PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTAGRISSO®

osimertinib tablets

Tablets, 40 mg and 80 mg osimertinib (as osimertinib mesylate), Oral

Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor, L01XE35

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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

EGFR Mutation-Positive NSCLC

Adjuvant
TAGRISSO (osimertinib) is indicated as adjuvant therapy after tumour resection in patients with stage IB-IIIA[1] non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations (see 14 CLINICAL TRIALS).

- A validated test is required to identify EGFR mutation-positive status prior to treatment (see 7 WARNINGS AND PRECAUTIONS, Assessment of EGFR Mutation Status).

Metastatic
TAGRISSO is indicated for the first-line treatment of patients with locally advanced (not amenable to curative therapies), or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (either alone or in combination with other EGFR mutations).

- A validated test is required to identify EGFR mutation-positive status prior to treatment (see 7 WARNINGS AND PRECAUTIONS, Assessment of EGFR Mutation Status).

EGFR T790M Mutation-Positive NSCLC

TAGRISSO is indicated for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

- A validated test is required to identify EGFR T790M mutation-positive status prior to treatment (see 7 WARNINGS AND PRECAUTIONS, Assessment of EGFR T790M Mutation Status, and Monitoring and Laboratory Tests).
- Marketing authorization was based on results from a randomized Phase III trial (AURA3) demonstrating that TAGRISSO is superior to chemotherapy in prolonging progression-free survival (PFS) as assessed by investigator using RECIST v1.1.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

[1] According to American Joint Committee on Cancer (7th edition)

1.2 Geriatrics

Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (10.7% versus 7.6%) in the ADAURA, FLAURA and AURA trials (n=1479). No overall differences in efficacy or predicted steady state exposure of osimertinib were observed between these patients and younger patients. See 7.1 Special Populations, 4.1 Dosing Considerations and 10.3 Pharmacokinetics.

2 CONTRAINDICATIONS

Do not use TAGRISSO (osimertinib) in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing of ingredients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Treatment with TAGRISSO (osimertinib) should be initiated by a qualified physician experienced in the use of anticancer therapies.
- Interstitial lung disease (e.g., pneumonitis), including fatal cases (see 7 WARNINGS AND PRECAUTIONS, Respiratory and 8 ADVERSE REACTIONS).
- QTcF interval prolongation (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Monitoring and Laboratory Tests; 8 ADVERSE REACTIONS, QT Interval Prolongation and ECG Findings; 9.4 Drug-Drug Interactions and 4 DOSAGE AND ADMINISTRATION).
- Left Ventricular Dysfunction and Cardiomyopathy (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Monitoring and Laboratory Tests; 8 ADVERSE REACTIONS, Left Ventricular

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Age, body weight, gender, race and smoking status: No dosage adjustment is required due to patient age, body weight, gender, ethnicity and smoking status (see 10.3 Pharmacokinetics).

Hepatic Impairment: Based on clinical studies, no dose adjustments are necessary in patients with mild hepatic impairment (Child Pugh A) or moderate hepatic impairment (Child Pugh B). Similarly, based on population PK analysis, no dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin between 1.0 to 1.5x ULN and any AST) or moderate hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST). The appropriate dose of TAGRISSO has not been established in patients with severe hepatic impairment (see 10.3 Pharmacokinetics).

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

should be exercised when treating patients with severe and end-stage renal impairment (see 10.3 Pharmacokinetics).

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of TAGRISSO (osimertinib) is 80 mg tablet taken orally once a day.

Patients in the adjuvant setting should receive treatment for up to 3 years or until disease recurrence or unacceptable toxicity.

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

Dose adjustments are not necessary for generally manageable adverse reactions. If dose reduction or modification is necessary based on individual safety and tolerability, then the dose of TAGRISSO should be reduced to 40 mg taken once daily. Dose reduction guidelines for adverse reactions toxicities are provided in Table 1.

Table 1 Recommended dose modifications for TAGRISSO

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary	ILD/Pneumonitis	Permanently discontinue TAGRISSO if ILD is confirmed. See 7 WARNINGS AND PRECAUTIONS, Interstitial Lung Disease (ILD) for further guidance and management.
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.
	Asymptomatic, absolute decrease in LVEF of 10% from baseline and below 50%	Withhold TAGRISSO for up to 4 weeks. If improved to baseline LVEF, resume. If not improved to baseline, permanently discontinue.
	Symptomatic congestive heart failure	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).

Target Organ	Adverse Reaction[a]	Dose Modification
	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.

Pediatrics (<18 years age): The safety and efficacy of TAGRISSO in children below 18 years of age have not been established. There are currently no available data. Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years age): Population pharmacokinetic (PK) analysis indicated that age did not have an impact on the exposure of osimertinib and hence, no dosage adjustment is required in this patient population (see 10.3 Pharmacokinetics).

4.4 Administration

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

The tablet 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 (room temperature). The tablet should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional 50 mL of water should be added to ensure that no residue remains in the glass 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 total volume of 30 mL of liquid should be immediately administered as per the nasogastric tube manufacturer's instructions with appropriate water flushes (see 10 CLINICAL PHARMACOLOGY). The dispersion and residues should be administered within 30 minutes of the addition of the tablets to water.

4.5 Missed Dose

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

5 OVERDOSAGE

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 trials, 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-inhibitor induced AEs (primarily diarrhea and skin rash) compared to the 80 mg dose.

There is no specific treatment in the event of TAGRISSO overdose. Physicians should treat symptomatically and follow general supportive measures, including ECG monitoring.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets, 40 mg and 80 mg	Tablet core: low-substituted hydroxpropyl cellulose, mannitol, microcrystalline cellulose, sodium stearyl fumarate Tablet coat: black iron oxide, macrogol 3350, polyvinyl alcohol, red iron oxide, talc, titanium dioxide, yellow iron oxide

Dosage Forms:

- TAGRISSO 40 mg tablets are beige, round and biconvex tablets marked with "AZ" and "40" on one side and plain on the other side.
- TAGRISSO 80 mg tablets are beige, oval and biconvex tablets marked with "AZ" and "80" on one side and plain on the other side.

Packaging: Both strengths of TAGRISSO are available in aluminum foil/foil blister in cartons of 30 tablets (3 packs of 10 tablets).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Assessment of EGFR Mutation Status: Prior to the use of TAGRISSO as an adjuvant therapy after tumour resection in patients with NSCLC, it is necessary that EGFR mutation-positive status [EGFR exon 19 deletions or exon 21 (L858R) substitution mutations] in tumour tissue DNA from diagnostic tumour biopsy specimen or tumour tissue taken during surgery is determined using a validated test method by laboratories with demonstrated proficiency in the specific technology being used.

Prior to the use of TAGRISSO as a first-line treatment for patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations, it is necessary that EGFR mutation-positive status (EGFR exon 19 deletions or exon 21 (L858R) substitution mutations) in tumour specimens is determined using a validated test method by laboratories with demonstrated proficiency in the specific technology being used.

Prior to the use of TAGRISSO as a treatment for locally advanced or metastatic NSCLC that has progressed on or after EGFR TKI therapy, it is necessary that EGFR T790M mutation-positive status in tumour specimens is determined using a validated test method by laboratories with demonstrated proficiency in the specific technology being used. See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 14 CLINICAL TRIALS. A validated and robust methodology is necessary to minimize false negative and false positive results.

Drug Interactions: Strong CYP3A4 inducers decrease osimertinib exposure (see 9 DRUG INTERACTIONS). Avoid co-administration of strong CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine and St. John's Wort) with TAGRISSO. If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when co-administering with a strong CYP3A4 inducer and continue dosage at 160 mg daily for 3 weeks following discontinuation of the strong CYP3A4 inducer. Resume TAGRISSO dosage at 80 mg daily 3 weeks after discontinuation of a strong CYP3A4 inducer.

TAGRISSO increases the exposure of breast cancer resistant protein (BCRP) and/or P-glycoprotein (P-gp) substrates. Patients taking concomitant medications with disposition dependent upon BCRP or P-gp and with narrow therapeutic indices should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving TAGRISSO (see 9 DRUG INTERACTIONS).

Cardiovascular

QT Interval Prolongation: QTc interval prolongation has been reported in 6.3% (93 of 1479) of patients treated with TAGRISSO. Of the 1479 patients in ADAURA, FLAURA and AURA trials 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 in QTc from baseline of greater than 60 msec.
A pharmacokinetic/pharmacodynamic analysis with TAGRISSO predicted a concentration-dependent increase in QTc interval prolongation. No QTc-related arrhythmias were reported in the ADAURA, FLAURA or AURA trials. Patients with clinically important abnormalities in rhythm and conduction and patients with resting QTc interval greater than 470 msec were excluded from these trials.

QTc prolongation may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age ≥65 years; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

Treatment with TAGRISSO is not recommended in patients with congenital long QT syndrome, or who are taking medicinal products known to prolong the QTc interval (see 9 DRUG INTERACTIONS). Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to TAGRISSO administration.

Particular care should be exercised when administering TAGRISSO to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug (see 9 DRUG INTERACTIONS).

In a Phase II trial (AURA2), during steady-state treatment on Day 43, mean changes from baseline in the QTc interval ranged from 13.0 msec (95% CI: 11.0, 14.9) to 16.2 msec (95% CI: 14.1, 18.3) over the course of the day.

When possible, avoid use of TAGRISSO in patients with congenital long QT syndrome. Monitor electrocardiograms (ECGs) prior to initiating and periodically during treatment (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). 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 baseline QTc interval is greater than or equal to 481 msec, then resume TAGRISSO at a reduced dose as described in 4.2 Recommended Dose and Dosage Adjustment. 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 (see 4 DOSAGE AND ADMINISTRATION).

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug. Patients should be advised to contact their healthcare provider immediately to report any new chest pain or discomfort, changes in heartbeat, palpitations, dizziness, light-headedness, fainting, or changes in or new use of other medications.

Left Ventricular Dysfunction and Cardiomyopathy: Across the AURA clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases ≥10 percentage points and a drop to <50% occurred in 3.2% (40/1233) of patients treated with TAGRISSO who had baseline and at least one follow-up LVEF assessment. Across clinical trials, a total of 3.0% of the 1479 TAGRISSO-treated patients reported cardiomyopathy events (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema, ejection fraction decreased); including 1 fatal event of congestive heart failure. 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%.

Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and TAGRISSO has not been established, however, causality cannot be completely ruled out. 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. Discontinuation of treatment with TAGRISSO should be considered in patients who develop congestive heart failure. See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; 4.2 Recommended Dose and Dosage Adjustment.

Driving and Operating Machinery

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

Hepatic/Biliary/Pancreatic

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 a pharmacokinetic analysis of 134 patients with baseline mild hepatic impairment (total bilirubin ≤ ULN and AST >ULN or total bilirubin between 1.0 to 1.5 x ULN and any AST), 8 patients with moderate hepatic impairment (total bilirubin between 1.5 x to 3.0 x ULN and any AST) and 1216 patients with normal hepatic function (total bilirubin

≤ ULN and AST ≤ ULN), osimertinib exposures were similar in these groups. Osimertinib is eliminated via hepatic metabolism. There are no data in patients with severe hepatic impairment. An appropriate dose of TAGRISSO has not been established in patients with severe hepatic impairment (see 4 DOSAGE AND ADMINISTRATION, Hepatic Impairment and 10.3 Pharmacokinetics).

Monitoring and Laboratory Tests

ECG Monitoring: ECG evaluations should be performed prior to initiating therapy with TAGRISSO, and periodically during treatment to monitor for QTc prolongation (see 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 8.2 Clinical Trial Adverse Reactions, ECG Findings; 9 DRUG INTERACTIONS).

Electrolyte Monitoring: Electrolyte levels (calcium, potassium, and magnesium) should be assessed prior to initiating therapy with TAGRISSO, and monitored periodically during treatment with TAGRISSO, particularly in patients at risk for these electrolyte abnormalities (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 9 DRUG INTERACTIONS). Hypocalcemia, hypokalemia, and hypomagnesemia should be corrected prior to TAGRISSO administration.

Left Ventricular Ejection Fraction Monitoring: Cardiac monitoring including an assessment of left ventricular ejection fraction (LVEF) at baseline and during treatment should be considered for patients with cardiac risk factors. Consider cardiac monitoring including LVEF assessment in patients who develop relevant cardiac signs/symptoms during treatment. Discontinuation of treatment with TAGRISSO should be considered in patients who develop congestive heart failure (see 4.2 Recommended Dose and Dosage Adjustment; 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 8.2 Clinical Trial Adverse Reactions, Left Ventricular Performance).

Ophthalmologic Monitoring: 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 4.2 Recommended Dose and Dosage Adjustment; 8 ADVERSE REACTIONS).

Ophthalmologic

Keratitis was reported in 0.7% (n=10) of the 1479 patients treated with TAGRISSO in the ADAURA, FLAURA and AURA trials. 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 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Contact lens use is also known to be an independent risk factor for ocular toxicity, including keratitis. Caution should be exercised when driving or operating machinery by patients who experience vision disorder (see 4.2 Recommended Dose and Dosage Adjustment; 8 ADVERSE REACTIONS).

Renal

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 baseline mild renal impairment (CLcr 60 to <90 mL/min), 254 patients with moderate renal impairment (CLcr 30 to <60 mL/min), 5 patients with severe renal impairment (CLcr 15 to <30 mL/min) and 502 patients with normal renal function (≥90 mL/min), osimertinib exposures were similar. The safety and efficacy of TAGRISSO has not been established in patients with end-stage renal

disease (CLcr <15 mL/min) or on dialysis. Caution should be exercised when treating patients with severe and end-stage renal impairment (see 4.1 Dosing Considerations, Renal Impairment and 10.3 Pharmacokinetics).

Reproductive Health: Female and Male Potential

- **Fertility**

  There are no data on the effect of TAGRISSO on human fertility. Results from animal studies have shown that TAGRISSO has effects on male and female reproductive organs and could impair fertility (see 16 NON-CLINICAL TOXICOLOGY).

Respiratory

Interstitial Lung Disease (ILD): Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g., pneumonitis) were reported in 3.7% and were fatal in 0.3% (n=5) of the 1479 patients who received TAGRISSO 80 mg in the ADAURA, FLAURA and AURA trials.

Patients with past medical history of ILD or evidence of clinically active ILD, or patients with radiation pneumonitis requiring steroid treatment were excluded from these trials.

The incidence of ILD was 10.9% 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 reactions was 2.8 months (see 8 ADVERSE REACTIONS; 4.1 Dosing Considerations; 10.3 Pharmacokinetics).

Withhold TAGRISSO and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed (see 8 ADVERSE REACTIONS and 4.2 Recommended Dose and Dosage Adjustment).

Skin

Skin and subcutaneous tissue disorders with TAGRISSO have been mainly mild in nature, including rash, dry skin, paronychia, pruritus, palmar-plantar erythrodysesthesia syndrome, alopecia and erythema multiforme. CTCAE Grade 3 events of rash occurred in 11/1479 (0.7%) patients, which consisted of erythema in 3/1479 (0.2%) patients, rash erythematous in 2/1479 (0.1%) patients, rash macular in 1/1479 (0.1%) patients, rash maculo-papular in 3/1479 (0.2%) patients and rash papular in 2/1479 (0.1%) patients.

Bullous and exfoliative skin disorders: Rare, non-fatal cases of Stevens-Johnson syndrome have been reported with the use of TAGRISSO treatment (see 8.5 Post-Market Adverse Reactions). Before initiating treatment, patients should be advised of signs and symptoms of Stevens-Johnson syndrome. TAGRISSO should be interrupted or discontinued immediately if the patient develops severe bullous, blistering or exfoliating conditions.

Erythema multiforme: Based on the pooled dataset analysis of the clinical trial data, uncommon cases of erythema multiforme have been identified with the use of TAGRISSO treatment (see 8.5 Post-Market Adverse Reactions). Before initiating treatment, patients should be advised of signs and symptoms of erythema multiforme. If signs and symptoms suggestive of erythema multiforme develop, close patient monitoring and drug interruption or discontinuation of TAGRISSO should be considered.

Paronychia: Paronychia was observed in 481/1479 (32.5%) patients who received TAGRISSO 80 mg in the ADAURA, FLAURA and AURA trials (n=1479) and was generally mild (309/1479, 20.9%, CTCAE Grade

1) or moderate (166/1479, 11.2%, CTCAE Grade 2) in nature. In the AURA3 trial, paronychia led to dose reduction in 0.4% (1/279) of patients with no treatment discontinuations. In the FLAURA trial, paronychia led to dose reduction in 0.4% (1/279) of patients; 0.4% (1/279) of patients discontinued due to paronychia. In the ADAURA trial, paronychia led to dose reduction in 1.2% (4/337) of patients with no treatment discontinuations. See 8 ADVERSE REACTIONS. Physicians should advise patients to use moisturizers regularly on the skin and nails and to keep hands clean and dry as prevention measures. Physicians should treat paronychia accordingly.

7.1 Special Populations

Females and Males of Reproductive Potential

Females: Advise females of childbearing potential to avoid becoming pregnant while receiving TAGRISSO and use effective contraception for at least 2 months after final dose.

Males: Male patients with female partners of reproductive potential should be advised that pregnancy should be avoided while receiving TAGRISSO and for at least 4 months after final dose.

7.1.1 Pregnant Women

There are no data in pregnant women using TAGRISSO. Studies in animals have shown reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY).

Based on its mechanism of action and preclinical data, TAGRISSO may cause fetal harm when administered to a pregnant woman. Administration of osimertinib to pregnant rats was associated with embryolethality, reduced fetal growth and neonatal death at exposures similar to what is expected in humans (see 16 NON-CLINICAL TOXICOLOGY).

Pregnant women must be advised of the potential risk of TAGRISSO to the fetus or potential risk for miscarriage. TAGRISSO should not be used during pregnancy unless clearly necessary and after a careful consideration of the need of the mother and the risk to the fetus. Women should avoid becoming pregnant (see 7.1 Special Populations, Females and Males of Reproductive Potential, Females).

7.1.2 Breast-feeding

It is not known whether TAGRISSO or its metabolites are excreted in human milk. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death. There is insufficient information on the excretion of osimertinib or its metabolites in animal milk. A risk to the breastfed child cannot be excluded. Breastfeeding should be discontinued during treatment with TAGRISSO therapy.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

In the ADAURA, FLAURA and AURA trials (n=1479), 43% of patients were ≥65 years of age, of whom 12% were ≥75 years of age. Compared with younger patients (<65 years of age), more patients ≥65

years old had reported adverse reactions that led to study drug dose modifications (interruptions or reductions) (14.3% versus 8.4%). The types of adverse reactions reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (10.7% versus 7.6%). No overall differences in efficacy or predicted steady state exposure of osimertinib were observed between these patients and younger patients. See 4.1 Dosing Considerations; 10.3 Pharmacokinetics.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The data described below reflect exposure to TAGRISSO (80 mg daily) from pooled Phase I [AURA1 (n=173)], Phase II [AURA extension (n=201), AURA2 (n=210)] and Phase III [ADAURA (n=337), FLAURA (n=279) and AURA3 (n=279)] data from 1479 patients with EGFR mutation-positive NSCLC (see 14 CLINICAL TRIALS). In ADAURA, the median duration of study treatment was 22.5 months for patients receiving TAGRISSO (n=337) and 18.7 months for patients receiving placebo. In FLAURA, the median duration of study treatment was 16.2 months for patients receiving TAGRISSO (n=279) and 11.5 months for patients receiving EGFR TKI comparator. In AURA3, the median duration of exposure was 8.1 months for patients receiving TAGRISSO (n=279) and 4.2 months for patients receiving chemotherapy (n=136).

Across all treatment settings [ADAURA, FLAURA and AURA trials (n=1479)], the majority of adverse events (AEs) were mild or moderate in severity (CTCAE Grade 1 and 2). Grade 3 or higher adverse events with TAGRISSO were reported in 33.1% of patients. Serious Adverse Events (SAEs) were reported in 24.9% of patients. AEs leading to death were reported in 2.8% of patients.

The most commonly reported (in ≥10% of patients, n=1479) adverse drug reactions (ADRs) by grouped terms include diarrhea (47.2%), rash (44.7%), paronychia (32.5%), dry skin (31.7%), stomatitis (23.5%) and pruritus (17.3%). ADRs by grouped terms with a Grade ≥3 severity (in ≥1% of patients, n=1479) include diarrhea (1.4%) and ILD (1.1%). ILD (1.8%) was also reported as a serious adverse reaction (SAR).

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 trials. Patients with clinically important abnormalities in rhythm and conduction as measured by resting electrocardiogram (ECG) (e.g., QTc interval greater than 470 msec) were excluded from these trials. Patients had LVEF evaluation at screening and every 12 weeks thereafter.

In the ADAURA, FLAURA and AURA trials, the incidence of ILD-like adverse reactions was 10.9% 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 reactions was 2.8 months (see 7 WARNINGS AND PRECAUTIONS, Respiratory; 4.1 Dosing Considerations; 10.3 Pharmacokinetics).

In patients treated with TAGRISSO 80 mg once daily, ADRs that led to dose modification (interruption or reduction) occurred in 11.0% (162/1479) of the patients. Dose reductions due to ADRs occurred in 3.2% (48/1479) of the patients. Discontinuation due to adverse reactions was 4.6% (68/1479). The most frequent adverse drug reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3.2% [48/1479]).

Fatal adverse drug reactions were reported in 0.3% (5/1479) of TAGRISSO-treated patients. SARs were reported in 24.9% (369/1479) of TAGRISSO-treated patients.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

ADAURA Trial

Tables below summarize the adverse drug reactions regardless of investigator assessed causality (Table 3) and laboratory abnormalities observed in EGFR mutation positive NSCLC patients treated with 80 mg TAGRISSO as adjuvant therapy in the ADAURA Phase III clinical trial.

Table 3 Adverse drug reactions reported in ADAURA[a] (Safety analysis set)

Preferred term	**TAGRISSO (N=337)**		**Placebo (N=343)**	
CTCAE Grade[b]	Any Grade n (%)	Grade 3 or Higher n (%)[c]	Any Grade n (%)	Grade 3 or Higher n (%)[c]
Eye Disorders				
Keratitis[d]	2 (0.6)	0 (0)	1 (0.3)	0 (0)
Gastrointestinal Disorders				
Diarrhea	156 (46.3)	8 (2.4)	68 (19.8)	1 (0.3)
Stomatitis[e]	95 (28.2)	6 (1.8)	22 (6.4)	0 (0)
Investigations				
Electrocardiogram QT prolonged[f]	2 (0.6)		0 (0)	
Respiratory, Thoracic and Mediastinal Disorders				
Epistaxis	19 (5.6)	0 (0)	3 (0.9)	0 (0)
Interstitial lung disease[g]	10 (3.0)	0 (0)	0 (0)	0 (0)
Skin and Subcutaneous Tissue Disorders				
Rash[h]	132 (39.2)	1 (0.3)	65 (19.0)	0 (0)
Paronychia[i]	123 (36.5)	3 (0.9)	13 (3.8)	0 (0)
Dry skin[j]	99 (29.4)	1 (0.3)	25 (7.3)	0 (0)
Pruritus[k]	65 (19.3)	0 (0)	30 (8.7)	0 (0)
Alopecia	19 (5.6)	0 (0)	7 (2.0)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	6 (1.8)	0 (0)	0 (0)	0 (0)
Urticaria	5 (1.5)	0 (0)	1 (0.3)	1 (0.3)

Findings based on test results presented as CTCAE grade shifts

Preferred term	TAGRISSO (N=337)		Placebo (N=343)	
Leukocytes decreased[l]	175 (54.0)	0 (0)	85 (25.4)	0 (0)
Platelet count decreased[l]	153 (47.2)	0 (0)	22 (6.6)	1 (0.3)
Lymphocytes decreased[l]	142 (43.8)	7 (2.2)	48 (14.4)	3 (0.9)
Neutrophils decreased[l]	83 (25.6)	1 (0.3)	34 (10.2)	1 (0.3)
Blood creatinine increased[l]	32 (9.8)	(0)	15 (4.5)	1 (0.3)

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

[a] Only events for patients receiving at least one dose of TAGRISSO as their randomized treatment are summarized. Frequency reported in this table are regardless of causality.

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

[c] All events were Grade 3. There were no deaths.

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

[e] Includes: stomatitis, mouth ulceration.

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

[g] Cases reported within the clustered terms: interstitial lung disease, pneumonitis.

[h] Cases reported within the clustered terms for rash AEs: rash, rash generalized, 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.

[i] Cases reported within the clustered terms: nail bed disorder, nail bed inflammation, nail bed infection, nail discolouration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.

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

[k] Cases reported within the clustered terms: pruritus, pruritus generalized, eyelid pruritus.

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

In the ADAURA study, the incidence of patients with adverse events leading to discontinuations or dose modifications (treatment interruption and/or a dose reduction) was 11.0% and 28.8% in patients treated with TAGRISSO 80 mg once daily vs. 2.9% and 11.4%, respectively, in patients on the placebo arm.

FLAURA Trial

Tables below summarize the adverse drug reactions regardless of investigator assessed causality (Table 4) and laboratory abnormalities (Table 4 and Table 7) observed in previously untreated EGFR mutation positive NSCLC patients treated with 80 mg TAGRISSO in the FLAURA Phase III clinical trial.

Table 4 Adverse drug reactions reported in FLAURA[a] (Safety analysis set)

Preferred term	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
CTCAE Grade[b] n(%)	All	3 or Higher	All	3 or Higher
Eye Disorders				
Keratitis[c]	1 (0.4)	0 (0)	4 (1.4)	0 (0)
Gastrointestinal Disorders				

Preferred term	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
Diarrhea[d]	161 (57.7)	6 (2.2)	159 (57.4)	7 (2.5)
Stomatitis[e]	88 (31.5)	2 (0.7)	60 (21.7)	3 (1.1)
Infection and Infestation				
Upper respiratory tract infection	28 (10.0)	0	18 (6.5)	0
Investigations				
Electrocardiogram QT prolonged[f]	28 (10.0)	6 (2.2)	11 (4.0)	2 (0.7)
Respiratory, Thoracic and Mediastinal Disorders				
Epistaxis	17 (6.1)	0 (0)	14 (5.1)	0 (0)
Interstitial lung disease[g]	11 (3.9)	3 (1.1)	6 (2.2)	4 (1.4)
Skin disorders				
Rash[h]	161 (57.7)	3 (1.1)	216 (78.0)	19 (6.9)
Dry skin[i]	100 (35.8)	1 (0.4)	100 (36.1)	3 (1.1)
Paronychia[j]	97 (34.8)	1 (0.4)	91 (32.9)	2 (0.7)
Pruritus[k]	48 (17.2)	1 (0.4)	46 (16.6)	0 (0)
Alopecia	20 (7.2)	0 (0)	35 (12.6)	0 (0)
Urticaria	6 (2.2)	2 (0.7)	1 (0.4)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	4 (1.4)	0 (0)	7 (2.5)	0 (0)
Erythema Multiforme	1 (0.4)	0 (0)	0 (0)	0 (0)
Findings based on test results presented as CTCAE grade shifts				
Leukocytes decreased[l]	191 (71.8)	1 (0.4)	82 (31.4)	1 (0.4)
Lymphocytes decreased[l]	168 (62.9)	15 (5.6)	94 (35.7)	11 (4.2)
Platelet count decreased[l]	138 (50.5)	2 (0.7)	33(12.3)	1 (0.4)
Neutrophils decreased[l]	109 (40.8)	8 (3.0)	27 (10.3)	0 (0)
Blood creatinine increased[l]	24 (8.8)	0 (0)	18 (6.7)	1 (0.4)

[a] Only events for patients receiving at least one dose of TAGRISSO as their randomized treatment are summarized. Frequency reported in this table are regardless of causality.

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

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

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

[e] Includes cases reported within the clustered terms: stomatitis, mouth ulceration.

[f] The frequency of "Electrocardiogram QT prolonged" represents reported adverse events in the FLAURA study. Frequencies of QTc intervals of >500 ms or >60 ms are presented under QT Interval Prolongation (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, QT Interval Prolongation).

[g] Cases reported within the clustered terms: interstitial lung disease, pneumonitis.
[h] Cases reported within the clustered terms for rash AEs: rash, rash generalized, 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.
[i] Cases reported within the clustered terms: dry skin, skin fissures, xerosis, eczema, xeroderma.
[j] Cases reported within the clustered terms: nail bed disorder, nail bed inflammation, nail bed infection, nail discolouration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.
[k] Cases reported within the clustered terms: pruritus, pruritus generalized, eyelid pruritus.
[l] Represents the incidence of laboratory findings, not of reported adverse events.

AURA3 Trial

Tables below summarize the adverse drug reactions regardless of causality (Table 5) and laboratory abnormalities (Table 8) observed in TAGRISSO-treated patients in a randomized, open label, active-controlled Phase III trial (AURA3) in 419 patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy.

The most common all-causality adverse reactions (≥20%) in patients treated with TAGRISSO were diarrhea (41%), rash (34%), dry skin (23%), nail toxicity (22%), and fatigue/asthenia (23%). The most common (≥1%) all-causality adverse events of CTCAE Grade ≥3 for patients treated with TAGRISSO were pulmonary embolism (1.4%), neutrophil count decreased, asthenia, decreased appetite, diarrhea, fatigue, alanine aminotransferase increased, aspartate aminotransferase increased and dyspnea (1.1% each).

The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval (1.8%), neutropenia (1.1%) and diarrhea (1.1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3.2%). Serious adverse reactions were reported in 18% of patients treated with TAGRISSO and 26% in the chemotherapy group. No single serious adverse reaction was reported in 2% or more patients treated with TAGRISSO. SAEs reported in more than 2 patients in the TAGRISSO arm were pulmonary embolism (1.4%), pneumonia (1.1%), dyspnea (1.1%), vomiting, cardiac failure, ILD, respiratory failure, back pain, road traffic accident and pyrexia (0.7% each). One patient (0.4%) treated with TAGRISSO experienced a fatal adverse reaction (ILD/pneumonitis).

Table 5 Adverse drug reactions reported in AURA3[a] (Safety analysis set)

Preferred term	TAGRISSO 80 mg once daily (N=279)				Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=136)			
CTCAE Grade[b] n(%)[c]	All	1	2	3 or Higher	All	1	2	3 or Higher
Eye Disorders								
Dry eye	10 (3.6)	8 (2.9)	2 (0.7)	0 (0.0)	4 (2.9)	4 (2.9)	0 (0.0)	0 (0.0)
Vision blurred	9 (3.2)	8 (2.9)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Preferred term	TAGRISSO 80 mg once daily (N=279)				Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=136)			
Keratitis[f,m]	3 (1.1)	1 (0.4)	2 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)
Conjunctival disorders[l]	22 (7.9)	16 (5.7)	6 (2.1)	0 (0.0)	10 (7.4)	8 (0.7)	2 1.5	0 (0.0)
Gastrointestinal Disorders								
Diarrhea[m]	113 (40.5)	96 (34.4)	14 (5.0)	3 (1.1)	15 (11.0)	10 (7.4)	3 (2.2)	2 (1.5)
Nausea	45 (16.1)	36 (12.9)	7 (2.5)	2 (0.7)	67 (49.3)	41 (30.1)	21 (15.4)	5 (3.7)
Stomatitis[m, n]	52 (18.6)	43 (15.4)	9 (3.2)	0 (0.0)	21 (15.4)	13 (9.6)	6 (4.4)	2 (1.5)
Constipation	39 (14.0)	35 (12.5)	4 (1.4)	0 (0.0)	47 (34.6)	40 (29.4)	7 (5.1)	0 (0.0)
Vomiting	31 (11.1)	25 (9.0)	5 (1.8)	1 (0.4)	27 (19.9)	15 (11.0)	9 (6.6)	3 (2.2)
General Disorders and Administration Site Conditions								
Fatigue	44 (15.8)	31 (11.1)	10 (3.6)	3 (1.1)	38 (27.9)	23 (16.9)	14 (10.3)	1 (0.7)
Asthenia	20 (7.2)	14 (5.0)	3 (1.1)	3 (1.1)	20 (14.7)	10 (7.4)	4 (2.9)	6 (4.4)
Infections and Infestations								
Nasopharyngitis	28 (10.0)	24 (8.6)	4 (1.4)	0 (0.0)	7 (5.1)	3 (2.2)	4 (2.9)	0 (0.0)
Investigations								
QTc interval prolongation[k,m]	4 (1.4)				0 (0.0)			
Metabolism and Nutrition Disorders								
Decreased appetite	50 (17.9)	41 (14.7)	6 (2.2)	3 (1.1)	49 (36.0)	35 (25.7)	10 (7.4)	4 (2.9)
Musculoskeletal and Connective Tissue Disorders								
Back pain	29 (10.4)	20 (7.2)	8 (2.9)	1 (0.4)	12 (8.8)	10 (7.4)	1 (0.7)	1 (0.7)
Nervous System Disorders								
Headache	28 (10.0)	23 (8.2)	5 (1.8)	0 (0.0)	15 (11.0)	14 (10.3)	1 (0.7)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders								
Cough	46 (16.5)	39 (14.0)	7 (2.5)	0 (0.0)	19 (14.0)	13 (9.6)	6 (4.4)	0 (0.0)
Dyspnea	24 (8.6)	15 (5.4)	6 (2.2)	3 (1.1)	18 (13.2)	12 (8.8)	6 (4.4)	0 (0.0)

Preferred term	TAGRISSO 80 mg once daily (N=279)				Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=136)			
Epistaxis	15 (5.4)	15 (5.4)	0 (0.0)	0 (0.0)	2 (1.5)	2 (1.5)	0 (0.0)	0 (0.0)
Interstitial lung disease[d,e,m]	10 (3.6)	3 (1.1)	6 (2.2)	1 (0.4)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)
Skin disorders								
Rash[g,m]	94 (33.7)	82 (29.4)	10 (3.6)	2 (0.7)	8 (5.9)	7 (5.1)	1 (0.7)	0 (0.0)
Dry skin[h,m]	65 (23.3)	58 (20.8)	7 (2.5)	0 (0.0)	6 (4.4)	5 (3.7)	1 (0.7)	0 (0.0)
Paronychia [i,m]	61 (21.9)	47 (16.8)	14 (5.0)	0 (0.0)	2 (1.5)	1 (0.7)	1 (0.7)	0 (0.0)
Pruritus[j,m]	36 (12.9)	33 (11.8)	3 (1.1)	0 (0.0)	7 (5.1)	5 (3.7)	2 (1.5)	0 (0.0)
Alopecia	10 (3.6)	8 (2.9)	2 (0.7)	0 (0.0)	4 (2.9)	3 (2.2)	1 (0.7)	0 (0.0)
Urticaria	7 (2.5)	5 (1.8)	2 (0.7)	0 (0.0)	2 (1.5)	2 (1.5)	0 (0.0)	0 (0.0)
Palmar-plantar erthrodysesthesia syndrome	5 (1.8)	4 (1.4)	1 (0.4)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)
Erythema Multiforme	2 (0.7)	2 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a] Data is cumulative from AURA3 trial; only events for patients receiving at least one dose of TAGRISSO are summarized. Frequency reported in this table are regardless of causality.

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

[c] Percentages rounded to 1 decimal place.

[d] Includes cases reported within the clustered terms: interstitial lung disease and pneumonitis.

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

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

[g] Includes cases reported within the clustered terms for rash AEs: rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis and dermatitis acneiform.

[h] Includes cases reported within the clustered terms: dry skin, skin fissures, xerosis, eczema.

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

[j] Includes cases reported within the clustered terms: pruritus, pruritus generalized, eyelid pruritus.

[k] Represents the incidence of patients who had a QTcF prolongation >500msec, See 8.2 Clinical Trial Adverse Reactions, QT Interval Prolongation below.

[l] Includes cases reported within the clustered terms: dry eye, conjunctivitis, keratitis, conjunctival hemorrhage, conjunctival hyperaemia.

[m] Adverse reactions associated with TAGRISSO.

[n] Includes cases reported within the clustered terms: Stomatitis, mouth ulceration.

ADAURA, FLAURA, and AURA Trials

The safety findings in the single-arm Phase I AURA1, Phase II AURAex and AURA2 trials were generally consistent with those observed in the TAGRISSO arm of the Phase III ADAURA, FLAURA and AURA3

trials. No additional or unexpected toxicity has been observed and adverse events have been aligned in type, severity and frequency.

Adverse drug reactions are presented in Table 6 regardless of investigator assessed causality based on adverse event reports in a pooled dataset from the 1479 patients who received TAGRISSO at a dose of 80 mg daily in the ADAURA, FLAURA and AURA trials.

Table 6 Adverse drug reactions reported in patients treated with TAGRISSO 80 mg in the ADAURA, FLAURA and AURA[a] trials

Preferred term[a]	TAGRISSO 80 mg once daily N=1479	
	All Grades[b] n(%)	Grade 3 and higher n(%)
Eye disorders		
Keratitis[c]	10 (0.7)	1 (0.1)
Gastrointestinal disorders		
Diarrhea	698 (47.24)	21(1.4)
Stomatitis[d]	348 (23.5)	7 (0.5)
Investigations		
QTc interval prolongation[e]	12 (0.8)	
Respiratory, thoracic and mediastinal disorders		
Epistaxis	79 (5.3)	0 (0)
Interstitial lung disease[f]	55 (3.7)	17 (1.1)[g]
Skin and subcutaneous tissue disorders		
Rash[h]	661 (44.7)	11 (0.7)
Paronychia[i]	481 (32.5)	6 (0.4)
Dry skin[j]	469 (31.7)	2 (0.1)
Pruritus[k]	256 (17.3)	1 (0.1)
Alopecia	68 (4.6)	0 (0)
Urticaria	28 (1.9)	2 (0.1)
Palmar-plantar erythrodysesthesia syndrome	25 (1.7)	0 (0)
Erythema Multiforme	5 (0.3)	0 (0)
Cutaneous Vasculitis[l]	3 (0.26)	0 (0)
Findings based on test results presented as CTCAE grade shifts		
Platelet count decreased[m]	767 (52.6)	18 (1.2)
Neutrophils count decreased[m]	474 (32.6)	47 (3.2)
Lymphocytes decreased[m]	898 (61.9)	88 (6.1)
Leukocytes count decreased[m]	940 (64.7)	17 (1.2)
Blood creatinine increased[m]	137 (9.4)	0 (0)

[a] Data is pooled from Phase III (ADAURA, FLAURA and AURA3), Phase II (AURAex and AURA2) and Phase I (AURA1) trials; only events for patients receiving at least one dose of TAGRISSO are summarized. Frequency reported in this table are regardless of causality.

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

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

[d] Includes cases reported within the clustered terms: stomatitis, mouth ulceration.

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

[f] Includes cases reported within the clustered terms: Interstitial lung disease and pneumonitis.

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

[h] Includes cases reported within the clustered terms for rash AEs: rash, rash generalized, 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.

[i] Includes cases reported within the clustered terms: nail bed disorders, 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.

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

[k] Includes cases reported within the clustered terms: pruritus, pruritus generalized, eyelid pruritus.

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

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

Hematological Events: Early reductions in the median laboratory counts of leukocytes, lymphocytes, neutrophils and platelets have been observed in patients treated with TAGRISSO, which stabilized over time and then remained above the lower limit of normal. Adverse events of leukopenia, lymphopenia, neutropenia and thrombocytopenia have been reported, most of which were mild or moderate in severity and did not lead to dose interruptions.

QT Interval Prolongation: Of the 1479 patients in the pooled ADAURA (n=337), FLAURA (n=279) and AURA Phase I (n=173), II (n=411) and III (n=279) trials treated with TAGRISSO 80 mg, 12 patients (0.8%) were found to have a QTc greater than 500 msec, 61 patients (4.1%) had a QTc greater than 480 msec, 5 patients (0.3%) had an increase from baseline QTc greater than 90 msec, and 46 patients (3.1%) had an increase from baseline QTc greater than 60 msec. No ventricular arrhythmias were reported in these trials. Consider periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, QT Interval Prolongation; 4.2 Recommended Dose and Dosage Adjustment).

ECG Findings: The effects of TAGRISSO 80 mg/day on cardiac electrophysiology were assessed in 210 patients in AURA2, which included serial ECGs at baseline following a single dose and steady-state.

In AURA2, TAGRISSO 80 mg/day was associated with a concentration-dependent prolongation of the QTcF interval ($QTcF=QT/RR^{1/3}$). During steady-state treatment on Day 43, mean changes from baseline in the QTcF interval ranged from 13.0 msec (95% CI: 11.0, 14.9) to 16.2 msec (95% CI: 14.1, 18.3) over the course of the day (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Heart Rate: TAGRISSO 80 mg/day was also associated with a concentration-dependent reduction in RR-derived ventricular heart rate. During steady-state treatment on Day 43 in AURA2, mean changes from baseline in RR-derived ventricular heart rate ranged from -2.1 (95% CI: -3.6, -0.5) to -5.9 bpm (95% CI: -7.5, -4.3) over the course of the day. In a pooled analysis of data from AURA2 and AURAex, the mean changes from baseline in pre-dose RR-derived ventricular heart rate were -1.7 bpm (95% CI: -

2.8, -0.5), -2.1 bpm (95% CI: -3.2, -0.9), -0.7 (95% CI: -1.8, 0.4) and -0.7 bpm (95% CI: -1.8, 0.5), on days 64, 85, 106 and day 127, respectively. No events of ventricular bradycardia were reported in the Phase II or III trials.

Left Ventricular Performance: The effects of TAGRISSO 80 mg daily on ventricular performance were assessed in patients in the ADAURA, FLAURA and AURA trials. Left ventricular ejection fraction (LVEF) was determined at screening and every 12 weeks relative to the first dose until treatment discontinuation. In those trials, LVEF decreases ≥10 percentage points and a drop to <50% occurred in 3.2% (40/1233) of patients treated with TAGRISSO who had baseline and at least one follow-up LVEF assessment. Consider cardiac monitoring, including an assessment of LVEF at baseline and during treatment in patients with cardiac risk factors. Assessment of LVEF in patients who develop relevant cardiac signs or symptoms during treatment should be considered. Discontinuation of treatment with TAGRISSO should be considered in patients who develop congestive heart failure (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 4.2 Recommended Dose and Dosage Adjustment).

Geriatrics (≥65 years of age): In the ADAURA, FLAURA and AURA trials (n=1479), 43% of patients were ≥65 years of age, of whom 12% were ≥75 years of age. Compared with younger patients (<65 years of age), more patients ≥65 years old had reported adverse reactions that led to study drug dose modifications (interruptions or reductions) (14.3% versus 8.4%). The types of adverse reactions reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (10.7% versus 7.6%). No overall differences in efficacy or predicted steady state exposure of osimertinib were observed between these patients and younger patients. See 7.1 Special Populations; 4.1 Dosing Considerations; 10.3 Pharmacokinetics.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 1 includes a summary of hematologic findings from the FLAURA trial (see 8 ADVERSE REACTIONS). Table 7 summarizes the grade shift change in clinical chemistry parameters in previously untreated first-line patients treated with TAGRISSO 80 mg and standard of care.

FLAURA Trial

Table 7 Clinical chemistry, maximum CTCAE grade shift from baseline during treatment in FLAURA (Safety analysis set)

Parameter	TAGRISSO 80 mg once daily (N=279)					Standard of Care (SoC) (N=277)				
CTCAE grade change n(%) of patients	All	1	2	3	4	All	1	2	3	4
ALT (increased) (TAGRISSO, n=272) (SoC, n=268)	56 (20.6)	49 (18.0)	5 (1.8)	2 (0.7)	0	138 (51.5)	90 (33.6)	27 (10.1)	19 (7.1)	2 (0.7)
AST (increased) (TAGRISSO, n=272) (SoC, n=268)	59 (21.7)	52 (19.1)	4 (1.5)	3 (1.1)	0	114 (42.5)	87 (32.5)	16 (6.0)	10 (3.7)	1 (0.4)

Parameter	TAGRISSO 80 mg once daily (N=279)					Standard of Care (SoC) (N=277)				
CTCAE grade change n(%) of patients	All	1	2	3	4	All	1	2	3	4
Total bilirubin (TAGRISSO, n=272) (SoC, n=266)	39 (14.3)	36 (13.2)	3 (1.1)	0	0	78 (29.3)	51 (19.2)	24 (9.0)	3 (1.1)	0

AURA 3 Trial

Decreases from baseline in median values for platelets, neutrophils and leucocytes were observed early in treatment with TAGRISSO. Median values appeared to stabilize after the initial drop [time of steady state (cycle 3 day 1)] with the majority of patients experiencing no change in CTCAE grade, or a single grade change from baseline. Table 8 below summarizes the shift changes in these hematologic parameters in patients treated with TAGRISSO 80 mg in the AURA3 trial.

Table 8 Hematology, maximum CTCAE grade shift from baseline occurring in patients during treatment in AURA3 (Safety analysis set)

Parameter	TAGRISSO 80 mg once daily (N=279)					Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131[a])				
	All[b]	1	2	3	4	All[b]	1	2	3	4
	CTCAE grade change n(%) of patients					CTCAE grade change n(%) of patients				
Hematology										
Blood creatinine increase	18 (6.5)	18 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	12 (9.2)	12 (9.2)	0 (0.0)	0 (0.0)	0 (0.0)
Leukocytes decreased	170 (60.9)	127 (45.5)	40 (14.3)	3 (1.1)	0 (0.0)	98 (74.8)	58 (44.3)	33 (25.2)	5 (3.8)	2 (1.5)
Lymphopenia	171 (61.3)	87 (31.2)	63 (22.6)	18 (6.5)	3 (1.1)	76 (58.0)	25 (19.1)	39 (29.8)	10 (7.6)	2 (1.5)
Neutrophils decreased	75 (26.9)	37 (13.3)	32 (11.5)	5 (1.8)	1 (0.4)	64 (48.9)	19 (14.5)	29 (22.1)	8 (6.1)	8 (6.1)
Platelet count decreased	127 (45.5)	123 (44.1)	2 (0.7)	1 (0.4)	1 (0.4)	63 (48.1)	43 (32.8)	10 (7.6)	7 (5.3)	3 (2.3)

a Based on the number of patients with available follow-up laboratory data.
CTCAE = Common Terminology Criteria for Adverse Events (version 4.0).

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported during post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably.

The following single isolated cases were reported in other clinical trials with TAGRISSO though causality could not be determined due to confounding factors: potential Hy's Law, bronchiolitis obliterans organizing pneumonia (BOOP), blindness and endophthalmitis/uveitis, and pneumonia (fatal).

Skin and subcutaneous tissue disorders: Rare, non-fatal post-marketing case reports of Stevens-Johnson syndrome have been reported in association with TAGRISSO. A frequency of 'Rare' has been derived from the single report received from a dataset of 5057 patients in the ADAURA, FLAURA and AURA studies and a post-marketing study.

Uncommon cases of erythema multiforme have been reported in association with TAGRISSO. A frequency of 'uncommon' has been derived from a dataset of 1479 patients in the ADAURA, FLAURA and AURA studies. Post-marketing reports consistent with erythema multiforme minor and major have been received, including reports from a post-marketing surveillance study (n=3578).

Cases of cutaneous vasculitis have also been reported.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In vitro studies have demonstrated that the Phase I metabolism of osimertinib is predominantly via CYP3A4 and CYP3A5. Clinical studies demonstrate that strong CYP3A4 inducers can decrease the exposure of osimertinib and that osimertinib may increase the exposure of BCRP and P-gp substrates. The related findings and precautions are discussed further below.

9.4 Drug-Drug Interactions

Effect of Other Drugs on TAGRISSO

Strong CYP3A4/5 Inhibitors: In a clinical pharmacokinetic trial in NSCLC patients, co-administration of 80 mg single dose of osimertinib with a strong CYP3A4 inhibitor itraconazole (200 mg b.i.d for 5 days) decreased the osimertinib maximum plasma concentration (C_{max}) by approximately 20% and increased the area under the curve (AUC) by approximately 24%. Given the inter-patient variability of 46% in the osimertinib exposure in the population PK analysis, this change of 24% is not clinically significant. Due to the dose proportional, linear and time independent PK of osimertinib, the effect of a strong CYP3A4 inhibitor at steady state is likely to be similar to that seen after a single dose. Hence, CYP3A4 inhibitors are unlikely to affect the exposure of osimertinib.

Strong CYP3A Inducers*:* Strong CYP3A4 inducers can decrease the exposure of osimertinib. In a clinical pharmacokinetic study in patients, the steady-state AUC and C_{max} of osimertinib was reduced by -78% and by -73% respectively, 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 continue dosing at 160 mg for 3 weeks following discontinuation of the strong CYP3A inducer. Resume TAGRISSO dosage 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 TAGRISSO on Other Drugs

BCRP substrates*:* 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 with disposition 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 (see 7 WARNINGS AND PRECAUTIONS, Drug Interactions).

PXR/P-gp substrates: 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% and 76% after a single dose and 27% and 25% 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 7 WARNINGS AND PRECAUTIONS, Drug Interactions).

CYP3A4/5 substrates: Based on *in vitro* studies, osimertinib is a competitive inhibitor of CYP3A4/5 and may induce CYP3A enzymes. 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 by -23% respectively. These changes are small and not likely to be of clinical significance. Clinical PK interactions with CYP3A4 substrates are unlikely.

Interactions with Drug Transport Systems

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

Effects of osimertinib on P-gp and BCRP: *In vitro* studies show that osimertinib is a substrate of P-gp and BCRP transporter but an interaction with co-administered P-gp or BCRP inhibitors or inducers seems unlikely (see 7 WARNINGS AND PRECAUTIONS, Drug Interactions and 9.4 Drug-Drug Interactions).

Gastric Acid Reducing Agents

In a clinical pharmacokinetic trial, co-administration of omeprazole did not result in clinically relevant changes in osimertinib exposures (see 10 CLINICAL PHARMACOLOGY). Gastric pH modifying agents (e.g., proton pump inhibitors, H2 antagonists and antacids) can be concomitantly used with TAGRISSO without any restrictions.

QT Interval Prolonging Drugs

The concomitant use of TAGRISSO with QTc interval-prolonging drugs should be avoided to the extent possible (See 7 WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; 8.2 Clinical Trial Adverse Reactions, QT Interval Prolongation and ECG Findings). Drugs that have been associated with QT interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc interval prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone)
- Class 1C antiarrhythmics (e.g., flecainide, propafenone)
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone, risperidone)
- antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants [e.g., amitriptyline, imipramine, maprotiline])
- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, azithromycin, tacrolimus)
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin)
- pentamidine
- antimalarials (e.g., quinine, chloroquine)
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- domperidone
- 5-hydroxytryptamine $(5\text{-HT})_3$ receptor antagonists (e.g., ondansetron)
- tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, ceritinib, vandetanib)
- arsenic trioxide
- histone deacetylase inhibitors (e.g., vorinostat)
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

Drugs that Affect Electrolytes

The use of TAGRISSO with drugs that can disrupt electrolyte levels should be avoided to the extent possible. Drugs that can disrupt electrolyte levels include, but are not limited to, the following:

- loop, thiazide, and related diuretics
- laxatives and enemas
- amphotericin B
- high-dose corticosteroids.

The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly approved drugs that decrease heart rate, prolong the QT/QTc interval, or decrease electrolytes, as well as for older drugs for which these effects have recently been established.

9.5 Drug-Food Interactions

Based on a clinical pharmacokinetic trial in patients at 80 mg, food (high-calorie, high-fat meal) does not alter osimertinib bioavailability to a clinically meaningful extent (AUC increase 6% (90% CI: -5, 19) and C_{max} decrease -7% (90% CI: -19, 6)). Hence, it is recommended that TAGRISSO be taken with or without food.

9.6 Drug-Herb Interactions

Avoid co-administering St. John's Wort and other herbs which are strong inducers of CYP3A4 with TAGRISSO (see 9.4 Drug-Drug Interactions).

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

TAGRISSO (osimertinib), a Tyrosine Kinase Inhibitor (TKI), is an oral, potent, and selective irreversible inhibitor of both Epidermal Growth Factor Receptor (EGFR) sensitizing-mutations (EGFRm) and T790M resistance mutation (T790M) that has limited activity against wild-type EGFR.

10.2 Pharmacodynamics

TAGRISSO (osimertinib) has been evaluated in preclinical *in vitro* and *in vivo* models to determine its primary pharmacology and mode of action. *In vitro* studies have demonstrated that TAGRISSO 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). This leads to inhibition of cell growth, while showing significantly less activity against EGFR in wild-type cell lines (apparent IC_{50}s 480 nM to 1.8 µM against phospho-EGFR). *In vivo* oral administration of TAGRISSO led to profound and durable tumour shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumour models.

Cardiovascular**:** Osimertinib inhibited the hERG (human ether-a-go-go-related gene)-encoded potassium channel in Chinese Hamster Ovary cells (N=4) with an IC_{50} of 0.69 µM. Osimertinib caused statistically significant decreases in heart rate (15-20%) and increases in the QT interval (5-7%) in conscious telemetry dogs (N=4) following oral administration of single ascending doses of 0, 6, 20 and 60 mg/kg, which produced mean osimertinib C_{max} values of 1, 0.52, 1.71 and 2.51 µmol/L, respectively.

CNS Distribution and *In Vivo* Intracranial Tumour Regression**:** TAGRISSO crosses the blood-brain barrier and is active in the Central Nervous System in non-clinical models.

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

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

Drug interactions**:** Based on *in vitro* studies, osimertinib is a competitive inhibitor of CYP 3A4/5 but not 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at clinically relevant concentrations. *In vitro*, 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.

10.3 Pharmacokinetics

The pharmacokinetics of TAGRISSO have been studied in healthy volunteers after single dose and in NSCLC patients after both single and multiple doses. The summary of steady state PK parameters of TAGRISSO is shown in Table 9.

Table 9 Summary of 80 mg Osimertinib Pharmacokinetic Parameters in NSCLC Patients Across AURA Trials

	$C_{ss,max}$ (nM)	$t_{½}$ (h)	AUC_{ss} (nM*h)	Clearance (L/h)	Volume of distribution (L)
Steady State	509	44	11040	14.3	918

The values are based on a population PK simulation of 100000 patients age (range: 25 to 91 years), gender (males 35%), ethnicity [including White (27.5%), Asian non-Japanese or non-Chinese (23.6%), Japanese (18.7%), Chinese (20.3%), other (9.95%)] and smoking status (current smokers (2.5%), former smokers (30.7%)) were calculated for an 80-mg AZD9291 simulated dose from the final PPK model (with inter-individual variability) along with patient demographics taken from AURA Phase I, AURA extension, AURA2, AURA3 and FLAURA.

The AUC and C_{max} increased dose proportionally over 20 to 240 mg dose range.

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 (objective response rate (ORR), Duration of Response (DoR) and Progression-Free Survival (PFS)) relationship for osimertinib was identified. Over the same dose range, increased exposure led to increased probability of adverse reactions, specifically rash, diarrhoea and ILD.

Administration of TAGRISSO once daily results in approximately 3 fold accumulation with steady-state exposures achieved by 15 days of dosing.

At steady-state, circulating plasma concentrations are typically maintained within a 1.6 fold range over the 24-hour dosing interval.

Absorption:

Following oral administration of TAGRISSO, peak plasma concentrations of osimertinib were achieved with a median (min-max) t_{max} of 6 (3-24) hours, with several peaks observed over the first 24 hours in some patients. The absolute bioavailability of TAGRISSO is 70% (90% CI: 67, 73).

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 C_{max} increase by 7% and 2%, respectively) with the 90% CI for exposure ratio contained within the 80-125% limit. [text]

Distribution:

Population estimated mean volume of distribution at steady-state (V_{ss}/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.

Metabolism:

In vitro studies indicate that Phase I metabolism of osimertinib is predominantly via CYP3A4, and CYP3A5. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in the plasma of animal species and in human 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. The systemic exposure of each metabolite (AZ7550 and AZ5104) was approximately 10% of the osimertinib exposure at steady-state. Both metabolites appeared slowly in plasma after administration of TAGRISSO to patients, with a median (min-max) t_{max} of 24 (4-72) and 24 (6-72) hours, respectively. In human plasma, parent osimertinib accounted for 0.8%, with the 2

metabolites contributing 0.08% and 0.07% of the total radioactivity with the majority of the radioactivity being covalently bound to plasma proteins. The geometric mean exposure of both AZ5104 and AZ7550, based on AUC, was approximately 10% each of the exposure of osimertinib at steady-state.

The main metabolic pathway of osimertinib was oxidation and dealkylation. Other metabolites detected in human hepatocytes included glutathione and cysteinylglycine adduct. 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 1A2, 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:

Osimertinib is primarily eliminated via the feces (68%) and to a lesser extent in the urine (14%). Unchanged osimertinib accounted for approximately 2% of the elimination with 0.8% in urine and 1.2% in feces.

Special Populations and Conditions

- **Pediatrics** The safety and efficacy of TAGRISSO in children below 18 years of age have not been established.
- **Geriatrics** 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.
- **Age, Sex, Ethnic Origin, Smoking Status** In a population based PK analysis (n=1367), no clinically significant relationships were identified between predicted steady-state exposure (AUC_{ss}) 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 (34 (2.5%) current smokers, n=419 (30.7%) former smokers).
- **Hepatic Insufficiency** Osimertinib is metabolized in 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. The AUC and C_{max} for osimertinib were reduced to 63.3% and 51.4% respectively in patients in mild hepatic impairment and to 68.4% and 60.7% respectively in patients with moderate hepatic impairment when compared to patients with normal liver function. For the metabolite AZ5104, the AUC and C_{max} were 66.5% and 66.3% respectively in patients with mild hepatic impairment, and 50.9% and 44.0% respectively in patients with moderate hepatic impairment when compared to the exposure in patients with normal liver function (see 4.1 Dosing Considerations). 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 trials 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. Data from 134

patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin between 1.0 to 1.5 x ULN and any AST), 8 patients with moderate hepatic impairment (total bilirubin between 1.5 x to 3.0 x ULN and any AST) and 1216 patients with normal hepatic function (total bilirubin ≤ ULN and AST ≤ ULN), showed similar osimertinib exposures. There are no data available on patients with severe hepatic impairment.

- **Renal Insufficiency** Urinary excretion of metabolites is <2% of the dose. 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 PK 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 10 mL/min were not included in the clinical trials. There are no data in patients with end stage renal disease (see 7.1 Special Populations).
- **Body Weight** Population PK analysis indicated that body weight was a significant covariate with a less than 20% change in osimertinib AUC_{ss} expected across a body weight range of 88 kg to 43 kg, respectively (95% to 5% quantiles) when compared to the AUC_{ss} for the median body weight of 62 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. These exposure changes due to body weight differences are not considered clinically relevant.
- **Serum albumin** Based on population PK analysis, serum albumin was identified as a significant covariate with a less than 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 baseline albumin are not considered clinically relevant.

Non-clinical Pharmacokinetics: Quantitative whole body autoradiography study in rats upon single oral dosing demonstrated that [^{14}C]-osimertinib-related radioactivity was rapidly and well distributed into most tissues, including the central nervous system. The distribution of radioactivity in pigmented rats resembled that found in albino rats, except for that in melanin containing tissues, where the concentration of radioactivity was high, and still measurable 60 days post-dose.

Plasma protein binding has not been determined. Osimertinib binds covalently to human serum albumin.

In all species, osimertinib related material was primarily excreted in the feces with < 5% recovered in urine.

11 STORAGE, STABILITY AND DISPOSAL

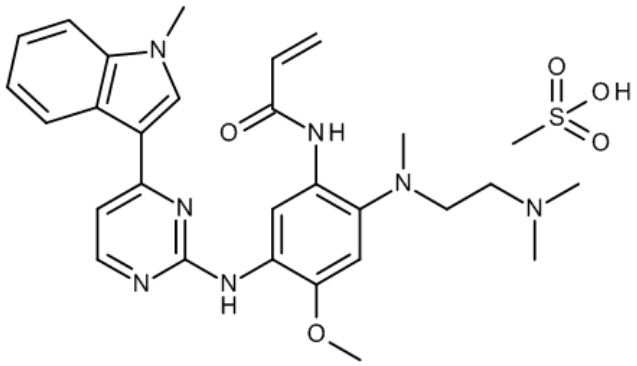
Store at controlled room temperature (15-30°C).

Keep in a safe place out of the reach of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	osimertinib mesylate
Chemical name:	*N*-(2-{[2-(Dimethylamino)ethyl](methyl)amino}-4-methoxy-5-{[4-(1-methyl-1*H*-indol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide methansulfonate (IUPAC)
Molecular formula and molecular mass:	$C_{28}H_{33}N_7O_2 \bullet CH_4O_3S$ 595.71 (as mesylate); 499.61 (as free base)
Structural formula:	
Physicochemical properties:	A white to brown powder with a melting point, defined as the onset temperature (differential scanning calorimetry) of approximately 248ºC. It has a high aqueous solubility across the physiological pH range of 1.2 to 7.0. It is an anhydrous and non-hygroscopic substance with a distribution coefficient (logD) of 3.4 (at pH 7.4) and pKa of 4.4 (aniline) and 9.5 (aliphatic amine).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

<u>Adjuvant Treatment of EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC), With or Without Prior Adjuvant Chemotherapy</u>

Trial Design and Study Demographics (ADAURA)

Table 10 Summary of patient demographics for clinical trials in ADAURA

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D5164C00001 (ADAURA)	Phase III, randomized (1:1), double-blind, placebo-controlled, that investigated TAGRISSO 80 mg once daily as adjuvant-treatment for EGFR mutation positive NSCLC with or without prior adjuvant Chemotherapy	80 mg tablets, once daily	TAGRISSO: n=339 Placebo: n=343	TAGRISSO: 62.5 (30-86) Placebo: 61.6 (31-82)	TAGRISSO: Female: n=230 Male: n=109 Placebo: Female: n=248 Male: n=95

The efficacy and safety of TAGRISSO (osimertinib) for the adjuvant treatment of patients with EGFR mutation-positive (exon 19 deletions or exon 21 L858R substitution mutations) NSCLC who have had complete tumour resection with or without prior adjuvant chemotherapy was demonstrated in a randomized, double-blind, placebo-controlled study (ADAURA).

Eligible patients with resectable tumours (stage IB-IIIA according to the American Joint Committee on Cancer (AJCC) 7th edition) were required to have EGFR exon 19 deletions or exon 21 L858R substitution mutations identified prospectively by the cobas® EGFR Mutation Test (Roche Molecular Systems) using diagnostic tumour biopsy specimen or tumour tissue taken during surgery, by central testing. The study excluded patients with clinically important ECG abnormalities identified on resting ECG (e.g. QTc interval >470 ms), history of ILD or prior treatment with neoadjuvant or adjuvant EGFR-TKIs.

Patients were randomized (1:1) to receive TAGRISSO 80 mg orally once daily or placebo following recovery from surgery and standard adjuvant chemotherapy. Patients not receiving adjuvant chemotherapy were randomized within 10 weeks and patients receiving adjuvant chemotherapy within 26 weeks following surgery. Randomization was stratified by mutation type (exon 19 deletions or exon 21 L858R substitution mutations), ethnicity (Asian or non-Asian) and staging based on TNM (IB or II or IIIA) according to the American Joint Committee on Cancer (AJCC) 7th edition. Treatment was given for 3 years or until disease recurrence or unacceptable toxicity.

The primary efficacy outcome measure was disease-free survival (DFS) by investigator assessment for stage II-IIIA. Secondary endpoints included DFS for the overall population (stage IB-IIIA) and overall survival (OS) for stage II-IIIA and stage IB-IIIA.

A total of 682 patients were randomized 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 and 72% were never smokers. Overall, study demographics and baseline characteristics were balanced between the treatment groups (see Table 11).

Table 11 Demographics and key baseline disease characteristics in ADAURA trial with TAGRISSO 80 mg (overall population)

	TAGRISSO (N=339)	Placebo (N=343)
Demographics		
Age (years)		
Mean (standard deviation)	62.5 (10.27)	61.6 (10.37)
Median (minimum-maximum)	64.0 (30-86)	62.0 (31-82)
Sex, n (%)		
Male	109 (32.2)	95 (27.7)
Female	230 (67.8)	248 (72.3)
Race, n (%)		
Asian	216 (63.7)	218 (63.6)
White	122 (36.0)	122 (35.6)
Other	1 (0.3)	2 (0.6)
Missing[a]	0 (0)	1 (0.3)
Ethnic group, n (%)		
Hispanic/Latino	12 (3.5%)	9 (2.6%)
Asian (other than Chinese or Japanese)	78 (23.0)	67 (19.5)
Chinese	95 (28.0)	100 (29.2)
Japanese	46 (13.6)	51 (14.9)
Other	108 (31.9)	116 (33.8)
Body mass index (kg/m^2)[b]		
Mean (standard deviation)	24.8 (4.29)	24.9 (4.36)
Median (minimum-maximum)	24.4 (15.1-41.8)	24.1 (16.6-42.0)
Key baseline disease characteristics		
WHO performance status		
0	216 (63.7)	218 (63.6)
1	123 (36.3)	125 (36.4)
AJCC stage at diagnosis[c]		
IB	107 (31.6)	109 (31.8)
IIA	86 (25.4)	90 (26.2)
IIB	29 (8.6)	26 (7.6)
IIIA	117 (34.5)	118 (34.4)
EGFR mutations by central cobas test[d]		
Exon 19 deletions	185 (54.6)	188 (54.8)
L858R	153 (45.1)[e]	155 (45.2)
Histology type		
Adenocarcinoma[f]	326 (96.2)	332 (96.8)
Bronchial gland carcinoma (NOS)	1 (0.3)	2 (0.6)
Carcionoma, adenosquamous, malignant	4 (1.2)	5 (1.5)
Other	8 (2.4)	4 (1.2)
Lung cancer resection type		
Lobectomy	328 (96.8)	322 (93.9)
Sleeve Resection	1 (0.3)	3 (0.9)

	TAGRISSO (N=339)	Placebo (N=343)
Bilobectomy	7 (2.1)	8 (2.3)
Pneumonectomy	3 (0.9)	10 (2.9)
Adjuvant platinum-based chemotherapy (prior to randomization) [g]	202 (59.6)	207 (60.3)
IB[h]	27 (25.2)	30 (27.5)
IIA[h]	60 (69.8)	65 (72.2)
IIB[h]	20 (69.0)	20 (76.9)
IIIA[h]	95 (81.2)	92 (78.0)

DCO: 17 January 2020

a One patient had missing race information due to local law.

b Body mass index = weight(kg)/[height(m)]^2

c AJCC TNM lung cancer staging 7th edition.

d Patients may have more than one EGFR mutation. Note: There were 12 mis-stratified patients in the IVRS. The data presented here show actual numbers confirmed by prospective central testing.

e Note: One patient was negative for both mutations and was discontinued from the study before receiving osimertinib.

f Includes: Adenocarcinoma: acinar; Adenocarcinoma: papillary, malignant; Adenocarcinoma: malignant; Adenocarcinoma: bronchiolo-alveolar; and Adenocarcinoma: solid with mucus formation

g Excludes 1 patient who received non-platinum based adjuvant chemotherapy

h Percentages are calculated from number of patients in full analysis set with the corresponding AJCC Staging (7th edition)

Study Results (ADAURA)

Efficacy results from ADAURA are summarized in Table 12, Figure 1 and Figure 2. Patients with stage II-IIIA disease treated with TAGRISSO compared to placebo, achieved 83% reduction in the risk of disease recurrence or death (median not calculable (NC) and 19.6 months, respectively, HR=0.17, 99.06% CI:0.11, 0.26; P<0.0001). The overall population (IB-IIIA) treated with TAGRISSO compared to placebo demonstrated 80% reduction in the risk of disease recurrence or death (median NC and 27.5 months, respectively, HR=0.20, 99.12% CI: 0.14, 0.30; P<0.0001). At time of DFS analysis, the median duration of exposure to TAGRISSO and placebo was 22.5 months and 18.7 months, respectively. Overall survival data were not mature at the time of DFS analysis.

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

Table 12 Efficacy results in the overall patient population (stage IB-IIIA) by investigator assessment

	Stage IB-IIIA population	
Efficacy Parameter	**TAGRISSO (n=339)**	**Placebo (n=343)**
Disease Free Survival		
Number of Events (%)	37 (10.9)	159 (46.4)
Recurrent disease (%)	37 (10.9)	157 (45.8)
Deaths (%)	0	2 (0.6)

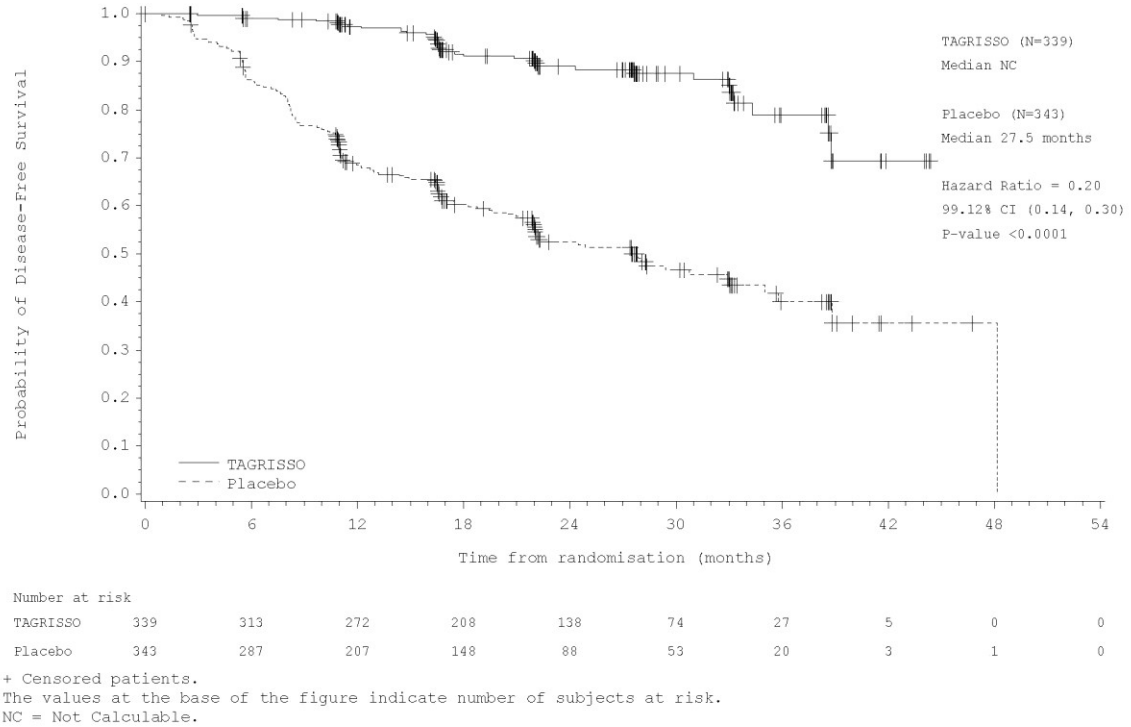
	Stage IB-IIIA population	
Efficacy Parameter	**TAGRISSO (n=339)**	**Placebo (n=343)**
Median, months (95% CI)	NC (NC, NC)	27.5 (22.0, 35.0)
HR (99.12% CI); P-value[a]	0.20 (0.14, 0.30); P-value <0.0001	
DFS rate at 12 months (%) (95% CI)	97.4 (94.9, 98.7)	68.5 (63.2, 73.2)
DFS rate at 24 months (%) (95% CI)	89.1 (84.5, 92.4)	52.4 (46.4, 58.1)
DFS rate at 36 months (%) (95% CI)[b]	78.9 (68.7, 86.1)	40.0 (32.1, 47.8)

HR=Hazard Ratio; CI=Confidence Interval, NC=Not Calculable
DFS results based on investigator assessment
Stage IB-IIIA: Median follow-up time for DFS was 22.1 months for patients receiving TAGRISSO and 16.6 months for patients receiving placebo.

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

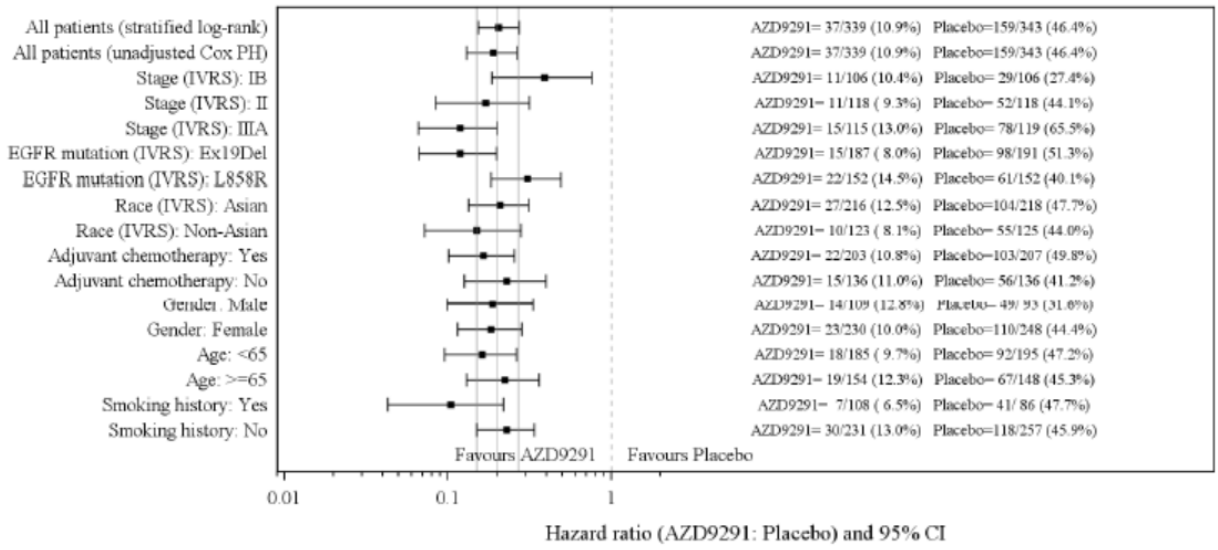
[b] The number of patients at risk at 36 months was 27 patients in the TAGRISSO arm, and 20 patients in the placebo arm.

Figure 1 Kaplan-Meier curve of Disease-Free Survival for the Overall Population (Stage IB-IIIA Patients) by investigator assessment



The DFS benefit of TAGRISSO compared to placebo was consistent across all predefined subgroups analysed (see Figure 2).

Figure 2 Disease-free survival, forest plot, by subgroup (for the overall population, Stage IB-IIIA)



The analysis was performed using a Cox proportional hazards model including treatment, subgroup and a treatment -by-subgroup interaction term. Subgroup categories with less than 20 events were excluded from the analysis. A hazard ratio <1 favours TAGRISSO (AZD9291).
DCO: 17 January 2020

EGFR Mutation-Positive NSCLC

Trial Design and Study Demographics (FLAURA)

Table 13 Summary of patient demographics for clinical trials for first-line treatment of EGFR mutation positive locally advanced or metastatic NSCLC patients

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex

D5160C00007 (FLAURA)	Phase III, randomized (1:1), double-blind, active-controlled, that investigated TAGRISSO 80 mg once daily as first line-treatment for EGFR mutation positive locally advanced or metastatic NSCLC	80 mg tablets, once daily	TAGRISSO: n=279 EGFR TKI: n=277	TAGRISSO: 62.7 (26-85) EGFR TKI: 63.3 (35-93)	TAGRISSO: Female: n=178 Male: n=101 EGFR TKI: Female: n=172 Male: n=105

The efficacy and safety of TAGRISSO for the treatment of patients with EGFR mutation positive locally advanced or metastatic NSCLC, who had not received previous systemic treatment for advanced disease, was demonstrated in a Phase III, randomized, double-blind, active-controlled trial (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 randomized 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). Randomization was stratified by EGFR mutation type (exon 19 deletion or L858R) and ethnicity (Asian or non-Asian). Patients received study therapy until intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. For patients receiving EGFR TKI comparator, post-progression crossover to open-label TAGRISSO was permitted provided tumour samples tested positive for the T790M mutation.

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

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

Table 14 Demographics and key baseline disease characteristics in FLAURA trial with TAGRISSO 80 mg (full analysis set)

	Osimertinib (N=279)	EGFR TKI comparator (gefitinib or erlotinib) (N=277)
Demographics		
Age (years)		
Mean (standard deviation)	62.7 (10.70)	63.3 (10.90)
Median (minimum-maximum)	64.0 (26-85)	64.0 (35-93)
Age group (years), n (%)		
<50	32 (11.5)	37 (13.4)
≥50-<65	121 (43.4)	108 (39.0)
≥65-<75	90 (32.3)	89 (32.1)
≥75	36 (12.9)	43 (15.5)
Sex, n (%)		
Male	101 (36.2)	105 (37.9)
Female	178 (63.8)	172 (62.1)
Race, n (%)		
Asian	174 (62.4)	173 (62.5)
Black or African American	2 (0.7)	2 (0.7)
White	101 (36.2)	100 (36.1)
American-Indian or Alaska Native	1 (0.4)	1 (0.4)
Missing	1 (0.4)	1 (0.4)
Smoking history, n (%)		
Never smokers	182 (65.2)	175 (63.2)
Current smokers	8 (2.9)	9 (3.2)
Former smokers	89 (31.9)	93 (33.6)
Key baseline disease characteristics		
WHO performance status		
0 (normal activity)	112 (40.1)	116 (41.9)
1 (restricted activity)	167 (59.9)	160 (57.8)
Missing	0	1 (0.4)
Overall disease classification		
Metastatic[a]	264 (94.6)	262 (94.6)
Locally-advanced[b]	14 (5.0)	15 (5.4)
Missing	1 (0.4)	0
CNS metastases[c]	53 (19.0)	63 (22.7)
Extra-thoracic visceral metastases	94 (33.7)	103 (37.2)
Liver metastases	41 (14.7)	37 (13.4)
Bone & locomotor metastases	97 (34.8)	102 (36.8)
EGFR mutations as used for randomization[d]		
Exon 19 deletion	175 (62.7)	174 (62.8)
Exon 21 L858R	104 (37.3)	103 (37.2)

[a] Metastatic disease - Patient had any metastatic site of disease.
[b] Locally advanced - Patient had only locally advanced sites of disease.
[c] This is a programmatically derived composite endpoint with a list of contributing data sources.
[d] EGFR mutations based on the test (local or central) used to determine randomisation strata (Ex19del or L858R).

Study Results (FLAURA)

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 summarized in Table 15, and the Kaplan-Meier curve for PFS is shown in Figure 3. The final analysis of overall survival (58% maturity) demonstrated a statistically significant improvement with an HR of 0.799 (95.05% CI: 0.641, 0.997; P=0.0462) in patients randomized to TAGRISSO compared to EGFR TKI comparator (Table 15 and Figure 4).

Table 15 Efficacy results from FLAURA by investigator assessment (Full analysis set)

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-value <0.0001	
Overall Survival		
Number of deaths, (58% maturity)	155 (56)	166 (60)
Median OS in months (95% CI)	38.6 (34.5, 41.8)	31.8 (26.6, 36.0)
HR (95.05% CI); P-value	0.799 (0.641, 0.997); P = 0.0462[†]	
Objective Response Rate[*a]		
Number of responses	223	210
Response Rate (95% CI)	80 (75, 85)	76 (70, 81)
Complete Response, n(%)	7 (2.5)	4 (1.4)
Partial Response, n(%)[b]	216 (77.4)	206 (74.4)
Odds ratio (95% CI); P-value	1.3 (0.9, 1.9); P-value = 0.2421	
Duration of Response (DoR)[*]		
Median, Months (95% CI)	17.2 (13.8, 22.0)	8.5 (7.3, 9.8)

HR=Hazard Ratio; CI=Confidence Interval

PFS, ORR and DoR results based on RECIST investigator assessment

[*] Based on unconfirmed response

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

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

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

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

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

[a] 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 3 Kaplan-Meier Curves of Progression-Free Survival as assessed by investigator in FLAURA

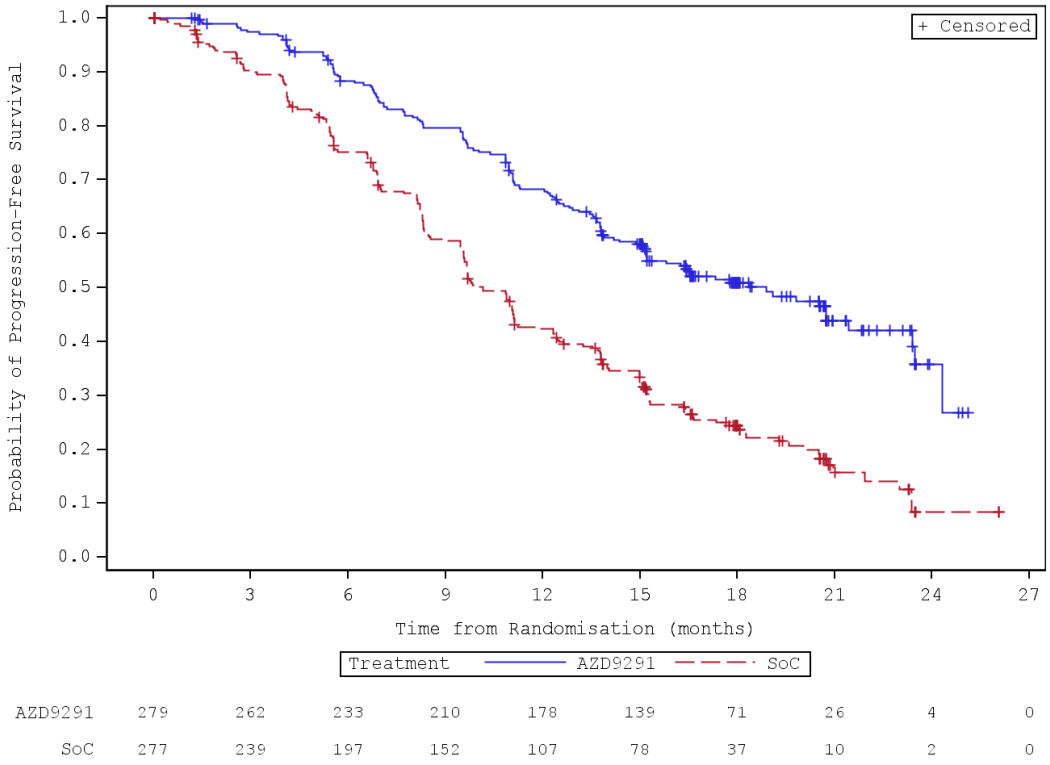
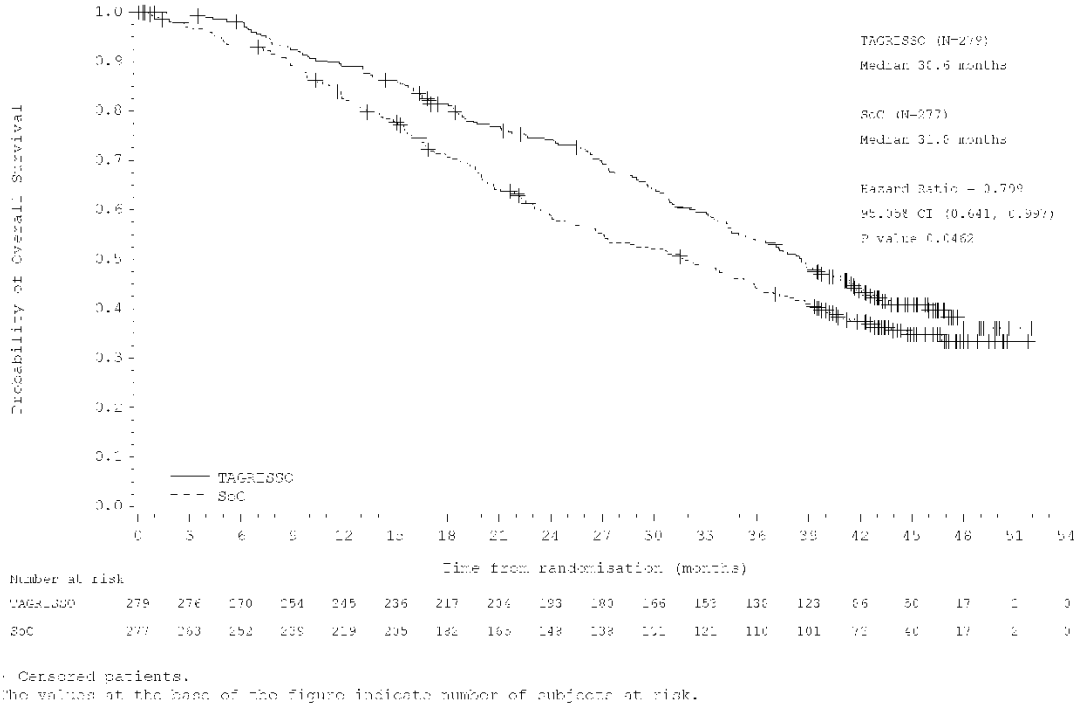


Figure 4 Kaplan-Meier Curves of Overall Survival in FLAURA



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

Patients randomized to TAGRISSO as first-line treatment also had clinically meaningful improvements in second PFS after start of first subsequent therapy (PFS2), time from randomization to first subsequent treatment of death (TFST) and time from randomization to second subsequent treatment or death (TSST) compared to patients randomized to EGFR TKI comparator. A continued clinical benefit beyond initial progression for patients treated with TAGRISSO was demonstrated by a clinically meaningful delay to PFS2 (HR: 0.58 [95% CI: 0.44, 0.78]; p=0.0004), TFST (HR: 0.51 [95% CI: 0.40, 0.64]; p < 0.0001) and TSST (HR: 0.60 [95% CI: 0.45, 0.80]; p=0.0005) for patients on TAGRISSO compared to patients on EGFR TKI comparator. The analysis of these post-progression endpoints demonstrated that PFS benefit was largely preserved through subsequent lines of therapy.

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

CNS metastases efficacy in the FLAURA trial

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 randomized 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 summarized in Table 16. EGFR mutation type (Ex19del or L858R) and ethnicity (Asian or non-Asian) was generally balanced within this analysis between the treatment arms. CNS efficacy by RECIST v1.1 in FLAURA demonstrated a statistically significant improvement in CNS PFS (HR=0.48, 95% CI: 0.26, 0.86; P=0.014).

Table 16 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[a]		
Number of Events (%)	18 (30)	30 (45)
Median, Months (95% CI)	NC (16.5, NC)	13.9 (8.3, NC)
HR (95% CI); P-value	0.48 (0.26, 0.86); P=0.014	
CNS progression free and alive at 6 months (%) 95% CI)	87 (74, 94)	71 (57, 81)
CNS progression free and alive at 12 months (%) (95% CI)	77 (62, 86)	56 (42, 68)
CNS Objective Response Rate[a]		
CNS Response Rate % (n) (95% CI)	66 (40) (52, 77)	43 (29) (31, 56)
Odds ratio (95% CI); P-value	2.5 (1.2, 5.2); P-value=0.011	
CNS Duration of Response[a]		
Median, Months (95% CI)	NC (12, NC)	14 (7, 19)
Patients remaining in response at 6 months (%) (95% CI)	86 (70, 94)	76 (55, 89)
Patients remaining in response at 12 months (%) (95% CI)	65 (46, 79)	67 (43, 82)

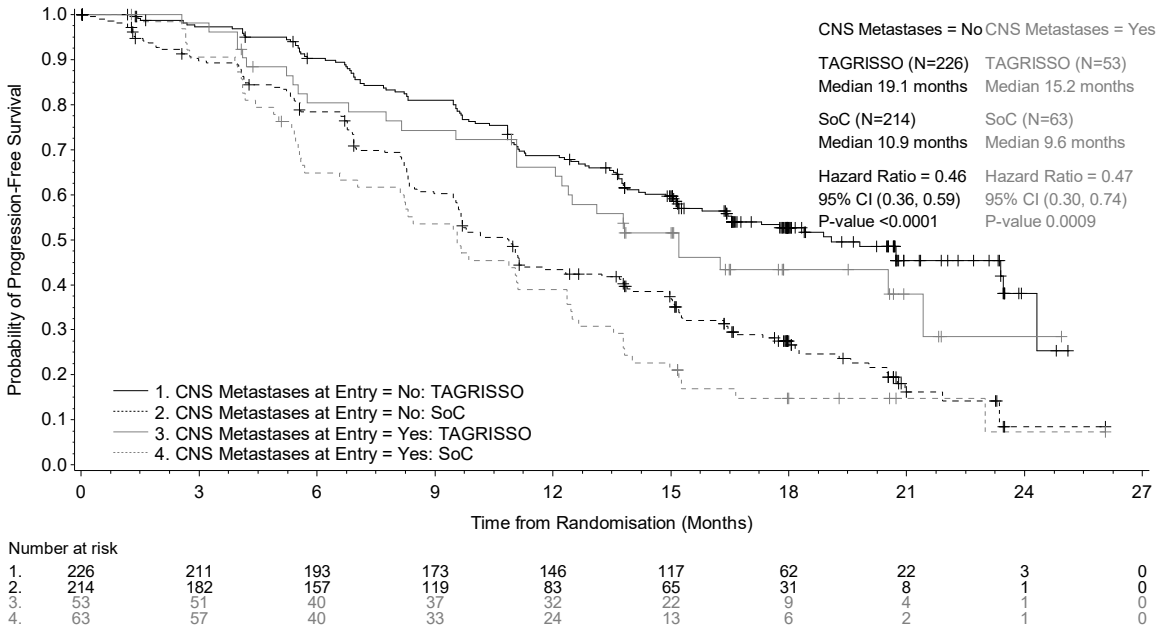
HR=Hazard Ratio; CI=Confidence Interval, NC=Not Calculable

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

a CNS PFS, ORR and DoR determined by RECIST v1.1by CNS BICR (CNS measurable and non-measurable lesions at baseline by BICR) n=61 for TAGRISSO and n=67 for EGFR TKI comparator; responses are unconfirmed

A pre-specified PFS subgroup based on CNS metastases status (identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases) at study entry was performed in FLAURA and is shown in Figure 5. Irrespective of CNS lesion status at study entry, patients in the TAGRISSO arm demonstrated an efficacy benefit over those in the EGFR TKI comparator arm.

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



Number at risk

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

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

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

Patient Reported Outcomes (PRO)

Patient-reported symptoms and health-related quality of life (HRQL) were electronically collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). At baseline, no differences in patient reported symptoms, function or HRQL were observed between TAGRISSO and EGFR TKI comparator (gefitinib or erlotinib) arms. 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, dyspnea, chest pain, fatigue, and appetite loss). Up to month 9, there were no clinically meaningful differences (as assessed by a difference of ≥10 points) between the TAGRISSO and EGFR TKI comparator groups in functioning or HRQL.

EGFR T790M Mutation-Positive Advanced NSCLC

Trial Design and Study Demographics (AURA3)

Table 17 Summary of patient demographics for clinical trials in EGFR T790M mutation positive NSCLC.

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
D5106C00003 (AURA3)	Phase III, randomized (2:1), open label, active-controlled study that investigated TAGRISSO 80 mg once daily as treatment for locally advanced or metastatic EGFR T790M mutation positive NSCLC.	80 mg Tablet, Once daily	TAGRISSO: n=279 Platinum-based doublet chemotherapy n=140	TAGRISSO: 62.0 (25-85) Platinum-based doublet chemotherapy 63.0 (20-90)	TAGRISSO: 107 Platinum-based doublet chemotherapy 172

The efficacy and safety of TAGRISSO 80 mg tablets for the treatment of patients with locally advanced or metastatic EGFR T790M NSCLC whose disease has progressed on or after EGFR TKI therapy, was demonstrated in a randomized, open label, active-controlled Phase III trial (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 randomization. The EGFR T790M mutation status was also assessed using ctDNA extracted from a plasma sample taken during screening. The primary efficacy endpoint was progression-free survival (PFS) as assessed by the investigator. Secondary efficacy endpoints included objective response rate (ORR), duration of response (DoR) and overall survival (OS) as assessed by the investigator.

Patients were randomized in a 2:1 (TAGRISSO: platinum-based doublet chemotherapy) ratio to receive TAGRISSO (n=279) or platinum-based doublet chemotherapy (n=140). Randomization 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/m2 with carboplatin AUC5 or pemetrexed 500 mg/m2 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/m2 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 cross over to receive treatment with TAGRISSO.

Demographic and disease characteristics for AURA3 are provided in Table 18.

Table 18 Demographic and disease characteristics in Phase III AURA3 trial (Full analysis set)

Characteristic		TAGRISSO 80mg (N=279)	Chemotherapy (N=140)	Total (N=419)
Age (years), n (%)				
	Median (range)	62.0 (25-85)	63.0 (20-90)	62.0 (20-90)
	<65	165 (59.2)	77 (55.0)	242 (57.8)
	≥65-<75	72 (25.8)	41 (29.3)	113 (27.0)
	≥75	42 (15.1)	22 (15.7)	64 (15.3)
Sex, n (%)				
	Male	107 (38.4)	43 (30.7)	150 (35.8)
	Female	172 (61.6)	97 (69.3)	269 (64.2)
Race, n (%)				
	White	89 (31.9)	45 (32.1)	134 (32.0)
	Black or African American	4 (1.4)	1 (0.7)	5 (1.2)
	Asian	182 (65.2)	92 (65.7)	274 (65.4)
	Other	4 (1.4)	2 (1.4)	6 (1.4)
Smoking status, n (%)				
	Never	189 (67.7)	94 (67.1)	283 (67.5)
	Current	14 (5.0)	8 (5.7)	22 (5.3)
	Former	76 (27.2)	38 (27.1)	114 (27.2)
WHO performance status, n (%)				
	0 (Normal activity)	102 (36.6)	56 (40.0)	158 (37.7)
	1 (Restricted activity)	177 (63.4)	84 (60.0)	261 (62.3)
Histology type				
	Squamous cell carcinoma (NOS)	3 (1.1)	0 (0.0)	3 (0.7)
	Adenocarcinoma[b]	274 (98.2)	139 (99.3)	413 (98.6)
	Non-small cell carcinoma	0 (0.0)	1 (0.7)	1 (0.2)
	Adenosquamous carcinoma	2 (0.7)	0 (0.0)	2 (0.5)
Overall disease classification				
	Metastatic	266 (95.3)	138 (98.6)	404 (96.4)
	Locally advanced	13 (4.7)	2 (1.4)	15 (3.6)
Metastases				
	CNS[a]	93 (33.3)	51 (36.4)	144 (34.4)
	Extra-thoracic Visceral	145 (52.0)	80 (57.1)	225 (53.7)
	Liver	56 (20.1)	41 (29.3)	97 (23.2)
	Bone/locomotor	105 (37.6)	71 (50.7)	176 (42.0)
Number of previous anti-cancer treatment regimens for advanced disease				
	1	269 (96.4)	134 (95.7)	403 (96.2)
	2	9 (3.2)	6 (4.3)	15 (3.6)
	3	1 (0.4)	0 (0.0)	1 (0.2)
	Median (range)	1.0 (1-3)	1.0 (1-2)	1.0 (1-3)
EGFR Mutations by cobas® central test				

Table 18 Demographic and disease characteristics in Phase III AURA3 trial (Full analysis set)

Characteristic		TAGRISSO 80mg (N=279)	Chemotherapy (N=140)	Total (N=419)
	EGFR EXON 20 T790M	275 (98.6)	138 (98.6)	413 (98.6)
	EGFR EXON 21 L858R	83 (29.7)	45 (32.1)	128 (30.5)
	EGFR EXON 19 Deletion	191 (68.5)	87 (62.1)	278 (66.3)
	G719X	4 (1.4)	2 (1.4)	6 (1.4)
	S768I	1 (0.4)	1 (0.7)	2 (0.5)
	EGFR EXON 20 Insertion	1 (0.4)	2 (1.4)	3 (0.7)
Duration of Prior EGFR TKI Therapy				
	<6 Months	17 (6.1)	7 (5.0)	24 (5.7)
	≥ 6 Months	262 (93.9)	133 (95.0)	395 (94.3)

[a] CNS metastases at study entry identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases.

[b] Includes: Adenocarcinoma (Not otherwise specified); Adenocarcinoma: acinar; Adenocarcinoma: papillary; Adenocarcinoma: bronchioloalveolar; Adenocarcinoma: solid with mucus formation and; Adenocarcinoma: bronchioloalveolar carcinoma (bac) and papillary.

Study Results (AURA3)

At the time of the primary PFS analysis, 43.9% of patients were ongoing on their randomised treatment (59.5% in the TAGRISSO arm and 11.8% in the chemotherapy arm).

AURA3 demonstrated a clinically meaningful and statistically significant improvement in PFS in the patients treated with TAGRISSO compared to chemotherapy. Efficacy results from AURA3 by investigator assessment are summarized in Table 19, and the Kaplan-Meier curve for PFS is shown in Figure 6.

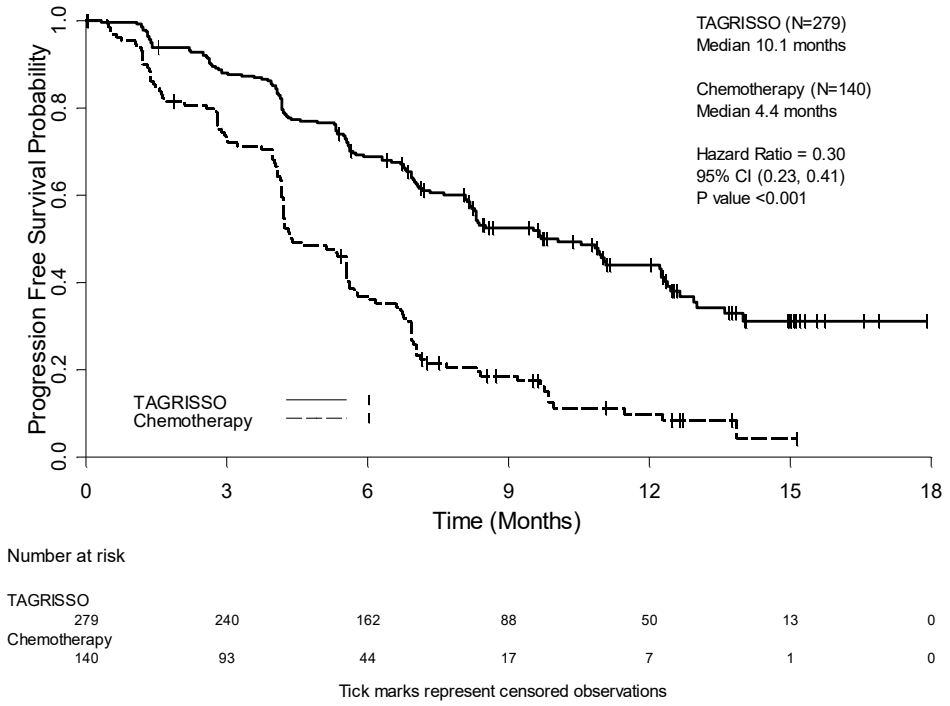
Table 19 Efficacy results from AURA3 by investigator assessment (Full analysis set)

Efficacy Parameter	TAGRISSO (n=279)	Chemotherapy (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	
Objective Response Rate		
Number of responses [a],	197	44
Response Rate (95% CI)	71 (65, 76)	31 (24, 40)
Complete Response, n(%)[a]	4 (1.4)	2 (1.4)
Partial Response, n(%)[a]	193 (69.2)	42 (30.0)
Odds ratio (95% CI); P-value	5.4 (3.5, 8.5); P-value <0.001	
Duration of Response		
Median, Months (95% CI)	9.7 (8.3, 11.6)	4.1 (3.0, 5.6)

CI=confidence interval; HR=Hazard Ratio
All efficacy results based on RECIST investigator assessment
A HR<1 favours TAGRISSO

[a] Response does not require confirmation

Figure 6 Kaplan-Meier Curves of Progression-Free Survival as assessed by investigator in AURA3



The AURA3 primary outcome measure included a sensitivity analysis of PFS using Blinded Independent Central Review (BICR); this analysis demonstrated a consistent treatment effect (HR 0.28; 95% CI: 0.20, 0.38; p<0.0001) 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.

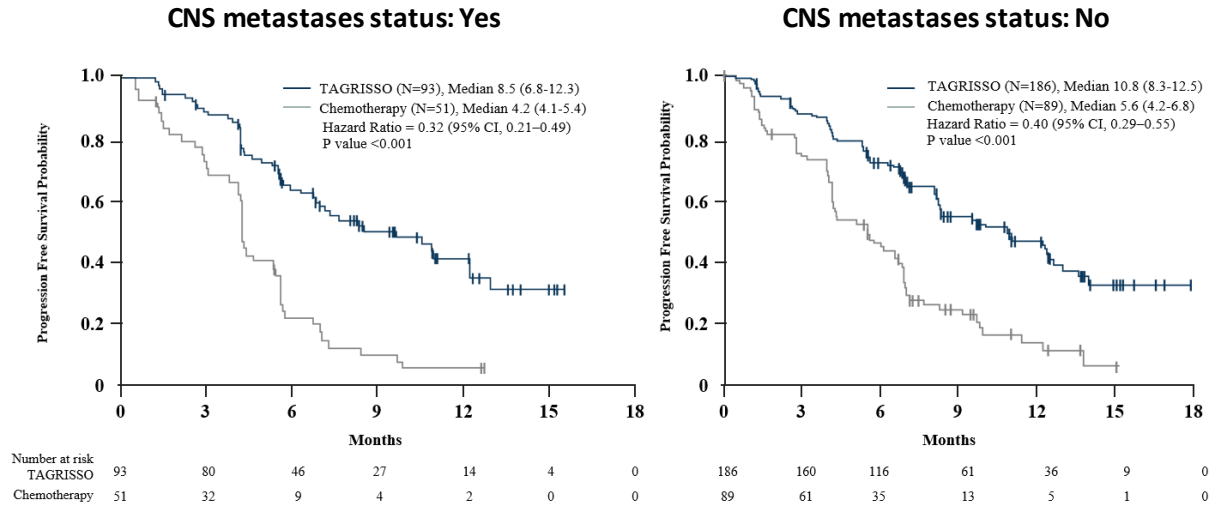
Among the patients in AURA3 treated with TAGRISSO with objective responses, 81.7% (161/279) had documentation of response at 6 weeks, and 94.9% (187/279) had documentation of response at 12 weeks.

The overall survival (OS) data was not mature at the time of the final PFS analysis (25% of patients had died). The final OS analysis was performed based on 281 death events (67% maturity, at which time 99 patients (71%) randomized to chemotherapy had crossed over to TAGRISSO treatment). Median OS in the TAGRISSO arm was 26.8 months compared to 22.5 months in the chemotherapy arm [Hazard ratio 0.87 (95% CI 0.67, 1.12), not statistically significant.

CNS Metastasis Efficacy Data in AURA3 Trial

An analysis of PFS by investigator assessment using RECIST v1.1 was performed in 419 patients based on CNS metastases status (Yes or No) at study entry (see Figure 7). The benefit of TAGRISSO was reported in patients with or without CNS metastases at baseline.

Figure 7 Kaplan-Meier curve of overall PFS by CNS metastases status at study entry in AURA3 as assessed by investigator (Full analysis set)



A BICR assessment of CNS efficacy by RECIST v1.1 was performed in a subgroup of 116/419 (28%) patients identified to have CNS metastases on a baseline brain scan are summarized in Table 20.

Table 20 CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in AURA3 (Full analysis set)

Efficacy Parameter	TAGRISSO	Chemotherapy
CNS Objective Response Rate[a]		
CNS response rate %, (n/N) (95% CI)	70% (21/30) (51, 85)	31% (5/16) (11, 59)
Complete Response, n (%)	2 (6.7)	1 (6.3)
Partial Response, n (%)	19 (63.3)	4 (25.0)
Odds Ratio (95% CI); P-value	5.1 (1.4, 21); P-value = 0.015	
CNS Duration of Response[b]		
Median, Months (95% CI)	8.9 (4.3, NC)	5.7 (NC, NC)
CNS Disease Control Rate (DCR)		
DCR (Number with CNS disease control) (95% CI)	87% (65/75) (77, 93)	68% (28/41) (52, 82)
Odds Ratio (95% CI); P-value	3 (1.2, 7.9); P-value = 0.021	
CNS Progression-free survival[c]	N=75	N=41

Efficacy Parameter	TAGRISSO	Chemotherapy
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-value = 0.004	

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

A HR< 1 favours TAGRISSO

[a] CNS ORR and DoR determined by RECIST v1.1 by CNS BICR in the evaluable for response population (CNS measurable lesions at baseline by BICR) n=30 for TAGRISSO and n=16 for Chemotherapy.

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

[c] CNS PFS determined by RECIST v1.1by CNS BICR in the full analysis set population (CNS measurable and non-measurable lesions at baseline by BICR) N=75 for TAGRISSO and N=41 for Chemotherapy.

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

TAGRISSO decreased the appearance of new CNS metastases (4.7%) as compared with chemotherapy (14.3%) according to RECIST v1.1 by investigator assessment; 2.5% compared to 9.3%, respectively based on BICR assessment.

EGFR T790M Mutation-Positive Advanced NSCLC - Phase II (AURAex and AURA2) Trials

The use of TAGRISSO 80 mg in the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who progressed on prior systemic therapies, including an EGFR TKI was investigated in two Phase II, multicenter, single-arm, open-label clinical trials, AURAex (Phase II Extension cohort of 201 patients) and AURA2 (210 patients). 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.

The primary efficacy endpoint of both trials was objective response rate (ORR) based on BICR using RECIST v1.1. Secondary efficacy endpoints included DoR.

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%) had received 1 prior line of therapy (EGFR-TKI treatment only, second line, chemotherapy naïve), 69% 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.

With a median duration of follow-up of 13 months (AURAex and AURA2) in the 411 patients, the ORR was 66% (95% CI: 61, 71). In patients with a confirmed response, the median DoR was 12.5 months (95% CI: 11.1, non-evaluable).

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

CNS Metastases Efficacy Data in Phase II Trials (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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity:

Repeat dose toxicity

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

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

Carcinogenesis and mutagenesis

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

Reproductive and Developmental Toxicology: Based on studies in animals, male fertility may be impaired by treatment with TAGRISSO. 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 lesions in dogs cannot be made.

Based on studies in animals, female fertility may be impaired by treatment with TAGRISSO. In repeat dose toxicity studies, an increased incidence of anestrus, 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 estrus 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 embryofetal 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 fetal weights but no adverse effects on external or visceral fetal 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).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

TAGRISSO®

Osimertinib tablets

Read this carefully before you start taking **TAGRISSO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TAGRISSO**.

Serious Warnings and Precautions

TAGRISSO should only be prescribed by a doctor with experience in the use of anti-cancer drugs.

These are rare but serious side effects that have been seen in patients taking TAGRISSO:

- Serious Lung Problems (interstitial lung disease (including pneumonitis)): This can cause inflamed or scarred lungs and death in some cases.
- Serious Electrical Problems with the Heart: Abnormal electrical signal of the heart (QT interval prolongation).
- Heart Failure and an Enlarged Heart: When your heart is weak and can't pump well enough to get blood to the body. It may lead to death.

What is TAGRISSO used for?

TAGRISSO is used in adults to treat a type of cancer called 'non-small cell lung cancer' (NSCLC). The cancer must have tumour changes (mutations) in a gene called EGFR (epidermal growth factor receptor).

TAGRISSO is used after the tumours are removed by surgery, to prevent the cancer from coming back, if:

- the tumours have 'EGFR exon 19 deletion' or 'EGFR exon 21 (L858R) substitution' mutations. This is checked by a test before TAGRISSO is used.

TAGRISSO is used when the tumours have spread to other parts of the body or cannot be removed by surgery if:

- the tumours have 'EGFR exon 19 deletion' or 'EGFR exon 21 (L858R) substitution' mutations. This is checked by a test before TAGRISSO is used for the first treatment of your cancer.
- the tumours have an 'EGFR T790M mutation'. This is checked by a test before TAGRISSO is used. You may have been treated before with other EGFR inhibitor medicines.

How does TAGRISSO work?

TAGRISSO is a type of drug that targets EGFR sensitising mutations and T790M mutations. TAGRISSO may help prevent your lung cancer from coming back after removal of the tumour by surgery. It may also help to slow or stop your lung cancer from growing or help to shrink the tumour. TAGRISSO has

been shown to produce effects on the tumour within 6 to 12 weeks of starting therapy. However, this may vary from patient to patient.

What are the ingredients in TAGRISSO?

Medicinal ingredient: osimertinib (as osimertinib mesylate)
Non-medicinal ingredients: black iron oxide, low-substituted hydroxypropyl cellulose, macrogol 3550, mannitol, microcrystalline cellulose, polyvinyl alcohol, red iron oxide, sodium stearyl fumarate, talc, titanium dioxide, and yellow iron oxide.

TAGRISSO comes in the following dosage forms:

Tablets, 40 and 80 mg.

Do not use TAGRISSO if:

- you are allergic to osimertinib or any of the other ingredients of TAGRISSO or the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TAGRISSO. Talk about any health conditions or problems you may have, including if you:

- have suffered from interstitial lung disease (including pneumonitis) which means that your lungs were inflamed or scarred.
- have ever had heart problems.
- have a family history of sudden cardiac death before 50 years of age.
- are dehydrated or suffer from excessive vomiting or eating disorders.
- have problems with your electrolytes such as low levels of potassium in the blood (hypokalemia), low levels of magnesium in the blood (hypomagnesemia) or low levels of calcium in the blood (hypocalemia).
- have a history of fainting.
- have liver disease or kidney disease.
- have a history of eye problems.
- wear contact lenses.
- have any other medical conditions.

Other warnings you should know about:

- You will need to have your cancer tested to see if you have the EGFR mutation before taking TAGRISSO.
- TAGRISSO should not be used in children and adolescents under 18 years of age.

Skin and nail problems can occur. You may get rash, dry skin, itching and problems with your nails. These are more likely in areas exposed to the sun. This can include **paronychia** which is red, hot, painful pus-filled blisters or swelling around the nail or an infection where the nail and skin meet at the side or the base of a fingernail or toenail. Consider using moisturizers regularly on your skin and nails to help control these problems.
Eye problems can occur. You should tell your doctor right away if you get any symptoms of eye problems: eye pain, swelling, redness with a gritty feeling, watery eyes; blurred vision, sensitivity to light, sudden changes in your eyesight, or other eyesight changes. If left untreated, your eye problems

may worsen and may lead to loss of eyesight. You may be at increased risk if you wear contact lenses.

Pregnancy, contraception and breastfeeding – information for women and men

Pregnancy – information for women

- You must not take TAGRISSO if you are pregnant. This is because it may harm your unborn baby.
- TAGRISSO can cause miscarriage.
- Do not get pregnant while taking TAGRISSO. If you are able to get pregnant, you must use effective birth control.
- If you get pregnant during treatment, tell your doctor immediately. Your doctor will decide with you if you should continue to take TAGRISSO.
- If you plan to get pregnant after taking the last dose of TAGRISSO, ask your doctor for advice. This is because TAGRISSO may remain in your body after the last dose.

Pregnancy – information for men
Avoid fathering a child during treatment. If your partner gets pregnant while you are taking TAGRISSO, tell her doctor right away.

Birth Control - information for women and men
You must use effective birth control during treatment.
Men taking TAGRISSO must use a condom because the drug may pass into the sperm.

After you finish treatment with TAGRISSO:

- Women must keep using birth control for at least 2 months.
- Men must keep using birth control for at least 4 months.

Breastfeeding
Do not breastfeed while taking TAGRISSO. It may get into breast milk and harm your baby.

Driving and using machines: Do not drive or use any tools or machines if you feel dizzy or get any symptoms that affect your eyesight, ability to concentrate or react.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. This is because TAGRISSO can affect the way some other medicines work. Also, some other medicines can affect the way TAGRISSO works. For example:

The following may interact with TAGRISSO:

- Some drugs that may reduce how well TAGRISSO works:
- Phenytoin, carbamazepine or phenobarbital. They are used for seizures or fits.
- Rifabutin or rifampicin. They are used for tuberculosis (TB).
- St. John's Wort (Hypericum perforatum). It is an herbal medicine used for depression. You should avoid using this product while taking TAGRISSO.

TAGRISSO may affect how well the following medicines work or may lead to increased side effects:

- Rosuvastatin – used to lower cholesterol
- Daunorubicin, doxorubicin, paclitaxel and topotecan - used for cancer
- Dabigatran etexilate – used to prevent blood clots
- Digoxin – used to treat irregular heart beat or other heart problems
- Aliskiren – used for high blood pressure

In addition, the following list includes some, but not all, medicines that may increase the risk of heart rhythm problems while receiving TAGRISSO:

- Medicines for heart rhythm problems (antiarrhythmics) such as quinidine, amiodarone and flecainide
- Antipsychotics such as chlorpromazine, pimozide haloperidol, droperidol, ziprasidone and risperidone
- Antidepressants such as fluoxetine and citalopram
- Opioids such as methadone
- Macrolide antibiotics and analogues such as erythromycin and tacrolimus
- Quinolone antibiotics such as moxifloxacin and levofloxacin
- Pentamidine – used to treat pneumonia
- Antimalarials such as quinine and chloroquine
- Antifungals such as ketoconazole and fluconazole
- Medicines for nausea and vomiting such as domperidone and ondansetron
- Other cancer medicines such as sunitinib, nilotinib, arsenic trioxide and vorinostat
- Medicines for asthma such as salmeterol and formoterol
- Medicines that decrease electrolyte levels such as loop, thiazide and related diuretics; laxatives and enemas; amphotericin B and high-dose corticosteroids

How to take TAGRISSO:

Always take this medicine exactly as your doctor or pharmacist has told you. Do not stop taking this medicine - talk to your doctor first. It is important to take this medicine **every day**, for as long as your doctor prescribes it for you. If you do not take this medicine as prescribed by your doctor, your cancer may grow again. Check with your doctor or pharmacist if you are not sure.

Take TAGRISSO:

- By mouth, with or without food, every day at about the same time.
- Swallow the tablet whole with water. Do NOT crush, split or chew the tablet.

If you have trouble swallowing the tablet, you can mix it in water:

- Put the tablet in a glass - do not crush, split or chew the tablet.
- Add 50 mL of non-carbonated, room temperature water - do not use any other liquids.
- Stir the water until the tablet breaks-up into very small pieces - the tablet will not completely dissolve.
- Drink the liquid immediately.
- To make sure you have taken all of the medicine, rinse the glass thoroughly with another 50 mL of water and drink it.

Usual dose:

Adults: One 80 mg tablet every day in a single dose.

If necessary, your doctor may need to adjust your dose:

- Reduced Adult Dose: One 40 mg tablet every day in a single dose.
- Increased Adult Dose: Two 80 mg tablets (160 mg) every day in a single dose.

Overdose:

If you think you, or a person you are caring for, have taken too much TAGRISSO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget a dose, take it as soon as you remember it. However, if it is less than 12 hours until your next dose is due, skip the missed dose. Take your next normal dose at its scheduled time.

What are possible side effects from using TAGRISSO?

These are not all the possible side effects you may feel when taking TAGRISSO. If you experience any side effects not listed here, contact your healthcare professional. Please also see the Serious Warnings and Precautions Box above. Side effects may include:

- Decrease in appetite, sores inside the mouth
- Vomiting
- Headache, dizziness, decreased ability to concentrate or react
- Weakness, feeling tired
- Back pain
- Cough
- Nose or throat infection, runny or stuffy nose
- Nose bleeds
- Changes in eyesight
- Hair loss

TAGRISSO can cause abnormal test results. Your doctor will decide when to do necessary tests. They include heart tests such as Echocardiogram and Electrocardiogram (ECG). Eye exams may be needed. Blood tests are needed before you start and while taking TAGRISSO. Your doctor will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Diarrhea that comes and goes: At least 3 loose liquid bowel movements a day.	✓		
Nausea, Constipation	✓		
Stomatitis: ulcer or sore, red and inflamed areas on the lips or inside the mouth.	✓		
Decreased white blood cells (leukocytes, lymphocytes or neutrophils): infections, fatigue, fever, aches, pains, and flu-like symptoms.		✓	
Decreased platelets: bruising, bleeding, fatigue, and weakness.		✓	
Skin and nail problems: itching, dry skin, rash, redness. **Paronychia (nail infection):** red, hot, painful pus-filled blisters around the nail, with swelling. Detached, discoloured or abnormally shaped nails.		✓	
COMMON			
Lung problems (interstitial lung disease, pneumonitis, pneumonia): serious or suddenly worse shortness of breath, wheezing, tiredness, possibly with a cough or fever. Painful breathing. This can cause death in some cases.			✓
Electrical problems with the heart (QT interval prolongation) that could lead to heart rhythm disturbances: fatigue, weakness, dizziness, fainting, being lightheaded or loss of consciousness, irregular heartbeat.			✓
Heart failure and an enlarged heart (left ventricular dysfunction, cardiomyopathy and congestive heart failure): tiredness along with swollen ankles, shortness of breath especially when lying down.			✓
Liver disorder, jaundice, toxicity, or failure: yellow skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite.		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Eye infection (conjunctivitis): itchy, red eyes with discharge, and swelling. **Eye problems:** trouble seeing, blurred vision, dry eye.		✓	
Pulmonary embolism: shortness of breath, chest pain particularly upon breathing in, and coughing up blood.			✓
Shortness of breath		✓	
Acute respiratory failure: sudden worsening of shortness of breath, bluish colour on skin, lips, and fingernails, irregular heartbeats, feel sleepy, loss of consciousness.			✓
Palmar-plantar erythrodysesthesia syndrome (Hand-foot syndrome): redness, swelling, tingling or burning sensation with cracking of the skin on the palms of hands and/or soles of feet.		✓	
Hives (Urticaria): itchy, raised patches anywhere on the skin, which may be pink or red and round in shape.		✓	
UNCOMMON			
Pulmonary edema (fluid in the air spaces of the lungs)**:** difficulty breathing that is worse when you lie down. Cough up blood or blood-tinged froth.		✓	
Reduced kidney function: change in frequency of urination, pain when you urinate, nausea, vomiting, swelling of extremities, fatigue.	✓		
Keratitis (red eye with a 'gritty' sensation): eye pain, eye swelling and redness, watery eyes, vision changes, and sensitivity to light.		✓	
Erythema multiforme: skin reaction with target lesions that look like rings.			✓
RARE			
Stevens-Johnson syndrome: Severe blistering or peeling of skin.			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN			
Allergic reactions: itch, rash, hives, swelling of the lips, tongue or throat, difficulty swallowing or breathing.			✓
Cutaneous vasculitis (inflammation of blood vessels): red spots on skin that don't change colour when pressed, bruise-like marks on the skin, raised skin lumps.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep TAGRISSO out of sight and reach of children.
- Do not use this medicine after the expiry date (EXP) which is stated on the blister foil and carton. The expiry date refers to the last day of that month.
- Keep TAGRISSO tablets at room temperature (15-30°C).
- Do not use any pack that is damaged or shows signs of tampering.

If you want more information about TAGRISSO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website:

(https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.astrazeneca.ca, or by contacting the sponsor, AstraZeneca Canada Inc. at:
Questions or concerns - 1 (800) 668-6000.

- This Patient Medication Information is current at the time of printing. The most up-to date version can be found at www.astrazeneca.ca.

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