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) is indicated for:

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

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

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

The recommended dose of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity.

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

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	ILD/Pneumonitis	Permanently discontinue treatment
Cardiac	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
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 4.0.

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 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 3.9% and were fatal in 0.4% (n=5) of the 1142 patients who received TAGRISSO in FLAURA 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 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.

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.

Erythema multiforme and Stevens-Johnson syndrome

Case reports of Erythema multiforme (EM) and Stevens-Johnson syndrome (SJS) have been uncommonly and rarely reported, respectively, in association with TAGRISSO treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM and SJS. 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 appear, TAGRISSO should be interrupted or discontinued immediately.

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 3.9% (35/908) of patients treated with TAGRISSO who had baseline and at least one follow-up LVEF assessment. Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and TAGRISSO has not been established. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

Keratitis

Keratitis was reported in 0.7% (n=8) of the 1142 patients treated with TAGRISSO in the FLAURA and AURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist (see section 4.2 Dose and Method of Administration).

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

Studies in EGFR mutation positive NSCLC patients

The data described below reflect exposure to TAGRISSO in 1142 patients with EGFR mutation-positive NSCLC. These patients received TAGRISSO at a dose of 80 mg daily in two

randomised Phase 3 studies (FLAURA, 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 (49%) and rash (47%). Grade 3 and Grade 4 adverse reactions with TAGRISSO were 9.7% and 0.9%, respectively. In patients treated with TAGRISSO 80 mg once daily, dose reductions due to adverse reactions occurred in 2.1% of the patients. Discontinuation due to adverse reactions or abnormal laboratory parameters was 4.3%.

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 1142 previously treated EGFR mutation positive patients who received TAGRISSO at a dose of 80 mg daily in the FLAURA, AURA3, AURAex, AURA2 and AURA1 studies.

Adverse reactions are listed according to system organ class (SOC) in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse 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 FLAURA and AURA studies[a]

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (all CTCAE grades[b])	Frequency of CTCAE grade 3-4 or higher
Respiratory, thoracic and mediastinal disorders	Interstitial Lung Disease[c]	Common (3.9%)[d]	1.5%
Gastrointestinal disorders	Diarrhoea	Very common (49%) [e]	1.2%
	Stomatitis	Very common (20%)[e]	0.2%
Eye disorders	Keratitis[e]	Uncommon (0.7%)	0.1%
Skin and subcutaneous tissue disorders	Rash[f,]	Very common (47%) [e]	0.9%
	Dry Skin[g]	Very common (33%) [e]	0.1%
	Paronychia[h]	Very common (31%)	0.3%
	Pruritus[i]	Very common (17%)	0.1%
	Erythema multiforme[j]	Uncommon (0.35%)	0%
	Stevens-Johnson syndrome[k]	Rare (0.02%)	
	Cutaneous Vasculitis[l]	Uncommon (0.26%)	
Investigations	QTc interval prolongation[m]	Uncommon (0.9%)	
Findings based on test results presented as CTCAE grade shifts	Platelet count decreased[n]	Very common (54%)	1.6%
	Leukocytes decreased[n]	Very common (68%)	1.5%
	Lymphocytes decreased[n]	Very common (67%)	7.2%
	Neutrophils decreased[n]	Very common (35%)	4.1%

[a] Data is cumulative from FLAURA 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 4.0.

[c] Includes cases reported within the clustered terms: Interstitial lung disease, pneumonitis.

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

[e] Includes cases reported within the clustered terms: Keratitis, punctate keratitis, corneal erosion, corneal epithelium defect.

[f] Includes cases reported within the clustered terms for rash AEs: 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 and skin erosion.

[g] Includes cases reported within the clustered terms: Dry skin, skin fissures, xerosis, eczema, xeroderma.

[h] Includes cases reported within the clustered terms: Nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.

[i] Includes cases reported within the clustered terms: Pruritus, pruritus generalised, eyelid pruritus.

[j] Four of the 1142 patients in the AURA and FLAURA studies reported erythema. Post-marketing reports of erythema multiforme have also been received, including 7 reports from a post-marketing surveillance study (N=3578).

[k] One event reported in a post-marketing study, and the frequency has been derived from the FLAURA and AURA studies and the post-marketing study (N=4720)

[l] Estimated frequency. The upper limit of the 95% CI for the point estimate is 3/1142 (0.26%).

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

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

Table 3. Adverse reactions reported in FLAURA[a] study

MedDRA SOC	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)**	**Any Grade (%)**	**Grade 3 or higher (%)**
MedDRA Preferred Term				
Respiratory, thoracic and mediastinal disorders				
Interstitial Lung Disease[c]	3.9	1.1	2.2	1.4
Eye disorders				
Keratitis[d]	0.4	0	1.4	0
Gastrointestinal disorders				
Diarrhoea[e]	58	2.2	57	2.5
Stomatitis	29	0.7	20	0.4
Skin and subcutaneous tissue disorders				
Rash[f]	58	1.1	78	6.9
Dry skin[g]	36	0.4	36	1.1
Paronychia[h]	35	0.4	33	0.7
Pruritus[i]	17	0.4	17	0
Investigations				
QTc interval prolongation[j,]	1.1		0.7	
(Findings based on test results presented as CTCAE grade shifts)				
Platelet count decreased[k]	51	0.7	12	0.4
Leukocytes decreased[k]	72	0.4	31	0.4
Lymphocytes decreased[k,]	63	5.6	36	4.2
Neutrophils decreased[k]	41	3.0	10	0

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

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

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

[c] Cases reported within the clustered terms: Interstitial lung disease, pneumonitis.

[d] Cases reported within the clustered terms: Keratitis, punctate keratitis, corneal erosion, corneal epithelium defect.

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

[f] Cases reported within the clustered terms for rash AEs: 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.

[g] Cases reported within the clustered terms: Dry skin, skin fissures, xerosis, eczema, xeroderma.

[h] Cases reported within the clustered terms: 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.

[i] Cases reported within the clustered terms: Pruritus, pruritus generalised, eyelid pruritus.

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

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

Table 4. Adverse reactions reported in AURA3[a] study

MedDRA SOC	TAGRISSO overall frequency (N=279)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) overall frequency (N=136)	
NCI Grade[b]	**Any Grade (%)**	**Grade 3 or higher (%)**	**Any Grade (%)**	**Grade 3 or higher (%)**
MedDRA Preferred Term				
Respiratory, thoracic and mediastinal disorders				
Interstitial Lung Disease[c,d]	3.6	0.4	0.7	0.7
Eye disorders				
Keratitis[e]	1.1	0	0.7	0
Gastrointestinal disorders				
Diarrhoea	41	1.1	11	1.5
Stomatitis	15	0	15	1.5
Skin and subcutaneous tissue disorders				
Rash[f]	34	0.7	5.9	0
Dry skin[g]	23	0	4.4	0
Paronychia[h]	22	0	1.5	0
Pruritus[i]	13	0	5.1	0
Investigations				
QTc interval prolongation[j]	1.4		0	
(Findings based on test results presented as CTCAE grade shifts)				
Platelet count decreased[k]	46	0.7	48	7.4
Leukocytes decreased[k]	61	1.1	75	5.3
Neutrophils decreased[k]	27	2.2	49	12

a Only events for patients receiving at least one dose of TAGRISSO are summarised.

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

c Includes cases reported within the clustered terms: Interstitial lung disease and pneumonitis.

d 1 CTCAE grade 5 event (fatal) was reported.

e Includes cases reported within the clustered terms: keratitis, punctate keratitis, corneal epithelium defect and corneal erosion.

f Includes cases reported within the clustered terms for rash AEs: Rash, rash generalised, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis and dermatitis acneiform.

g Includes cases reported within the clustered terms: Dry skin, skin fissures, xerosis, eczema.

[h] Includes cases reported within the clustered terms: Nail disorders, nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, onychalgia, onychoclasis, onycholysis, onychomadesis, paronychia.

[i] Includes cases reported within the clustered terms: Pruritus, pruritus generalised, eyelid pruritus.

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

[k] 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 1142 patients in the FLAURA and AURA studies treated with TAGRISSO 80 mg, 0.9% of patients (n=10) were found to have a QTc greater than 500 msec, and 3.6% of patients (n=41) 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 FLAURA 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 FLAURA and AURA3 (n=1142), 43% of patients were 65 years of age and older, and 13% were 75 years of age and older. Compared with younger subjects (<65), more subjects ≥65 years old had reported adverse reactions that led to study drug dose modifications (interruptions or reductions) (13.4% versus 7.6%). 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 (13.4% versus 9.3%). No overall differences in efficacy were observed between these subjects and younger subjects. A consistent pattern in safety and efficacy results was observed in the analysis of AURA Phase 2 studies.

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://nzphvc.otago.ac.nz/reporting/.

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

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

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

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

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

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

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

TAGRISSO demonstrated a clinically meaningful and highly statistically significant improvement in PFS compared to EGFR TKI comparator (median 18.9 months and 10.2 months, respectively, HR=0.46, 95% CI: 0.37, 0.57; P<0.0001). Efficacy results from FLAURA by investigator assessment are summarised in Table 5, and the Kaplan-Meier curve for PFS is shown in Figure 1. 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 5 and Figure 2). 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 5. Efficacy results from FLAURA by investigator assessment

Efficacy Parameter	**TAGRISSO (N=279)**	**EGFR TKI comparator (gefitinib or erlotinib) (N=277)**
Progression-Free Survival		
Number of events (62% maturity)	136 (49)	206 (74)
Median, months (95% CI)	18.9 (15.2, 21.4)	10.2 (9.6, 11.1)
HR (95% CI); P-value	0.46 (0.37, 0.57); P<0.0001	
Overall Survival		
Number of deaths, (58% maturity)	155 (56)	166 (60)
Median OS in months (95% CI)	38.6 (34.5, 41.8)	31.8 (26.6, 36.0)
HR (95% CI); P-value	0.799 (0.641, 0.997); P=0.00462 †	
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)[1],		
Median, Months (95% CI)	17.2 (13.8, 22.0)	8.5 (7.3, 9.8)
Second PFS after start of first subsequent therapy (PFS2)		
Number of patients with second progression (%)	73 (26)	106 (38)
Median PFS2, months (95% CI)	NC (23.7, NC)	20.0 (18.2, NC)
HR (95% CI); P-value	0.58 (0.44, 0.78); P=0.0004	
Time from randomisation to first subsequent treatment or death (TFST)		
Number of patients who had first subsequent treatment or died (%)	115 (41)	175 (63)
Median TFST, months (95% CI)	23.5 (22.0, NC)	13.8 (12.3, 15.7)
HR (95% CI); P-value	0.51 (0.40, 0.64); P<0.0001	
Time from randomisation to second subsequent treatment or death (TSST)		
Number of patients who had second subsequent treatment or died (%)	74 (27)	110 (40)

Efficacy Parameter	TAGRISSO (N=279)	EGFR TKI comparator (gefitinib or erlotinib) (N=277)
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

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

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

Figure 1. Kaplan-Meier Curves of Progression-Free Survival as assessed by investigator in FLAURA

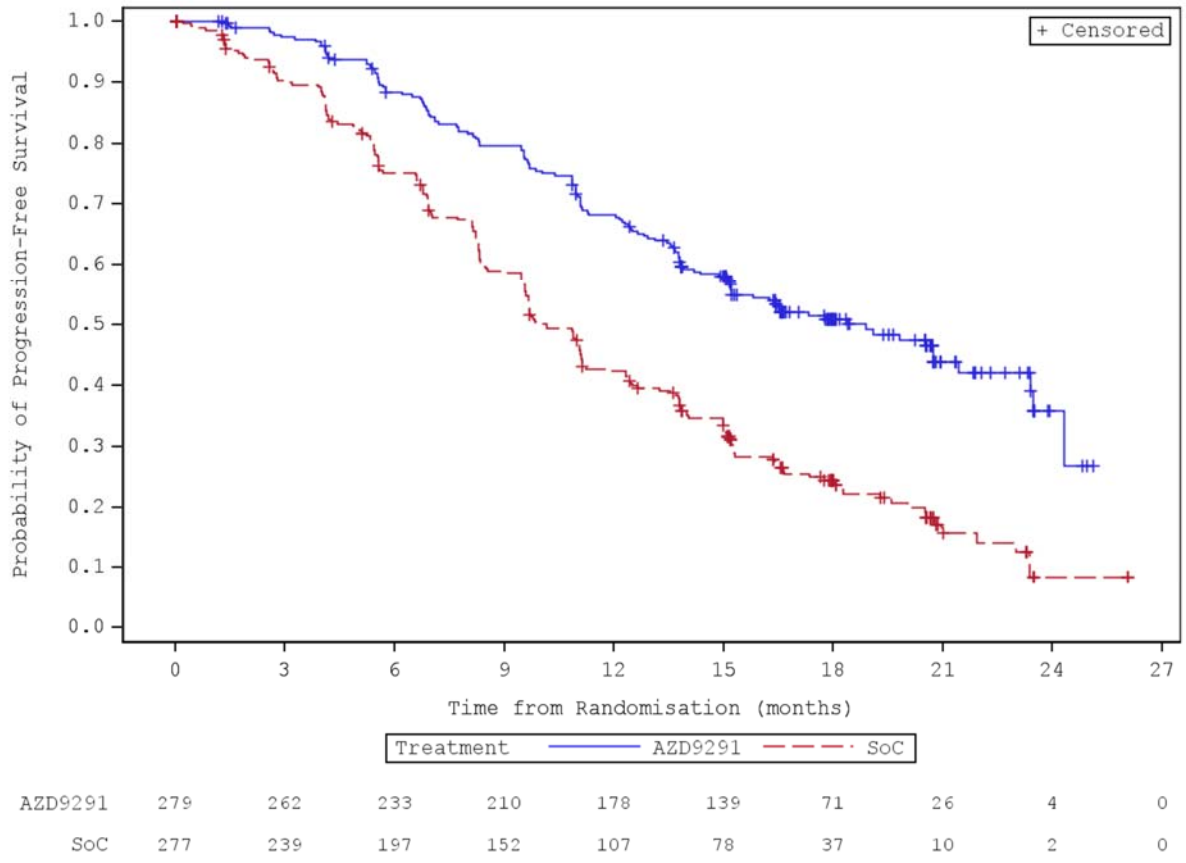
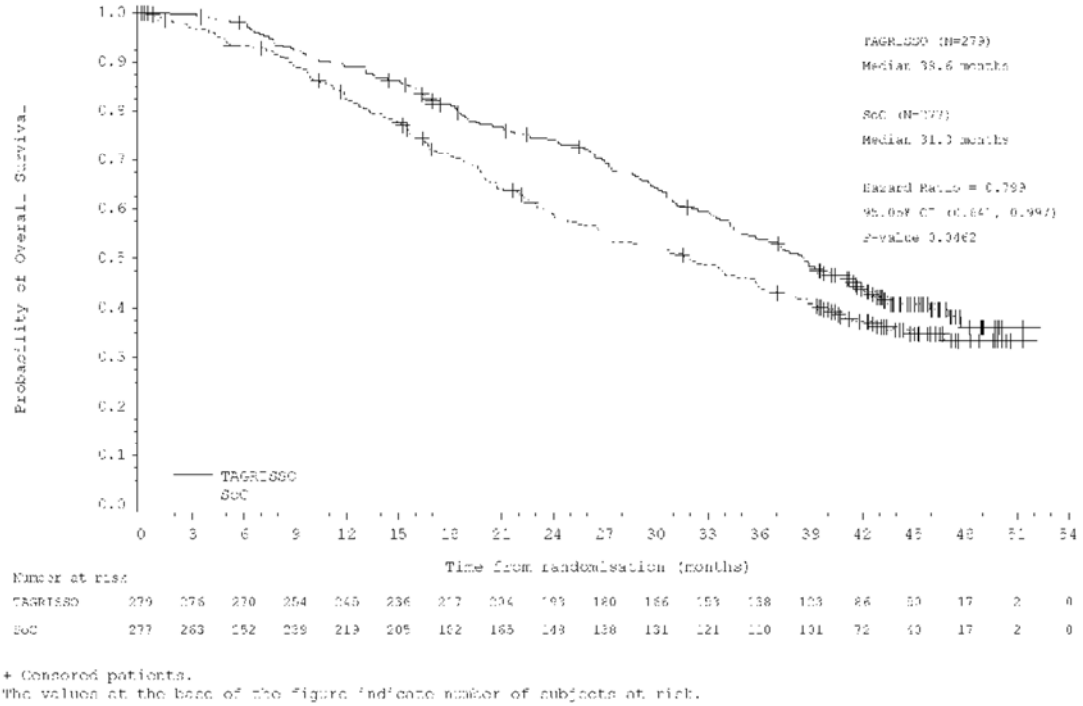


Figure 2. Kaplan-Meier Curves of Overall Survival in FLAURA



+ 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 6. EGFR mutation type (Ex19del or L858R) and ethnicity (Asian or non-Asian) was generally balanced within this analysis between the treatment arms. CNS efficacy by RECIST v1.1 in FLAURA demonstrated a statistically significant improvement in CNS PFS (HR=0.48, 95% CI 0.26, 0.86; P=0.014).

Table 6. CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in FLAURA

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

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

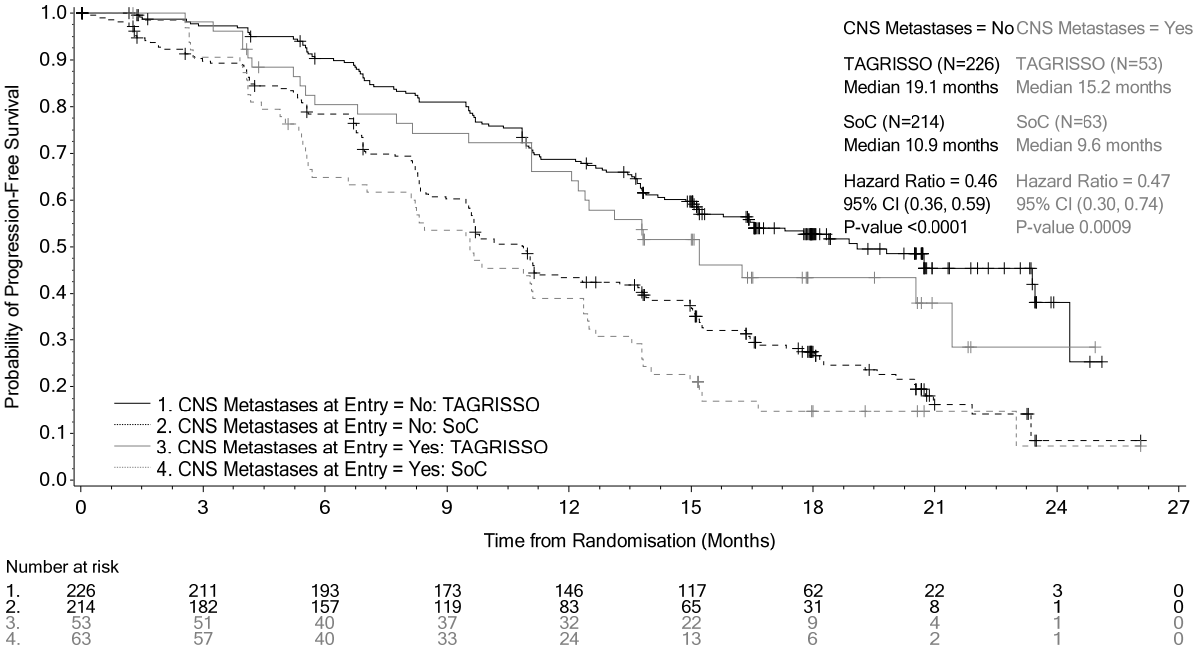
A HR< 1 favours TAGRISSO, an Odds ratio of >1 favours TAGRISSO

[1] CNS PFS, ORR and DoR determined by RECIST v1.1by 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

† Nominally statistically significant

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 3. Irrespective of CNS lesion status at study entry, patients in the TAGRISSO arm demonstrated an efficacy benefit over those in the EGFR TKI comparator arm.

Figure 3 Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in FLAURA



Number at risk

1.	226	211	193	173	146	117	62	22	3	0
2.	214	182	157	119	83	65	31	8	1	0
3.	53	51	40	37	32	22	9	4	1	0
4.	63	57	40	33	24	13	6	2	1	0

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

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

Patient Reported Outcomes (PRO)

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

Key lung cancer symptoms analysis

Data collected from baseline up to month 9 showed similar improvements in TAGRISSO and EGFR TKI comparator groups for the five pre-specified primary PRO symptoms (cough, dyspnoea, chest pain, fatigue, and appetite loss) with improvement in cough reaching the established clinically relevant cutoff. Up to month 9 there were no clinically meaningful differences in patient-reported symptoms between TAGRISSO and EGFR TKI comparator groups (as assessed by a difference of ≥ 10 points). Data are presented in Table 7.

Table 7. Mixed Model Repeated Measures – Key lung cancer symptoms - mean change from baseline in TAGRISSO patients compared with EGFR TKI comparator (gefitinib or erlotinib)

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

HRQL and physical functioning improvement analysis

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

Pretreated T790M positive NSCLC patients-AURA3

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

Patients were randomised in a 2:1 (TAGRISSO: platinum-based doublet chemotherapy) ratio to receive TAGRISSO (n=279) or platinum-based doublet chemotherapy (n=140). Randomisation was stratified by ethnicity (Asian and non-Asian). Patients in the TAGRISSO arm received TAGRISSO 80 mg orally once daily until intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Chemotherapy consisted of pemetrexed 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 World Health Organization (WHO) performance status of 0 or 1. Fifty-four percent (54%) of patients had extra-thoracic visceral metastases, including 34% with CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases) and 23% with liver metastases. Forty-two percent (42%) of patients had metastatic bone disease.

AURA3 demonstrated a statistically significant improvement in PFS in the patients treated with TAGRISSO compared to chemotherapy. Efficacy results from AURA3 by investigator assessment are summarised in Table 8, and the Kaplan-Meier curve for PFS is shown in Figure 4. 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 8. Efficacy results from AURA3 by investigator assessment

Efficacy Parameter	**TAGRISSO (N=279)**	**Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=140)**
Progression-Free Survival		
Number of Events (% maturity)	140 (50)	110 (79)
Median, Months (95% CI)	10.1 (8.3, 12.3)	4.4 (4.2, 5.6)
HR (95% CI) ; P-value	0.30 (0.23,0.41) ; P < 0.001	
Overall Survival (OS)[1]		
Number of Deaths (% maturity)	188 (67.4)	93 (66.4)
Median OS, Months (95% CI)	26.8 (23.5, 31.5)	22.5 (20.2, 28.8)
HR (95.56% CI); P-value	0.87 (0.67, 1.13); P= 0.277	
Objective Response Rate[2]		
Number of responses, Response Rate (95% CI)	197 71% (65, 76)	44 31% (24, 40)
Odds ratio (95% CI) ; P-value	5.4 (3.5, 8.5); P <0.001	
Duration of Response (DoR)		
Median, Months (95% CI)	9.7 (8.3, 11.6)	4.1 (3.0, 5.6)

HR=Hazard Ratio; CI=confidence interval; OS = Overall Survival

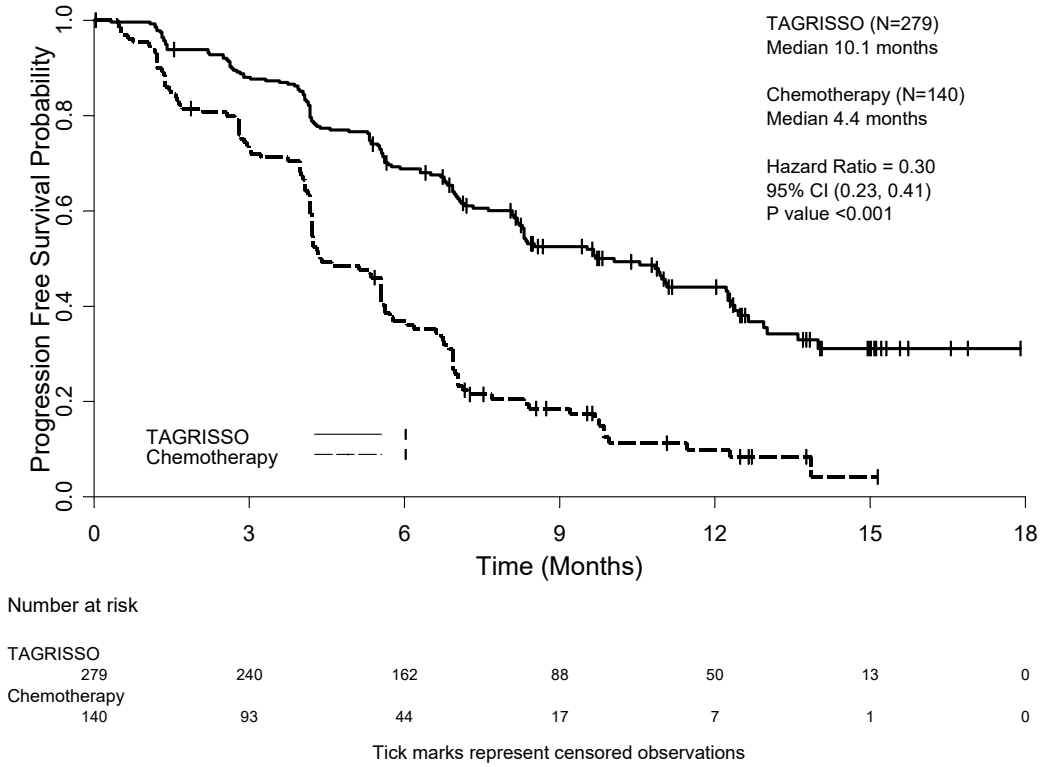
All efficacy results based on RECIST investigator assessment

A HR< 1 favours TAGRISSO

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

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

Figure 4. Kaplan-Meier Curves of Progression-Free Survival as assessed by investigator in AURA3



Number at risk

TAGRISSO						
279	240	162	88	50	13	0
Chemotherapy						
140	93	44	17	7	1	0

Tick marks represent censored observations

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

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

<u>CNS metastases efficacy data in AURA3 study</u>

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 summarized in Table 9.

Table 9. CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in AURA3

Efficacy Parameter	TAGRISSO	Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin)
CNS Objective Response Rate[1]		
CNS response rate % (n/N) (95% CI)	70% (21/30) (51, 85)	31% (5/16) (11, 59)
Odds ratio (95% CI); P-value	5.1 (1.4, 21); p=0.015	
CNS Duration of Response[2]		
Median, 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[3]	N=75	N=41
Number of Events (% maturity)	19 (25)	16 (39)
Median, Months (95% CI)	11.7 (10, NC)	5.6 (4.2, 9.7)
HR (95% CI); P value	0.32 (0.15, 0.69); p=0.004	

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

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

3 CNS Progression Free Survival determined by RECIST v1.1by 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

NC=non-calculable; HR< 1 favours TAGRISSO

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 5 and Table 10.

Figure 5. Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in AURA3

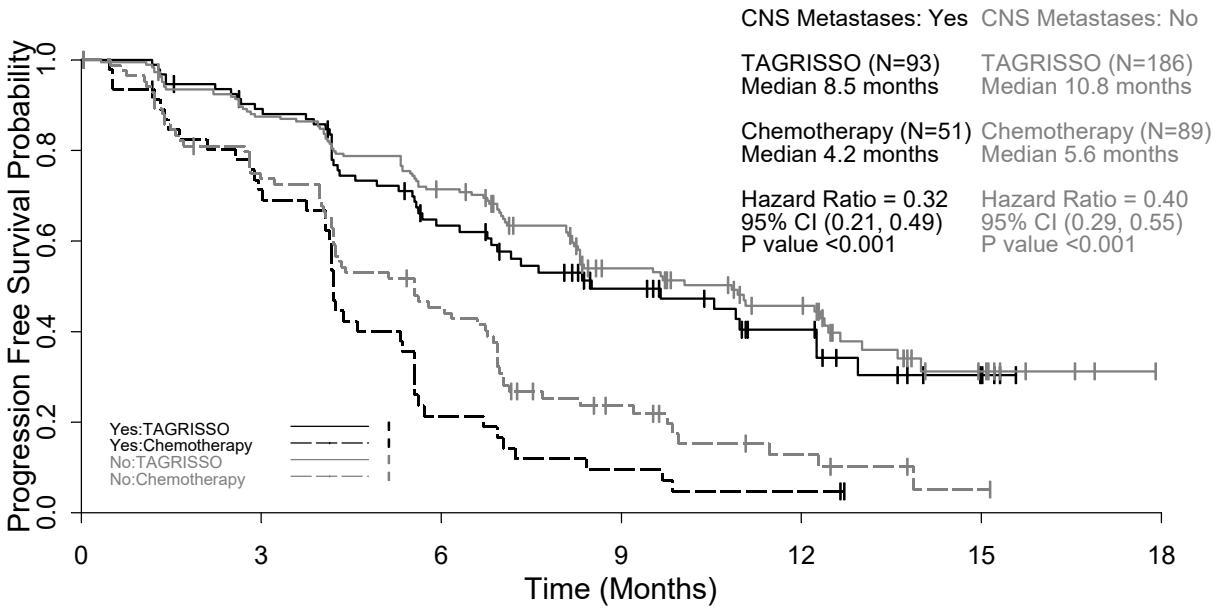


Table 10. PFS by CNS metastases at study entry based on investigator assessment (full analysis set) in AURA3

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

Baseline characteristics of the overall study population (AURAex and AURA2) were as follows: median age 63 years, 13% of patients were ≥75 years old, female (68%), White (36%), Asian (60%). All patients received at least one prior line of therapy. Thirty-one percent (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 World Health Organization (WHO) performance status of 0 or 1. Fifty-nine percent (59%) of patients had extra-thoracic visceral metastasis including 39% with CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery and/or prior radiotherapy to CNS metastases) and 29% with liver metastases. Forty-seven percent (47%) of patients had metastatic bone disease. The median duration of follow up for PFS was 12.6 months.

In the 411 pre-treated EGFR T790M mutation positive patients, the ORR by 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 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.

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.

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

Carcinogenicity

Carcinogenicity studies have not been performed with osimertinib.

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).

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 TAGRISSO 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: (09) 306 5650

9. DATE OF FIRST APPROVAL

5 October 2017

9. DATE OF REVISION OF TEXT

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Changes in contractility section – minor text adjustments to improve clarity for LVEF changes
4.8	Cutaneous vasculitis added to Table 2 Onychalgia is added to the footnote of Table 3 and 4