NEW ZEALAND DATA SHEET

1. PRODUCT NAME

TAGRISSO® 40 mg Film Coated Tablets
TAGRISSO® 80 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TAGRISSO 40 mg Tablets: Each tablet contains 40 mg osimertinib (as mesilate)

TAGRISSO 80 mg Tablets: Each tablet contains 80 mg osimertinib (as mesilate)

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

TAGRISSO 40 mg Tablets: round, biconvex, beige, film-coated tablets with a diameter of approximately 9 mm. The tablets are debossed with 'AZ' over '40' on 1 side and plain on the reverse.

TAGRISSO 80 mg Tablets: oval, biconvex, beige, film-coated tablets measuring approximately 7.25 × 14.5 mm. The tablets are debossed with 'AZ 80' on 1 side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TAGRISSO (osimertinib) as monotherapy is indicated for:

- The adjuvant treatment after tumour resection in adult patients with non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations. (see section 5.1 Pharmacodynamic Properties – Clinical Efficacy and Safety).

- the treatment of adult patients with locally advanced, unresectable (stage III) NSCLC whose tumours have EGFR mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy.

- the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations.

- the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

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TAGRISSO (osimertinib) is indicated in combination with:

- pemetrexed and platinum-based chemotherapy for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

When considering the use of TAGRISSO, EGFR mutation status in tumour or plasma specimens should be determined using a validated test method (see section 4.4 Special Warnings and Precautions for Use).

Dosage in adults

Monotherapy

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

TAGRISSO can be taken without regard to food at the same time each day.

Combination therapy

The recommended dose of TAGRISSO is 80 mg osimertinib once a day when taken with pemetrexed and platinum-based chemotherapy.

Refer to the Data Sheets for pemetrexed and cisplatin or carboplatin for the respective dosing information.

Duration of treatment

Patients in the adjuvant setting should receive treatment until disease recurrence or unacceptable toxicity. Treatment duration for more than 3 years was not studied.
Patients with locally advanced or metastatic lung cancer should receive treatment until disease progression or unacceptable toxicity.

Missed dose

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

Dose adjustments

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

Table 1. Dose adjustment information for adverse reactions

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary[b]	Interstitial Lung Disease (ILD)/Pneumonitis[c]	Permanently discontinue TAGRISSO
	Grade 1 radiation pneumonitis[d]	Consider withholding or continue TAGRISSO, as clinically indicated.
	Grade 2[c] radiation pneumonitis[d]	Withhold TAGRISSO until symptoms resolve. TAGRISSO may be restarted. Permanently discontinue if symptoms do not resolve after 4 weeks or Grade 2 Radiation Pneumonitis recurs
	Grade 3 or 4 radiation pneumonitis[d]	Permanently discontinue TAGRISSO
Cardiac[b]	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold treatment 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 treatment
Cutaneous[b]	Stevens-Johnson Syndrome and Toxic epidermal necrolysis	Permanently discontinue treatment
Blood and lymphatic system[b]	Aplastic anaemia	Permanently discontinue treatment
Other	Grade 3 or higher adverse reaction	Withhold treatment for up to 3 weeks
	Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of treatment for up to 3 weeks	Treatment 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 treatment

[a] Note: The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
[b] Refer to Section 4.4 Special warnings and special precautions for use for further details.
[c] The definition of Grade 2 pneumonitis as per NCI-CTCAE version 5.0 is symptomatic; medical intervention indicated; limiting instrumental activities of daily living (ADL).
[d] Radiation pneumonitis is not considered an ADR

Combination therapy

When TAGRISSO is used in combination with pemetrexed and platinum-based chemotherapy, any one of the treatments should be dose modified, as appropriate. For TAGRISSO dose modification instructions, see Table 1. Pemetrexed, cisplatin or carboplatin should be withheld,

dose reduced, or discontinued in accordance with the instructions in the pemetrexed, cisplatin or carboplatin Data Sheets, respectively.

Special patient populations

No dosage adjustment is required according to patient age, body weight, gender, ethnicity and smoking status.

Paediatric and Adolescents

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

Elderly (>65 years)

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

Hepatic impairment

Based on clinical studies, no dose adjustments are necessary in patients with mild hepatic impairment (Child Pugh A) or moderate hepatic impairment (Child Pugh B). Similarly, based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild or moderate hepatic impairment. The appropriate dose of TAGRISSO has not been established in patients with severe hepatic impairment. Until additional data become available, use of TAGRISSO in patients with severe hepatic impairment is not recommended.

Renal Impairment

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

Method of Administration

The tablets should be swallowed whole with water. The tablet should not be crushed, split or chewed.

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

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 nasogastric 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 – List of Excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Assessment of EGFR mutation status

When considering the use of TAGRISSO as an adjuvant therapy after complete tumour resection in patients with NSCLC, EGFR mutation positive status 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 (stage III) NSCLC, EGFR mutation positive status 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 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.

Only robust, reliable and sensitive test(s) with demonstrated utility for the determination of EGFR mutation status of tumour-derived DNA (from a tissue sample or plasma sample) should be used.

Positive determination of EGFR mutation status using either a tissue-based or plasma-based test indicates eligibility for treatment with TAGRISSO. However, if a plasma-based ctDNA test is used and the result is negative, it is advisable to follow-up with a tissue test wherever possible due to the potential for false negative results using a plasma-based test.

Interstitial Lung Disease (ILD)

Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) were reported in 4.0% and were fatal in 0.4% (n=7) of the 1813 patients who received TAGRISSO monotherapy in ADAURA, FLAURA, FLAURA2 and AURA studies. Most cases improved or resolved with discontinuation 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.

The incidence of ILD was 11.2% in patients of Japanese ethnicity, 2.3% in patients of non-Japanese Asian ethnicity and 2.7% in non-Asian patients. The median time from first dose to onset of ILD or ILD-like adverse reactions was 2.8 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 5.3 months.

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

TAGRISSO is not approved for use in combination with PD1/PDL1 checkpoint inhibitors. In an uncontrolled phase 1 study, an increased incidence of pneumonitis was observed with the combination of osimertinib with a PDL1 checkpoint inhibitor treatment.

ILD following definitive platinum-based chemoradiation therapy

In the LAURA study, following definitive platinum-based chemoradiation therapy, ILD or ILD-like adverse reactions (e.g. pneumonitis) were reported in 7.7% of the 143 patients who received TAGRISSO and 1.4% of the 73 patients who received placebo. In the TAGRISSO arm of the LAURA study, the incidence of ILD or ILD-like adverse reactions was 6.6% (6 of 91 patients) in patients of non-Japanese Asian ethnicity and 17.2% (5 of 29 patients) 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 in the TAGRISSO arm. The median time from last dose of radiotherapy to onset of ILD or ILD-like adverse reactions was 3.0 months in the TAGRISSO arm. There were 0.7% fatal cases reported for ILD or ILD-like adverse reactions in the TAGRISSO arm and no fatal cases in the placebo arm. See Section 4.2, Table 1.

Radiation pneumonitis

Radiation pneumonitis is usually observed for up to a year after patients receive radiation therapy to the lungs. 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. 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. 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. See Section 4.2, Table 1.

Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

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

QTc Interval Prolongation

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

Changes in cardiac contractility

Across clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases greater than or equal to 10 percentage points and a drop to LVEF below 50% occurred in 4.2% (65/1557) of patients treated with TAGRISSO monotherapy who had baseline and at least one follow-up LVEF assessment. In a placebo-controlled trial (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 below 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 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%.

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

Keratitis

Keratitis was reported in 0.6% (n=10) of the 1813 patients treated with TAGRISSO monotherapy in the ADAURA, FLAURA, FLAURA2 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 Dose and Method of Administration).

Aplastic anaemia

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

Skeletal Muscles

Case reports of blood creatine phosphokinase (CPK) increased have been reported with TAGRISSO in pooled clinical trials (n=1813), including CTCAE Grades ≥3 (0.3%). There were no CTCAE grade 5 adverse events reported. Uncommon case reports of myositis have been reported in 0.2% (n=3) of the 1813 patients treated with TAGRISSO monotherapy in the ADAURA, FLAURA, FLAURA2 and AURA studies (see section 4.8).

In postmarketing experience, rhabdomyolysis has been reported. Since these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Before initiating treatment, patients should be advised to report any unexplained muscle pain, tenderness, weakness, trouble moving arms or legs, dark tea-coloured urine, or decreased urination. Sign and symptoms of increased CPK, myositis, or rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated (see section 4.2).

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Strong CYP3A4 inducers can decrease exposure to 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 1 metabolism of osimertinib is predominantly via CYP3A4 and CYP3A5. In a clinical pharmacokinetic study in patients, TAGRISSO co-administered with 200 mg itraconazole twice daily (a strong CYP3A4 inhibitor) had no clinically significant effect on the exposure to osimertinib (area under the curve (AUC) increased by 24% and C_{max} decreased 20%). Therefore, CYP3A4 inhibitors are not likely to affect the exposure of osimertinib.

Active substances that may decrease osimertinib plasma concentrations

In a clinical pharmacokinetic study in patients, the steady-state AUC of osimertinib was reduced 78% when co-administered with rifampicin (600 mg daily for 21 days). It is recommended that concomitant use of strong CYP3A inducers (e.g. phenytoin, rifampicin, carbamazepine, St John's Wort) with TAGRISSO should be avoided. If not possible, then increase TAGRISSO dose to 160 mg during the treatment with strong CYP3A inducer and resume at 80 mg, 3 weeks after discontinuation of the strong CYP3A inducer.

Based on physiologically-based pharmacokinetic (PBPK) model simulations, no dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.

Effect of gastric acid reducing active substances on osimertinib

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

Active substances whose plasma concentrations may be altered by TAGRISSO

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

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

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Category D

There are no adequate and well-controlled studies in pregnant women using TAGRISSO. Based on its mechanism of action and preclinical data, osimertinib may cause foetal harm when administered to a pregnant woman. If TAGRISSO is used during pregnancy or if the patient

becomes pregnant while receiving TAGRISSO, she should be informed of the potential hazard to the foetus or potential risk for miscarriage.

Due to the risk of foetal harm, women of childbearing potential should be advised to avoid becoming pregnant while receiving TAGRISSO. Patients should be advised to use effective contraception and continue to use the contraception for the following periods after completion of treatment with TAGRISSO: at least 6 weeks in female patients and longer in male patients (4 months).

Breast-feeding

It is not known whether osimertinib or its metabolites are present in human milk. When osimertinib was administered to lactating rats, osimertinib and its metabolites were detected in the suckling pups and there were adverse effects on pup growth and survival. Due to potential for transfer through breast milk, breast-feeding mothers are advised to discontinue breast-feeding infants while receiving TAGRISSO therapy.

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. Due to the potential for effects on egg and sperm development women should not conceive and men should not father a child while receiving TAGRISSO.

Based on studies in animals, male and female fertility may be impaired by treatment with TAGRISSO.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. If patients experience symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

4.8 UNDESIRABLE EFFECTS

Overall Summary of the Safety Profile

<u>Studies in EGFR mutation positive NSCLC patients</u>

The safety of TAGRISSO as a monotherapy is based on pooled data from 1813 patients with EGFR mutation-positive NSCLC. These patients received TAGRISSO at a dose of 80 mg daily in four randomised Phase 3 studies (ADUARA, adjuvant; FLAURA and FLAURA2 (monotherapy arm), first-line; AURA3, second line only) two single-arm Phase 2 studies (AURAex and AURA2-second line or greater) and one Phase 1 study (AURA1, first-line or greater) (see section 5.1 Pharmacodynamic Properties – Clinical Efficacy and Safety).

Most adverse reactions were Grade 1 or 2 in severity. The most commonly reported adverse drug reactions (ADRs) were diarrhoea (47%), rash (46%), paronychia (34%), dry skin (32%), and stomatitis (24%). Grade 3 and Grade 4 adverse reactions with TAGRISSO were 9.2% and 0.2%, respectively. In patients treated with TAGRISSO 80 mg once daily, dose reductions due to adverse reactions occurred in 3.6% of the patients. Discontinuation due to adverse reactions or abnormal laboratory parameters was 4.7%.

The safety of TAGRISSO (80 mg once daily) following platinum-based chemoradiation therapy is based on data from 143 patients with EGFR mutation-positive NSCLC. It was manageable and was consistent with TAGRISSO monotherapy and the known safety profile of treatment following platinum-based chemoradiation therapy. Most adverse reactions were Grade 1 or 2

in severity and did not lead to dose reductions or discontinuations. See Table 4 - Adverse Reactions reported in LAURA study.

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.

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 ms) were excluded from these studies. Patients were evaluated for LVEF at screening and every 12 weeks thereafter.

Tabulated list of adverse reactions

Adverse reactions have been assigned to the frequency categories in Table 2 where possible based on the incidence of comparable adverse event reports in a pooled dataset from the 1813 previously treated EGFR mutation positive patients who received TAGRISSO at a dose of 80 mg daily in the ADAURA, FLAURA, FLAURA2, AURA3, AURAex, AURA2 and AURA1 studies.

Adverse reactions are listed according to system organ class (SOC) in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the CIOMS III convention and is defined as: very common (≥1/10); common (>1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data).

Table 2. Adverse Reactions Reported in ADAURA, FLAURA, FLAURA2 monotherapy arm and AURA studies[a]

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (all CTCAE grades[b])	Frequency of CTCAE grade 3-4 or higher
Blood and lymphatic system disorders	Aplastic anaemia	Rare (0.06%)	0.06%
Eye disorders	Keratitis[c]	Uncommon (0.6%)	0.06%
Respiratory, thoracic and mediastinal disorders	Epistaxis	Common (6%)	0%
	Interstitial lung disease[d]	Common (4.0%)[e]	1.4%
Gastrointestinal disorders	Diarrhoea	Very common (47%)	1.4%
	Stomatitis[f]	Very common (24%)	0.4%
Skin and subcutaneous tissue disorders	Rash[g,]	Very common (46%)	0.8%
	Paronychia[h]	Very common (34%)	0.4%
	Dry Skin[i]	Very common (32%)	0.1%
	Pruritus[j]	Very common (17%)	0.06%
	Alopecia	Common (5%)	0%

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (all CTCAE grades[b])	Frequency of CTCAE grade 3-4 or higher
	Palmar-plantar erythrodysaesthesia syndrome	Common (2.1%)	0%
	Urticaria	Common (1.9%)	0.1%
	Skin hyperpigmentation[k]	Common (1.0%)	0%
	Erythema multiforme[l]	Uncommon (0.3%)	0%
	Toxic epidermal necrolysis[m]	Uncommon (0.2%)	
	Cutaneous vasculitis[m]	Uncommon (0.2%)	
	Stevens-Johnson syndrome[n]	Rare (0.02%)	
Musculoskeletal and connective tissue disorders	Myositis	Uncommon (0.2%)	
Investigations	Blood creatine phosphokinase increased	Common (1.9%)	0.3%
	QTc interval prolongation[o]	Uncommon (1.1%)	
Findings based on test results presented as CTCAE grade shifts	Leukocytes decreased[p]	Very common (65%)	1.8%
	Lymphocytes decreased[p]	Very common (64%)	8%
	Platelet count decreased[p]	Very common (53%)	1.3%
	Neutrophils decreased[p]	Very common (36%)	4.0%
	Blood creatinine increased[p]	Common (9%)	0.2%

[a] Data is pooled from ADAURA, FLAURA, FLAURA2 (monotherapy arm) 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 summarised.

[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

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

[d] Includes Interstitial lung disease, pneumonitis, organising pneumonia. Cases of eosinophilic pneumonia have additionally been reported in the post-marketing setting.

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

[f] Includes: Stomatitis, mouth ulceration

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

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

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

[j] Includes: eyelid pruritus, pruritus.

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

[l] Six of the 1813 patients in the ADAURA, FLAURA, FLAURA2 (monotherapy arm) 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).

[m] Estimated frequency. The upper limit of the 95% CI for the point estimate is 3/1813 (0.17%). No reports in clinical trials.

[n] One event reported in a post-marketing study, and the frequency has been derived from the ADAURA, FLAURA, FLAURA2 (monotherapy arm) and AURA studies and the post-marketing study (N=5391)

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

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

Table 3. Adverse reactions reported in the ADAURA[a] study

MedDRA SOC	TAGRISSO (N=337)		Placebo (N=343)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)[c]**	**Any Grade (%)**	**Grade 3 or higher (%)[c]**
MedDRA Preferred Term				
Eye disorders				
Keratitis[d]	0.6	0	0.3	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	5.6	0	0.9	0
Interstitial lung disease[e]	3.0	0	0	0
Gastrointestinal disorders				
Diarrhoea	46.3	2.4	19.8	0.3
Stomatitis[f]	28.2	1.8	6.4	0
Skin and subcutaneous tissue disorders				
Rash[g]	39.2	0.3	19.0	0
Paronychia[h]	36.5	0.9	3.8	0
Dry skin[i]	29.4	0.3	7.3	0
Pruritus[j]	19.3	0	8.7	0
Alopecia	5.6	0	2.0	0
Palmar-plantar erythrodysaesthesia syndrome	1.8	0	0	0
Skin hyperpigmentation	1.8	0	0	0
Urticaria	1.5	0	0.3	0.3
Musculoskeletal and connective tissue disorders				
Myositis	0.3	0	0.3	0
Investigations				
Blood creatine phosphokinase increased	3.3		0.9	
QTc interval prolongation[k]	0.6		0	
(Findings based on test results presented as CTCAE grade shifts)				
Leukocytes decreased[l]	54.0	0	25.4	0
Platelet count decreased[l]	47.2	0	6.6	0.3

MedDRA SOC	TAGRISSO (N=337)		Placebo (N=343)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)[c]**	**Any Grade (%)**	**Grade 3 or higher (%)[c]**
MedDRA Preferred Term				
Lymphocytes decreased[l]	43.8	2.2	14.4	0.9
Neutrophils decreased[l]	25.6	0.3	10.2	0.3
Blood creatinine increased[l]	9.8	0	4.5	0.3

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

[a] Only events for patients receiving at least one dose of their randomised treatment are summarised.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[c] All events were Grade 3. There were no deaths
[d] Includes: Keratitis, punctate keratitis, corneal erosion, corneal epithelium defect.
[e] Includes: Interstitial lung disease, pneumonitis.
[f] Includes: Stomatitis, mouth ulceration.
[g] Includes: acne, dermatitis, dermatitis acneiform, drug eruption, erythema, folliculitis, pustule, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin erosion.
[h] Includes: nail bed disorder, nail bed infection, nail bed inflammation, nail discolouration, nail disorder, nail dystrophy, nail infection, nail pigmentation, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.
[i] Includes: dry skin, eczema, skin fissures, xeroderma, xerosis.
[j] Includes: eyelid pruritus, pruritus, pruritus generalised.
[k] Represents the incidence of patients who had a QTcF prolongation >500 msec.
[l] Represents the incidence of laboratory findings, not of reported adverse events.

Table 4. Adverse reactions reported in LAURA[a] study

MedDRA SOC	TAGRISSO (N=143)		Placebo (N=73)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)**	**Any Grade (%)**	**Grade 3 or higher (%)**
MedDRA Preferred Term				
Eye disorders				
Keratitis[c]	0.7	0	1.4	0
Respiratory, thoracic and mediastinal disorders				
Interstitial lung disease[d]	8	2.1[e]	1.4	0
Epistaxis	0.7	0	0	0
Gastrointestinal disorders				
Diarrhoea	36	2.1	14	0
Stomatitis[f]	15	0	4.1	0
Skin and subcutaneous tissue disorders				
Rash[g]	36	0.7	19	0
Paronychia[h]	23	0	1.4	0

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MedDRA SOC	TAGRISSO (N=143)		Placebo (N=73)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)**	**Any Grade (%)**	**Grade 3 or higher (%)**
MedDRA Preferred Term				
Dry skin[i]	17	0.7	5	0
Pruritus[j]	13	0	7	0
Alopecia	1.4	0	0	0
Urticaria	1.4	0	1.4	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	0	0
Skin hyperpigmentation	0	0	0	0
Erythema multiforme	0	0	0	0
Musculoskeletal and connective tissue disorders				
Myositis	0	0	0	0
Investigations				
Blood creatine phosphokinase increased	3.5	1.4	0	0
QTc interval prolongation[k]	0.7		0	
(Findings based on test results presented as CTCAE grade shifts)				
Lymphocytes decreased[l]	70	3.5	40	1.4
Leukocytes decreased[l]	66	2.8	24	0
Platelet count decreased[l]	51	1.4	8	1.4
Neutrophils decreased[l]	42	2.1	15	1.4
Blood creatinine increased[l,m]	19	0	12	0

In LAURA, the median duration of study treatment was 24.0 months for patients in the TAGRISSO arm and 8.3 months for patients in the placebo arm.

[a] Only events for patients receiving at least one dose of their randomised treatment are summarised.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.
[c] Includes: corneal erosion, corneal epithelium defect, keratitis, punctuate keratitis.
[d] Includes: interstitial lung disease, pneumonitis, organising pneumonia.
[e] One CTCAE Grade 5 event (fatal) was reported.
[f] Includes: mouth ulceration, stomatitis.
[g] Includes: acne, dermatitis, dermatitis acneiform, drug eruption, erythema, folliculitis, pustule, rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin erosion.
[h] Includes: nail bed disorder, nail bed infection, nail bed inflammation, nail discolouration, nail disorder, nail dystrophy, nail infection, nail pigmentation, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.
[i] Includes: dry skin, eczema, skin fissures, xeroderma, xerosis.
[j] Includes: eyelid pruritus, pruritus.
[k] Represents the incidence of patients who had a QTcF prolongation >500 msec.
[l] Represents the incidence of laboratory findings, not of reported adverse events.
[m] A lower baseline blood creatinine clearance (<30 mL/min) was used in the LAURA study compared to other monotherapy TAGRISSO studies (<50 mL/min) so grade shifts were more likely to occur.

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Table 5. Adverse reactions reported in FLAURA[a] study

MedDRA SOC	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)**	**Any Grade (%)**	**Grade 3 or higher (%)**
MedDRA Preferred Term				
Eye disorders				
Keratitis[c]	0.4	0	1.4	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	6.1	0	5.1	0
Interstitial lung disease[d]	3.9	1.1	2.2	1.4
Gastrointestinal disorders				
Diarrhoea[e]	58	2.2	57	2.5
Stomatitis[f]	32	0.7	22	1.1
Skin and subcutaneous tissue disorders				
Rash[g]	58	1.1	78	6.9
Dry skin[h]	36	0.4	36	1.1
Paronychia[i]	35	0.4	33	0.7
Pruritus[j]	17	0.4	17	0
Alopecia	7.2	0	13	0
Urticaria	2.2	0.7	0.4	0
Palmar-plantar erythrodysaesthesia syndrome	1.4	0	2.5	0
Skin hyperpigmentation	0.4	0	1.1	0
Musculoskeletal and connective tissue disorders				
Myositis	0.4	0	0	0
Investigations				
Blood creatine phosphokinase increased	0.4		0.4	
QTc interval prolongation[k,]	1.1		0.7	
(Findings based on test results presented as CTCAE grade shifts)				
Leukocytes decreased[l]	72	0.4	31	0.4
Lymphocytes decreased[l]	63	5.6	36	4.2

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MedDRA SOC	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)**	**Any Grade (%)**	**Grade 3 or higher (%)**
MedDRA Preferred Term				
Platelet count decreased[l]	51	0.7	12	0.4
Neutrophils decreased[l]	41	3.0	10	0
Blood creatinine increased	8.8	0	6.7	0.4

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

[a] Only events for patients receiving at least one dose of their randomised treatment are summarised.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0
[c] Includes: corneal erosion, corneal epithelium defect, keratitis, punctate keratitis.
[d] Includes: interstitial lung disease, pneumonitis.
[e] 1 CTCAE Grade 5 event (fatal) was reported in the EGFR TKI comparator arm.
[f] Includes cases reported within the clustered terms: Stomatitis, mouth ulceration
[g] Includes: Rash, rash generalised, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, skin erosion, pustule.
[h] Includes: Dry skin, skin fissures, xerosis, eczema, xeroderma.
[i] Includes: Nail bed disorder, nail bed inflammation, nail bed infection, nail discolouration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.
[j] Includes: Pruritus, pruritus generalised, eyelid pruritus.
[k] Represents the incidence of patients who had a QTcF prolongation >500 msec.
[l] Represents the incidence of laboratory findings, not of reported adverse events.

Table 6 Adverse reactions reported in FLAURA2[a] study

MedDRA SOC	TAGRISSO with pemetrexed and platinum-based chemotherapy (N=276)		TAGRISSO (N=275)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)**	**Any Grade (%)**	**Grade 3 or higher (%)**
MedDRA Preferred Term				
Eye disorders				
Keratitis[c]	0.7	0	0	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	7	0.4	7	0
Interstitial lung disease[d]	3.3	0.7[e]	3.6	1.8[e]
Gastrointestinal disorders				
Diarrhoea	43	2.9	41	0.4
Stomatitis[f]	31	0.4	21	0.4
Skin and subcutaneous tissue disorders				
Rash[g]	49	2.5	44	1.5
Paronychia[h]	27	0.7	32	0.4

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MedDRA SOC	TAGRISSO with pemetrexed and platinum-based chemotherapy (N=276)		TAGRISSO (N=275)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)**	**Any Grade (%)**	**Grade 3 or higher (%)**
MedDRA Preferred Term				
Dry skin[i]	24	0	31	0
Alopecia	9	0	5	0
Pruritus[j]	8	0	11	0
Palmar-plantar erythrodysaesthesia syndrome	5	0	3.3	0
Skin hyperpigmentation	2.5	0	1.1	0
Urticaria	1.4	0.4	1.5	0
Erythema multiforme	1.4	0.7	0.4	0
Musculoskeletal and connective tissue disorders				
Myositis	0	0	0.4	0
Investigations				
Blood creatine phosphokinase increased	3.3	1.1	3.3	0
QTc interval prolongation[k]	1.8		1.8	
(Findings based on test results presented as CTCAE grade shifts)				
Leukocytes decreased[l]	88	20	53	3.3
Platelet count decreased[l]	85	16	44	1.8
Neutrophils decreased[l]	85	36	40	4.7
Lymphocytes decreased[l]	78	16	55	7
Blood creatinine increased[l]	22	0.4	8	0

In FLAURA2, the median duration of study treatment was 22.3 months for patients in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm and 19.3 months for patients in the TAGRISSO monotherapy arm.

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

[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0

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

[d] Includes: interstitial lung disease, pneumonitis, organising pnuemonia.

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

[f] Includes: mouth ulceration, stomatitis.

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

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

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

[j] Includes: eyelid pruritus, pruritus.

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

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

Table 7. Adverse reactions reported in AURA3[a] study

MedDRA SOC	**TAGRISSO overall frequency (N=279)**		**Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) overall frequency (N=136)**	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)**	**Any Grade (%)**	**Grade 3 or higher (%)**
MedDRA Preferred Term				
Eye disorders				
Keratitis[c]	1.1	0	0.7	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	5.4	0	1.5	0
Interstitial lung disease[d,e]	3.6	0.4	0.7	0.7
Gastrointestinal disorders				
Diarrhoea	41	1.1	11	1.5
Stomatitis[f]	19	0	15	1.5
Skin and subcutaneous tissue disorders				
Rash[g]	34	0.7	5.9	0
Dry skin[h]	23	0	4.4	0
Paronychia[i]	22	0	1.5	0
Pruritus[j]	13	0	5.1	0
Alopecia	3.6	0	2.9	0
Urticaria	2.5	0	1.5	0
Palmar-plantar erythrodysaesthesia syndrome	1.8	0	0.7	0
Skin hyperpigmentation	0.4	0	3.7	0
Musculoskeletal and connective tissue disorders				
Myositis	0	0	0	0
Investigations				
QTc interval prolongation[k]	1.4		0	
Blood creatine phosphokinase increased	0.7		0.7	
(Findings based on test results presented as CTCAE grade shifts)				
Leukocytes decreased[l]	61	1.1	75	5.3

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

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

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

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

Description of selected adverse reactions

Interstitial lung disease (ILD)

In the FLAURA and AURA studies, the incidence of ILD was 10.4% in patients of Japanese ethnicity, 1.8% in patients of non-Japanese Asian ethnicity and 2.8% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 2.8 months. (see section 4.4 Special Warnings and Precautions for Use).

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.

QT Interval Prolongation

Of the 1813 patients in the ADAURA, FLAURA, FLAURA2 and AURA studies treated with TAGRISSO monotherapy (80 mg), 1.1% of patients (n=20) were found to have a QTc greater than 500 msec, and 4.3% of patients (n=78) had an increase from baseline QTc greater than

60 msec. A pharmacokinetic analysis with TAGRISSO predicted a concentration-dependent increase in QTc interval prolongation. No QTc-related arrhythmias were reported in the ADAURA, LAURA, FLAURA, FLAURA2 or AURA studies (see section 4.4 Special Warnings and Precautions for Use).

Cardiac Contractility

Left Ventricular Ejection Fraction (LVEF) Analysis

Across clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases greater than or equal to 10% and a drop to less than 50% occurred in 3.9% (35/908) of patients treated with TAGRISSO who had baseline and at least one follow-up LVEF assessment (see section 4.4 Special Warnings and Precautions for Use).

Cardiac adverse events

In the Phase 2 studies, 5 patients (1.2%) were reported to have 6 adverse events consistent with cardiac failure or cardiomyopathy. The reported adverse events were; Congestive heart failure (2 events in 1 patient with fatal outcome; 0.2%), ejection fraction decreased (3 events; 0.7%) and pulmonary oedema (1 event; 0.2%).

Special populations

Elderly

In ADAURA, FLAURA, FLAURA2 and AURA3 (TAGRISSO monotherapy n=1813), 42% 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 drug dose modifications (interruptions or reductions) (14% versus 10%). The types of adverse reactions reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (11% versus 9%). No overall differences in efficacy were observed between older and younger patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://pophealth.my.site.com/carmreportnz/s.

4.9 OVERDOSE

In TAGRISSO clinical trials a limited number of patients were treated with daily doses of up to 240 mg without dose limiting toxicities. In these studies, patients who were treated with TAGRISSO daily doses of 160 mg and 240 mg experienced an increase in the frequency and severity of a number of typical EGFR-induced AEs (primarily diarrhoea and skin rash) compared to the 80 mg dose. There is 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, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

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5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors; ATC code: L01XE35

Mechanism of Action

TAGRISSO is an orally administered Tyrosine Kinase Inhibitor (TKI). It is a selective and irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harbouring single (L858R or del746-750) or double (L858R/T790M or del746-750/T790M) mutations.

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 non-small cell lung cancer (NSCLC) cell lines (apparent IC_{50}s from 6 nM to 54 nM against phospho-EGFR). This leads to inhibition of cell growth, while showing significantly less activity against EGFR in wild-type cell lines (apparent IC_{50}s 480 nM to 1.8 μM against phospho-EGFR). In vivo oral administration of TAGRISSO leads to tumour shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumour models.

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

Clinical Efficacy and Safety

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

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

Patients with resectable tumours (except for stage IA), were required to have EGFR exon 19 deletions or exon 21 L858R substitution mutations identified by the cobas EGFR Mutation Test performed prospectively using biopsy or surgical specimen in a central laboratory.

Patients were randomised (1:1) to receive TAGRISSO 80 mg orally once daily or placebo 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 mutation type (exon 19 deletions or exon 21 L858R substitution mutations), ethnicity (Asian or non-Asian) and staging based on pTNM (IB or II or IIIA) according to AJCC 7th edition. Treatment was given until disease recurrence, unacceptable toxicity, or for 3 years.

The major efficacy outcome measure was disease-free survival (DFS) by investigator assessment. Additional efficacy outcome measures include DFS rate, overall survival (OS), OS rate, and time to deterioration in health-related quality of life (HRQL) SF-36.

A total of 682 patients were randomised to TAGRISSO (n=339) or to placebo (n=343). The median age was 63 years (range 30-86 years), 11% were ≥75 years of age; 70% were female, 64% were Asian and 72% were never smokers. Baseline World Health Organisation (WHO) performance status was 0 (64%) or 1 (36%); 31% had stage IB, 34% II, and 35% IIIA. With regard to EGFR mutation status, 55% were exon 19 deletions and 45% were exon 21 L858R substitution mutations; 9 patients (1%) also had a concurrent de novo T790M mutation. The majority (60%) of patients received adjuvant chemotherapy prior to randomisation (26% IB; 71% IIA; 73% IIB; 80% IIIA).

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

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

The final analysis of OS demonstrated a highly statistically significant and clinically meaningful improvement in OS with a 51% reduction in the risk of death for patients treated with TAGRISSO compared to placebo for both the stage II-IIIA population (21.3% maturity; HR=0.49; 95.03% CI: 0.33, 0.73; p value=0.0004) and the overall population (IB-IIIA; 18.2% maturity; HR=0.49; 95.03% CI: 0.34, 0.70; p-value < 0.0001). In the overall population (IB-IIIA), the median follow-up time in censored patients was 61.5 months in both treatment arms.

Efficacy results from ADAURA by investigator assessment are summarised in Table 8 and Table 9 and the Kaplan-Meier curves for DFS and OS in stage II-IIIA patients and in the overall population (IB-IIIA) are shown in Figure 1 to Figure 4.

Table 8. Disease Free Survival Efficacy Results in Stage II-IIIA Patients by Investigator Assessment

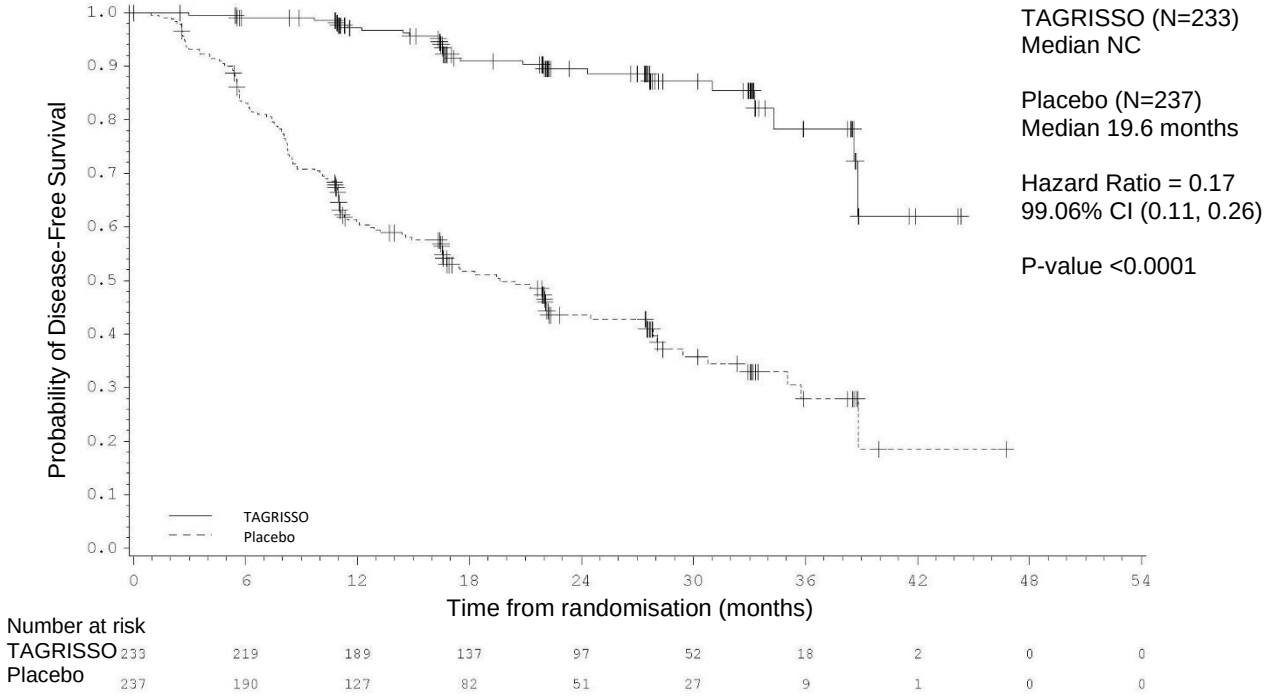
Efficacy Parameter	**TAGRISSO (N=233)**	**Placebo (N=237)**
Disease Free Survival		
Number of events (%)	26 (11.2)	130 (54.9)
Recurrent disease (%)	26 (11.2)	129 (54.4)
Deaths (%)	0	1 (0.4)
Median DFS, months (95% CI)	NC (38.8, NC)	19.6 (16.6, 24.5)

Efficacy Parameter	**TAGRISSO (N=233)**	**Placebo (N=237)**
HR (99.06% CI); P-value[a]	0.17 (0.11, 0.26); <0.0001	
DFS rate at 12 months (%) (95% CI)	97.2 (93.9, 98.7)	60.8 (54.1, 66.8)
DFS rate at 24 months (%) (95% CI)	89.5 (84, 93.2)	43.6 (36.5, 50.6)
DFS rate at 36 months (%) (95% CI)[b]	78.3 (64.5, 87.3)	27.9 (18.9, 37.6)
Overall Survival		
Number of deaths (21% maturity)	35 (15.0)	65 (27.4)
Median OS, months (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95.03% CI); P-value[c]	0.49 (0.33, 0.73); 0.0004	
OS rate at 24 months (%) (95% CI)[d]	99.5 (96.8, 99.9)	92.6 (88.3, 95.3)
OS rate at 36 months (%) (95% CI)[d]	94.1 (90.1, 96.5)	85.9 (80.6, 89.8)
OS rate at 48 months (%) (95% CI)[d]	91.0 (86.3, 94.1)	79.9 (74.0, 84.6)
OS rate at 60 months (%) (95% CI)[d]	85.0 (79.3, 89.2)	72.6 (66.0, 78.1)

HR=Hazard Ratio; CI=Confidence Interval; NC= Not Calculable
DFS results based on investigator assessment
A HR< 1 favours TAGRISSO
Median follow-up time for DFS was 22.1 months for patients receiving TAGRISSO and 14.9 months for patients receiving placebo.
Median follow-up time for OS in censored patients was 61.7 months (stage II-IIIA population) in the TAGRISSO arm and 60.4 months in the placebo arm.
DFS results are from the primary analysis (17 January 2020). OS results are from the final analysis (27 January 2023).

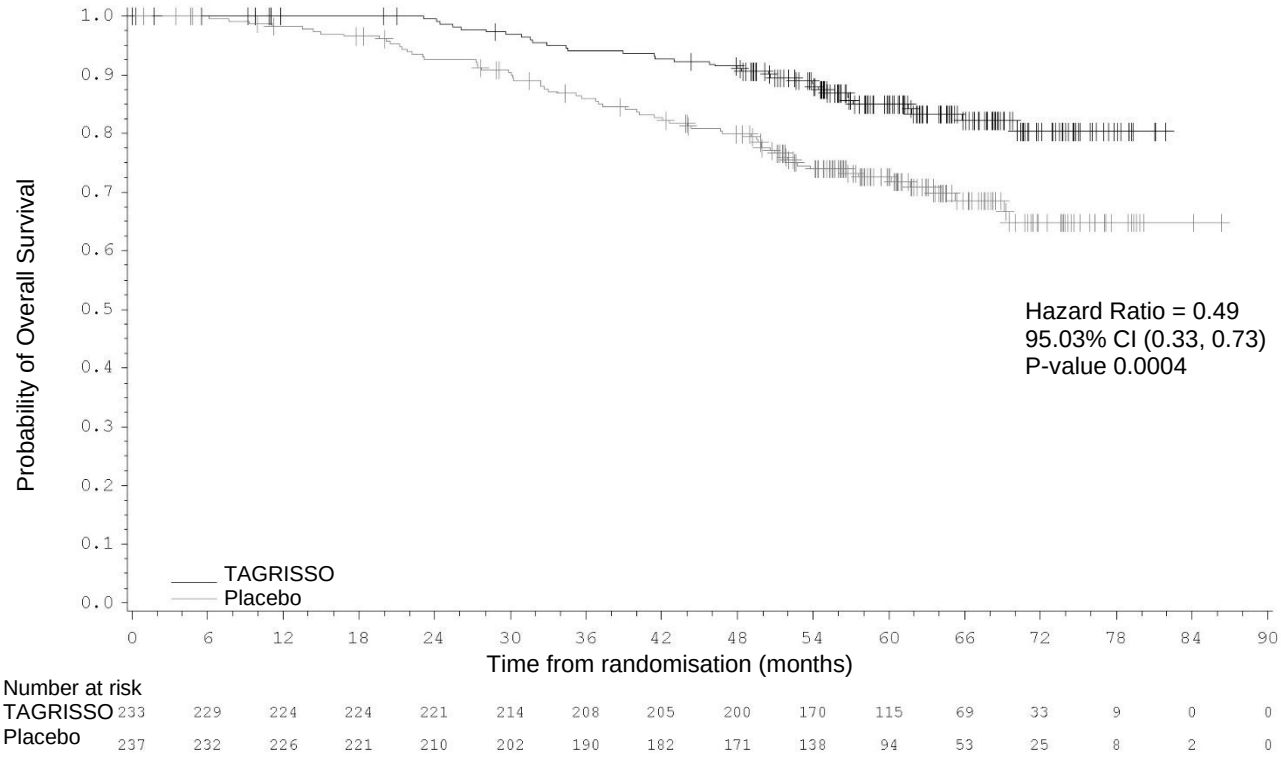
[a] Adjusted for an interim analysis (33% maturity) a p-value < 0.0094 was required to achieve statistical significance.
[b] The number of patients at risk at 36 months was 18 patients in the osimertinib arm, and 9 patients in the placebo arm.
[c] Adjusted for interim analyses a p-value < 0.0497 was required to achieve statistical significance.
[d] Calculated using the Kaplan-Meier method.

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



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

Figure 2. Kaplan-Meier Curve of Overall Survival (Stage II-IIIA Patients)



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

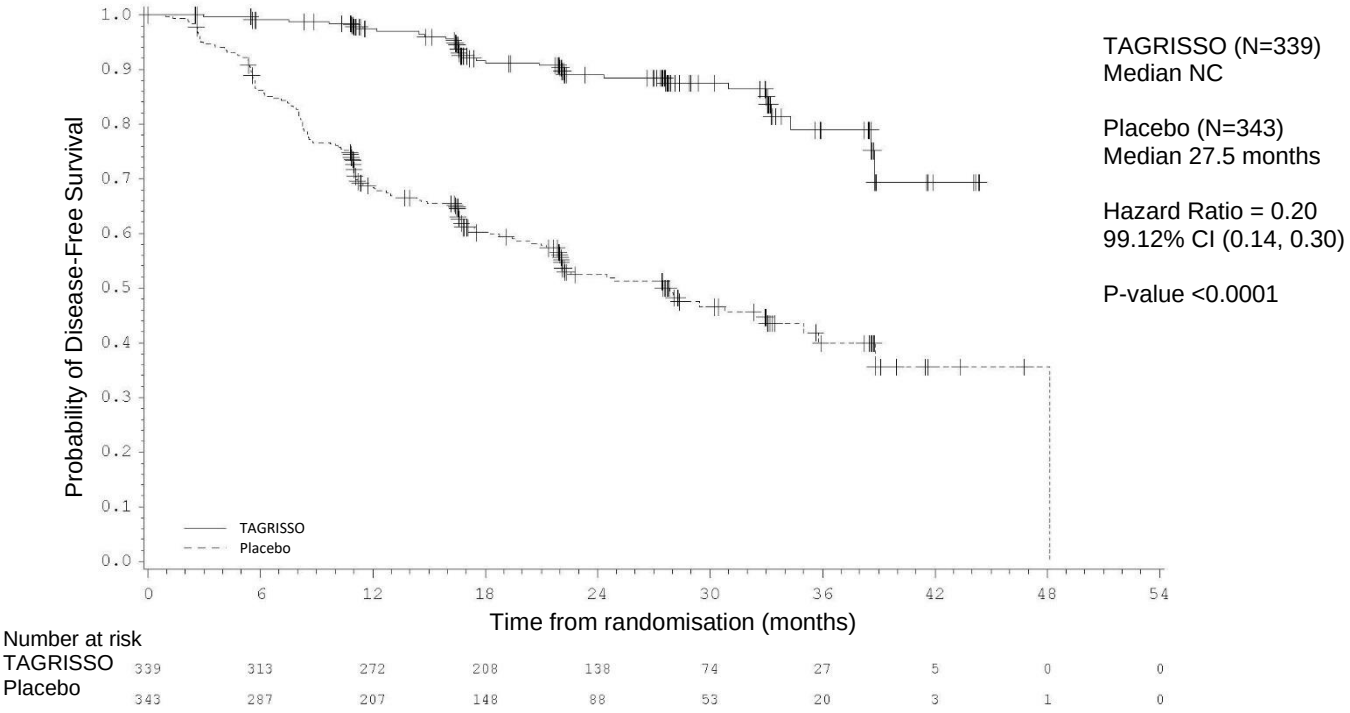
Table 9. Disease Free Survival Efficacy Results in Overall (IB-IIIA) Patients by Investigator Assessment

Efficacy Parameter	TAGRISSO (N=339)	Placebo (N=343)
Disease Free Survival		
Number of events (%)	37 (10.9)	159 (46.4)
Recurrent disease (%)	37 (10.9)	157 (45.8)
Deaths (%)	0	2 (0.6)
Median DFS, months (95% CI)	NC (NC, NC)	27.5 (22.0, 35.0)
HR (99.12% CI); P-value[a]	0.20 (0.14, 0.30); <0.0001	
DFS rate at 12 months (%) (95% CI)	97.4 (94.9, 98.7)	68.5 (63.2, 73.2)
DFS rate at 24 months (%) (95% CI)	89.1 (84.5, 92.4)	52.4 (46.4, 58.1)
DFS rate at 36 months (%) (95% CI)[b]	78.9 (68.7, 86.1)	40.0 (32.1, 47.8)
Overall Survival		
Number of deaths (18% maturity)	42 (12.4)	82 (23.9)
Median OS, months (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95.03% CI); P-value[c]	0.49 (0.34, 0.70); <0.0001	
OS rate at 24 months (%) (95% CI)[d]	99.4 (97.5, 99.8)	94.3 (91.2, 96.3)
OS rate at 36 months (%) (95% CI)[d]	95.3 (92.3, 97.1)	88.8 (84.9, 91.8)
OS rate at 48 months (%) (95% CI)[d]	92.8 (89.4, 95.2)	83.9 (79.4, 87.4)
OS rate at 60 months (%) (95% CI)[d]	87.6 (83.3, 90.9)	77.7 (72.7, 81.9)

HR=Hazard Ratio; CI=Confidence Interval; NC= Not Calculable
DFS results based on investigator assessment
A HR< 1 favours TAGRISSO
Median follow-up time for DFS was 22.1 months for patients receiving TAGRISSO and 16.6 months for patients receiving placebo.
Median follow-up time for OS in censored patients was 61.5 months in both the TAGRISSO arm and the placebo arm.
DFS results are from the primary analysis (17 January 2020). OS results are from the final analysis (27 January 2023)

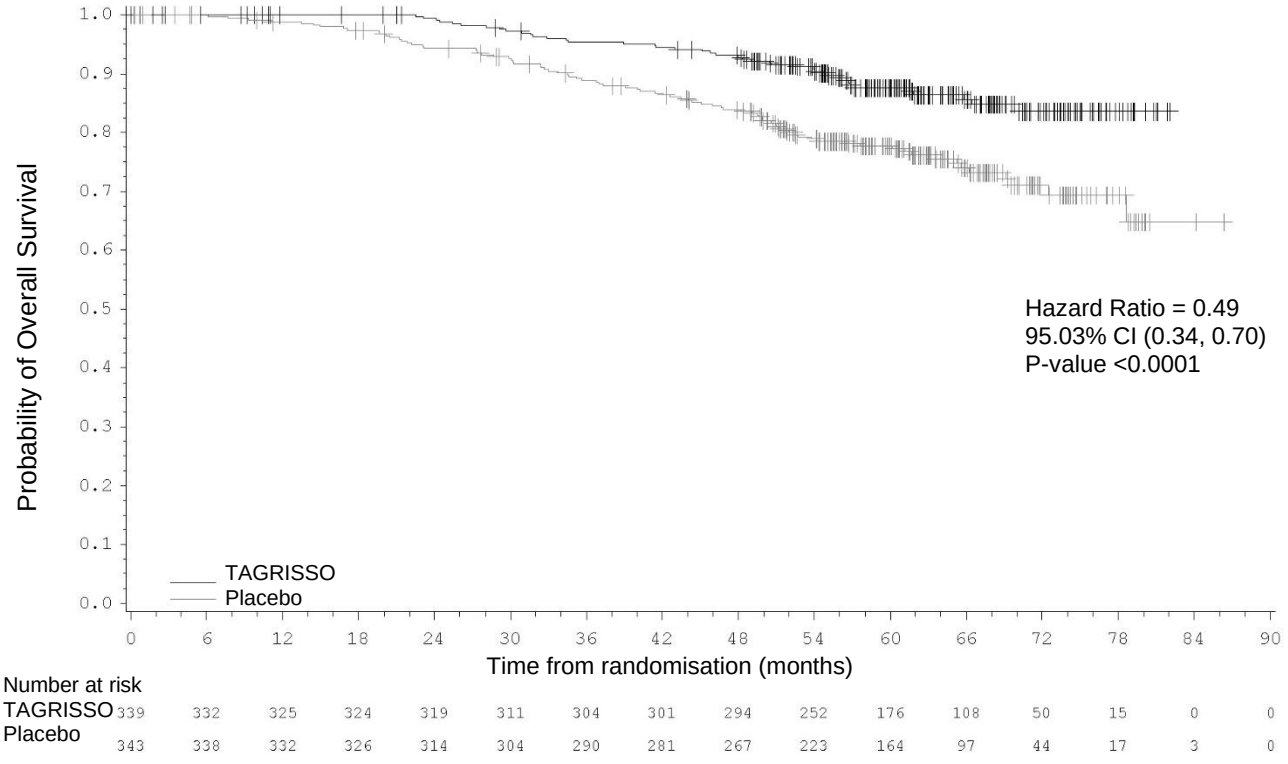
[a] Adjusted for an interim analysis (29% maturity) a p-value < 0.0088 was required to achieve statistical significance.
[b] The number of patients at risk at 36 months was 27 patients in the osimertinib arm, and 20 patients in the placebo arm.
[c] Adjusted for interim analyses a p-value < 0.0497 was required to achieve statistical significance.
[d] Calculated using the Kaplan-Meier method.

Figure 3. Kaplan-Meier Curve of Disease-Free Survival (Overall Population) by Investigator Assessment



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

Figure 4. Kaplan-Meier Curve of Overall Survival (Overall Population)



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

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

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

Patient Reported Outcomes (PRO)

Health-related quality of life (HRQoL) 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, HRQoL was maintained in both arms, with more than 75% of patients in the stage II-IIIA population not experiencing a clinically meaningful deterioration in the physical component of the SF-36 or death (75.1% vs 83.5% for TAGRISSO vs placebo), or in the mental component of the SF-36 or death (77.7% vs 78.1% for TAGRISSO vs placebo). A trend of shorter time to deterioration (TTD) for the physical component of SF-36 or death was observed in the TAGRISSO arm (HR=1.43, 95% CI: 0.96, 2.13), with a median TTD that was not reached in either arm. There was no difference between the arms in the TTD for the mental component of SF-36 or death (HR=0.90, 95% CI: 0.61, 1.33), with a median TTD of 39.0 months (95% CI: NC, NC) in the TAGRISSO arm and not reached in the placebo arm.

Locally advanced, unresectable (stage III) EGFR mutation-positive NSCLC – LAURA

The efficacy and safety of TAGRISSO for the treatment of patients with EGFR mutation-positive, locally advanced, unresectable (stage III) NSCLC, who had not progressed during or following definitive platinum-based chemoradiation therapy, was demonstrated 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. Post progression, all patients were offered open-label TAGRISSO in accordance with local clinical practice if, in the opinion of the treating physician, there was an expected clinical benefit.

The primary efficacy endpoint was PFS as assessed by blinded independent central review (BICR). Additional efficacy endpoints included CNS PFS, OS, ORR, DoR, time to death or distant metastases (TTDM), second PFS after start of first subsequent therapy (PFS2), time to first subsequent treatment or death (TFST), and time to second subsequent treatment or death (TSST). CNS PFS, ORR, DoR, and TTDM were all assessed by BICR. Patient-reported outcomes were also assessed.

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 and clinically meaningful 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). A greater proportion of patients treated with TAGRISSO were alive and progression free at 6, 12, 18, 24 and 36 months (84%, 74%, 67%, 65% and 58%, respectively) compared to patients treated with placebo (45%, 22%, 14%, 13% and 10%, 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. There was a nominally statistically significant and clinically meaningful improvement in CNS PFS (based on neuroradiologist BICR assessment) in patients treated with TAGRISSO compared to placebo (27% maturity; HR=0.17; 95% CI: 0.09, 0.32; P<0.001 [nominal]). 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 interim analysis of overall survival, there was a positive trend in favour of TAGRISSO (20% maturity; HR=0.81; 95% CI: 0.42, 1.56; P=0.530), which was not statistically significant. Efficacy results from LAURA are summarised in Table 10, and the Kaplan-Meier curves for PFS and CNS PFS are shown in Figure 5 and Figure 6, respectively.

Table 10. Efficacy results from LAURA

Efficacy Parameter	**TAGRISSO (N=143)**	**Placebo (N=73)**
Progression-Free Survival		
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	
CNS Progression-Free Survival		
Number (%) of events	29 (20)	30 (41)
Median CNS PFS, months (95% CI)	NC (NC, NC)	14.9 (7.4, NC)
HR (95% CI); P-value	0.17 (0.09, 0.32); P<0.001	
CNS progression free and alive at 12 months, % (95% CI)	87 (79, 92)	53 (38, 66)

Efficacy Parameter	**TAGRISSO (N=143)**	**Placebo (N=73)**
CNS progression free and alive at 24 months, % (95% CI)	83 (75, 89)	43 (28, 58)
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]	
Objective Response Rate[b]		
Number of responses (n), Response rate % (95% CI)	82 57 (49, 66)	24 33 (22, 45)
Odds ratio (95% CI); P-value[c]	2.77 (1.54, 5.08); P<0.001	
Duration of Response (DoR)[b]		
Median DoR, months (95% CI)[d]	36.9 (30.1, NC)	6.5 (3.6, 8.3)
Time to death or distant metastases (TTDM)		
Number (%) of patients	33 (23)	31 (43)
Median TTDM, months (95% CI)	NC (39.3, NC)	13.0 (9.0, NC)
HR (95% CI); P-value	0.21 (0.11, 0.38); P<0.001	
Second PFS after start of first subsequent therapy (PFS2)		
Number (%) of PFS2 events	34 (24)	24 (33)
Median PFS2, months (95% CI)	48.2 (44.4, NC)	47.4 (28.2, NC)
HR (95% CI); P-value	0.62 (0.35, 1.08); P=0.088	
Time from randomisation to first subsequent treatment or death (TFST)		
Number of patients who had first subsequent treatment or died (%)	53 (37)	61 (84)
Median TFST, months (95% CI)	43.8 (38.9, NC)	9.5 (6.6, 11.5)
HR (95% CI); P-value	0.13 (0.08, 0.21); P<0.001	
Time from randomisation to second subsequent treatment or death (TSST)		
Number of patients who had second subsequent treatment or died (%)	32 (22)	24 (33)
Median TSST, months (95% CI)	NC (44.4, NC)	47.4 (34.1, NC)

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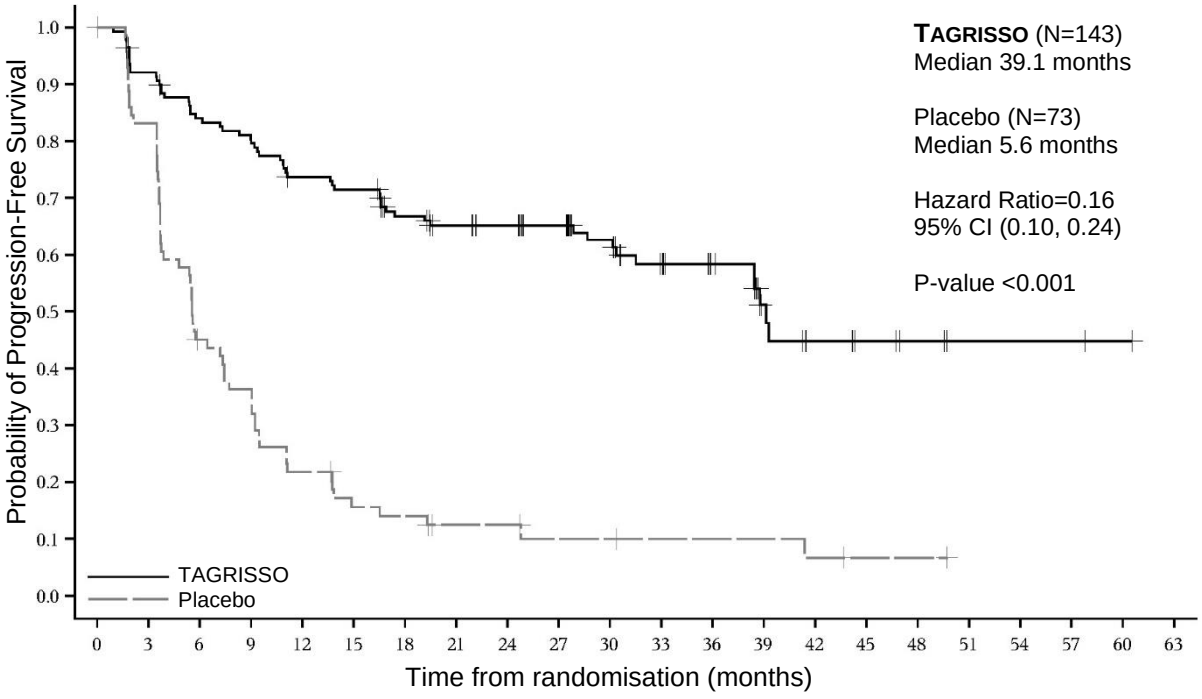
Efficacy Parameter	TAGRISSO (N=143)	Placebo (N=73)
HR (95% CI); P-value	0.51 (0.28, 0.91); P=0.022	

HR=Hazard Ratio; CI=Confidence Interval, NC=Not Calculable
PFS, CNS PFS, ORR, DoR, and TTDM 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 HR <1 favours TAGRISSO, an Odds ratio of >1 favours TAGRISSO.

[a] Adjusted for an interim analysis (20% maturity) a p-value <0.00036 was required to achieve statistical significance.
[b] Based on unconfirmed response.
[c] The analysis was performed using a logistic regression stratified by disease stage prior to chemotherapy (IIIA vs IIIB/IIIC).
[d] Calculated using the Kaplan-Meier method.

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



Number at risk

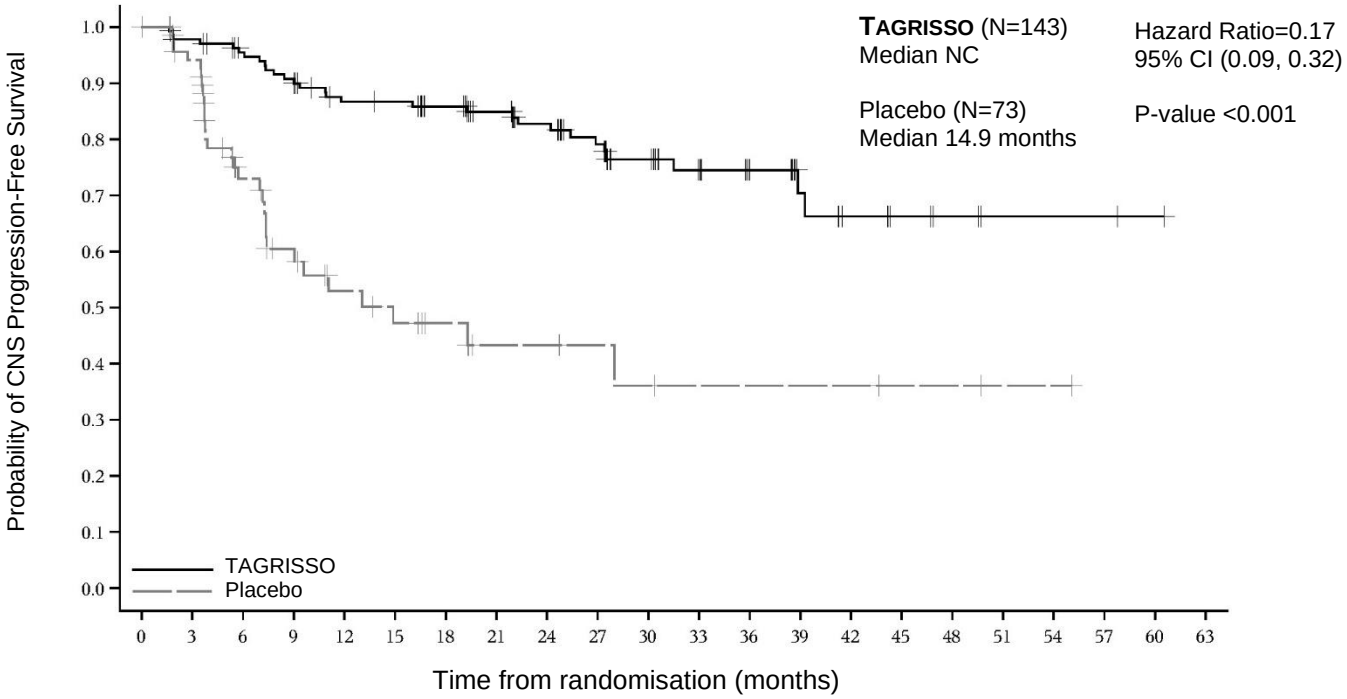
TAGRISSO	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

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

A sensitivity analysis of PFS assessed by investigator according to RECIST v1.1 (HR=0.19; 95% CI: 0.12, 0.29; P<0.001) showed a median PFS of 38.9 months with TAGRISSO compared with 7.3 months with placebo. This analysis was consistent with the primary PFS analysis by BICR.

The PFS benefit of TAGRISSO compared to placebo was consistent across all predefined subgroups analysed including gender, age at randomisation, smoking history, ethnicity, prior chemoradiation strategy (CCRT vs SCRT), disease stage prior to chemoradiation (IIIA vs IIIB/IIIC), response to prior chemoradiation, and EGFR mutation type (exon 19 deletion or L858R).

Figure 6. Kaplan-Meier Curves of CNS PFS as assessed by BICR in LAURA



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

Patients randomised to TAGRISSO had clinically meaningful improvements in TTDM by BICR compared to patients randomised to placebo.

Patients randomised to TAGRISSO had clinically meaningful improvements in PFS2, TFST and TSST compared to patients randomised to placebo. The analysis of these post progression endpoints demonstrated that PFS benefit was largely preserved through subsequent lines of therapy despite the high level of cross-over to TAGRISSO.

Patient-Reported Outcomes

Patient-reported symptoms and HRQL data were electronically collected using the EORTC QLQ-C30 (C30) and a lung cancer module EORTC QLQ-LC13 (LC13). At baseline, patient-reported symptoms, physical function and global health status/quality of life (GHS/QoL) were comparable between the TAGRISSO and placebo arms. There was no clinically meaningful difference in the overall mean change from baseline for the five key patient-reported lung cancer and treatment-related symptoms (cough, dyspnoea, chest pain, fatigue, and appetite loss) and for physical functioning domains and GHS/QoL. No meaningful difference in the risk of deterioration in these patient-reported symptoms, physical function or GHS/QoL was observed between the treatment arms.

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 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. Additional efficacy end-points included OS, ORR, DoR, PFS2, TFST and TSST as assessed by investigator. CNS PFS, CNS ORR and CNS DoR as assessed by BICR, and PRO were also assessed.

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

TAGRISSO demonstrated a clinically meaningful and highly statistically significant improvement in PFS compared to EGFR TKI comparator (median 18.9 months and 10.2 months, respectively, HR=0.46, 95% CI: 0.37, 0.57; P<0.0001). Efficacy results from FLAURA by investigator assessment are summarised in Table 11, and the Kaplan-Meier curve for PFS is shown in Figure 7. The final analysis of overall survival (58% maturity) demonstrated a statistically significant improvement with an HR of 0.799 (95.05%CI: 0.641, 0.997; P=0.0462) and a clinically meaningful longer median survival time in patients randomised to TAGRISSO compared to EGFR TKI comparator (Table 11 and Figure 8). A greater proportion of patients treated with Tagrisso were alive at 12, 18, 24 and 36 months (89%, 81%, 74% and 54% respectively) compared to patients treated with EGFR TKI comparator (83%, 71%, 59% and 44% respectively).

Table 11. 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)

Efficacy Parameter	**TAGRISSO (N=279)**	**EGFR TKI comparator (gefitinib or erlotinib) (N=277)**
Median OS months (95% CI)	38.6 (34.5, 41.8)	31.8 (26.6, 36.0)
HR (95% CI); P-value	0.799 (0.641, 0.997); P=0.00462[a]	
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)[b],		
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 (18.2, NC)
HR (95% CI); P-value	0.58 (0.44, 0.78); P=0.0004	
Time from randomisation to first subsequent treatment or death (TFST)		
Number of patients who had first subsequent treatment or died (%)	115 (41)	175 (63)
Median TFST, months (95% CI)	23.5 (22.0, NC)	13.8 (12.3, 15.7)
HR (95% CI); P-value	0.51 (0.40, 0.64); P<0.0001	
Time from randomisation to second subsequent treatment or death (TSST)		
Number of patients who had second subsequent treatment or died (%)	74 (27)	110 (40)
Median TSST, months (95% CI)	NC (NC, NC)	25.9 (20.0, NC)
HR (95% CI); P-value	0.60 (0.45, 0.80); P=0.0005	

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

PFS, ORR, DoR and PFS2 results based on RECIST investigator assessment

* Based on unconfirmed response

Median follow-up time was 15.0 months for patients receiving TAGRISSO and 9.7 months for patients receiving EGFR TKI comparator.

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

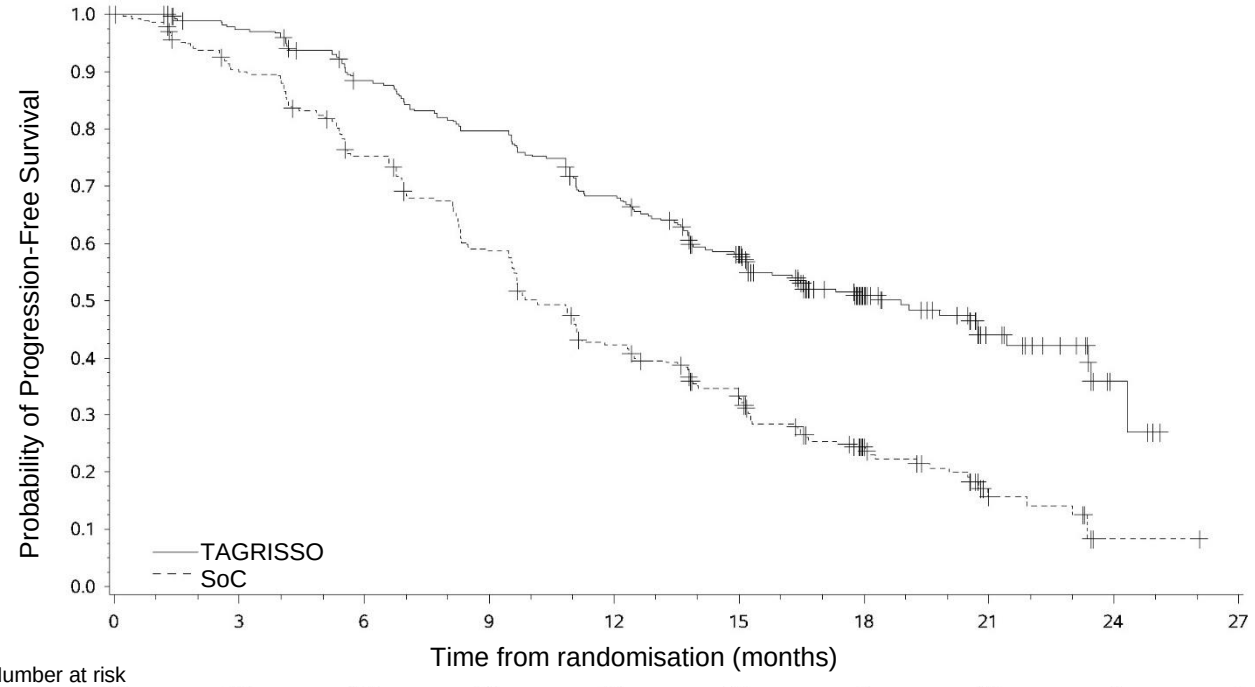
PFS, ORR, DoR, PFS2, TFST and TSST results are from data cut-off 12 June 2017. OS results are from data cut-off 25 June 2019.

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

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

[b] 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.

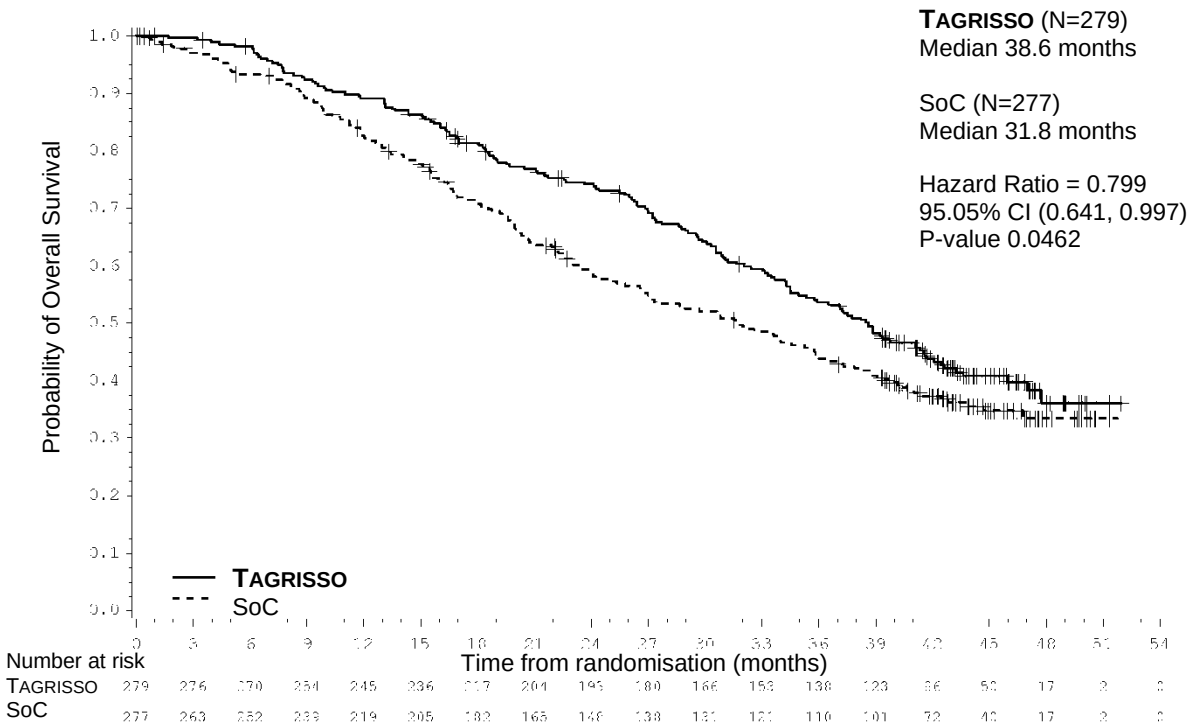
Figure 7. Kaplan-Meier Curves of Progression-Free Survival as assessed by investigator in FLAURA



Number at risk										
TAGRISSO	279	262	233	210	178	139	71	26	4	0
SoC	277	239	197	152	107	78	37	10	2	0

+ Censored patients.
SoC = Standard of Care
The values at the base of the figure indicate number of subjects at risk.

Figure 8. Kaplan-Meier Curves of Overall Survival in FLAURA



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

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

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

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

CNS metastases efficacy data in FLAURA study

Patients with CNS metastases not requiring steroids and with stable neurologic status for at least two weeks after completion of the definitive therapy and steroids were eligible to be randomised in the FLAURA study. Of 556 patients, 200 patients had available baseline brain scans. A BICR assessment of these scans resulted in a subgroup of 128/556 (23%) patients with CNS metastases and these data are summarised in Table 12. EGFR mutation type (Ex19del or L858R) and ethnicity (Asian or non-Asian) was generally balanced within this analysis between the treatment arms. CNS efficacy by RECIST v1.1 in FLAURA demonstrated a statistically significant improvement in CNS PFS (HR=0.48, 95% CI 0.26, 0.86; P=0.014).

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Table 12. 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)
CNS Objective Response Rate[a]		
CNS response rate % (n) (95% CI)	66 (40) (52,77)	43 (29) (31,56)
Odds ratio (95% CI); P-value	2.5 (1.2, 5.2); P=0.011	
CNS Duration of Response[a]		
Median CNS DoR, months (95% CI)	NC (12, NC)	14 (7, 19)
Patients remaining in response at 6 months (%) (95% CI)	86 (70, 94)	76 (55, 89)
Patients remaining in response at 12 months (%) (95% CI)	65 (46, 79)	67 (43, 82)

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

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

[a] CNS PFS, ORR and DoR 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 9. 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.

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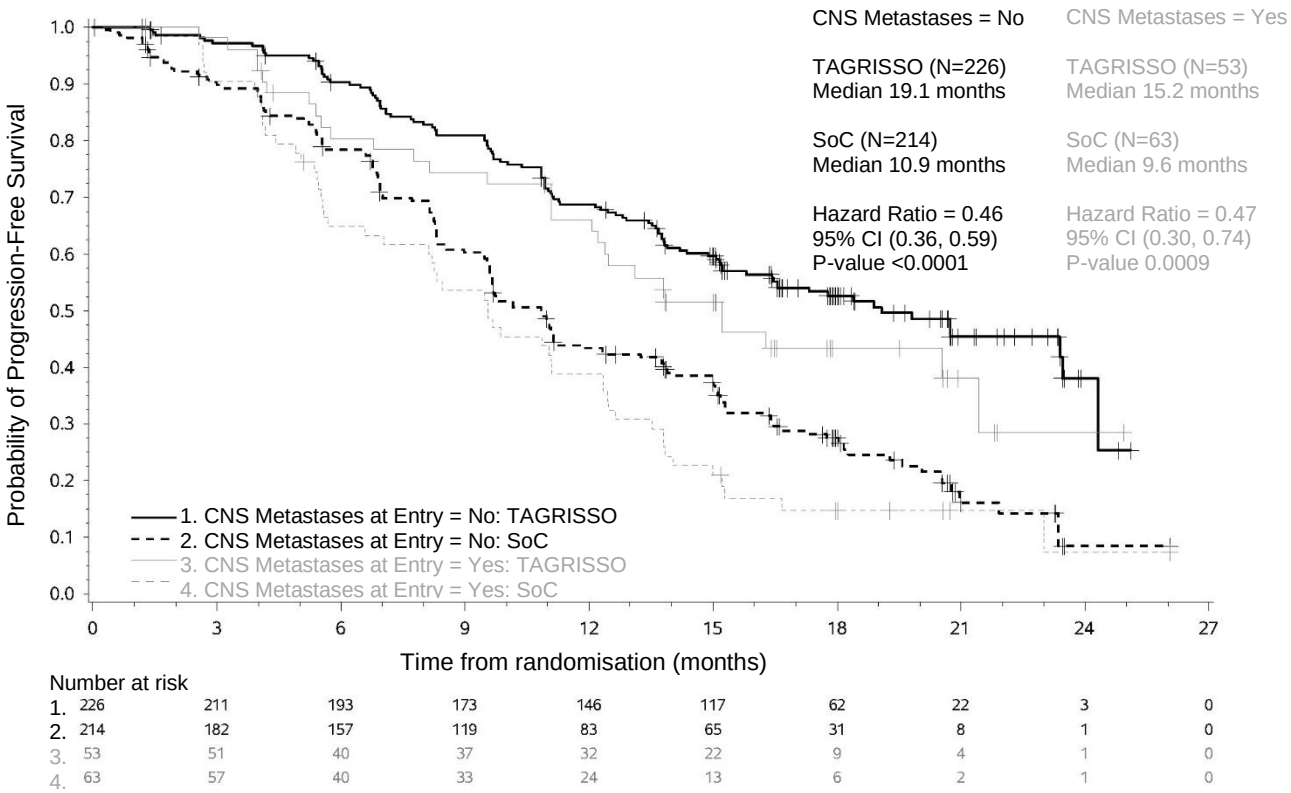
Figure 9. Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in FLAURA



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

Patient Reported Outcomes

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.

<u>Key lung cancer symptoms analysis</u>

Data collected from baseline up to month 9 showed similar improvements in TAGRISSO and EGFR TKI comparator groups for the five pre-specified primary PRO symptoms (cough, dyspnoea, chest pain, fatigue, and appetite loss) with improvement in cough reaching the established clinically relevant cutoff. Up to month 9 there were no clinically meaningful differences in patient-reported symptoms between TAGRISSO and EGFR TKI comparator groups (as assessed by a difference of ≥ 10 points). Data are presented in Table 13.

Table 13. Mixed Model Repeated Measures – Key lung cancer symptoms - mean change from baseline in TAGRISSO patients compared with EGFR TKI comparator (gefitinib or erlotinib)

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

HRQL and physical functioning improvement analysis

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

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 21-day cycles 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. Additional efficacy endpoints included OS, ORR, DoR, disease control rate (DCR), depth of response, PFS2, TFST and TSST as assessed by investigator. CNS PFS, CNS ORR, CNS DoR, and CNS depth of response as assessed by BICR, and PRO were also assessed.

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%). All patients had a WHO performance status of 0 or 1; 49% of patients had metastatic bone disease, 53% of patients 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).

TAGRISSO in combination with pemetrexed and platinum-based chemotherapy demonstrated a clinically meaningful and statistically significant improvement in PFS compared to TAGRISSO monotherapy (51% maturity; HR=0.62, 95% CI: 0.49, 0.79; P<0.0001; median 25.5 months and 16.7 months, respectively).

The final OS analysis demonstrated a clinically meaningful and statistically significant improvement in the OS for patients randomised to TAGRISSO plus pemetrexed and platinum-based chemotherapy compared to TAGRISSO monotherapy (57% maturity; HR=0.77, 95% CI: 0.61, 0.96; P=0.0202; median 47.5 months and 37.6 months, respectively).

Efficacy results from FLAURA2 by investigator assessment are summarised in Table 14, and the Kaplan-Meier curves for PFS and OS are shown in Figure 10 and Figure 11, respectively.

Table 14 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)	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 (57% maturity)	144 (52)	171 (62)
Median OS, months (95% CI)	47.5 (41.0, NC)	37.6 (33.2, 43.2)
HR (95% CI); P-value	0.77 (0.61, 0.96); P=0.0202[a]	
Objective Response Rate[b,c]		
Number of responses (n), Response Rate % (95% CI)	232 83 (78, 87)	210 76 (70, 80)
Odds ratio (95% CI); P-value[d]	1.61 (1.06, 2.44); P=0.0261	
Duration of Response (DoR)[b]		

Efficacy Parameter	**TAGRISSO with Pemetrexed and Platinum-based Chemotherapy (N=279)**	**TAGRISSO (N=278)**
Median DoR, months (95% CI)[e]	24.0 (20.9, 27.8)	15.3 (12.7, 19.4)
Disease Control Rate		
Number of patients with disease control (n), Control Rate % (95% CI)	266 95 (92, 98)	261 94 (90, 96)
Odds ratio (95% CI); P-value[d]	1.33 (0.63, 2.81); P=0.4483	
Second PFS after start of first subsequent therapy (PFS2)		
Number (%) of PFS2 events	81 (29)	110 (40)
Median PFS2, months (95% CI)	30.6 (29.0, NC)	27.8 (26.0, NC)
HR (95% CI); P-value	0.70 (0.52, 0.93); P=0.0132	
Time from randomisation to first subsequent treatment or death (TFST)		
Number of patients who had first subsequent treatment or died (%)	104 (37)	129 (46)
Median TFST, months (95% CI)	30.7 (27.3, NC)	25.4 (22.8, NC)
HR (95% CI); P-value	0.73 (0.56, 0.94); P=0.0159	
Time from randomisation to second subsequent treatment or death (TSST)		
Number of patients who had second subsequent treatment or died (%)	74 (27)	103 (37)
Median TSST, months (95% CI)	NC (NC, NC)	33.2 (28.2, NC)
HR (95% CI); P-value	0.69 (0.51, 0.93); P=0.0157	

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

PFS, ORR, DoR and DCR results 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, ORR, DoR, DCR, PFS2, TFST and TSST results are from DCO 03 April 2023. OS results are from DCO 12 June 2025.

A HR < 1 favours TAGRISSO with pemetrexed and platinum-based chemotherapy, an Odds ratio of >1 favours TAGRISSO with pemetrexed and platinum-based chemotherapy.

[a] Adjusting for the interim analyses, at the OS final analysis a p-value < 0.04953 was required to achieve statistical significance.

[b] Based on unconfirmed response.

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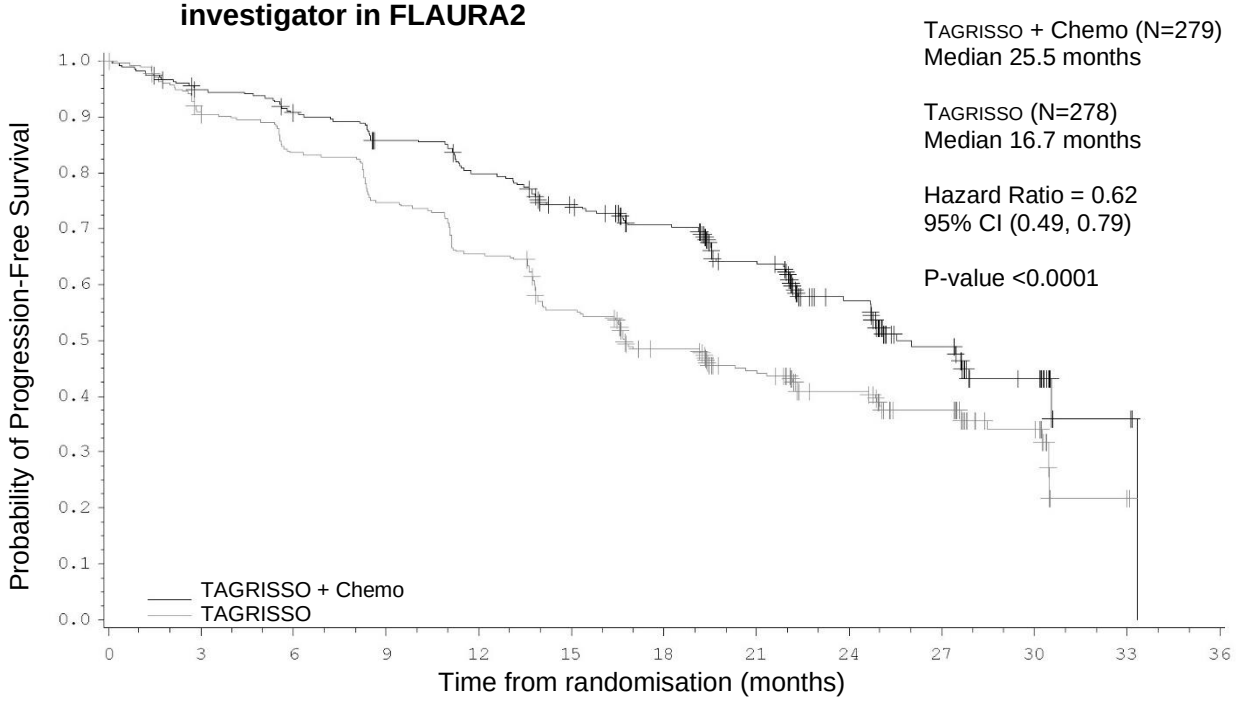
[c] ORR results by BICR were consistent with those reported via investigator assessment; ORR by BICR assessment was 92% (95% CI: 88, 95) for patients in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm and 83% (95% CI: 78, 87) for patients in the TAGRISSO monotherapy arm.

[d] The analysis was performed using a logistic regression stratified by race (Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian), WHO performance status (0 vs. 1), and method used for tissue testing (central vs. local).

[e] Calculated using the Kaplan-Meier method.

Figure 10 Kaplan-Meier Curves of Progression-Free Survival as assessed by investigator in FLAURA2



Number at risk

TAGRISSO + Chemo	279	254	241	225	207	187	165	133	84	42	21	3	0
TAGRISSO	278	246	227	203	178	148	119	94	67	48	21	1	0

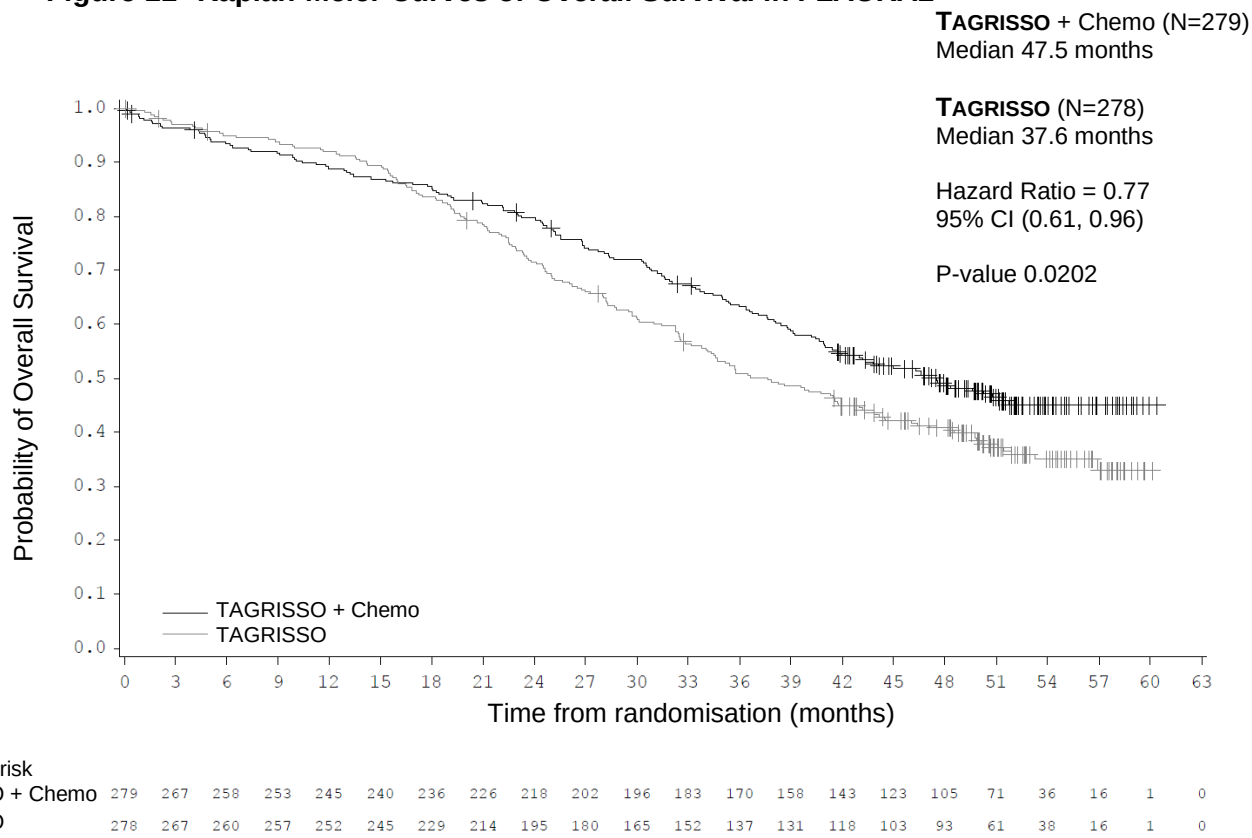
+ Censored patients.
Chemo = Pemetrexed and platinum-based chemotherapy.
The values at the base of the figure indicate number of patients at risk.

A sensitivity analysis of PFS was conducted by a BICR and showed a median PFS of 29.4 months with TAGRISSO in combination with pemetrexed and platinum-based chemotherapy compared with 19.9 months with TAGRISSO monotherapy. This analysis demonstrated a consistent treatment effect (HR 0.62; 95% CI: 0.48, 0.80; P=0.0002 [nominal]) with that observed by investigator assessment.

The PFS benefit of TAGRISSO in combination with pemetrexed and platinum-based chemotherapy compared to TAGRISSO monotherapy 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).

The median best percentage change in target lesion size from baseline was -53% (range: -100% to 20%) in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm and -50% (range: -100% to 40%) in the TAGRISSO monotherapy arm.

Figure 11 Kaplan-Meier Curves of Overall Survival in FLAURA2



Number at risk

TAGRISSO + Chemo	279	267	258	253	245	240	236	226	218	202	196	183	170	158	143	123	105	71	36	16	1	0
TAGRISSO	278	267	260	257	252	245	229	214	195	180	165	152	137	131	118	103	93	61	38	16	1	0

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

Patients randomised to TAGRISSO in combination with pemetrexed and platinum-based chemotherapy as first-line treatment also had clinically meaningful improvements in PFS2, TFST and TSST compared to patients randomised to TAGRISSO monotherapy. The analysis of these post-progression endpoints demonstrated that PFS benefit was largely preserved through subsequent lines of therapy.

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). CNS efficacy assessment by BICR in FLAURA2 demonstrated a clinically meaningful improvement in CNS PFS in patients in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm compared to patients in the TAGRISSO monotherapy arm for both the cFAS and cEFR (cFAS: 27% maturity; HR=0.58, 95% CI 0.33, 1.01; P=0.0548 [nominal] and cEFR: 37% maturity; HR=0.40, 95% CI 0.19, 0.84; P=0.0157 [nominal]). The CNS efficacy data are summarised in Table 15.

Table 15 CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in FLAURA2

Efficacy Parameter	CNS Measurable and/or Non-measurable Lesions (cFAS)		CNS Measurable Lesions (cEFR)	
	TAGRISSO with Pemetrexed and Platinum-based Chemotherapy (N=118)	TAGRISSO (N=104)	TAGRISSO with Pemetrexed and Platinum-based Chemotherapy (N=40)	TAGRISSO (N=38)
CNS Progression-Free Survival[a]				
Number (%) of events	28 (24)	31 (30)	11 (28)	18 (47)
Median CNS PFS, months (95% CI)	30.2 (28.4, NC)	27.6 (22.1, NC)	NC (23.0, NC)	17.3 (13.9, NC)
HR (95% CI); P-value[b]	0.58 (0.33, 1.01); P=0.0548		0.40 (0.19, 0.84); P=0.0157	
CNS progression free and alive at 12 months (%) (95% CI)	87 (79, 92)	83 (73, 89)	89 (74, 96)	73 (55, 85)
CNS progression free and alive at 24 months (%) (95% CI)	74 (63, 82)	54 (39, 67)	65 (43, 80)	37 (18, 57)
CNS Objective Response Rate[a]				
Number of CNS responses (n), CNS Response Rate % (95% CI)	86 73 (64, 81)	72 69 (59, 78)	35 88 (73, 96)	33 87 (72, 96)
Complete response	70 (59)	45 (43)	19 (48)	6 (16)
Partial response	16 (14)	27 (26)	16 (40)	27 (71)
Odds ratio (95% CI); P-value[b,c]	1.19 (0.67, 2.14); P=0.5492		1.06 (0.28, 4.00); P=0.9308	
CNS Duration of Response[a]				
Median CNS DoR, months (95% CI)	NC (23.8, NC)	26.2 (19.4, NC)	NC (21.6, NC)	20.9 (12.6, NC)
Patients remaining in response at 12 months (%) (95% CI)	93 (85, 97)	81 (68, 89)	93 (75, 98)	74 (53, 87)
Patients remaining in response at 24 months (%) (95% CI)	62 (40, 77)	57 (38, 72)	57 (27, 78)	45 (22, 65)

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

A HR< 1 favours TAGRISSO with pemetrexed and platinum-based chemotherapy, an Odds ratio of >1 favours TAGRISSO with pemetrexed and platinum-based chemotherapy.

[a] Based on unconfirmed responses.

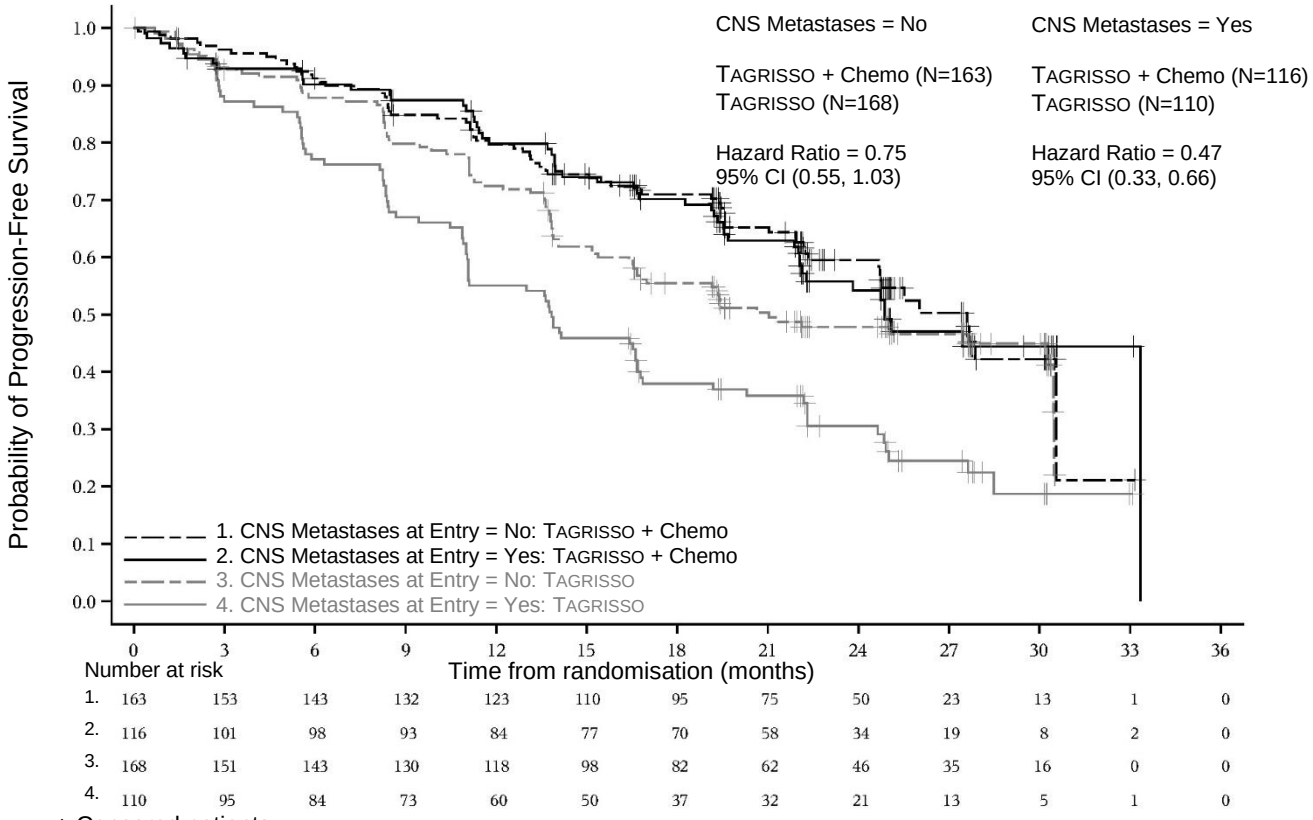
[b] Nominal P-value.

[c] The analysis was performed using logistic regression with a factor for treatment.

The median best percentage change in target CNS lesion size from baseline was -94% (range: -100% to 7%) in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm and -61% (range: -100% to 68%) in the TAGRISSO monotherapy arm.

A pre-specified PFS subgroup based on CNS metastases status (identified by investigator based on CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases) at study entry was performed in FLAURA2. Irrespective of CNS metastases status at study entry, an improvement of PFS in patients in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm was demonstrated compared to those in the TAGRISSO monotherapy arm. The Kaplan-Meier curve for PFS by CNS metastases status at study entry 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 FLAURA2



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

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 8 weeks, then every 3 weeks before progression and every 8 weeks after progression. The C30 was assessed every 3 weeks for the first 8 weeks, then every 6 weeks before progression and every 8 weeks after progression. At baseline, no differences in patient-reported symptoms, physical function or GHS/QoL were observed between the TAGRISSO with pemetrexed and platinum-based chemotherapy arm and the TAGRISSO monotherapy arm. Compliance over the first 19 months was generally high (≥80%) and similar in both arms.

Key lung cancer symptoms analysis

Data collected from baseline up to month 19 showed similar improvements for three of the five pre-specified primary PRO symptoms (cough, dyspnoea, and chest pain) in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm compared with the TAGRISSO monotherapy arm, with improvement in cough reaching the established clinically relevant cutoff (change from baseline ≤-10) in both arms. There was a trend towards improvement for appetite loss and fatigue in the TAGRISSO monotherapy arm. In the TAGRISSO with pemetrexed and platinum-based chemotherapy arm, there was a trend towards worsening in fatigue during the first 4 cycles of chemotherapy followed by a trend towards improvement, and a trend towards worsening in appetite loss. The changes were not clinically meaningful. Data are presented in Table 16.

Table 16 Mixed Model Repeated Measures – Key lung cancer symptoms - mean change from baseline in patients treated with TAGRISSO with pemetrexed and platinum-based chemotherapy compared with patients treated with TAGRISSO monotherapy

	TAGRISSO with Pemetrexed and Platinum-based Chemotherapy (N=279)		**TAGRISSO (N=278)**		**Estimated Difference in Treatment (95%CI)**
	N	Adjusted mean	N	Adjusted mean	
Cough	253	-13.23	251	-11.19	-2.04 (-4.35, 0.26)
Dyspnoea	253	-3.09	251	-5.67	2.57 (0.28, 4.86)
Chest pain	253	-6.33	251	-6.61	0.29 (-1.62, 2.20)
Appetite loss	253	2.87	253	-4.58	7.45 (4.52, 10.38)
Fatigue	253	-0.03	253	-6.31	6.28 (3.60, 8.96)

Global health status/QoL and physical functioning improvement analysis

Both arms reported no clinically meaningful changes in physical functioning and GHS/QoL.

Pretreated T790M positive NSCLC patients - AURA3

The efficacy and safety of TAGRISSO for the treatment of patients with locally advanced or metastatic T790M NSCLC whose disease has progressed on or after EGFR TKI therapy, was demonstrated in a randomised, open label, active-controlled Phase 3 study (AURA3). All patients were required to have EGFR T790M mutation positive NSCLC identified by the cobas® EGFR mutation test performed in a central laboratory prior to randomisation. The T790M mutation status was also assessed using ctDNA extracted from a plasma sample taken during screening. The primary efficacy outcome was PFS as assessed by investigator. Additional efficacy outcome measures included ORR, DoR and 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 500mg/m^2 with carboplatin AUC5 or pemetrexed 500mg/m^2 with cisplatin 75mg/m^2) on Day 1 of every 21d 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 500mg/m^2 on Day 1 of every 21d cycle). Subjects on the chemotherapy arm who had objective radiological progression (by the investigator and confirmed by independent central imaging review) were given the opportunity to begin treatment with TAGRISSO.

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

AURA3 demonstrated a statistically significant improvement in PFS in the patients treated with TAGRISSO compared to chemotherapy. Efficacy results from AURA3 by investigator assessment are summarised in Table 17, and the Kaplan-Meier curve for PFS is shown in Figure 13. No statistically significant difference was observed between the treatment arms at the final OS analysis (conducted at 67% maturity), at which time 99 patients (71%) randomised to chemotherapy had crossed over to TAGRISSO treatment.

Table 17. 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 (OS)[a]		
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[b]		

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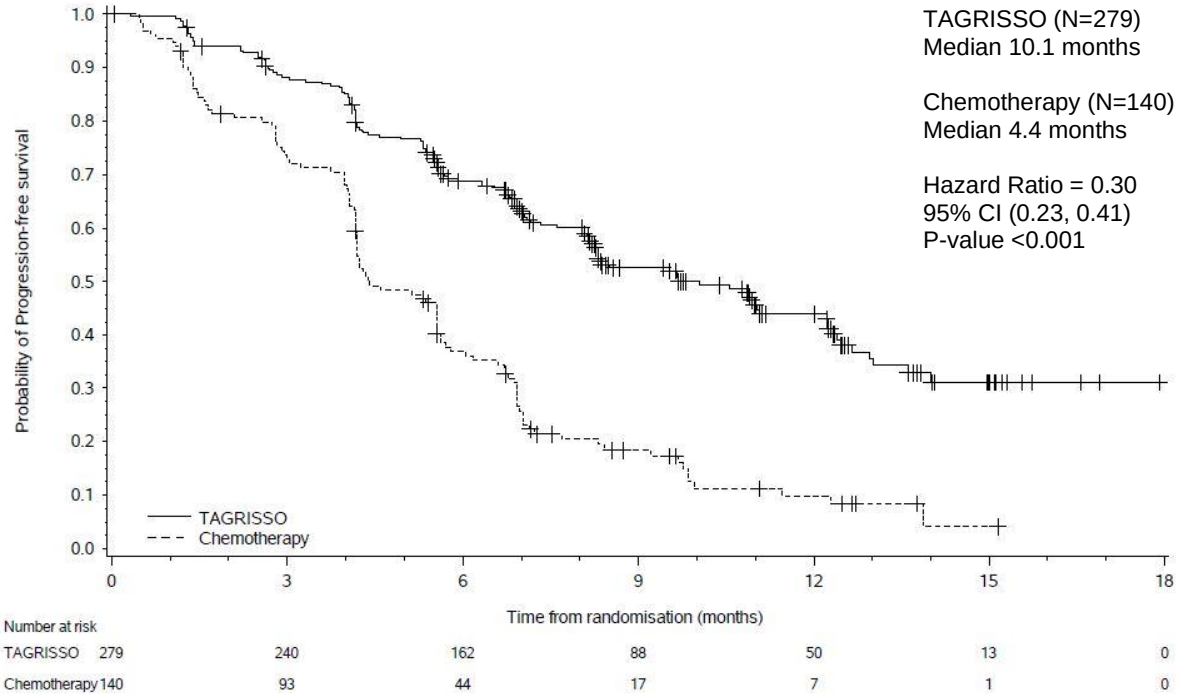
Efficacy Parameter	TAGRISSO (N=279)	Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=140)
Number of responses, Response Rate (95% CI)	197 71% (65, 76)	44 31% (24, 40)
Odds ratio (95% CI) ; P-value	5.4 (3.5, 8.5); P < 0.001	
Duration of Response (DoR)		
Median DoR, months (95% CI)	9.7 (8.3, 11.6)	4.1 (3.0, 5.6)

HR=Hazard Ratio; CI=confidence interval; OS = Overall Survival
All efficacy results based on RECIST investigator assessment
A HR< 1 favours TAGRISSO
[a] 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).
[b] ORR and DoR results by investigator assessment were consistent with those reported via Blinded Independent Central Review (BICR); ORR by BICR assessment was 64.9% [95% CI: 59.0, 70.5] on osimertinib and 34.3% [95% CI: 26.5, 42.8] on chemotherapy; DoR by BICR assessment was 11.2 months (95% CI: 8.3, NC) on osimertinib and 3.1 months (95% CI: 2.9, 4.3) on chemotherapy.

Figure 13. Kaplan-Meier Curves of Progression-Free Survival as assessed by investigator in AURA3



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

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

Clinically meaningful improvements in PFS with HRs less than 0.50 in favour of patients receiving TAGRISSO compared to those receiving chemotherapy were consistently observed in all predefined subgroups analysed, including ethnicity, age, gender, smoking history, CNS metastases status at study entry, EGFR mutation (Exon 19 deletion and L858R), and duration of first-line therapy with an EGFR-TKI.

CNS metastases efficacy data in AURA3 study

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 18.

Table 18. 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[a]		
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[b]		
Median CNS DoR, months (95% CI)	8.9 (4.3, NC)	5.7 (NC, NC)
CNS Disease control rate		
Number with disease control CNS disease control rate	87% (65/75) (77, 93)	68% (28/41) (52, 82)
Odds ratio (95% CI) ; P-value	3 (1.2, 7.9); p=0.021	
CNS Progression-free survival[c]	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	

NC=non-calculable.

HR < 1 favours TAGRISSO.

[a] 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

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

[c] CNS Progression Free Survival determined by RECIST v1.1by 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

Thirty-seven (37%) percent (28/75) of patients treated with TAGRISSO and with BICR identified CNS metastases had received prior brain radiation, including 19% (14/75) who completed radiation treatment within 6 months before starting treatment. CNS responses were observed irrespective of prior brain radiation status.

A pre-specified PFS subgroup based on CNS metastases status at study entry was performed in AURA3 and is shown in Figure 14 and Table 19 .

Figure 14. Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in AURA3

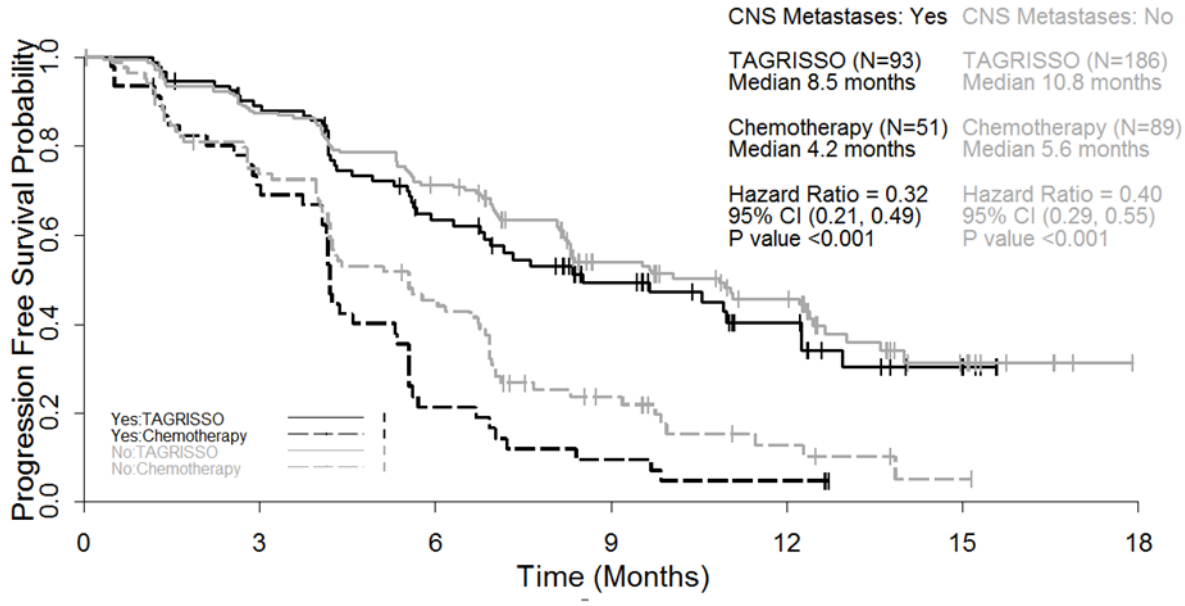


Table 19. PFS by CNS metastases at study entry based on investigator assessment (full analysis set) in AURA3

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

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

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

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

Pretreated T790M positive NSCLC patients-AURAex and AURA2

Two single-arm, open-label clinical studies, AURAex (Phase 2 Extension cohort, (n=201)) and AURA2 (n=210) were conducted in patients with EGFR T790M mutation-positive lung cancer

who have progressed on one or more prior systemic therapy, 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 dosing T790M mutation status was also assessed retrospectively using ctDNA extracted from a plasma sample taken during screening. All patients received TAGRISSO at a dose of 80 mg once daily. The primary efficacy outcome measure of these two trials was ORR according to RECIST v1.1 as evaluated by a BICR. Secondary efficacy outcome measures included DoR and 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 (N=129) had received 1 prior line of therapy (EGFR-TKI treatment only, second line, chemotherapy naïve), 69% (N=282) had received 2 or more prior lines. Seventy-two percent of patients were never smokers, 100% of patients had a WHO performance status of 0 or 1. Fifty-nine percent (59%) of patients had extra-thoracic visceral metastasis including 39% with CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery and/or prior radiotherapy to CNS metastases) and 29% with liver metastases. Forty-seven percent (47%) of patients had metastatic bone disease. The median duration of follow up for PFS was 12.6 months.

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

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

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

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

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

5.2 PHARMACOKINETIC PROPERTIES

Osimertinib pharmacokinetic parameters have been characterized in healthy subjects and NSCLC patients. Based on population PK 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 C_{max} 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

In a relative bioavailability study against an oral solution of osimertinib mesilate, both TAGRISSO and the oral solution produced peak plasma concentrations of osimertinib with median (min-

max) t_{max} of 6 (3 - 24) hours, with several peaks observed over the first 24 hours in some patients. The AUC and C_{max} values for TAGRISSO and the oral solution were also similar, indicating similar relative bioavailability. The absolute bioavailability of TAGRISSO is 70% (90% CI 67, 73). A food effect study conducted with a 20 mg dose of TAGRISSO tablets showed minimal effect on C_{max} and AUC (14% and 19%, increased with a high fat, high calorie meal). In the AURAex and AURA2 studies (see section 5.1 Pharmacodynamic Properties - Clinical Efficacy and Safety), patients were instructed to take TAGRISSO when fasted. 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 with the 90% CI for exposure ratio contained within the 80-125% limit.

Distribution

Population estimated mean volume of distribution at steady state (V_{ss}/F) of osimertinib is 918 L indicating extensive distribution into tissue. Plasma protein binding could not be measured due to instability, but based on the physicochemical properties of osimertinib plasma protein binding is likely to be high.

Biotransformation

In vitro studies indicate that osimertinib is metabolised predominantly by CYP3A4 and CYP3A5. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in plasma after oral dosing with osimertinib; AZ7550 showed a similar pharmacological profile to osimertinib while AZ5104 showed greater potency across both mutant and wild-type EGFR. Both metabolites appeared slowly in plasma after administration of osimertinib to patients, with a median (min-max) t_{max} of 24 (4-72) and 24 (6-72) hours, respectively. In a pharmacokinetic and mass balance study of orally administered radio-labelled osimertinib mesilate, 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 remaining 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. Minor glutathione, cysteinylglycine, glucuronide and sulphate conjugates were also observed in rat and dog in vitro. 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, 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.

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Transporter interactions

In vitro studies have shown that osimertinib is a substrate of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but is not a substrate of the hepatocyte uptake transporters OATP1B1 and OATP1B3.

In vitro, osimertinib does not inhibit P-gp, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2-K and OCT2 at clinically relevant concentrations, but does inhibit BCRP (see section 4.5 Interactions).

Special populations

In a population based pharmacokinetic analyses (n=1367), no clinically significant relationships were identified between predicted steady state exposure (AUC_{ss}) and patient's age, gender, ethnicity, line of therapy and smoking status. Population PK analysis indicated that body weight and serum albumin were significant covariates but the exposure changes due to body weight or baseline albumin differences are not considered clinically relevant.

Hepatic impairment

Osimertinib is eliminated mainly via the liver. In a clinical trial, patients with mild hepatic impairment (Child Pugh A, n=7) or moderate hepatic impairment (Child Pugh B, n=5) had no increase in exposure compared to patients with normal hepatic function (n=10) after a single 80 mg dose of TAGRISSO. Based on population PK analysis, there was no relationship between markers of hepatic function (ALT, AST, bilirubin) and osimertinib exposure. Clinical studies that were conducted excluded patients with AST or ALT >2.5 x upper limit of normal (ULN), or if due to underlying malignancy, >5.0 x ULN or with total bilirubin >1.5 x ULN. Based on a pharmacokinetic analysis of 134 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST), 8 patients with moderate hepatic impairment (total bilirubin between 1.5 times to 3.0 times ULN and any AST) and 1216 patients with normal hepatic function (total bilirubin less than or equal to ULN and AST less than or equal to ULN), osimertinib exposures were similar. There are no data available on patients with severe hepatic impairment (see section 4.2 Dose and Method of Administration).

Renal impairment

In a clinical trial, patients with severe renal impairment (CLcr 15 to less than 30 mL/min; n=7) compared to patients with normal renal function (CLcr greater than or equal to 90 mL/min; n=8) after a single 80 mg dose of TAGRISSO showed a 1.85-fold increase in AUC (90% CI: 0.94, 3.64) and a 1.19-fold increase in C_{max} (90% CI: 0.69, 2.07). Furthermore, based on a population 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 trials.

Patients with brain metastases

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

Cardiac electrophysiology

The QT interval prolongation potential of osimertinib 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 QT intervals (see section 4.4 Special Warnings and Precautions for Use – QTc interval prolongation). A pharmacokinetic/pharmacodynamic analysis with osimertinib predicted a drug-related QTc interval prolongation at 80 mg of 14 msec with an upper bound of 16 msec (90% CI).

5.3 PRECLINICAL SAFETY DATA

Repeat dose toxicity

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

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

Carcinogenicity and mutagenesis

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

Genotoxicity

Osimertinib showed no activity in in vitro bacterial and mouse lymphoma cell mutation assays and in in vivo rat bone marrow micronucleus assays, suggesting that it is neither a mutagen nor a clastogen.

CNS distribution and in vivo intracranial tumour regression

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

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

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Reproductive toxicity

Degenerative changes were present in the testes in rats and dogs exposed to osimertinib for ≥4 weeks and there was a reduction in male fertility in rats following exposure to osimertinib for ~2.5 months. These findings were seen at exposure similar to the clinical exposure at 80 mg daily (based on AUC). Pathology findings in the testes seen in rats following 4 weeks dosing were reversible.

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 ≥4 weeks at 10 mg/kg/day (total exposure 0.3 times the clinical exposure). Findings in the ovaries seen following 4 weeks 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 embryo-foetal development study in the rat, osimertinib caused embryolethality when administered to pregnant rats prior to embryonic implantation. These effects were seen at a maternally tolerated dose of 20 mg/kg/day where exposure was equivalent to the human exposure at the recommended dose of 80 mg daily (based on total AUC). Exposure at doses of 20 mg/kg and above during organogenesis caused reduced foetal weights. Teratogenicity has not been adequately assessed in animal studies. When osimertinib was administered to pregnant female rats throughout gestation and then through early lactation, there was demonstrable excretion in milk and 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

- Mannitol
- Microcrystalline cellulose
- Hydroxypropylcellulose
- Sodium stearyl fumarate
- Polyvinyl alcohol
- Titanium dioxide
- Talc
- Iron oxide black
- Iron oxide red
- Iron oxide yellow
- Macrogol 3350

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

The tablets are packed into PVC/aluminium/polyamide laminate blister strips in cartons of 30 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: 0800 684 432

9. DATE OF FIRST APPROVAL

5 October 2017

9. DATE OF REVISION OF TEXT

1 April 2026

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	New section titled Skeletal Muscles
4.8	Myositis added to AE tables.
4.9	Minor editorial change in line with Medsafe guidelines.
5.1	FLAURA2 final OS study data added.