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1. NAME OF THE MEDICINAL PRODUCT

TAGRISSO 40mg film-coated tablets

TAGRISSO 80mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TAGRISSO 40 mg tablets

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

TAGRISSO 80 mg tablets

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

Excipient with known effect

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

TAGRISSO 40 mg tablets:

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

TAGRISSO 80 mg tablets

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tagrisso as monotherapy is indicated for:

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

4.2 Posology and method of administration

Treatment with TAGRISSO should be initiated by a physician experienced in the use of anticancer therapies.
When considering the use of TAGRISSO, EGFR mutation status in tumour or plasma specimens should be determined using a validated test method (see section 4.4).

Posology

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

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

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

Dose adjustments

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose should be reduced to 40 mg taken once daily.

Dose reduction guidelines for adverse reactions toxicities are provided in Table 1.

Table 1. Recommended dose modifications for TAGRISSO

Target organ	Adverse reaction[a]	Dose modification

Pulmonary	ILD/Pneumonitis	Permanently discontinue TAGRISSO
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue TAGRISSO
Other	Grade 3 or higher adverse reaction	Withhold TAGRISSO for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of TAGRISSO for up to 3 weeks	TAGRISSO may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue TAGRISSO

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

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

Special populations

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

Hepatic impairment

No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin <upper limit of normal (ULN) and aspartate aminotransferase (AST) between 1 to 1.5x ULN or total bilirubin between 1.0 to 1.5xULN and any AST) but caution should be used when administering TAGRISSO to these patients. The safety and efficacy of this medicinal product has not been established in patients with severe hepatic impairment. Until additional data become available, use in patients with moderate or severe hepatic impairment is not recommended (see section 5.2).

Renal impairment

No dose adjustment is recommended in patients with mild and moderate renal impairment. Limited data are available in patients with severe renal impairment. The safety and efficacy of this medicinal product has not been established in patients with end-stage renal disease [creatinine clearance (CLcr) <15

mL/min, calculated by the Cockcroft and Gault equation], or on dialysis. Caution should be exercised when treating patients with severe and end stage renal impairment (see section 5.2).

Paediatric population

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

Method of administration

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

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

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
St. John's wort should not be used together with TAGRISSO (see section 4.5).

4.4 Special warnings and precautions for use

Assessment of EGFR mutation status

When considering the use of TAGRISSO as 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 tests with demonstrated utility for the determination of EGFR mutation status of tumour derived DNA (from a tissue or a 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)

Severe, life-threatening or fatal Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) have been observed in patients treated with TAGRISSO in clinical studies. Most cases improved or resolved with interruption of treatment. Patients with a past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from clinical studies (see section 4.8).

Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) were reported in 3.9% and were fatal in 0.4% of the 1142 patients who received TAGRISSO in FLAURA and AURA studies. The incidence of ILD was 10.4% in patients of Japanese ethnicity, 1.8% in patients of Asian ethnicity and 2.8% in non-Asian patients. (See Section 4.8).

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

Stevens-Johnson syndrome

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

QTc interval prolongation

QTc interval prolongation occurs in patients treated with TAGRISSO. QTc interval prolongation may lead to an increased risk for ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death. No arrhythmic events were reported in FLAURA or AURA studies (see section 4.8). Patients with clinically important abnormalities in rhythm and conduction as measured by resting electrocardiogram (ECG) (e.g. QTc interval greater than 470 ms) were excluded from these studies (see section 4.8).

When possible, the use of osimertinib in patients with congenital long QT syndrome should be avoided. Periodic monitoring with electrocardiograms (ECGs) and electrolytes should be considered in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products that are known to prolong the QTc interval. Treatment should be withheld in patients who develop a QTc interval greater than 500 msec on at least 2 separate ECGs until the QTc interval is less than 481 msec or recovery to baseline if the QTc interval is greater than or equal to 481 msec, then resume TAGRISSO at a reduced dose as described in Table 1. Osimertinib should be permanently discontinued in patients who develop QTc interval prolongation in combination with any of the following: Torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia.

Changes in cardiac contractility

Across clinical 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. 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 Table 1).

Age and body weight

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

Sodium

This medicine contains < 1 mmol sodium (23 mg) per 40 mg or 80 mg tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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

Active substances that may increase osimertinib plasma concentrations

In vitro studies have demonstrated that the Phase I metabolism of osimertinib is predominantly via CYP3A4 and CYP3A5. In a clinical pharmacokinetic study in patients, co-administration with 200 mg itraconazole twice daily (a strong CYP3A4 inhibitor) had no clinically significant effect on the exposure of osimertinib (area under the curve (AUC) increased by 24% and Cmax decreased by 20%). Therefore, CYP3A4 inhibitors are not likely to affect the exposure of osimertinib. Further catalyzing enzymes have not been identified.

Active substances that may decrease osimertinib plasma concentrations

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

Effect of gastric acid reducing active substances on osimertinib

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

Active substances whose plasma concentrations may be altered by TAGRISSO

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

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

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

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

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving TAGRISSO. Patients should be advised to use effective contraception for the following periods after completion of treatment with this medicinal product: at least 2 months for females and 4 months for males. A risk for decreased exposure of hormonal contraceptives cannot be excluded.

Pregnancy

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

Breast-feeding

It is not known whether osimertinib or its metabolites are excreted in human milk. There is insufficient information on the excretion of osimertinib or its metabolites in animal milk. However, osimertinib and its metabolites were detected in the suckling pups and there were adverse effects on pup growth and survival (see section 5.3). A risk to the suckling child cannot be excluded.
Breast-feeding should be discontinued during treatment with TAGRISSO.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Studies in EGFR mutation-positive NSCLC patients

The data described below reflect exposure to TAGRISSO in 1142 patients with EGFR mutation-positive non-small cell lung cancer. These patients received TAGRISSO at a dose of 80 mg daily in two randomised Phase 3 study (FLAURA, first line and AURA3, second line only), 2 single-arm studies (AURAex and AURA2-second line or greater) and one Phase 1 study (AURA1, first-line or greater) (see section 5.1).
Most adverse reactions were Grade 1 or 2 in severity. The most commonly reported adverse drug reactions (ADRs) were diarrhoea (49%) and rash (47%). Grade 3 and Grade 4 adverse events across both studies 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 of 1142 EGFR mutation positive NSCLC patients who received TAGRISSO at a dose of 80 mg daily in the FLAURA, AURA3, AURAex, AURA 2 and AURA1 studies.

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

Table 2. Adverse drug reactions reported in FLAURA and AURA studies[a]

MedDRA SOC	MedDRA term	CIOMS descriptor/ overall frequency (allCTCAE grades) [b]	Frequency of CTCAE grade 3 or higher
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[c]	Common (3.9%)[d]	1.5%
Gastrointestinal disorders	Diarrhoea	Very common (49%)	1.2%
	Stomatitis	Very common (20%)	0.2%
Eye disorders	Keratitis[e]	Uncommon (0.7%)	0.1%
Skin and subcutaneous tissue disorders	Rash[f]	Very common (47%)	0.9%
	Dry skin[g]	Very common (33%)	0.1%
	Paronychia[h]	Very common (31%)	0.3%
	Pruritus[i]	Very common (17%)	0.1%
	Stevens-Johnson syndrome[j]	Rare (0.02%)	

Investigations	QTc interval prolongation[k]	Uncommon (0.9%)	
(findings based on test results presented as CTCAE grade shifts)	Platelet count decreased[l]	Very common (54%)	1.6%
	Leucocytes decreased[l]	Very common (68%)	1.5%
	Lymphocytes decreased[l]	Very common (67%)	7.2%
	Neutrophils decreased[l]	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 summarized.

[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]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, 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, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.

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

[j]One event was 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).

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

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

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

Description of selected adverse reactions

Interstitial lung disease (ILD)

In the FLAURA and AURA studies, the incidence of ILD was 10.4% in patients of Japanese ethnicity, 1.8% in patients of non-Japanese Asian ethnicity and 2.8% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 85 days (see section 4.4).

QTc interval prolongation

Of the 1142 patients in 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 and AURA studies (see sections 4.4 and 5.1).

Gastrointestinal effects

In the FLAURA and AURA studies, diarrhoea was reported in 49% of patients of which 39% were Grade 1 events, 8.0% Grade 2 and 1.2% were Grade 3; no Grade 4 or 5 events were reported. Dose reduction was required in 0.2% of patients and dose interruption in 1.4%. One event (0.1%) led to discontinuation. In FLAURA and AURA3 the median time to onset was 19 days and 22 days respectively, and the median duration of the Grade 2 events was 19 days and 6 days, respectively.

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.

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 reported adverse reactions that led to study drug dose modifications (interruptions or reductions) (13.4% versus 7.6%). The types of adverse events reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (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.

Low body weight

Patients receiving TAGRISSO 80 mg with low body weight (<50 kg) reported higher frequencies of Grade ≥3 adverse events (52% versus 35%) and QTc prolongation (14% versus 4%) than patients with higher body weight (≥50 kg).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by an online form: http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

In TAGRISSO clinical trials limited number of patients were treated with daily doses of up to 240 mg without dose limiting toxicities. In these studies, patients who were treated with TAGRISSO daily doses of 160 mg and 240 mg experienced an increase in the frequency and severity of a number of typical EGFR TKI--induced AEs (primarily diarrhoea and skin rash) compared to the 80-mg dose. There is limited experience with accidental overdoses in humans. All cases were isolated incidents of patients taking an additional daily dose of TAGRISSO in error, without any resulting clinical consequences.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Pharmacodynamic effects

In vitro studies have demonstrated that osimertinib has high potency and inhibitory activity against EGFR across a range of all clinically relevant EGFR sensitising-mutant and T790M mutant 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 wildtype cell lines (apparent IC_{50}s from 480 nM to 1.8 μM against phospho-EGFR). In vivo oral administration of osimertinib lead to tumour shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumour models.

Cardiac electrophysiology

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

Clinical efficacy and safety

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

Patients were randomised 1:1 to receive either TAGRISSO (n=279, 80 mg orally once daily) or EGFR TKI comparator (n=277; gefitinib 250 mg orally once daily or erlotinib 150 mg orally once daily). Randomisation was stratified by EGFR mutation type (Ex19del or L858R) and ethnicity (Asian and 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.

The baseline demographic and disease characteristics of the overall study population were: median age 64 (range 26-93 years), ≥75 years old (14%), female (63%), white (36%), Asian (62%), never smoker (64%), World Health Organization (WHO) performance status 0 or 1 (100%), metastatic bone disease (36%), extra-thoracic visceral metastases (35%), CNS metastases (21%, identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases).

TAGRISSO demonstrated a clinically meaningful and statistically significant improvement in PFS compared to EGFR TKI comparator (median 18.9 months and 10.2 months, respectively, HR=0.46, 95% CI: 0.37, 0.57; P<0.0001). Efficacy results from FLAURA by investigator assessment are summarised in Table 3, and the Kaplan-Meier curve for PFS is shown in Figure 1. At the time of the interim analysis of overall survival (25% maturity), a HR of 0.63 favoured TAGRISSO (95% CI: 0.45, 0.88; P = 0.0068), which did not reach formal statistical significance. A greater proportion of patients treated with TAGRISSO were alive at 12 months and 18 months (89% and 83%, respectively) compared to patients treated with EGFR TKI comparator (83% and 71%, respectively). Analysis of post-progression end–points demonstrated that the PFS benefit was preserved through subsequent lines of therapy.

Table 3. 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, (25% maturity)	58 (21)	83 (30)
Median OS in months (95% CI)	NC	NC
HR (95% CI); P-value	0.63 (0.45, 0.88); P=0.0068 (NS) †	
Objective Response Rate		
Number of responses (n),Response Rate (95% CI)	223 80% (75, 85)	210 76% (70, 81)
Odds ratio (95% CI); P-value	1.3 (0.9, 1.9); P=0.2421	
Duration of Response (DoR)		
Median, Months (95% CI)	17.2 (13.8, 22.0).	8.5 (7.3, 9.8)
Second PFS after start of first subsequent therapy (PFS2)		
Number of patients with second progression (%)	73 (26)	106 (38)
Median PFS2, months (95% CI)	NC (23.7, NC)	20.0 (18.0, NC)
HR (95% CI); P-value	0.58 (0.44, 0.78); P=0.0004	
Time from randomisation to first subsequent treatment or death (TFST)		
Number of patients who had first subsequent treatment or died (%)	115 (41)	175 (63)
Median TFST, months (95% CI)	23.5 (22.0, NC)	13.8 (12.3, 15.7)
HR (95% CI); P-value	0.51 (0.40, 0.64); P<0.0001	
Time from randomisation to second subsequent treatment or death (TSST)		
Number of patients who had second subsequent treatment or died (%)	75 (27)	110 (40)
Median TSST, months (95% CI)	NC (NC, NC)	25.9 (20.0, NC)
HR (95% CI); P-value	0.60 (0.45, 0.80); P=0.0005	

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

All efficacy 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

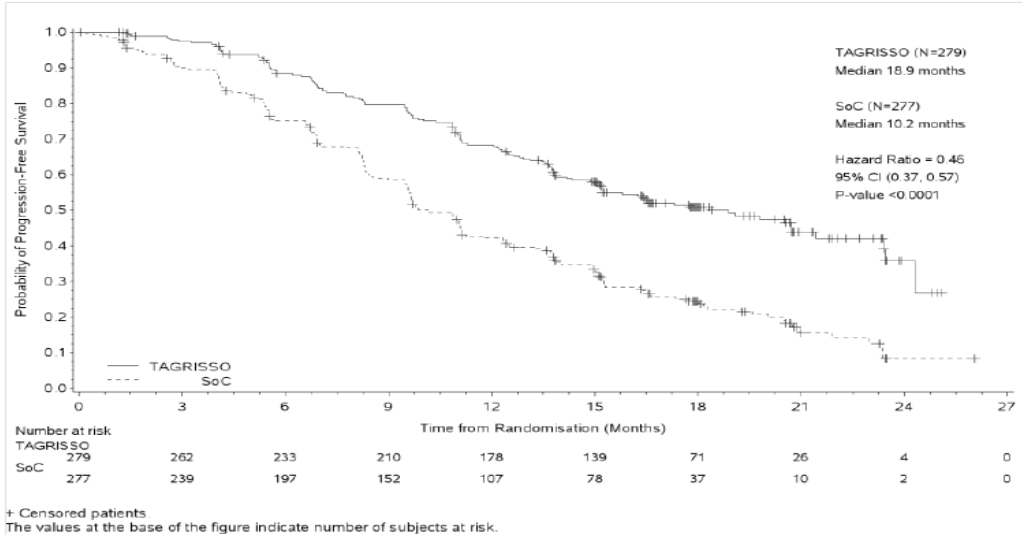
comparator

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

† Based on an interim analysis with 25% maturity a P-value < 0.0015 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



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

CNS metastases efficacy data in FLAURA study

Patients with CNS metastases not requiring steroids and with stable neurologic status for at least two weeks after completion of the definitive therapy and steroids were eligible to be randomised in the FLAURA study. Of 556 patients, 200 patients had available baseline brain scans. A BICR assessment of these scans resulted in a subgroup of 128/556 (23%) patients with CNS metastases and these data are summarised in Table 4. CNS efficacy by RECIST v1.1 in FLAURA demonstrated a nominal statistically significant improvement in CNS PFS (HR=0.48, 95% CI 0.26, 0.86; P=0.014).

Table 4. 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)

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

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

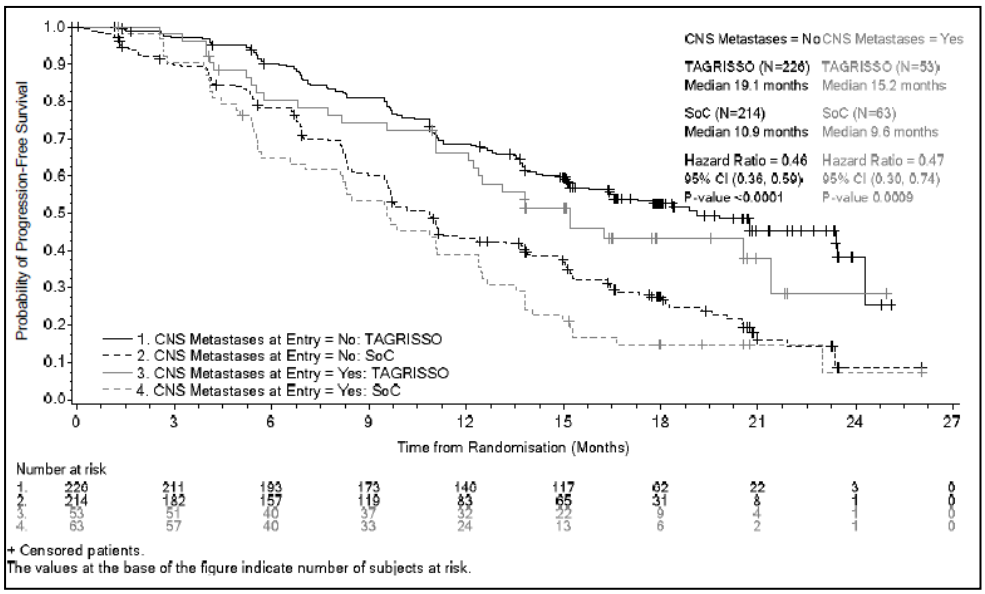
1 CNS PFS determined by RECIST v1.1by CNS BICR (CNS measurable and non-measurable lesions at baseline by BICR)

n=61 for TAGRISSO and n=67 for EGFR TKI comparator; responses are unconfirmed

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

Figure 2. Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in FLAURA



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).

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.

Pre-treated T790M positive NSCLC patients-AURA3

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

Patients were randomised in a 2:1 (TAGRISSO: platinum-based doublet chemotherapy) ratio to receive TAGRISSO (n=279) or platinum-based doublet chemotherapy (n=140). Randomisation was stratified by ethnicity (Asian and non-Asian). Patients in the TAGRISSO arm received TAGRISSO 80 mg orally once daily until intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Chemotherapy consisted of pemetrexed 500 mg/m^2 with carboplatin AUC5 or pemetrexed 500 mg/m^2 with cisplatin 75 mg/m2 on Day 1 of every 21-day cycle for up to 6 cycles. Patients whose disease has not progressed after four cycles of platinum-based chemotherapy may receive pemetrexed maintenance therapy (pemetrexed 500 mg/m^2 on Day 1 of every 21-day cycle). Subjects on the chemotherapy arm who had objective radiological progression (by the investigator and confirmed by independent central imaging review) were given the opportunity to begin treatment with TAGRISSO.

The baseline demographic and disease characteristics of the overall study population were: median age 62, ≥75 years old (15%), female (64%), white (32%), Asian (65%), never smoker (68%), WHO performance status 0 or 1 (100%). Fifty-four percent (54%) of patients had extra-thoracic visceral metastases, including 34% with CNS metastases (identified by CNS lesion site at baseline, medical

history, and/or prior surgery, and/or prior radiotherapy to CNS metastases) and 23% with liver metastases. Forty-two percent (42%) of patients had metastatic bone disease.

AURA3 demonstrated a statistically significant improvement in PFS in the patients treated with TAGRISSO compared to chemotherapy. Efficacy results from AURA3 by investigator assessment are summarised in Table 5, and the Kaplan-Meier curve for PFS is shown in Figure 3. Overall survival data were not mature at the time of this initial OS analysis.

Table 5. 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-value <0.001	
Overall Survival[1]		
Number of Deaths (% maturity)	69 (24.7)	40 (28.6)
Median OS, Months (95% CI)	NC (20.5, NC)	NC (20.5, NC)
HR (95% CI); P-value	0.72 (0.48, 1.09); P-value = 0.121	
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-value <0.001	
Duration of Response (DoR)[2]		
Median, Months (95% CI)	9.7 (8.3, 11.6)	4.1 (3.0, 5.6)

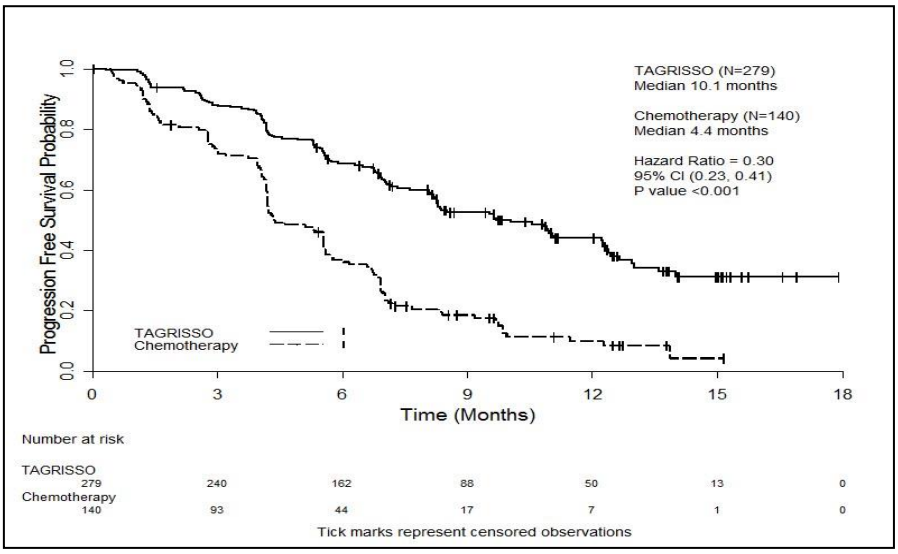
HR=Hazard Ratio; CI=confidence interval; NC=non-calculable

All efficacy results based on RECIST investigator assessment

[1] The first analysis of OS was performed approximately 4 months after the primary analysis of PFS. The OS analysis was not adjusted for the potentially confounding effects of crossover (94 [67%] patients on the chemotherapy arm received subsequent osimertinib treatment).

[2] ORR and DoR results by investigator assessment are 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 3. Kaplan-Meier curves of Progression-Free Survival as assessed by investigator in AURA3



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

Clinically meaningful improvements in PFS with HRs less than 0.50 in favour of patients receiving TAGRISSO compared to those receiving chemotherapy were consistently observed in all predefined subgroups analysed, including ethnicity, age, gender, smoking history and EGFR mutation (Exon 19 deletion and L858R).

CNS metastases efficacy data in AURA3 study

Patients with asymptomatic, stable brain metastases not requiring steroids for at least 4 weeks prior to the start of study treatment were eligible to be randomised in the study. A BICR assessment of CNS efficacy by RECIST v1.1 in the subgroup of 116/419 (28%) patients identified to have CNS metastases on a baseline brain scan are summarised in Table 6.

Table 6. CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in AURA3

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

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

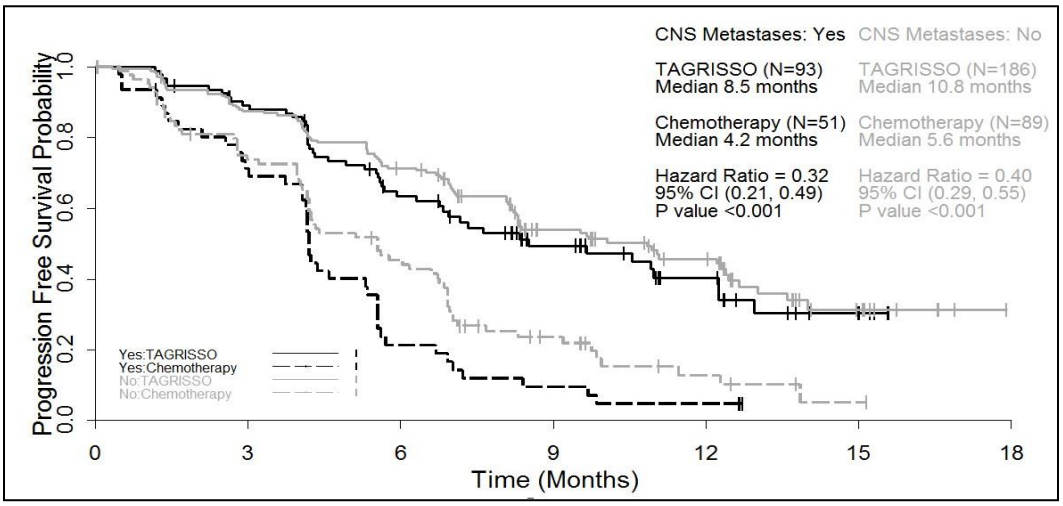
[2]Based on patients with response only; DoR defined as the time from the date of first documented response (complete response or partial response) until progression or death event; DCR definedas the proportion of patients with response (complete response or partial response), or stable disease ≥ 6 weeks

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

A HR<1 favours TAGRISSO

A pre-specified PFS subgroup analysis based on CNS metastases status at study entry was performed in AURA3 and is shown in Figure 4.

Figure 4. Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in AURA3



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

Patient Reported Outcomes

Patient-reported symptoms and 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 7.

Table 7. Mixed Model Repeated Measures – Key lung cancer symptoms - mean change from baseline in TAGRISSO patients compared with chemotherapy

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

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

HRQL and physical functioning improvement analysis

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

Pre-treated T790M positive NSCLC patients - AURAex and AURA2

Two single-arm, open-label clinical studies, AURAex (Phase 2 Extension cohort, (n=201)) and AURA2 (n=210) were conducted in patients with EGFR T790M mutation-positive lung cancer who have progressed on one or more prior systemic therapies, including an EGFR TKI. All patients were required

to have EGFR T790M mutation-positive NSCLC identified by the cobas EGFR mutation test performed in a central laboratory prior to treatment. The T790M mutation status was also assessed retrospectively using ctDNA extracted from a plasma sample taken during screening. All patients received TAGRISSO at a dose of 80 mg once daily. The primary efficacy outcome measure of these two trials was ORR according to RECIST v1.1 as evaluated by a Blinded Independent Central Review (BICR). Secondary efficacy outcome measures included Duration of Response (DoR) and Progression-Free Survival (PFS).

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

In the 411 pre-treated EGFR T790M mutation-positive patients, the total ORR by Blinded Independent Central Review (BICR) was 66% (95% CI: 61, 71). In patients with a confirmed response by BICR, the median DoR was 12.5 months (95% CI: 11.1, NE). The ORR by BICR in AURAex was 62% (95% CI: 55, 68) and 70% (95% CI: 63, 77) in AURA2. The median PFS was 11.0 months 95% CI (9.6, 12.4).

Objective response rates by BICR above 50% were observed in all predefined subgroups analysed, including line of therapy, ethnicity, age and region.

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

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

A BICR assessment of CNS efficacy by RECISTv 1.1 was performed in a subgroup of 50 (out of 411) patients identified to have measurable CNS metastases on a baseline brain scan. A CNS ORR of 54%

(27/50 patients; 95% CI: 39.3, 68.2) was observed with 12% of these responses being complete responses.

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

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

Biotransformation

In vitro studies indicate that osimertinib is metabolized predominantly by CYP3A4, and CYP3A5.

However, with current available data, alternative metabolic pathways cannot be fully ruled out. Based on in vitro studies, 2 pharmacologically active metabolites (AZ7550 and AZ5104) have subsequently been identified in the plasma of preclinical species and in humans after oral dosing with osimertinib; AZ7550 showed a similar pharmacological profile to TAGRISSO while AZ5104 showed greater potency across both mutant and wild-type EGFR. Both metabolites appeared slowly in plasma after administration of TAGRISSO to patients, with a median (min-max) tmax of 24 (4-72) and 24 (6-72) hours, respectively. In human plasma, parent osimertinib accounted for 0.8%, with the 2 metabolites contributing 0.08% and 0.07% of the total radioactivity with the majority of the radioactivity being covalently bound to plasma proteins. The geometric mean exposure of both AZ5104 and AZ7550, based on AUC, was approximately 10% each of the exposure of osimertinib at steady-state.

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

Based on in vitro studies, osimertinib is a competitive inhibitor of CYP 3A4/5 but not CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at clinically relevant concentrations. Based on in vitro studies, osimertinib is not an inhibitor of UGT1A1 and UGT2B7 at clinically relevant concentrations hepatically. Intestinal inhibition of UGT1A1 is possible but the clinical impact is unknown.

Elimination

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

Interactions with transport proteins

In vitro studies have shown that osimertinib is not a substrate of OATP1B1 and OATP1B3. In vitro, osimertinib does not inhibit OAT1, OAT3, OATP1B1, OATP1B3 MATE1, OCT2 and MATE2K at clinically relevant concentrations.

Effects of osimertinib on P-gp and BCRP

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

Special populations

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

Hepatic impairment

Osimertinib is eliminated mainly via the liver. In a clinical trial, patients with different types of advanced solid tumours and with mild hepatic impairment (Child Pugh A, mean score = 5.3, n=7) or moderate hepatic impairment (Child Pugh B, mean score = 8.2, n=5) had no increase in exposure compared to patients with normal hepatic function (n=10) after a single 80 mg dose of TAGRISSO. The geometric mean ratio (90% CI) of osimertinib AUC and Cmax was 63.3% (47.3, 84.5) and 51.4% (36.6, 72.3) in patients with mild hepatic impairment and 68.4% (49.6, 94.2) and 60.7% (41.6, 88.6) in patients with moderate hepatic impairment; for the metabolite AZ5104 the AUC and Cmax were 66.5% (43.4, 101.9) and 66.3% (45.3, 96.9) in patients with mild hepatic impairment and 50.9% (31.7, 81.6) and 44.0% (28.9, 67.1) in patients with moderate hepatic impairment, compared to the exposure in patients with normal hepatic function. Based on population PK analysis, there was no relationship between markers of hepatic function (ALT, AST, bilirubin) and osimertinib exposure. The hepatic impairment marker serum albumin showed an effect on the PK of osimertinib. Clinical studies that were conducted excluded patients with AST or ALT >2.5x upper limit of normal (ULN), or if due to underlying

malignancy, >5.0x ULN or with total bilirubin >1.5x ULN. Based on a pharmacokinetic analysis of 134 patients with mild hepatic impairment, 8 patients with moderate hepatic impairment and 1216 patients with normal hepatic function osimertinib exposures were similar. There are no data available on patients with severe hepatic impairment (see section 4.2).

Renal impairment

A pharmacokinetic study in patients with renal impairment has not been conducted. 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 <than 60 mL/min),5 patients with severe renal impairment (CLcr 15 to <than 30 mL/min) and 502 patients with normal renal function (greater than or equal to 90 mL/min), osimertinib exposures were similar. Severe renal impairment may influence the elimination of hepatically eliminated medicinal products. Patients with CLcr less than 15 mL/min were not included in the clinical trials.

5.3 Preclinical safety data

The main findings observed in repeat dose toxicity studies in rats and dogs comprised atrophic, inflammatory and/or degenerative changes affecting the epithelia of the cornea (accompanied by corneal translucencies and opacities in dogs at ophthalmology examination), GI tract (including tongue), skin, and male and female reproductive tracts with secondary changes in spleen. These findings occurred at plasma concentrations that were below those seen in patients at the 80 mg therapeutic dose. The findings present following 1 month of dosing were largely reversible within 1 month of cessation of dosing with the exception of partial recovery for some of the corneal changes.

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

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

Carcinogenesis and mutagenesis

Carcinogenicity studies have not been performed with osimertinib. Osimertinib did not cause genetic damage in in vitro and in vivo assays.

Reproductive toxicity

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol

Microcrystalline cellulose

Low-substituted hydroxpropyl cellulose

Sodium stearyl fumarate

Tablet coating

Polyvinyl alcohol

Titanium dioxide (E 171)

Macrogol 3350

Talc

Yellow iron oxide (E 172)

Red iron oxide (E 172)

Black iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

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

7. Marketing authorisation holder

AstraZeneca (Israel) Ltd.,

PO Box 1455 Hod Hasharon 4524075

8. Manufacturer

AstraZeneca AB

Gärtunavägen

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