AUSTRALIAN PRODUCT INFORMATION

TAGRISSO®

osimertinib mesilate tablets

1 NAME OF THE MEDICINE

Osimertinib mesilate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains either 40 mg or 80 mg of osimertinib as the mesilate salt.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

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

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TAGRISSO is indicated:

- as adjuvant therapy after tumour resection in patients with non-small cell lung cancer (NSCLC) whose tumours have activating epidermal growth factor receptor (EGFR) mutations, as detected by a validated test.

- for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have activating EGFR mutations, as detected by a validated test.

- for the treatment of patients with locally advanced or metastatic NSCLC that is EGFR T790M mutation-positive, as detected by a validated test.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Patient selection
Select patients for adjuvant treatment of NSCLC based on the presence of an activating EGFR mutation in tumour tissue DNA using a validated test. Only patients with exon 19 deletions or exon 21 L858R mutations were included in the pivotal study (see Section 5.1, Pharmacodynamic properties – Clinical trials).

Select patients for the first line treatment of locally advanced or metastatic NSCLC based on the presence of an activating EGFR mutation in tumour tissue DNA or circulating tumour DNA (ctDNA, obtained from a plasma sample) using a validated test. Only patients with exon 19 deletions or exon 21 L858R mutations were included in the pivotal study (see Section 5.1, Pharmacodynamic properties – Clinical trials).

Select patients for the treatment of locally advanced or metastatic NSCLC based on the presence of a T790M EGFR mutation in tumour tissue DNA or ctDNA using a validated test (see Section 5.1, Pharmacodynamic properties – Clinical trials).

If a plasma-based ctDNA test is used and the result is negative, this does not rule out the presence of an activating mutation: follow-up with a tissue test if possible.

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

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

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

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

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.

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 drug reactions are provided in Table 1.

Table 1 Dose adjustment information for adverse drug reactions[a]

Target Organ	Adverse Drug Reaction	Dose Modification
Pulmonary[b]	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue treatment
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 drug reaction	Withhold treatment for up to 3 weeks
	If Grade 3 or higher adverse drug 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 drug reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue treatment

[a] Adverse drug reaction grades refer to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
[b] Refer to Section 4.4, Special warnings and precautions for use for further details.

Strong CYP3A inducers

If co-administration of TAGRISSO with a strong CYP3A inducer can't be avoided, 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. See Section 4.5, Interactions with other medicines and other forms of interactions.

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

Paediatric and adolescent patients
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 PK analysis indicated that age did not have an impact on the exposure of osimertinib and hence, TAGRISSO can be used in adults without regard to age.

Hepatic impairment
Based on clinical studies and population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild hepatic impairment (Child Pugh A) or moderate hepatic impairment (Child Pugh B). 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 adjustment is recommended in patients with mild, moderate or severe renal impairment. As there are limited data in patients with severe renal impairment (n=12), caution should be exercised when treating these patients. As patients with creatinine clearance less than 15 mL/min or on dialysis were not included in the clinical trials, caution should be exercised when treating these patients.

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
Only robust, reliable and sensitive tests with demonstrated utility for the determination of EGFR mutation status should be used to select patients for treatment (see Section 4.2, Dose and method of administration – Patient selection).

Interstitial Lung Disease (ILD)
Interstitial Lung Disease (ILD) or ILD-like adverse events (e.g. pneumonitis) were reported in 3.8% and were fatal in 0.3% (n=5) of the 1479 patients who received TAGRISSO in ADAURA, FLAURA and AURA studies. Most cases improved (16.1%) or resolved (57.1%) 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 11.3% in patients of Japanese ethnicity, 1.6% in patients of non-Japanese Asian ethnicity and 2.5% in non-Asian patients. The median time to onset of ILD or ILD-like adverse events 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 (see Section 4.2, Dose and method of administration – Dose adjustments).

Severe cutaneous reactions
Severe cutaneous reactions have been reported with TAGRISSO including erythema multiforme (EM) and life-threatening reactions such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) (e.g. progressive skin rash often with blisters or mucosal lesions). Treatment with TAGRISSO should be interrupted if the patient develops severe bullous, blistering or exfoliative conditions, and discontinued if SJS or TEN are confirmed.

QTc interval prolongation
Prolongation of the heart rate-corrected QT (QTc) interval occurs in patients treated with TAGRISSO (see sections 4.8 and 5.2, Adverse effects – Description of selected adverse events and Pharmacokinetic properties – Cardiac electrophysiology). When possible, avoid use of TAGRISSO in patients with congenital long QT syndrome. 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 (see 4.2, Dose and method of administration). Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation in combination with any of the following: torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia.

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

In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

Keratitis
Keratitis was reported in 0.7% (n=10) of the 1479 patients treated with TAGRISSO in the ADAURA, FLAURA and AURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist (see Section 4.2, Dose and method of administration). Contact lens use may also be a risk factor for keratitis and ulceration.

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, infection and fatigue. If signs and symptoms suggestive of aplastic anaemia develop, close patient monitoring and drug interruption or discontinuation of TAGRISSO should be considered. TAGRISSO should be discontinued in patients with confirmed aplastic anaemia.

Use in the elderly
TAGRISSO can be used in adults without regard to age (see Sections 4.2 and 4.8, Dose and method of administration and Adverse effects).

Paediatric use
The safety and efficacy of TAGRISSO in children or adolescents aged less than 18 years have not been established. No data are available (see Section 4.2, Dose and method of administration).

Effects on laboratory tests
See Section 4.8, Adverse effects.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Active substances that may increase osimertinib plasma concentrations
In vitro studies have demonstrated that the phase 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 of 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

Effects on fertility
There are no data on the effect of TAGRISSO on human 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.

Results from animal studies have shown that osimertinib has effects on male and female reproductive organs and could impair fertility.

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 a female fertility study in rats, oral administration of TAGRISSO at 20 mg/kg/day (approximately equal to exposure in humans at 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 treatment-free period.

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.

Use in 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).

In a modified embryofoetal development study in the rat, osimertinib caused embryolethality when administered to pregnant rats prior to embryonic implantation. These effects were seen at a maternally tolerated dose of 20 mg/kg/day where exposure was equivalent to the human exposure at the recommended dose of 80 mg daily (based on total AUC). Exposure at doses of 20 mg/kg and above during organogenesis caused reduced foetal weights. 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).

Use in lactation
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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Overall summary of the safety profile

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

Most adverse events were Grade 1 or 2 in severity. The most commonly reported adverse events were diarrhoea (47%), rash (45%), musculoskeletal pain (36%), nail toxicity (33%), dry skin (32%), stomatitis (26%), fatigue (21%), and cough (20%). Grade 3 or higher adverse events with TAGRISSO 80 mg once daily were reported in 33.1% of patients. In patients treated with TAGRISSO 80 mg once daily, dose reductions due to adverse events occurred in 5.1% of the patients. Discontinuation due to adverse events was 9.9%.

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 lists of adverse drug reactions and adverse events

Adverse drug reactions across studies

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

Adverse drug reactions are listed according to system organ class (SOC) in MedDRA. 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 drug reactions reported in ADAURA, FLAURA and AURA studies[a]

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (all CTCAE grades[b])	Frequency of CTCAE grade 3 or higher[b]
Blood and lymphatic system disorders	Aplastic anaemia	Rare (0.07%)	0.07%
Respiratory, thoracic and mediastinal disorders	Epistaxis	Common (5.3%)	0%
	Interstitial lung disease[e]	Common (3.8%)[m]	1.1 %
Gastrointestinal disorders	Diarrhoea	Very common (47%)	1.4%
	Stomatitis[n]	Very common (24%)	0.5%
Eye disorders	Keratitis[g]	Uncommon (0.7%)	0.1%
Skin and subcutaneous tissue disorders	Rash[c]	Very common (45%)	0.7%
	Paronychia[h]	Very common (33%)	0.4%
	Dry skin[d]	Very common (32%)	0.1%
	Pruritus[i]	Very common (17%)	0.1%
	Alopecia	Common (4.6%)	0%
	Urticaria	Common (1.9%)	0.1%
	Skin hyperpigmentation[j]	Uncommon (0.8%)	0%
	Palmar-plantar erythrodysaesthesia syndrome	Common (1.7%)	0%
	Erythema multiforme[k]	Uncommon (0.3%)	0%
Investigations	Blood creatine phosphokinase increased	Common (1.6%)	0.3%
	QTc interval prolongation[l]	Uncommon (0.8%)	
Findings based on test results	Leukocytes decreased[f]	Very common (65%)	1.2%

presented as CTCAE grade shifts	Lymphocytes decreased[f]	Very common (62%)	6.1%
	Platelet count decreased[f]	Very common (53%)	1.2%
	Neutrophils decreased[f]	Very common (33%)	3.2%
	Blood creatinine increased[f]	Common (9.4%)	0%

a Data is pooled from ADAURA, FLAURA and AURA (AURA3, AURAex, AURA2 and AURA1) studies; only events for patients receiving at least one dose of TAGRISSO as their randomised treatment are summarised.
b National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
c Includes: Rash, rash generalised, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, rash maculovesicular, rash morbilliform, rash vesicular, rash follicular, acne pustular, erythema, folliculitis, eyelid folliculitis, acne, dermatitis acneiform, drug eruption, skin erosion, pustule.
d Includes: Dry skin, skin fissures, xerosis, and eczema, xeroderma.
e Includes: Interstitial lung disease, lung disorder, pneumonitis, diffuse alveolar damage, pulmonary fibrosis, alveolitis, idiopathic pulmonary fibrosis, acute interstitial pneumonitis, and pulmonary toxicity, organising pneumonia.
f Represents the incidence of laboratory findings, not of reported adverse drug reactions.
g Includes: Keratitis, punctate keratitis, corneal erosion, corneal epithelium defect, corneal defect.
h Includes: Nail bed disorders, 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 Includes: Pruritus, pruritus generalised, eyelid pruritus.
j Cases of erythema dyschromicum perstans have been reported in the post-marketing setting.
k Five of the 1479 patients in the ADAURA, AURA and FLAURA studies reported erythema multiforme.
l Represents the incidence of patients who had a QTcF prolongation >500msec.
m 5 CTCAE grade 5 events (fatal) were reported.
n Includes: Stomatitis, mouth ulceration.

Adverse events in ADAURA

Serious adverse events were reported in 16% of patients treated with TAGRISSO. The most common serious adverse event (≥1%) was pneumonia (1.5%). Adverse events leading to dose reductions occurred in 9% of patients treated with TAGRISSO. The most frequent adverse events leading to dose reductions or interruptions were diarrhoea (4.5%), stomatitis (3.9%), nail toxicity (1.8%) and rash (1.8%). Adverse events leading to permanent discontinuation occurred in 11% of patients treated with TAGRISSO. The most frequent adverse events leading to discontinuation of TAGRISSO were interstitial lung disease (2.7%), and rash (1.2%).

Table 3 and Table 4 summarise the most common adverse events and laboratory abnormalities that occurred in ADAURA.

Table 3 Adverse events reported in at least 10% of patients who received TAGRISSO in the ADAURA study[a]

Adverse Event	TAGRISSO (N=337)		PLACEBO (N=343)	
	All Grades (%)	Grade 3 or higher[b] (%)	All Grades (%)	Grade 3 or higher[b] (%)
Gastrointestinal Disorders				
Diarrhoea[c]	47	2.4	20	0.3
Stomatitis[d]	28	1.8	6	0
Abdominal pain[e]	12	0.3	7	0
Skin Disorders				
Rash[f]	39	0.3	19	0
Nail toxicity[g]	37	0.9	3.8	0
Dry skin[h]	29	0.3	7	0
Pruritus[i]	19	0	9	0
Skin hyperpigmentation	1.8	0	0	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough[j]	19	0	19	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[k]	18	0.3	25	0.3
Infection and Infestation Disorders				
Nasopharyngitis	14	0	10	0
Upper respiratory tract infection	13	0.6	10	0
Urinary tract infection[l]	10	0.3	7	0
General Disorders and Administration Site Conditions				
Fatigue[m]	13	0.6	9	0.3
Nervous System Disorders				
Dizziness[n]	10	0	9	0
Metabolism and Nutrition Disorders				
Decreased appetite	13	0.6	3.8	0

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]NCI CTCAE v4.0.

[b]All events were grade 3.

[c]Includes diarrhoea, colitis, enterocolitis, enteritis.

[d]Includes stomatitis and mouth ulceration.

[e]Includes abdominal discomfort, abdominal pain, abdominal lower pain, abdominal upper pain, epigastric discomfort, hepatic pain.

[f]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.

[g]Includes 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.

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

[i]Includes pruritus, pruritus generalised, eyelid pruritus.

[j]Includes cough, productive cough, upper-airway cough syndrome
[k]Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain.
[l]Includes cystitis, urinary tract infection, and urinary tract infection bacterial.
[m]Includes asthenia, fatigue
[n]Includes dizziness, vertigo, and vertigo positional.

Clinically relevant adverse drug reactions in ADAURA in <10% of patients receiving TAGRISSO were alopecia (6%), epistaxis (6%), interstitial lung disease (3%), palmar-plantar erythrodysaesthesia syndrome (1.8%), urticaria (1.5%), keratitis (0.6%), QTc interval prolongation (0.6%), and erythema multiform (0.3%). QTc interval prolongation represents the incidence of patients who had a QTcF prolongation >500msec.

Table 4 Laboratory abnormalities worsening from baseline in at least 20% of patients in ADAURA

Laboratory Abnormality[a,b]	TAGRISSO (N=337)		PLACEBO (N=343)	
	All Grades (%)	Grade 3 or Grade 4 (%)	All Grades (%)	Grade 3 or Grade 4 (%)
Hematology				
Leukopenia	54	0	25	0
Thrombocytopenia	47	0	7	0.3
Lymphopenia	44	3.4	14	0.9
Neutropenia	26	0.6	10	0.3

[a]NCI CTCAE v4.0
[b]Based on the number of patients with available follow-up laboratory data

Laboratory abnormalities in ADAURA that occurred in <20% of patients receiving TAGRISSO was increased blood creatinine (10%) and blood CPK increased (3.3%).

Adverse drug reactions in FLAURA

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

MedDRA SOC	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
NCI Grade[b]	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
MedDRA Preferred Term				
Respiratory, thoracic and mediastinal disorders				
Epistaxis	6.1	0	5.1	0
Interstitial lung disease[c]	3.9	1.1	2.2	1.4

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[d]	0.4	0	1.4	0
Gastrointestinal disorders				
Diarrhoea[e]	58	2.2	57	2.5
Stomatitis[f]	32	0.7	22	1.1
Skin and subcutaneous tissue disorders				
Rash[g]	58	1.1	78	6.9
Dry skin[h]	36	0.4	36	1.1
Paronychia[i]	35	0.4	33	0.7
Pruritus[j]	17	0.4	17	0
Alopecia	7.2	0	13	0
Urticaria	2.2	0.7	0.4	0
Palmar-plantar erythrodysaesthesia syndrome	1.4	0	2.5	0
Skin hyperpigmentation	0.4	0	1.1	0
Investigations				
QTc interval prolongation[k]	1.1		0.7	
Blood creatinine phosphokinase increased	0.4		0.4	
(Findings based on test results presented as CTCAE grade shifts)				
Leukocytes decreased[l]	72	0.4	31	0.4
Lymphocytes decreased[l]	63	5.6	36	4.2
Platelet count decreased[l]	51	0.7	12	0.4

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				
Neutrophils decreased[l]	41	3.0	10	0
Blood creatinine increased[l]	8.8	0	6.7	0.4

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

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

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

[c] Includes: Interstitial lung disease, pneumonitis.

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

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

[f] Includes: 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 drug reactions.

Adverse drug reactions in AURA3

Table 6 Adverse drug reactions reported in AURA3[a] study

MedDRA SOC	TAGRISSO overall frequency (N=279)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) overall frequency (N=136)	
NCI Grade[b]	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
MedDRA Preferred Term				
Respiratory, thoracic and mediastinal disorders				
Epistaxis	5.4	0	1.5	0
Interstitial lung disease[c,d]	3.6	0.4	0.7	0.7
Eye disorders				
Keratitis[e]	1.1	0	0.7	0
Gastrointestinal disorders				
Diarrhoea	41	1.1	11	1.5
Stomatitis[f]	19	0	15	1.5
Skin and subcutaneous tissue disorders				
Rash[g]	34	0.7	5.9	0
Dry skin[h]	23	0	4.4	0
Paronychia[i]	22	0	1.5	0
Pruritus[j]	13	0	5.1	0
Alopecia	3.6	0	2.9	0
Urticaria	2.5	0	1.5	0
Palmar-plantar erythrodysaesthesia syndrome	1.8	0	0.7	0
Skin hyperpigmentation	0.4	0	3.7	0
Investigations				
QTc interval prolongation[k]	1.4		0	

Blood creatinine 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
Platelet count decreased[l]	46	0.7	48	7.4
Neutrophils decreased[l]	27	2.2	49	12
Blood creatinine increase[l]	6.5	0	9.2	0

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

[a] Data is cumulative from AURA3 study; only events for patients receiving at least one dose of TAGRISSO are summarised.

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

[c] Includes: Interstitial lung disease and pneumonitis.

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

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

[f] Includes: Stomatitis, mouth ulceration.

[g] Includes: Rash, rash generalised, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis and dermatitis acneiform, pustule.

[h] Includes: Dry skin, skin fissures, xerosis, eczema.

[i] Includes: 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.

[j] Includes: Pruritus, pruritus generalised, eyelid pruritus.

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

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

Description of selected adverse events

Interstitial lung disease (ILD)

In ADAURA, FLAURA and AURA studies, the incidence of ILD was 11.3% in patients of Japanese ethnicity, 1.6% in patients of non-Japanese Asian ethnicity and 2.5% in non-Asian patients. The median time to onset of ILD or ILD-like adverse events 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 (see Table 2, Findings based on test results presented as CTCAE grade shifts). Dose interruption is required for such events if they are CTCAE grade 3 or higher (see Table 1, Dose adjustment information for adverse drug reactions [Target Organ: other]; Section 4.2, Dose and method of administration).

QTc interval prolongation
Of the 1479 patients in ADAURA, FLAURA and AURA studies treated with TAGRISSO 80 mg, 0.8% of patients (n=12) were found to have a QTc greater than 500 msec, and 3.1% of patients (n=46) had an increase from baseline QTc greater than 60 msec. A pharmacokinetic analysis with TAGRISSO predicted a concentration-dependent increase in QTc interval prolongation (see Section 5.2, Pharmacokinetic properties – Cardiac electrophysiology). No QTc-related arrhythmias were reported in ADAURA, 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 3.2% (40/1233) of patients treated with TAGRISSO who had baseline and at least one follow-up LVEF assessment. In a placebo controlled trial (ADAURA), 1.6% (5/312) of patients treated with TAGRISSO and 1.5% (5/331) of patients treated with placebo experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%. 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 patients
In ADAURA, FLAURA and AURA (n = 1479), 43% of patients were 65 years of age and older, and 12% were 75 years of age and older. Compared with younger subjects (<65), exploratory analysis suggested that more subjects ≥65 years old had adverse events that led to study drug dose modifications (interruptions or reductions) (32% versus 21%). The types of adverse events reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse events compared to younger patients (35% versus 27%). No overall differences in efficacy were observed between these subjects and younger subjects.

Postmarket experience
In addition to those seen in clinical trials, the following adverse drug reactions have been reported during post-approval use of TAGRISSO. Because 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.

Skin and subcutaneous tissue: Stevens-Johnson syndrome, toxic epidermal necrolysis, cutaneous vasculitis.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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 information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Osimertinib 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 common in NSCLC. Inhibitory activity at uncommon mutant forms of EGFR in NSCLC (G719A/C/S, L747S, S768I, L861Q [single or double]) has also been shown.

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 (EGFRm) and T790M mutant non-small cell lung cancer (NSCLC) cell lines (apparent IC_{50}s from 6 nM to 54 nM against phospho-EGFR) (see Section 5.2, Pharmacokinetics). 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 osimertinib leads to tumour shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumour models. Osimertinib also showed significant anti-tumour activity, associated with increased survival, in a mouse brain xenograft metastasis model (PC9; exon 19 del).

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 osimertinib was identified. Over the same dose range, increased exposure led to increased probability of adverse drug reactions, specifically rash, diarrhoea and ILD.

Clinical trials

Adjuvant treatment of EGFR mutation positive NSCLC – ADAURA

The efficacy and safety of TAGRISSO for the adjuvant treatment of patients with EGFR mutation-positive NSCLC after complete tumour resection (with or without prior adjuvant chemotherapy) was demonstrated in a randomised, double-blind, placebo-controlled study (ADAURA).

To be eligible, patients were required to have stage IB – IIIA NSCLC (according to American Joint Commission on Cancer [AJCC] 7th edition) that was predominantly of non-squamous histology and that harboured an EGFR exon 19 deletions or exon 21 L858R substitution mutations. EGFR mutations were identified prospectively from tumour tissue in a central laboratory by the cobas® EGFR Mutation Test. Patients with clinically significant uncontrolled cardiac disease, with a prior history of ILD/pneumonitis, or who had received prior treatment with an EGFR kinase inhibitor were not eligible.

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

The primary efficacy outcome measure was the hazard ratio (HR) of disease-free survival (DFS; defined as reduction in the risk of disease recurrence or death), determined by investigator assessment. Additional efficacy outcome measures included DFS rate, hazard ratio of overall survival (OS), OS rate, and time to deterioration in health-related quality of life (HRQoL) 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 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 (27% IB; 70% II; 79% IIIA).

ADAURA demonstrated a statistically significant and clinically meaningful difference in DFS for patients treated with TAGRISSO compared to patients treated with placebo. Overall survival (OS) data were not mature at the time of the DFS analysis.

Efficacy results from ADAURA are summarised in Table 7, and the Kaplan-Meier curve for DFS in stage II-IIIA patients and in the overall population (IB-IIIA) is shown in Figure 1 and Figure 2, respectively.

Table 7 Efficacy results in ADAURA by investigator assessment

	Stage II-IIIA population[a]		**Overall population (stage IB-IIIA)[b]**	
	TAGRISSO (N=233)	**Placebo (N=237)**	**TAGRISSO (N=339)**	**Placebo (N=343)**
Disease-free survival (investigator-assessed)				
Number of events (%)	26 (11)	130 (55)	37 (11)	159 (46)
Recurrent disease (%)	26 (11)	129 (54)	37 (11)	157 (46)
Deaths (%)	0	1 (0.4)	0	2 (0.6)
Median, months (95% CI)	NC (38.8, NC)	19.6 (16.6, 24.5)	NC (NC, NC)	27.5 (22.0, 35.0)
HR (95% CI); p-value[c]	0.17 (0.12, 0.23); <0.0001		0.20 (0.15, 0.27); <0.0001	

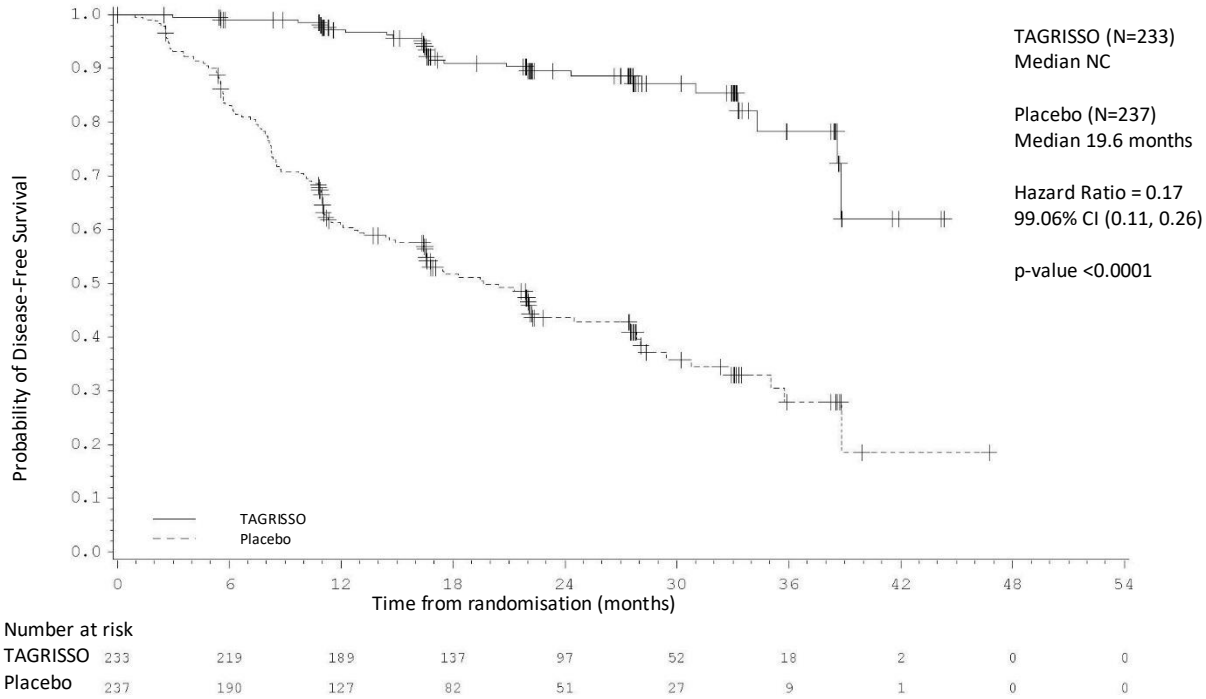
HR = hazard ratio; CI = confidence interval; NC = not calculable

[a] Median follow-up time for DFS in the stage II-IIIA population was 22.1 months for patients receiving TAGRISSO and 14.9 months for patients receiving placebo.

[b] Median follow-up time for DFS in the overall population (stage Ib-IIIA) was 22.1 months for patients receiving TAGRISSO and 16.6 months for patients receiving placebo.

[c] HR (Pike estimator) and p-value (log-rank test) were both stratified by race (Asian vs non-Asian), mutation status (Ex19del vs L858R), and pTNM staging

Figure 1 **Kaplan-Meier curve of disease-free survival (stage II-IIIA population) by investigator assessment in ADAURA**

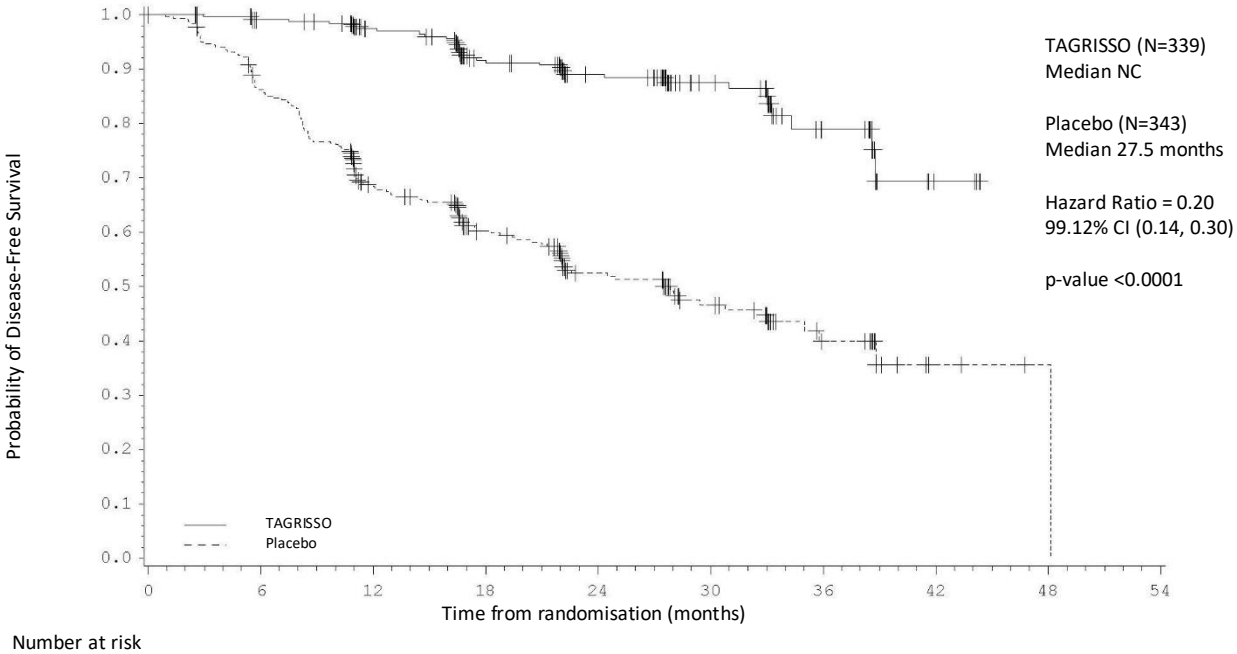


Number at risk

TAGRISSO	233	219	189	137	97	52	18	2	0	0
Placebo	237	190	127	82	51	27	9	1	0	0

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

Figure 2 **Kaplan-Meier curve of disease-free survival (overall population) by investigator assessment in ADAURA**



Number at risk

TAGRISSO	339	313	272	208	138	74	27	5	0	0
Placebo	343	287	207	148	88	53	20	3	1	0

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

In an exploratory analysis of site(s) of relapse, the proportion of patients with CNS involvement at the time of disease recurrence was 5 patients (1.5%) on the TAGRISSO arm and 34 patients (10%) on the placebo arm.

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).

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

The efficacy of TAGRISSO was demonstrated in a randomised, double-blind, active-controlled study (FLAURA) in patients with EGFR mutation-positive locally advanced or metastatic NSCLC, who had not received previous systemic treatment for advanced disease. 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), prospectively identified by central testing (using the cobas® EGFR Mutation Test) or locally in an accredited laboratory. Patients with CNS metastases not requiring steroids and with stable neurological status for at least two weeks after completion of definitive surgery or radiotherapy were eligible to enrol. Patients were assessed at the investigator's discretion for CNS metastases if they had a history of, or suspected, CNS metastases at study entry.

Patients were randomised 1:1 to receive either TAGRISSO 80 mg orally once daily or to receive an EGFR TKI comparator (gefitinib 250 mg orally once daily or erlotinib 150 mg orally once daily), until disease progression or unacceptable toxicity. Randomisation was stratified by EGFR mutation type (Ex19del or L858R) and ethnicity (Asian or non-Asian). Patients randomised to the control arm were offered TAGRISSO at the time of disease progression if tumour samples tested positive for the EGFR T790M mutation. The major efficacy outcome measure was progression-free survival (PFS), assessed by investigator. Additional efficacy outcome measures included overall survival (OS) and overall response rate (ORR), patient-reported outcomes (PRO) and blinded independent central review (BICR) assessment of central nervous system (CNS) ORR and DoR.

A total of 556 patients were randomised to TAGRISSO (n=279) or to control (gefitinib n=183; erlotinib n=94). The median age was 64 years (range 26-93 years); 54% were < 65 years of age; 63% were female; 62% were Asian and 64% were never smokers. Baseline WHO performance status was 0 (41%) or 1 (59%); 5% had Stage IIIb and 95% had Stage IV; and 7% received prior systemic cytotoxic chemotherapy as neoadjuvant or adjuvant therapy. EGFR tumour mutation was Ex19del in 63% and L858R in 37% of patients; 5 patients (<1%) also had a concomitant de novo T790M mutation. EGFR mutation status was confirmed centrally using the cobas EGFR Mutation Test in 90% of patients. Of those randomised to investigator's choice of erlotinib or gefitinib, 55 patients (20%) received TAGRISSO as the next line of antineoplastic therapy.

At the time of the primary efficacy analysis, the median follow-up time for PFS was 15.0 months for patients receiving TAGRISSO and 9.7 months for patients receiving an EGFR TKI comparator. TAGRISSO demonstrated a statistically significant improvement in PFS compared to erlotinib or gefitinib (see Table 8 and Figure 3). The final analysis of overall survival (58% maturity) demonstrated a statistically significant improvement and a clinically meaningful longer median survival time in patients randomized to TAGRISSO compared to EGFR TKI comparator (see Table 8 and Figure 4). The Median survival follow-up time was 35.8 months for patients receiving TAGRISSO and 27.0 months for patients receiving EGFR TKI comparator. A greater proportion of patients treated with TAGRISSO were alive at 12, 18, 24 and 36 months (89%, 81%, 74% and 54%, respectively) compared to patients treated with EGFR TKI comparator (83%, 71%, 59% and 44%, respectively).

Table 8 Efficacy results from FLAURA by investigator assessment

	TAGRISSO (N=279)	**EGFR TKI comparator (gefitinib or erlotinib) (N=277)**
Progression-free survival (PFS)		
Number of events (62% maturity)	136 (49)	206 (74)
Progressive disease (%)	125 (45)	192 (69)
Death[a] (%)	11 (4)	14 (5)
Median PFS, months (95% CI)	18.9 (15.2, 21.4)	10.2 (9.6, 11.1)
HR (95% CI)[b,c], p-value[b,d]	0.46 (0.37, 0.57), p<0.0001	
Overall survival (OS)		
Number of deaths (58% maturity)	155 (56)	166 (60)
Median OS in months (95% CI)	38.6 (34.5, 41.8)	31.8 (26.6, 36.0)
HR (95.05% CI); p-value	0.799 (0.641, 0.997); p=0.0462	
Objective response rate (ORR)[e]		
ORR, % (95% CI)[b]	77 (71,82)	69 (63, 74)
Complete response rate	2%	1%
Partial response rate	75%	68%

	TAGRISSO (N=279)	EGFR TKI comparator (gefitinib or erlotinib) (N=277)
Duration of response (DOR)[e]		
Median, months (95% CI)	17.6 (13.8, 22.0)	9.6 (8.3, 11.1)

HR=Hazard Ratio; CI=Confidence Interval

[a] Without documented radiological disease progression

[b] Stratified by ethnicity (Asian vs. non-Asian) and mutation status (Ex19del vs. L858R)

[c] Pike estimator

[d] Stratified log-rank test

[e] Confirmed responses

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

Figure 3 **Kaplan-Meier curves of progression-free survival as assessed by investigator in FLAURA**

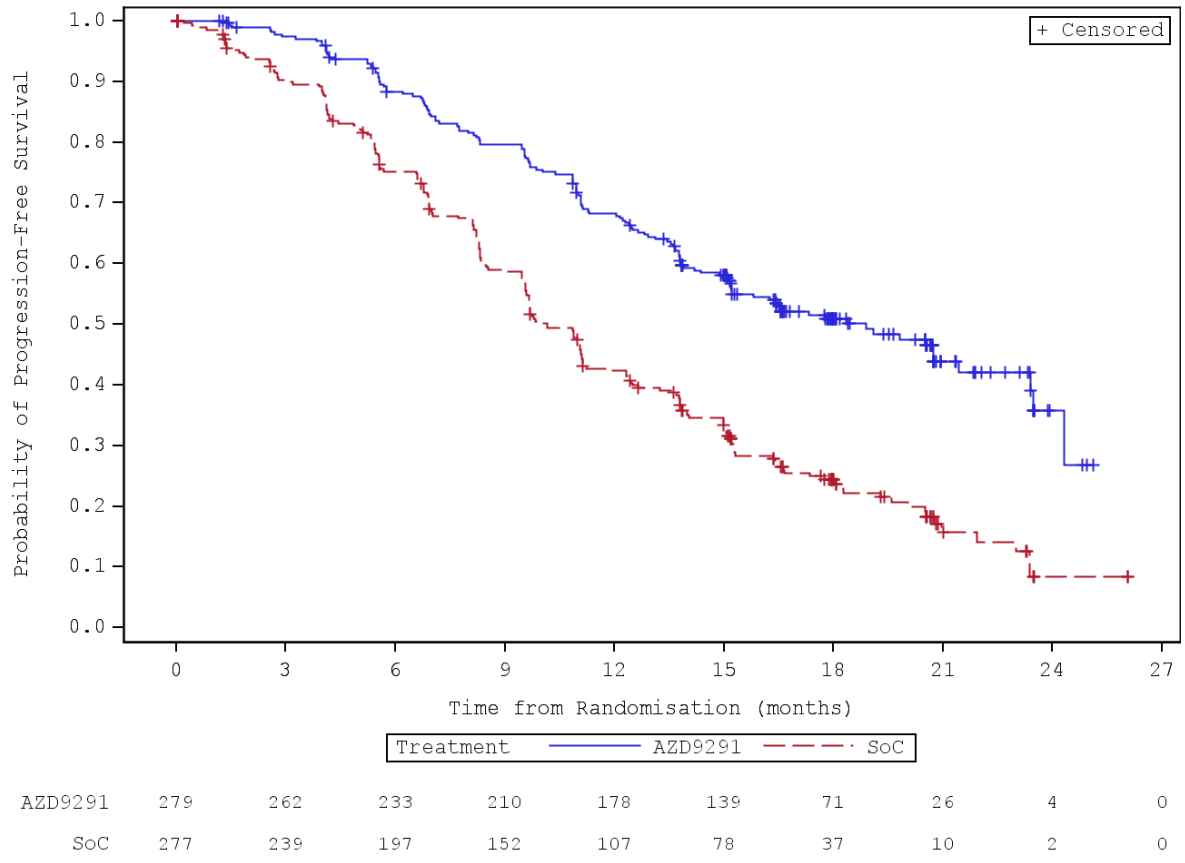
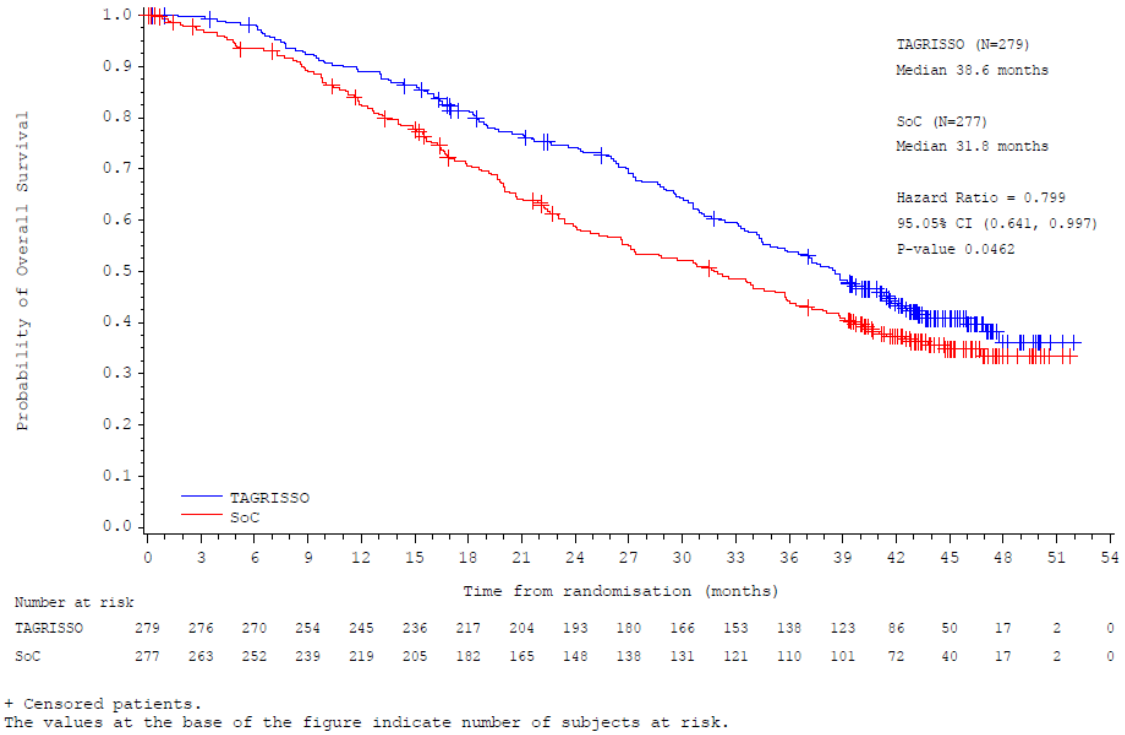


Figure 4 Kaplan-Meier curves of overall survival in FLAURA



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

In a supportive analysis of PFS according to BICR, median PFS was 17.7 months in the TAGRISSO arm compared to 9.7 months in the EGFR TKI comparator arm (HR=0.45; 95% CI: 0.36, 0.57).

CNS metastases efficacy data in FLAURA study

Of 556 patients, 200 patients (36%) had baseline brain scans reviewed by BICR; this included 106 patients in the TAGRISSO arm and 94 patients in the investigator choice of EGFR TKI arm. Of these 200 patients, 128 had at least one measurable or non-measurable lesion identified by BICR. Results of the pre-specified exploratory analysis of CNS PFS by RECIST v1.1 in FLAURA demonstrated a statistically significant improvement in CNS PFS with the median PFS time not reached in the TAGRISSO arm and 13.9 months in the investigator choice of EGFR TKI arm (see Table 9). Of the 128 patients, 41 had measurable CNS lesions at baseline per RECIST v1.1. Results of pre-specified exploratory analyses of CNS ORR and DoR by BICR in the subset of patients with measurable CNS lesions at baseline are summarised in Table 9.

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

	TAGRISSO	EGFR TKI (gefitinib or erlotinib)
CNS PFS[a]		
	N=61	N=67
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 ORR[b,c]		
	N=22	N=19
CNS ORR (%) (95% CI)	77 (55, 92)	63 (38, 84)
Complete response rate (%)	18	0
CNS Duration of Response[b, d]		
	N=22	N=19
Number of responders	17	12
Response Duration ≥6 months (%)	88	50
Response Duration ≥12 months (%)	47	33

[a] According to RECIST v1.1 by CNS BICR (CNS measurable and non-measurable lesions at baseline by BICR)
[b] According to RECIST v1.1 by CNS BICR (CNS measurable lesions at baseline by BICR)
[c] Based on confirmed response.
[d] Based on patients with response only; DoR defined as the time from the date of first documented response (complete response or partial response) until progression or death event.
NC= Not Calculable

Patient-reported outcomes (PRO)

PRO data was collected using the EORTC QLQ-C30 and the EORTC QLQ-LC13 questionnaire tools. From baseline, there was a sustained, clinically relevant improvement in cough and deterioration in diarrhoea in both study arms. No clinically meaningful differences were demonstrated between arms at baseline or during the first 9 months, during which time compliance was generally high (≥70%) and was similar in both arms.

T790M-positive advanced NSCLC

TAGRISSO has not been studied in previously untreated patients within EGFR T790M mutation positive NSCLC.

Previously treated T790M-positive NSCLC patients - AURA3

The efficacy and safety of TAGRISSO for the treatment of patients with locally advanced or metastatic T790M NSCLC whose disease has progressed on or after EGFR TKI therapy, was demonstrated in a randomised, open label, active-controlled Phase 3 study (AURA3). All patients were required to have EGFR T790M mutation positive NSCLC identified by the cobas EGFR mutation test performed in a central laboratory prior to randomisation. The T790M mutation status was also assessed using ctDNA extracted from a plasma sample taken during screening. The primary efficacy outcome was progression-free survival (PFS) as assessed by investigator. Additional efficacy outcome measures included 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 Organisation (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 as assessed by investigator (refer **Table 10** and **Figure 5**). No statistically significant difference in OS was observed between the treatment arms at the final analysis (conducted at 67% maturity), at which time 99 patients randomised to chemotherapy had crossed over to TAGRISSO treatment (refer **Table 10**).

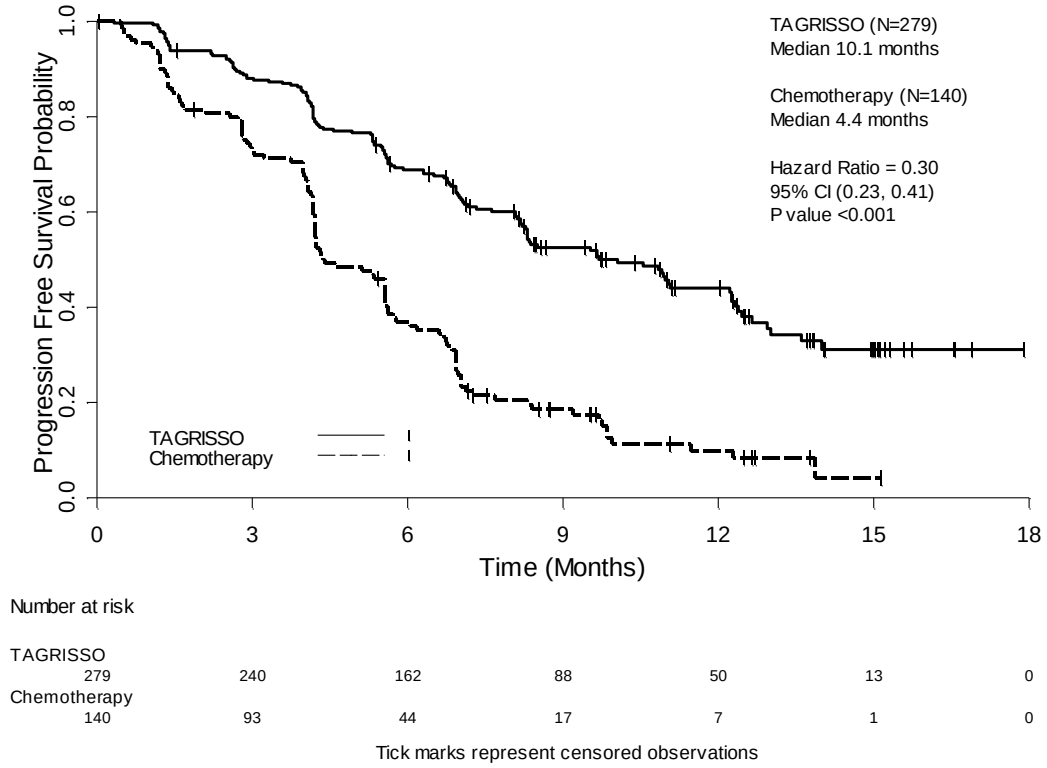
Table 10 Efficacy results from AURA3 by investigator assessment

	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[1]		
Number of Deaths (% maturity)	188 (67.4)	93 (66.4)
Median, 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		
Number of responses, Response Rate (95% CI)	197 71% (65, 76)	44 31% (24, 40)
Complete Response	1%	1%
Partial Response	69%	30%
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
All efficacy results based on RECIST investigator assessment. A HR<1 favours TAGRISSO
[1]The final analysis of overall survival (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).

Figure 5 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 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. The study was not powered for these subgroup analyses.

CNS metastasis efficacy data in AURA3 study

A BICR assessment of CNS efficacy by RECIST v1.1 in patients identified to have CNS metastases on a baseline brain scan are summarised in Table 11.

Table 11 CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in AURA3

	TAGRISSO N=30	**Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) N=16**
CNS objective response rate[1]		
CNS response rate % (95% CI)	57% (37%, 75%)	25% (7%, 52%)
Complete response rate	7%	0%
Partial response rate	50%	25%
CNS duration of response (DOR)[2]		
Median, months (95% CI)	NC (6.0, NC)	5.7 (NC, NC)
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 confirmed response only; DOR defined as the time from the date of first documented response (complete response or partial response, or stable disease ≥6 weeks)
[3] CNS progression free survival determined by RECIST v1.1 by CNS BICR in the full analysis set population (CNS measurable and non-measurable lesions at baseline by BICR): n=75 for TAGRISSO and n=41 for Chemotherapy
NC=non-calculable

Patient -reported outcomes

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

Key lung cancer symptoms analysis

TAGRISSO improved patient-reported lung cancer symptoms compared to chemotherapy by demonstrating a statistically significant difference in mean change from baseline versus chemotherapy during the overall time period from randomisation until 6 months for 5 pre-specified primary PRO symptoms (appetite loss, cough, chest pain, dyspnoea, and fatigue) as shown in Table 12.

Table 12 Mixed Model Repeated Measures – Key lung cancer symptoms - mean change from baseline in TAGRISSO patients compared with chemotherapy

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

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

HRQL and physical functioning improvement analysis

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

Previously treated T790M-positive NSCLC patients - AURAex and AURA2

Two single-arm, open-label clinical studies, AURAex (Phase 2 Extension cohort, (n=201)) and AURA2 (n=210) were conducted in patients with EGFR T790M mutation-positive lung cancer who have progressed on one or more prior systemic 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. 31% (N=129) had received 1 prior line of therapy (EGFR-TKI treatment only, second line, chemotherapy naïve), 69% (N=282) had received 2 or more prior lines. Seventy-two percent of patients were never smokers, 100% of patients had a World Health Organisation (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).

Overall response rates by BCIR 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 characterised 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, Clinical trials), 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 (Vss/F) of osimertinib is 918 L indicating extensive distribution into tissue. Osimertinib is highly plasma protein bound (approximately 95%). Penetration of the blood-brain barrier by osimertinib has been demonstrated in the mouse, rat and cynomolgus monkey, with exposure in the brain approximately 2–3 times higher than for blood (based on C_{max} or AUC).

Metabolism
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.

Excretion
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-gp and BCRP but is not a substrate of the hepatocyte uptake transporters OATP1B1 and OATP1B3.

In vitro, osimertinib does not inhibit OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2-K and OCT2 at clinically relevant concentrations, but does inhibit BCRP (see Section 4.5, Interactions with other medicines and other forms of interactions).

Special populations
In population based pharmacokinetic analyses, no clinically significant relationships were identified between predicted steady state exposure (AUC_{ss}) and patient's age, gender, ethnicity, line of therapy or smoking status. 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 1.5x ULN and any AST), 8 patients with moderate hepatic impairment (total bilirubin between 1.5 times to 3.0 times ULN and any AST) and 1216 patients with normal hepatic function (total bilirubin ≤ULN and AST ≤ULN), osimertinib exposures were similar. There are limited 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. See also section 4.2, Dosage and method of administration.

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– QT 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

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.

Carcinogenicity
Osimertinib showed no carcinogenic potential when administered orally to Tg rasH2 transgenic mice for 26 weeks. Systemic exposure (AUC) in mice at the highest dose tested (10 mg/kg/day) was less than that in patients at the maximum recommended clinical dose. 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. In addition, there was an increased incidence of malignant lymphomas in hemolymphoreticular tissue in male rats at exposures 0.2-times the AUC observed at the recommended clinical dose. The clinical relevance of this finding is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet contains mannitol, microcrystalline cellulose, hyprolose, sodium stearyl fumarate, polyvinyl alcohol, titanium dioxide, purified talc, iron oxide black, iron oxide red, iron oxide yellow and macrogol 3350.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

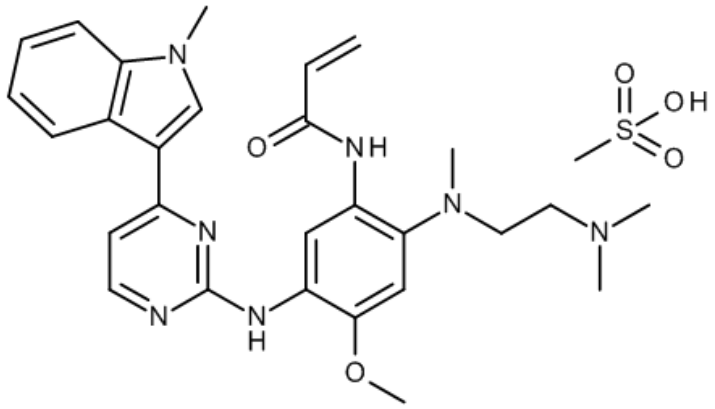
6.7 PHYSICOCHEMICAL PROPERTIES

Osimertinib mesilate is a single crystalline form solid, which is slightly soluble in water (3.1 mg/mL at 37°C) and has pKa values of 9.5 (aliphatic amine) and 4.4 (aniline).

Chemical structure

The chemical name of osimertinib mesilate is: N-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide mesilate salt.

The chemical structure of osimertinib mesilate is:



Molecular formula: $C_{28}H_{33}N_7O_2 \bullet CH_4O_3S$

Molecular weight: 595.71

CAS number

CAS number: 1421373-66-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4.

8 SPONSOR

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2, 4.3, 6.1, 6.7	Editorial changes
4.8	Addition of skin hyperpigmentation adverse drug reaction

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