated with TAGRISSO 80 mg once daily, dose reductions due to adverse reactions occurred in 3.4% of the patients. Discontinuation due to adverse reactions was 5.5%.

The safety of TAGRISSO given in combination with pemetrexed and platinum-based chemotherapy is based on data in 276 patients with EGFR mutation-positive NSCLC and was consistent with TAGRISSO monotherapy and known safety profiles of pemetrexed and platinum-based chemotherapy. The most commonly reported ADRs when TAGRISSO was given in combination with pemetrexed and platinum-based chemotherapy were rash (49%), diarrhoea (43%), decreased appetite (31%), stomatitis (31%), paronychia (27%) and dry skin (24%). When TAGRISSO is administered as combination therapy, refer to the Summary of Product Characteristics for the respective combination therapy components prior to initiation of treatment.

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 electrocardiogram (ECG) (e.g. QTc interval greater than 470 msec) 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 1956 EGFR mutation-positive NSCLC patients who received TAGRISSO monotherapy at a dose of 80 mg daily in the ADAURA, FLAURA, FLAURA2, LAURA, AURA3, AURAex, AURA 2 and AURA1 studies and in 276 patients treated with TAGRISSO in combination with pemetrexed and platinum-based chemotherapy in the FLAURA2 study.

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 <1/1,000); very rare (<1/10,000); not known (cannot be estimated from available data).

Table 2. Adverse reactions reported in ADAURA, LAURA, FLAURA, FLAURA2 and AURA studies

MedDRA SOC and MedDRA term	TAGRISSO[a]		TAGRISSO with pemetrexed and platinum-based chemotherapy[b]	
	CIOMS descriptor/ overall frequency (all CTCAE grades)[c]	Frequency of CTCAE grade 3 or higher[c]	CIOMS descriptor/ overall frequency (all CTCAE grades)[c]	Frequency of CTCAE grade 3 or higher[c]
Infections and infestations				
Hepatitis B reactivation[d]	Not known		0%	0%
Blood and lymphatic system disorders				
Aplastic anaemia	Rare (0.05%)	0.05%	0%	0%
Thrombocytopenia	Common (7%)	0.6%	Very common (18.5%)	6.9%
Neutropenia	Common (6%)	0.9%	Very common (24.6%)	13.4%
Leukopenia	Common (5%)	0.4%	Very common (12.7%)	2.9%
Lymphopenia	Common (1.6%)	0.3%	Common (2.5%)	1.1%
Metabolism and nutrition disorders				
Decreased appetite	Very common (19%)	1.1%	Very common (31%)	2.9%
Eye disorders				
Keratitis[e]	Uncommon (0.6%)	0.05%	Uncommon (0.7%)	0%
Cardiac disorders				
Cardiac failure	Uncommon (0.5%)	0.2%	Common (1.8%)	1.1%[f]
Respiratory, thoracic and mediastinal disorders				
Epistaxis	Common (6%)	0%	Common (7%)	0.4%
Interstitial lung disease	Common (4.3%)[g]	1.4%[h]	Common (3.3%)[i]	0.7%[j]
Radiation Pneumonitis[k]	Common (4%)	0.2%	0%	0%
Gastrointestinal disorders				
Diarrhoea	Very common (46%)	1.5%	Very common (43%)	2.9%
Stomatitis[l]	Very common (23%)	0.4%	Very common (31%)	0.4%
Skin and subcutaneous tissue disorders				
Rash[m]	Very common (45%)	0.8%	Very common (49%)	2.5%
Paronychia[n]	Very common (33%)	0.4%	Very common (27%)	0.7%
Dry skin[o]	Very common (31%)	0.2%	Very common (24%)	0%

Pruritus[p]	Very common (17%)	0.05%	Common (8%)	0%
Alopecia	Common (5%)	0%	Common (9%)	0%
Palmar-plantar erythrodysaesthesia syndrome	Common (1.9%)	0%	Common (5%)	0%
Urticaria	Common (1.9%)	0.1%	Common (1.4%)	0.4%
Skin hyperpigmentation[q]	Uncommon (0.9%)	0%	Common (2.5%)	0%
Erythema multiforme[r]	Uncommon (0.3%)	0%	Common (1.4%)	0.7%
Cutaneous vasculitis[s]	Uncommon (0.2%)		0%	0%
Stevens-Johnson syndrome[t]	Rare (0.02%)		0%	0%
Toxic Epidermal Necrolysis[d]	Not known		0%	0%
Investigations				
Left ventricular ejection fraction decreased[u,v]	Common (4.1%)		Common (8.0%)	
Blood creatine phosphokinase increased	Common (2%)	0.4%	Common (3.3%)	1.1%
QTc interval prolongation[w]	Common (1.1%)		Common (1.8%)	
Investigations (Findings based on test results presented as CTCAE grade shifts)				
Leukocytes decreased[u]	Very common (65%)	1.9%	Very common (88%)	20%
Lymphocytes decreased[u]	Very common (64%)	8%	Very common (78%)	16%
Platelet count decreased[u]	Very common (53%)	1.3%	Very common (85%)	16%
Neutrophils decreased[u]	Very common (36%)	4.0%	Very common (85%)	36%
Blood creatinine increased	Common (5.6%)	0.05%	Very common (22%)	0.4%
Musculoskeletal and connective tissue disorders				
Myositis	Uncommon (0.2%)	0%	0%	0%

[a] Data is pooled from ADAURA, FLAURA, FLAURA2 (monotherapy arm), LAURA and AURA (AURA3, AURAex, AURA 2 and AURA1) studies; only events for patients receiving at least one dose of TAGRISSO as their randomised treatment are summarized.

[b] Data is from the combination arm of the FLAURA2 study; only events for the patients receiving at least one dose of study treatment (TAGRISSO, pemetrexed, cisplatin or carboplatin) as their randomised treatment are summarised. The median duration of study treatment was 22.3 months for patients in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm.

[c] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

[d] Reported during post-marketing use.

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

[f] Two CTCAE Grade 5 events (fatal) were reported.

[g] Includes: interstitial lung disease (1.8%), pneumonitis (2.2%), pulmonary fibrosis (0.2%), organising pneumonia (0.1%).

[h] Eight CTCAE Grade 5 events (fatal) were reported.

[i] Includes: interstitial lung disease (1.8%), pneumonitis (1.1%), organising pneumonia (0.4%).

[j] One CTCAE Grade 5 event (fatal) was reported.

[k] Includes: radiation fibrosis-lung (0.05%).

[l] Includes: mouth ulceration, stomatitis.

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

[n] 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.

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

[p] Includes: eyelid pruritus, pruritus.

[q] Cases of erythema dyschromicum perstans have been reported in the post-marketing setting.

[r] Six of the 1956 patients in the ADAURA, AURA, FLAURA, FLAURA2 (monotherapy arm), LAURA and AURA 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).

[s] Estimated frequency. The upper limit of the 95% CI for the point estimate is 3/1956 (0.4%).

[t] One event was reported in a post-marketing study, and the frequency has been derived from the ADAURA, FLAURA, FLAURA2 (monotherapy arm), LAURA and AURA studies and the post-marketing study (N=5534).

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

[v] Represents decreases greater than or equal to 10 percentage points and a drop to less than 50%.

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

Description of selected adverse reactions

Interstitial lung disease (ILD)

In the ADAURA, FLAURA, FLAURA2 (monotherapy arm), AURA and LAURA studies, ILD or ILD-like adverse reactions were reported in 4.3% of the 1956 patients. Eight fatal cases were reported. No fatal cases were reported in the adjuvant setting. The incidence of ILD was 10.4% in patients of Japanese ethnicity, 2.8% in patients of non-Japanese Asian ethnicity and 3.2% in non-Asian patients. The median time from first dose to onset of ILD or ILD-like adverse reactions was 85 days (see section 4.4).

ILD or ILD-like adverse reactions were reported in 7.7% and were fatal in 0.7% (n=1) of the 143 patients who received TAGRISSO following definitive platinum-based chemoradiation therapy in LAURA. The incidence of ILD was 6.6% in patients of non-Japanese Asian ethnicity and 17.2% in non-Asian patients; no patients of Japanese ethnicity had an event of ILD. The median time from first dose to onset of ILD or ILD-like adverse reactions was 1.9 months. The median time from last dose of radiotherapy to onset of ILD or ILD-like adverse reactions was 3.0 months.

ILD or ILD-like adverse reactions were reported in 3.3% and were fatal in 0.4% (n=1) of the 276 patients who received TAGRISSO in combination with pemetrexed and platinum-based chemotherapy in FLAURA2. The incidence of ILD was 14.9% in patients of Japanese ethnicity and 1.7% in non-Asian patients; no patients of non-Japanese Asian ethnicity had an event of ILD in the FLAURA2 combination arm. The median time from first dose to onset of ILD or ILD-like adverse reactions was 161 days.

Radiation pneumonitis

In the LAURA study, following definitive platinum-based chemoradiation therapy, radiation pneumonitis was reported in 48% of the 143 patients who received TAGRISSO and 38% of the 73 patients who received placebo. Three (2.1%) patients had Grade 3 events, all in the TAGRISSO arm, and no Grade 4 or Grade 5 events were reported in either arm. The median time from first dose to onset of radiation pneumonitis was 1.7 months in the TAGRISSO arm and 1.8 months in the placebo arm. The median time from last dose of radiotherapy to onset of radiation pneumonitis was 2.5 months in the TAGRISSO arm and 2.6 months in the placebo arm.

QTc interval prolongation

Of the 1956 patients in ADAURA, FLAURA, FLAURA2, LAURA and AURA studies treated with TAGRISSO monotherapy 80 mg, 1.1% of patients (n=21) were found to have a QTc greater than 500 msec, and 4% of patients (n=79) had an increase from baseline QTc greater than 60 msec. A pharmacokinetic/pharmacodynamic analysis with TAGRISSO predicted a concentration-dependent increase in QTc interval prolongation. No QTc-related arrhythmias were reported in the ADAURA, LAURA, FLAURA, FLAURA2 or AURA studies (see sections 4.4 and 5.1).

In patients who received TAGRISSO in combination with pemetrexed and platinum-based chemotherapy, the proportion of patients who experienced a QTc interval prolongation of greater than 500 msec with a greater than 60 msec increase from baseline was low and was similar with monotherapy (1.8% versus 1.5%).

Gastrointestinal effects

In the ADAURA, FLAURA, FLAURA2, LAURA and AURA studies (TAGRISSO monotherapy; N=1956), diarrhoea was reported in 46% of patients of which 36% were Grade 1 events, 8.1% Grade 2 and 1.5% were Grade 3; no Grade 4 or 5 events were reported. Dose reduction was required in 0.6% of patients and dose interruption in 1.9%. Four events (0.2%) led to discontinuation. In ADAURA, FLAURA, FLAURA2 (monotherapy arm) and AURA3 the median time to onset was 22 days, 19 days, 22 days and 22 days, respectively, and the median duration of the Grade 2 events was 11 days, 19 days, 17 days and 6 days, respectively. In patients who received TAGRISSO in combination with pemetrexed and platinum-based chemotherapy, diarrhoea was reported in 43% of patients versus 41% of patients in monotherapy, most of these diarrhoea events were Grade 1 and Grade 2 events.

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. Rare cases of aplastic anaemia, including fatal events, have been reported in association with TAGRISSO treatment. TAGRISSO should be discontinued in patients with confirmed aplastic anaemia (see section 4.2 and 4.4).

Elderly

In ADAURA, FLAURA, FLAURA2, LAURA and AURA3 (TAGRISSO monotherapy; N=1956), 43% of patients were 65 years of age and older, and 11% were 75 years of age and older. Compared with younger patients (<65), more patients ≥65 years old had reported adverse reactions that led to study dose modifications (interruptions or reductions) (18% versus 13%). The types of adverse events reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (14% versus 9%). No overall differences in efficacy were observed between older and younger patients. A consistent pattern in safety and efficacy results was observed in the analysis of AURA Phase 2 studies. Of the 276 patients treated with TAGRISSO in combination with pemetrexed

and platinum-based chemotherapy, 104 patients were ≥65 years and 23 patients were ≥75 years of age. Older patients (≥65 years) reported similar Grade 3 or higher adverse reactions compared to <65 years old patients (36% versus 36%) respectively. Dose modification for adverse reactions were reported in a higher proportion of patients ≥65 years as compared to <65 years (34% vs 20%).

Low body weight

Patients receiving TAGRISSO monotherapy (80 mg; N=1956) with low body weight (<50 kg) reported higher frequencies of Grade ≥3 adverse reactions (20% versus 10%) and QTc prolongation (12% versus 6%) than patients with higher body weight (≥50 kg). Patients who received TAGRISSO in combination with pemetrexed and platinum-based chemotherapy with low body weight (<50 kg) reported similar frequencies of Grade ≥3 adverse reactions (32% versus 37%) when compared to patients with higher body weight (≥50 kg). In contrast, dry skin (34% versus 22%) and stomatitis (40% versus 30%) were reported at higher frequencies in patients with low body weight (<50 kg) versus higher body weight (≥50 kg).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by an online form: https://sideeffects.health.gov.il

4.9 Overdose

In TAGRISSO clinical studies 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 TKI-induced AEs (primarily diarrhoea and skin rash) compared to the 80-mg dose. There is limited experience with accidental overdoses in humans. All cases were isolated incidents of patients taking an additional daily dose of TAGRISSO in error, without any resulting clinical consequences.

There is no specific treatment in the event of TAGRISSO overdose. In case of suspected overdose, TAGRISSO should be withheld and symptomatic treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors; ATC code: L01EB04.

Mechanism of action

Osimertinib is a Tyrosine Kinase Inhibitor (TKI). It is an irreversible inhibitor of EGFRs harboring sensitising-mutations (EGFRm) and TKI-resistance mutation T790M.

Pharmacodynamic effects

In vitro studies have demonstrated that osimertinib has high potency and inhibitory activity against EGFR across a range of all clinically relevant EGFR sensitising-mutant and T790M mutant 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 from 480 nM to 1.8 μM against phospho-EGFR). *In vivo* oral administration of osimertinib lead to tumour shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumour models.

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 osimertinib on QTc intervals. A pharmacokinetic/pharmacodynamic analysis 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 (Ex19del or L858R) NSCLC who have had complete tumor resection, with or without prior adjuvant chemotherapy was demonstrated in a randomised, double-blind, placebo-controlled study (ADAURA).

Eligible patients with resectable tumors stage IB – IIIA (according to American Joint Commission on Cancer [AJCC] 7th edition) were required to have EGFR mutations (Ex19del or L858R), identified by the cobas EGFR Mutation Test performed prospectively using biopsy or surgical specimen in a central laboratory.

Patients were randomised 1:1 to receive TAGRISSO (n=339, 80 mg orally once daily) or placebo (n=343) following recovery from surgery and standard adjuvant chemotherapy where given. Patients not receiving adjuvant chemotherapy were randomised within 10 weeks and patients receiving adjuvant chemotherapy within 26 weeks following surgery. Randomisation was stratified by EGFR mutation type (Ex19del or L858R), ethnicity (Asian or non-Asian) and staging based on pathological tumor-node-metastasis (pTNM) (IB or II or IIIA) according to AJCC 7th edition. Treatment was given until disease recurrence, unacceptable toxicity, or for 3 years.

The major efficacy outcome measure was disease-free survival (DFS) by investigator assessment in the stage II-IIIA population. DFS by investigator assessment in the stage IB-IIIA population (overall population) was an additional efficacy outcome measure. Other additional efficacy outcome measures included DFS rate, overall survival (OS), OS rate, and time to deterioration in health-related quality of life (HRQoL) SF-36.

The baseline demographic and disease characteristics of the overall population were: median age 63 years (range 30-86 years), ≥75 years old (11%), female (70%), Asian (64%), never smokers (72%), World Health Organization (WHO) performance status of 0 (64%) or 1 (36%), stage IB (31%), stage II (34%), and IIIA (35%). With regards 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 randomization (26% IB; 71% IIA; 73% IIB; 80% IIIA). At the time of the DFS analysis, 205 (61%) patients were still on active treatment; of the 73 (11%) patients who had the opportunity to complete the 3-year treatment period, 40 (12%) were in the osimertinib arm and 33 (10%) in the placebo arm.

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 central nervous system (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).

ADAURA demonstrated a statistically significant reduction in the risk of disease recurrence or death for patients treated with TAGRISSO compared to patients treated with placebo in the stage II-IIIA population. Similar results were observed in the stage IB-IIIA population.

Efficacy results from ADAURA by investigator assessment are summarized in Table 3.

Table 3. Efficacy results from ADAURA by Investigator Assessment

	Stage II-IIIA population		**Stage IB-IIIA population**	
Efficacy parameter	**TAGRISSO (N=233)**	**Placebo (N=237)**	**TAGRISSO (N=339)**	**Placebo (N=343)**
Disease-free survival				
Number of events (%)	26 (11)	130 (55)	37 (11)	159 (46)
Recurrent disease (%)	26 (11)	129 (54)	37 (11)	157 (46)
Deaths (%)	0	1 (0.4)	0	2 (0.6)
Median DFS, months (95% CI)	NC (38.8, NC)	19.6 (16.6, 24.5)	NC (NC, NC)	27.5 (22.0, 35.0)
HR (99.06% CI); P-value	0.17 (0.11, 0.26); <0.0001[a]		0.20 (0.14, 0.30); <0.0001[b]	
DFS rate at 12 months (%) (95% CI)	97 (94, 99)	61 (54, 67)	97 (95, 99)	69 (63, 73)
DFS rate at 24 months (%) (95% CI)	90 (84, 93)	44 (37, 51)	89 (85, 92)	52 (46, 58)
DFS rate at 36 months (%) (95% CI)[c, d]	78 (65, 87)	28 (19, 38)	79 (69, 86)	40 (32, 48)

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, 14.9 months for patients receiving placebo (stage II-IIIA population) and 16.6 months for patients receiving placebo (stage IB-IIIA population).

DFS results are from the primary analysis (17 January 2020).

[a] Adjusted for an interim analysis (33% maturity) a p-value < 0.0094 was required to achieve statistical significance.

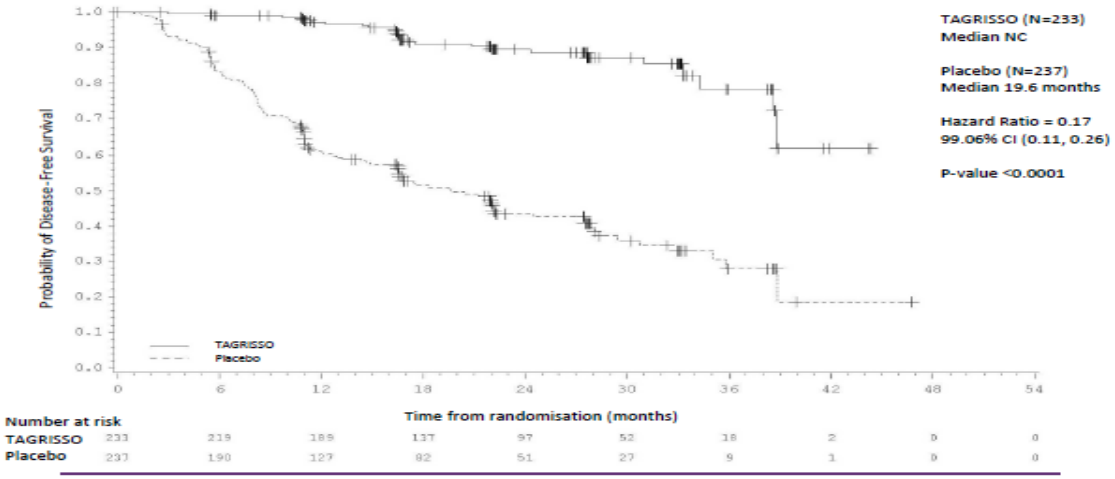
[b] Adjusted for an interim analysis (29% maturity) a p-value <0.0088 was required to achieve statistical significance.

[c] The number of patients at risk at 36 months was 18 patients in the TAGRISSO arm and 9 patients in the placebo arm (stage II-IIIA population).

[d] The number of patients at risk at 36 months was 27 patients in the TAGRISSO arm and 20 patients in the placebo arm (stage IB-IIIA population).

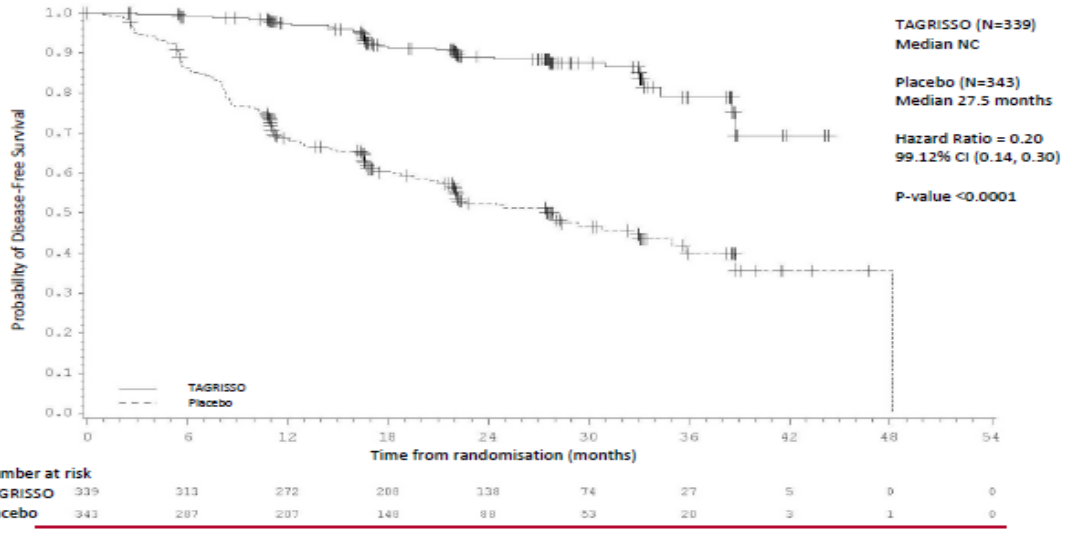
The final analysis of OS (data cut-off [DCO]: 27 January 2023) demonstrated a statistically significant improvement in OS for patients treated with TAGRISSO compared to placebo for both the stage II-IIIA population (100 OS events [21% maturity]; HR=0.49; 95.03% CI: 0.33, 0.73; p-value=0.0004) and the overall population (IB-IIIA; 124 OS events [18% maturity]; HR=0.49; 95.03% CI: 0.34, 0.70; p-value < 0.0001). For both populations, the median OS was not reached in either treatment arm and the 95% CIs were not calculable. The median follow-up time for OS in all patients was 59.9 months (stage II-IIIA population) and 60.4 months (stage IB-IIIA population) in the TAGRISSO arm and 56.2 months (stage II-IIIA population) and 59.4 months (stage IB-IIIA population) in the placebo arm.

Figure 1. Kaplan-Meier curve of disease-free survival in 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.

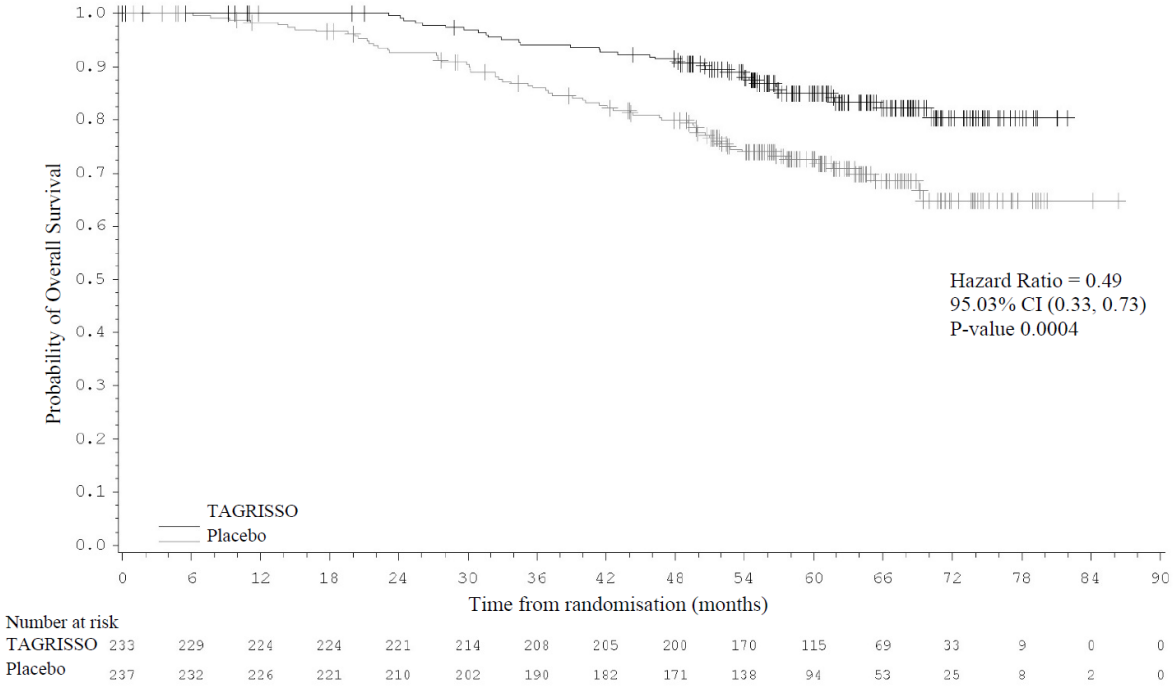
Figure 2. Kaplan-Meier curve of Disease-Free Survival in stage IB-IIIA (overall population) patients by investigator assessment



+ 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 (Ex19Del or L858R).

Figure 3. Kaplan-Meier curve of overall survival in stage II-IIIA patients



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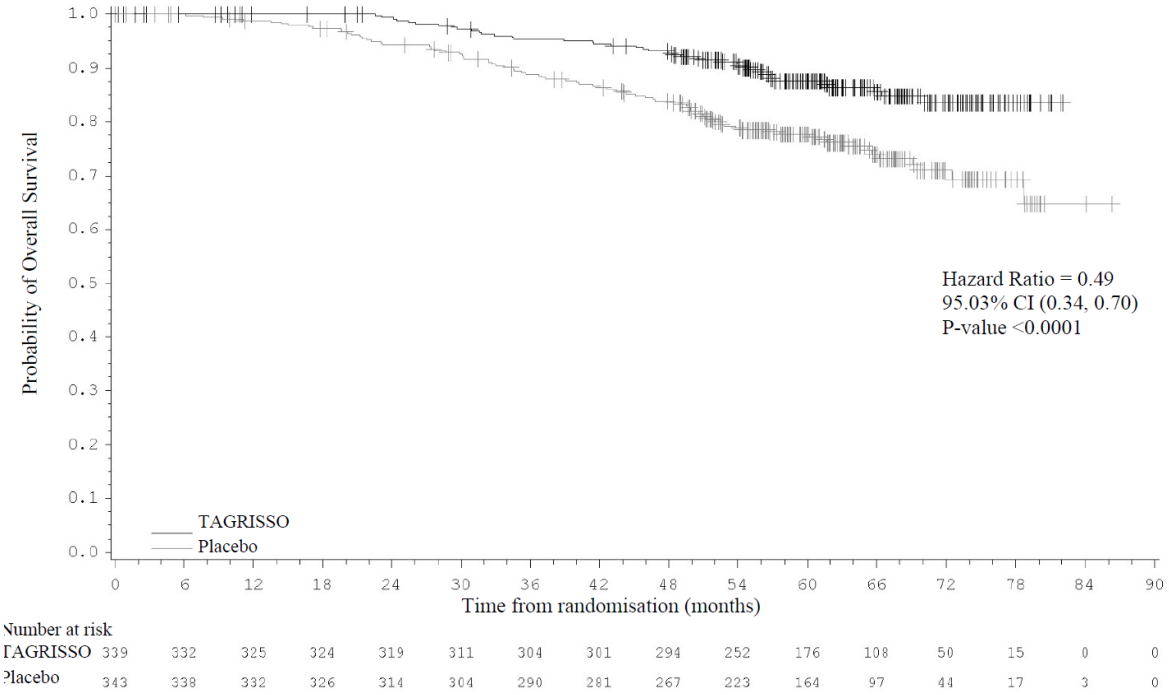
The values at the base of the figure indicate number of subjects at risk.

Figure 4. Kaplan-Meier curve of overall survival in stage IB-IIIA (overall population) patients



\+ Censored patients.
The values at the base of the figure indicate number of subjects at risk.

An exploratory analysis of CNS DFS (time to CNS recurrence or death) for patients on TAGRISSO compared to patients on placebo showed a HR of 0.18 (95% CI: 0.10, 0.33; p <0.0001) for the overall population (stage IB-IIIA).

Patient reported outcomes

Health-related quality of life (HRQL) in ADAURA was assessed using the Short Form (36) Health Survey version 2 (SF-36v2) questionnaire. SF-36v2 was administered at 12 weeks, 24 weeks and then every 24 weeks relative to randomisation until treatment completion or discontinuation. Overall, HRQL was maintained in both arms up to 30 months, with at least 70% of patients in the stage II-IIIA population not experiencing a clinically meaningful deterioration in the physical component of the SF-36 or death (70% vs 76% for TAGRISSO vs placebo), or in the mental component of the SF-36 or death (70% vs 71% for TAGRISSO vs placebo).

Locally advanced, unresectable EGFR mutation-positive NSCLC – LAURA

The efficacy and safety of TAGRISSO for the treatment of patients with EGFR mutation-positive, locally advanced, unresectable NSCLC, who had not progressed during or following definitive platinum-based chemoradiation therapy, were evaluated in a randomised, double-blind, placebo-controlled study (LAURA). Patients were to receive concurrent chemoradiation therapy (CCRT) or sequential chemoradiation therapy (SCRT) regimens, where at least 2 cycles or 5 weekly doses of platinum-based chemotherapy and a total dose of radiation of 60 Gy ±10% (54 Gy to 66 Gy), were to be completed ≤6 weeks prior to randomisation. Patient tumour tissue samples were required to have an EGFR exon 19 deletion or exon 21 L858R mutation, as identified by central or local testing using a certified/approved test.

Patients were randomised (2:1) to receive either TAGRISSO 80 mg orally once daily (n=143) or placebo (n=73). Randomisation was stratified by prior chemoradiation strategy (CCRT vs SCRT), tumour staging prior to chemoradiation (IIIA vs IIIB/IIIC), and by the China cohort. Patients continued to receive study treatment until intolerance to therapy or confirmed disease progression. Cross-over from placebo to TAGRISSO was permitted upon progressive disease.

The primary efficacy endpoint was progression-free survival (PFS) as assessed by blinded independent central review (BICR). Additional efficacy endpoints included OS and CNS PFS as assessed by neuroradiologist BICR.

The baseline demographic and disease characteristics of the overall study population were: median age 63 years (range 36-84 years), ≥75 years old (13%), female (61%), Asian (82%), White (14%), never smokers (70%). Baseline WHO performance status was 0 (51%) or 1 (49%); 35% of patients had stage IIIA, 49% of patients had stage IIIB and 16% of patients had stage IIIC NSCLC. With regard to EGFR mutation status, 54% were exon 19 deletions and 45% were exon 21 L858R mutations. Prior to randomisation, 89% of patients received CCRT and 11% of patients received SCRT. All patients received platinum-based chemotherapy (55% carboplatin-based chemotherapy and 44% cisplatin-based chemotherapy). The median total dose of radiation was 60 Gy for patients in both arms.

Treatment with TAGRISSO following platinum-based chemoradiation therapy resulted in a statistically significant improvement in PFS compared to placebo (56% maturity; HR=0.16; 95% CI: 0.10, 0.24; P<0.001, median 39.1 months and 5.6 months, respectively).

Per protocol, all patients underwent baseline magnetic resonance imaging (MRI) brain scans and all but one patient had scheduled on-treatment MRI brain scans. A lower proportion of patients had new CNS lesions by neuroradiologist review in the TAGRISSO arm compared to the placebo arm (17/143 [12%] vs. 26/73 [36%], respectively).

At the time of the interim analysis of OS (DCO: 05 January 2024), statistical significance was not reached. Fifty out of 62 patients (80.6%) in placebo arm were treated with TAGRISSO post-BICR confirmed disease progression.

Efficacy results from LAURA are summarised in Table 4, and the Kaplan-Meier curve for PFS is shown in Figure 5.

Table 4. Efficacy results from LAURA

Efficacy Parameter	**TAGRISSO (N=143)**	**Placebo (N=73)**
Progression-Free Survival[a]		
Number (%) of events	57 (40)	63 (86)
Median PFS, months (95% CI)	39.1 (31.5, NC)	5.6 (3.7, 7.4)
HR (95% CI); P-value	0.16 (0.10, 0.24); P<0.001	
Overall Survival		
Number (%) of deaths	28 (20)	15 (21)
Median OS, months (95% CI)	54.0 (46.5, NC)	NC (42.1, NC)
HR (95% CI); P-value	0.81 (0.42, 1.56); P=0.530[a]	

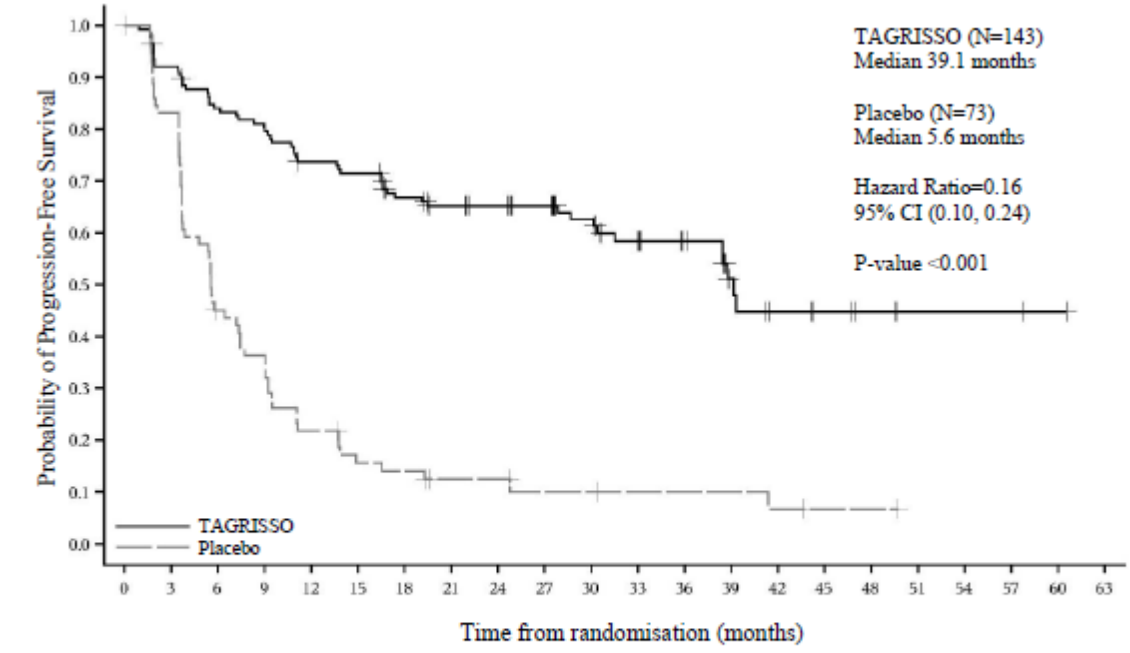
HR=Hazard Ratio; CI=Confidence Interval, NC=Not

Calculable PFS results as assessed by BICR.

Median follow-up time for PFS in all patients was 22.0 months in the TAGRISSO arm and 5.6 months in the placebo arm.

[a] Adjusted for an interim analysis (20% maturity) a p-value <0.000036 was required to achieve statistical significance.

Figure 5. Kaplan-Meier Curves of Progression-Free Survival as assessed by BICR in LAURA



Previously untreated EGFR mutation-positive locally advanced or metastatic NSCLC

FLAURA– Monotherapy

The efficacy and safety of TAGRISSO for the treatment of patients with EGFR mutation-positive locally advanced, not amenable to curative surgery or radiotherapy, 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 PFS as assessed by investigator.

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%), WHO performance status of 0 or 1 (100%), metastatic bone disease (36%), extra-thoracic visceral metastases (35%), CNS metastases (21%, 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 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 5, and the Kaplan-Meier curve for PFS is shown in Figure 6. The final analysis of OS, (58% maturity) demonstrated a statistically significant improvement with an HR of 0.799 (95.05% CI: 0.641, 0. 997) and a clinically meaningful longer median survival time in patients randomized to TAGRISSO compared to EGFR TKI comparator (Table 5 and Figure 7). 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). Analysis of post-progression endpoints demonstrated that the PFS benefit was preserved through subsequent lines of therapy**.**

Table 5. 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 PFS, 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, 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 DoR, 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 (18.0, 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 (%)	75 (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 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 DCO 12 June 2017. OS results are from DCO 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 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 6. Kaplan-Meier curves of progression-free survival as assessed by investigator in FLAURA

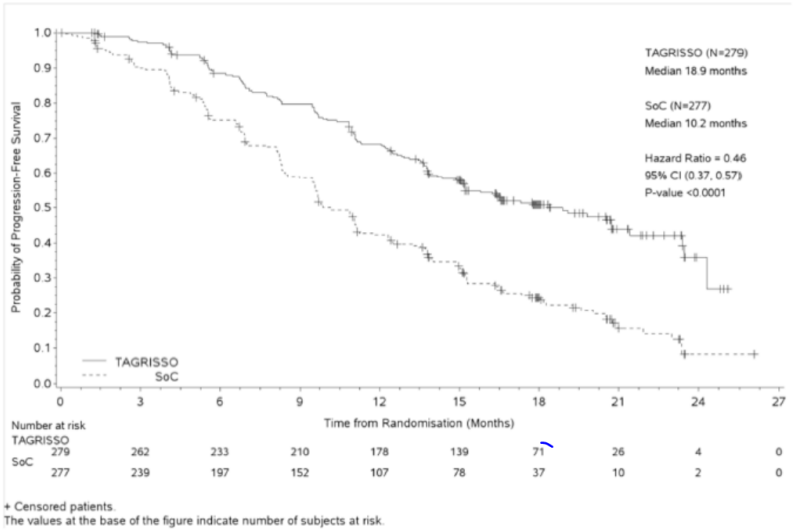
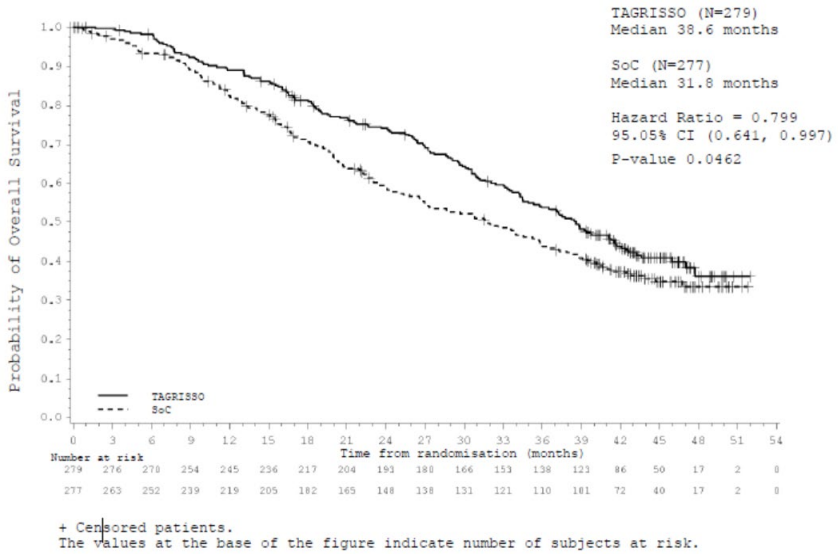


Figure 7. Kaplan-Meier curves of overall survival in FLAURA



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).

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 6. 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 6. 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 CNS PFS, 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)

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

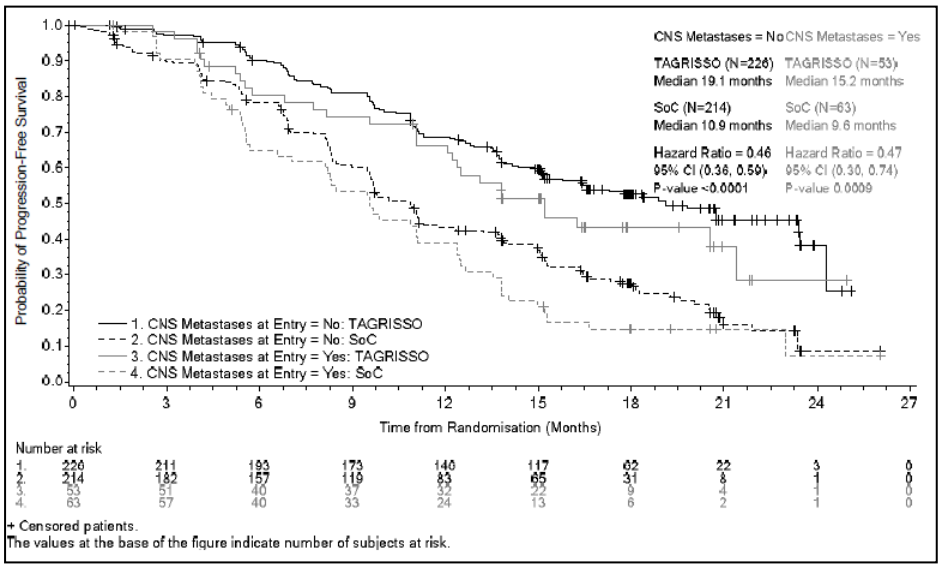
A HR< 1 favours TAGRISSO, an Odds ratio of >1 favours TAGRISSO

[1] CNS PFS determined by RECIST v1.1by 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 8. 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 and 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).

Figure 8. Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in FLAURA



Patient reported outcomes

Patient-reported symptoms and 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 cut-off.

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).

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.

FLAURA2 – Combination Therapy

The efficacy and safety of TAGRISSO in combination with pemetrexed and platinum-based chemotherapy 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, open-label, active-controlled study (FLAURA2). 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 one of the following treatment arms:

- TAGRISSO (80 mg) orally once daily with pemetrexed (500 mg/m^2) and the investigator's choice of cisplatin (75 mg/m^2) or carboplatin (AUC5) administered intravenously on Day 1 of every 21- day cycle for 4 cycles, followed by TAGRISSO (80 mg) orally once daily and pemetrexed (500 mg/m^2) administered intravenously every 3 weeks (n=279)
- TAGRISSO (80 mg) orally once daily (n=278)

Randomisation was stratified by race (Chinese/Asian, non-Chinese/Asian or non-Asian), WHO performance status (0 or 1), and method for tissue testing (central or local). Patients received study therapy until intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit.

The primary efficacy endpoint was PFS as assessed by investigator per RECIST 1.1 and the key secondary efficacy endpoint was OS.

The baseline demographic and disease characteristics of the overall study population were: median age 61 years (range 26-85 years), ≥75 years old (8%), female (61%), Asian (64%), White (28%), never smokers (66%). Baseline WHO performance status was 0 (37%) or 1 (63%); 98.7% had predominantly adenocarcinoma histology. Of the patients who had metastatic disease, 49% had metastatic bone disease, 53% had extra-thoracic metastases and 20% had liver metastases. Forty-one percent (41%) of patients had CNS metastases (identified by investigator based on CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases). With regard to tumour EGFR mutation type at randomisation, 60.5% were exon 19 deletions and 38.2% were exon 21 L858R; 0.7% of patients had tumours with both exon 19 deletions and exon 21 L858R.

TAGRISSO in combination with pemetrexed and platinum-based chemotherapy demonstrated a statistically significant improvement in PFS compared to TAGRISSO monotherapy. The PFS benefit was consistent across all subgroups analysed. At the time of the second interim analysis of OS (DCO 08 January 2024), statistical significance was not reached.

Efficacy results from FLAURA2 by investigator assessment are summarised in Table 7, the Kaplan-Meier curve for PFS is shown in Figure 9 and the Kaplan-Meier curve for OS is shown in Figure 10.

Table 7. Efficacy results from FLAURA2 by investigator assessment

Efficacy parameter	**TAGRISSO with pemetrexed and platinum-based chemotherapy (N=279)**	**TAGRISSO (N=278)**
Progression-Free Survival		
Number (%) of events	120 (43)	166 (60)
Median PFS, months (95% CI)[a]	25.5 (24.7, NC)	16.7 (14.1, 21.3)
HR (95% CI); P-value	0.62 (0.49, 0.79); P<0.0001	
Overall Survival		
Number (%) of deaths	100 (36)	126 (45)

Median OS, months (95% CI)	NC (38.0, NC)	36.7 (33.2, NC)
HR (95% CI); P-value	0.75 (0.57, 0.97); P=0.0280[b]	

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

PFS based on RECIST investigator assessment.

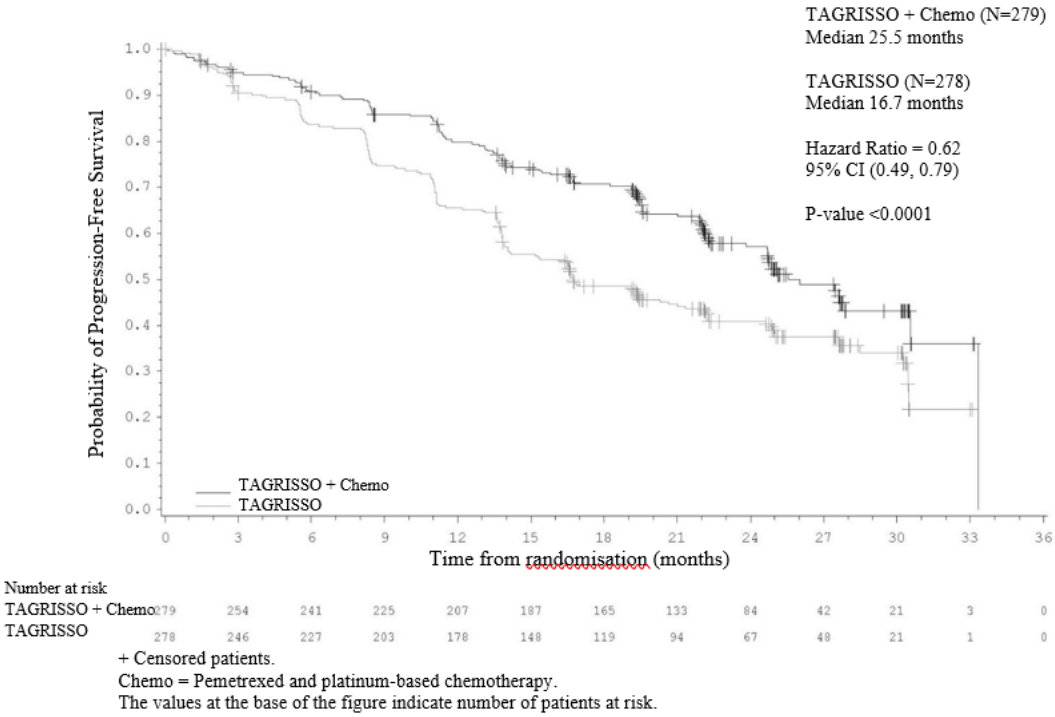
Median follow-up time for PFS in all patients was 19.5 months in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm and 16.5 months in the TAGRISSO monotherapy arm.

PFS results are from DCO 03 April 2023 (51% maturity). OS results are from DCO 08 January 2024 (41% maturity).

[a] PFS results by BICR were consistent with those reported via investigator assessment.

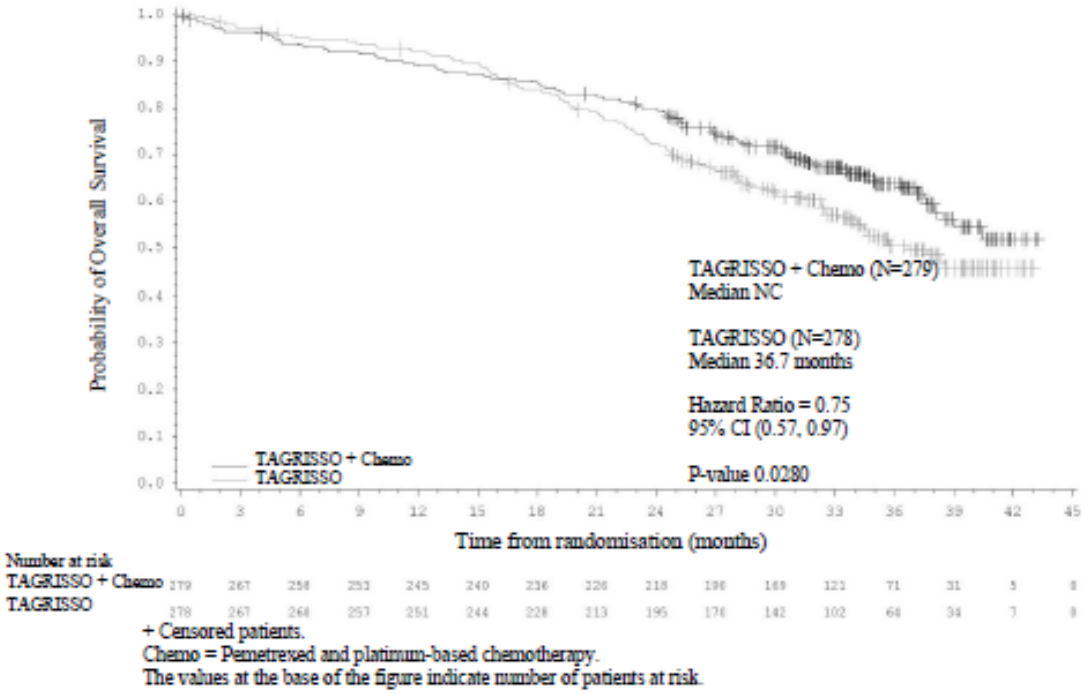
[b] Based on the second interim analysis (41% maturity) a p-value <0.000001 was required to achieve statistical significance.

Figure 9. Kaplan-Meier curves of progression-free survival as assessed by investigator in FLAURA2



+ Censored patients.
Chemo = Pemetrexed and platinum-based chemotherapy.
The values at the base of the figure indicate number of patients at risk.

Figure 10. Kaplan-Meier Curves of Overall Survival in FLAURA2



+ Censored patients.
Chemo = Pemetrexed and platinum-based chemotherapy.
The values at the base of the figure indicate number of patients at risk.

CNS metastases efficacy data in FLAURA2 study

Patients with asymptomatic 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 FLAURA2 study. All patients had available baseline brain scans. A BICR assessment, using modified RECIST, of these scans resulted in a subgroup of 222/557 (40%) patients with CNS measurable and/or non-measurable lesions (cFAS) and a further subgroup of 78/557 (14%) patients with CNS measurable lesions (cEFR). Based on an exploratory analysis, CNS response rate was >65% in both treatment arms with a higher complete response rate in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm (59.3% of patients) compared to the TAGRISSO monotherapy arm (43.3% of patients). Median DoR was not reached in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm and was 26.2 months in the TAGRISSO monotherapy arm. In the cEFR subgroup, 47.5% of patients in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm had a CNS complete response compared to 15.8% of patients in the TAGRISSO monotherapy arm.

Pre-treated 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 ORR, DoR 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 has not progressed after four cycles of platinum-based chemotherapy may 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, ≥75 years old (15%), female (64%), white (32%), Asian (65%), never smoker (68%), WHO performance status 0 or 1 (100%). 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 8, and the Kaplan-Meier curve for PFS is shown in Figure 11. No statistically significant difference was observed between the treatment arms at the final OS analysis.

Table 8. 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 PFS, 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[1] (OS)		
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 (95.56% 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 DoR, months (95% CI)	9.7 (8.3, 11.6)	4.1 (3.0, 5.6)

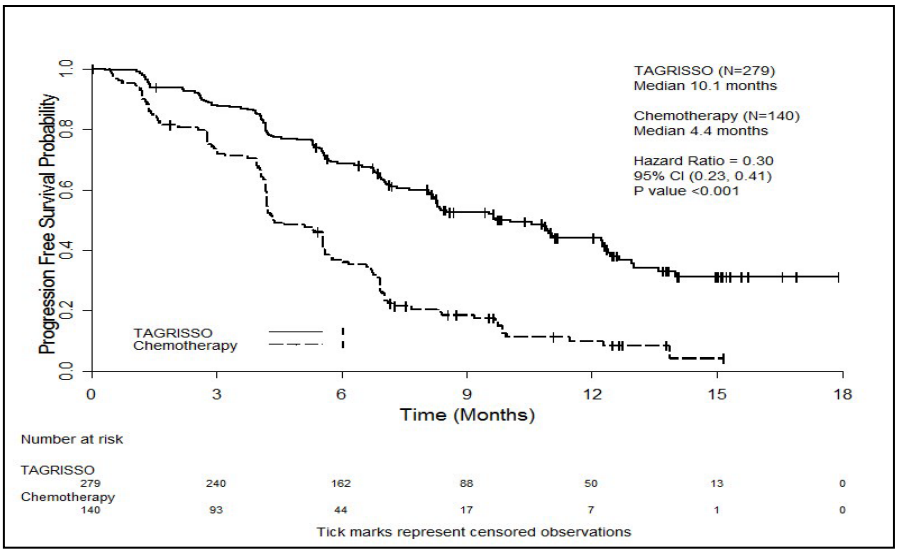
HR=Hazard Ratio; CI=confidence interval; NC=non-calculable; ; OS=Overall Survival

All efficacy results based on RECIST investigator assessment

[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: 25.6, 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.

Figure 11. 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 and EGFR mutation (Exon 19 deletion and L858R).

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 9.

Table 9. 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 CNS DoR, months (95% CI)	8.9 (4.3, NC)	5.7 (NC, NC)
CNS disease control rate		
CNS disease control rate % (n/N) (95% CI)	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 CNS PFS, 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

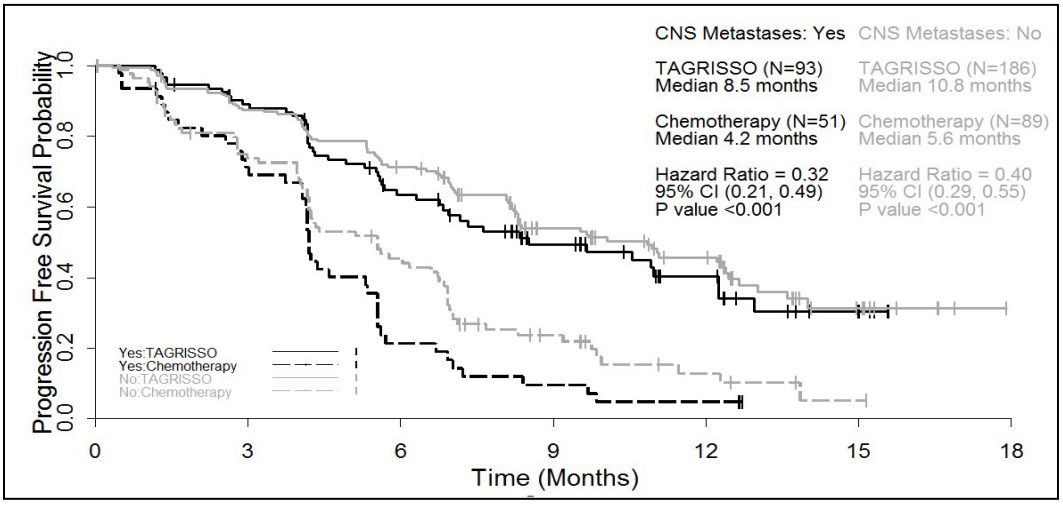
2 Based on patients with response only; DoR defined as the time from the date of first documented response (complete response or partial response) until progression or death event; DCR defined as the proportion of patients with response (complete response or partial response), or stable disease ≥ 6 weeks

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

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 12.

Figure 12. Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in AURA3



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

Patient reported outcomes

Patient-reported symptoms and 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 10.

Table 10. 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).

Pre-treated 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 the cobas EGFR mutation test performed in a central laboratory prior to treatment. The 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 studies was 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%). All patients received at least one prior line of therapy. Thirty-one percent (31%) (N=129) had received 1 prior line of therapy (EGFR-TKI treatment only), 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 total ORR by Blinded Independent Central Review (BICR) 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 ORR by BICR in AURAex was 62% (95% CI: 55, 68) and 70% (95% CI: 63, 77) in AURA2. The median PFS 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, ethnicity, age and region.

In the evaluable for response population, 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 v 1.1 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% of these responses being complete responses.

Clinical studies have not been conducted in patients with de novo EGFR T790M mutation-positive NSCLC.

5.2 Pharmacokinetic properties

Osimertinib pharmacokinetic parameters have been characterized 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 pharmacokinetics in patients treated with osimertinib in combination with pemetrexed and platinum-based chemotherapy are similar to those in patients treated with osimertinib monotherapy. The AUC and Cmax increased dose proportionally over 20 to 240 mg dose range. Administration of osimertinib 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 were 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 by 6% (90% CI -5, 19) and Cmax decrease by 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 Cmax 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 (Vss/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 metabolized predominantly by CYP3A4, and CYP3A5. However, with current available data, alternative metabolic pathways cannot be fully ruled out. 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 osimertinib; 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 CYP1A2, 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 OAT1, OAT3, OATP1B1, OATP1B3, MATE1, OCT2 and MATE2K at clinically relevant concentrations.

Based on *in vitro* studies osimertinib is a substrate of P-gp and BCRP but at clinical doses, clinically relevant interactions are unlikely. Based on *in vitro* data, osimertinib is an inhibitor of BCRP and P-gp. (See section 4.5).

Special populations

In a population based pharmacokinetic analyses (n=1367), no clinically significant relationships were identified between predicted steady-state exposure (AUCss) 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 AUCss expected across a body weight range of 88kg to 43kg respectively (95% to 5% quantiles) when compared to the AUCss 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 study, patients with different types of advanced solid tumours and with mild hepatic impairment (Child Pugh A, mean score = 5.3, n=7) or moderate hepatic impairment (Child Pugh B, mean score = 8.2, n=5) had no increase in exposure compared to patients with normal hepatic function (n=10) after a single 80 mg dose of TAGRISSO. The geometric mean ratio (90% CI) of osimertinib AUC and Cmax was 63.3% (47.3, 84.5) and 51.4% (36.6, 72.3) in patients with mild hepatic impairment and 68.4% (49.6, 94.2) and 60.7% (41.6, 88.6) in patients with moderate hepatic impairment; for the metabolite AZ5104 the AUC and Cmax were 66.5% (43.4, 101.9) and 66.3% (45.3, 96.9) in patients with mild hepatic impairment and 50.9% (31.7, 81.6) and 44.0% (28.9, 67.1) in patients with moderate hepatic impairment, compared to the exposure in patients with normal hepatic function. 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, 8 patients with moderate hepatic impairment and 1216 patients with normal hepatic function osimertinib exposures were similar. There are no data available on patients with severe hepatic impairment (see section 4.2).

Renal impairment

In a clinical study, 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 oral dose of TAGRISSO showed a 1.85-fold increase in AUC (90% CI; 0.94, 3.64) and a 1.19-fold increase in Cmax (90% CI: 0.69, 2.07). Furthermore, based on a population pharmacokinetic 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 studies.

Patients with brain metastases

PET images following administration of microdoses of [^{11}C]osimertinib in EGFR mutation-positive NSCLC patients with brain metastases (n=4) and healthy volunteers (n=7) demonstrated that the brain to plasma ratio (Kp) was similar and that [^{11}C]osimertinib crossed the blood brain barrier rapidly and was homogeneously distributed across all regions of the brain in both patients and healthy volunteers.

5.3 Preclinical safety data

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 cornea (accompanied by corneal translucencies and opacities in dogs at ophthalmology examination), GI tract (including tongue), skin, and male and female reproductive tracts with secondary changes in spleen. 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 with the exception of partial recovery for some of the corneal changes.

Lens fibre degeneration was found in the 104-week carcinogenicity rat study at exposures 0.2-times the human AUC, at the recommended clinical dose of 80 mg once a day. Lens opacities were first noted from week 52 of this study and showed a gradual increase in incidence and severity with increased duration of dosing. The clinical relevance of this finding cannot be ruled out.

Osimertinib penetrated the intact blood-brain barrier of the cynomolgus monkey (intravenous dosing), rat and mouse (oral administration).

Non-clinical data indicate that osimertinib and its metabolite (AZ5104) inhibit the h-ERG channel, and QTc prolonging effect cannot be excluded.

Osimertinib did not cause genetic damage in *in vitro* and *in vivo* assays. 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 at the recommended clinical dose of 80 mg once daily, and is unlikely to be relevant for humans.

Reproductive toxicity

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 osimertinib. 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 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Al/Al perforated unit dose blisters. Cartons of 30 x 1 tablets (3 blister strips).

6.6 Special precautions for disposal

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

7. Marketing authorisation holder

AstraZeneca (Israel) Ltd.,

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8. Manufacturer

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9. License number

Tagrisso 40 mg: 155-86-34627-00

Tagrisso 80 mg: 155-87-34654-00

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