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

TAGRISSO, indicated:

- for the treatment of patients with locally advanced, unresectable (stage III) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (either alone or in combination with other EGFR mutations) and whose disease has not progressed during or following platinum based chemoradiation therapy.

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for TAGRISSO please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html"

TAGRISSO, indicated:

- as adjuvant therapy after tumour resection in patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations
- 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)
- in combination with pemetrexed and platinum-based chemotherapy 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.
- 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

has been issued market authorization without conditions

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What is a Notice of Compliance with Conditions (NOC/c)?

A NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

1 INDICATIONS	04/2025
1 INDICATIONS, 1.2 Geriatrics	06/2024
4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations	06/2024
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	04/2025
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7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics	06/2024

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Sections or subsections that are not applicable at the time of authorization are not listed.

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 (see7 WARNINGS AND PRECAUTIONS, Assessment of EGFR Mutation Status).

NOC/c

Unresectable Stage III

TAGRISSO is indicated for the treatment of patients with locally advanced, unresectable (stage III) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (either alone or in combination with other EGFR mutations) and whose disease has not progressed during or following platinum based chemoradiation therapy.

- A validated test is required to identify EGFR mutation-positive status prior to treatment (see 7 WARNINGS AND PRECAUTIONS, Assessment of EGFR Mutation Status).
- Marketing authorization with conditions was based on the primary efficacy endpoint of progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in subsequent analyses (see 14 CLINICAL TRIALS).

Metastatic (monotherapy)

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).

Metastatic (in combination with chemotherapy)

TAGRISSO is indicated in combination with pemetrexed and platinum-based chemotherapy 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.

- 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.

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

- 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.

1.2 Geriatrics

Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (11% versus 9%) with TAGRISSO monotherapy in the ADAURA, FLAURA, FLAURA2 (monotherapy arm) and AURA trials (n=1813). 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, 7.1 Special Populations, and 10.3 Pharmacokinetics. Refer to the Product Monographs of pemetrexed and cisplatin/carboplatin when used in combination with TAGRISSO.

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 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Monitoring and Laboratory Tests; 8 ADVERSE REACTIONS, QT Interval Prolongation and ECG Findings; and 9.4 Drug-Drug Interactions).
- Left Ventricular Dysfunction and Cardiomyopathy (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Monitoring and Laboratory Tests; 8 ADVERSE REACTIONS, Left Ventricular Performance).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Age, body weight, gender, race and smoking status: No dosage adjustment is required, either as monotherapy or in combination with pemetrexed and platinum-based chemotherapy, due to patient age, body weight, gender, ethnicity and smoking status (see 10.3 Pharmacokinetics and 1.2 Geriatrics).

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.

TAGRISSO can be used as a monotherapy or in combination with pemetrexed and platinum-based (cisplatin or carboplatin) chemotherapy in patients with locally advanced or metastatic NSCLC. Refer to the Product Monographs for pemetrexed and cisplatin/carboplatin for dosing information when TAGRISSO is used in combination with chemotherapy.

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 TAGRISSO treatment until disease progression or unacceptable toxicity regardless of if prescribed as monotherapy or in combination with pemetrexed and platinum-based chemotherapy.

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[b]	ILD/Pneumonitis if no recent definitive chemoradiation therapy was received	Permanently discontinue TAGRISSO if ILD is confirmed. See 7 WARNINGS AND PRECAUTIONS, Interstitial Lung Disease (ILD) for further guidance and management.
	ILD/Pneumonitis following definitive platinum-based chemoradiation therapy: Asymptomatic (Grade 1)	Continue TAGRISSO or interrupt and restart, as appropriate.
	ILD/Pneumonitis following definitive platinum-based chemoradiation therapy: Grade ≥2	Permanently discontinue TAGRISSO
	Radiation Pneumonitis: Symptomatic (Grade 2)	Withhold TAGRISSO until symptoms resolve and restart, as appropriate.
	Radiation Pneumonitis if: Symptoms do not resolve after 4 weeks of interrupting TAGRISSO Symptoms (Grade 2) recur after restarting TAGRISSO Severe or life-threatening (Grade 3 or 4)	Permanently discontinue TAGRISSO
Cardiac[b]	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.

Target Organ	Adverse Reaction[a]	Dose Modification
Cutaneous[b]	Stevens-Johnson Syndrome and Toxic epidermal necrolysis	Permanently discontinue TAGRISSO.
Blood and Lymphatic system[b]	Aplastic Anemia	Permanently discontinue TAGRISSO.
Other	Grade 3 or higher adverse reaction	Withhold TAGRISSO for up to 3 weeks.
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of TAGRISSO for up to 3 weeks	TAGRISSO may be restarted at the same dose (80 mg) or a lower dose (40 mg).
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue TAGRISSO.

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

[b] See 7 WARNINGS AND PRECAUTIONS

When TAGRISSO is administered in combination with pemetrexed and platinum-based chemotherapy, modify the dose of any one of the treatments for the management of adverse reactions, as appropriate. For TAGRISSO dose modification instructions, see Table 1. Withhold, reduce the dose or permanently discontinue pemetrexed, cisplatin or carboplatin according to their respective Product Monographs.

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 in patients with locally advanced, unresectable (stage III) NSCLC following chemoradiation, 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 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 7.1% (129 of 1813) of patients treated with TAGRISSO monotherapy. Of the 1813 patients treated with TAGRISSO monotherapy in clinical trials treated with TAGRISSO 80 mg, 1.1% of patients (n=20) were found to have a QTc greater than 500 msec, and 4.3% of patients (n=78) had an increase in QTc from baseline of greater than 60 msec.

Of the 276 patients treated with TAGRISSO in combination with pemetrexed and platinum-based chemotherapy in the FLAURA2 study, 1.8% were found to have a QTc >500 msec, and 10.5% of patients had an increase from baseline QTc >60 msec.

No QTc-related arrhythmias were reported.

A pharmacokinetic/pharmacodynamic analysis with TAGRISSO predicted a concentration-dependent increase in QTc interval prolongation. No QTc-related arrhythmias were reported in the ADAURA, LAURA, 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.

Cardiomyopathy and Left Ventricular Dysfunction: Across clinical trials, cardiomyopathy (defined

as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 3.8% of the 1813 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal.

In the FLAURA2 study, cardiomyopathy occurred in 9% (mainly driven by events of Left Ventricular Ejection Fraction (LVEF) decreased) of the 276 patients who received TAGRISSO in combination with pemetrexed and platinum-based chemotherapy; 1.1% of cardiomyopathy cases were fatal mainly driven by incidence of LVEF decrease.

LVEF decreases ≥10 percentage points and a drop to <50% occurred in 4.2% (65/1557) of patients treated with TAGRISSO monotherapy who had baseline and at least one follow-up LVEF assessment. In the ADAURA study,1.5% (5/325) of patients treated with TAGRISSO experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%.

In the FLAURA2 study, 8% (21/262) of patients treated with TAGRISSO in combination with pemetrexed and platinum-based chemotherapy, who had baseline and at least one follow-up LVEF assessment, experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%. In the LAURA study, following platinum-based chemoradiation therapy, 3.0% (4/135) of patients treated with TAGRISSO and no patients treated with placebo experienced LVEF decreases greater than or equal to 10 % 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.

For patients who will be receiving TAGRISSO monotherapy, conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

For patients who will be receiving TAGRISSO in combination with pemetrexed and platinum-based chemotherapy, conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in all patients.

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.

Hematologic

Rare reports of aplastic anemia have been reported in association with TAGRISSO treatment. Some cases had a fatal outcome. Before initiating treatment, patients should be advised of signs and symptoms of aplastic anemia including but not limited to persistent fever, bruising, bleeding, pallor. If signs and symptoms suggestive of aplastic anemia develop, drug should be interrupted, and the patient should be closely monitored. TAGRISSO should be discontinued in patients with confirmed aplastic anemia.

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.

Hematologic Monitoring: Perform complete blood count with differential before starting TAGRISSO, periodically throughout treatment, and more frequently if indicated.

If aplastic anemia is suspected, withhold TAGRISSO and obtain hematology consultation.

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 when TAGRISSO is used as monotherapy and in all patients when TAGRISSO is used in combination with pemetrexed and platinum-based chemotherapy. 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 0.6% (n=10) of the 1813 patients treated with TAGRISSO monotherapy in the ADAURA, FLAURA, FLAURA2 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 4.0% and were fatal in 0.4% (n=7) of the 1813 patients who received TAGRISSO monotherapy 80 mg in the ADAURA, FLAURA, FLAURA2 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 11.2% in patients of Japanese ethnicity, 2.3% in patients of non-Japanese Asian ethnicity and 2.7% in non-Asian patients. The median time from first dose to onset of ILD or ILD-like adverse reactions was 2.8 months (see 4.1 Dosing Considerations; 8 ADVERSE REACTIONS and 10.3 Pharmacokinetics).

In the FLAURA2 study these events were reported in 3.3% of the 276 patients who received TAGRISSO in combination with pemetrexed and platinum-based chemotherapy; 0.4% were fatal.

The incidence of ILD was 14.9% in patients of Japanese ethnicity and 1.7% in non-Asian patients; no patients of non-Japanese Asian ethnicity had an event of ILD in the FLAURA2 TAGRISSO + chemotherapy arm. The median time from first dose to onset of ILD or ILD-like adverse reactions was 5.3 months.

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

ILD following definitive platinum-based chemoradiation therapy:

In the LAURA study, following definitive platinum-based chemoradiation therapy, ILD or ILD-like adverse reactions (e.g., pneumonitis) were reported in 7.7% (11 of 143) of patients who received TAGRISSO and 1.4% (1 of 73) of patients who received placebo. In the TAGRISSO arm, the incidence of ILD or ILD-like adverse reactions was 6.6% (6 of 91 patients) in patients of non-Japanese Asian ethnicity and 17.2% (5 of 29 patients) in non-Asian patients; no patients of

Japanese ethnicity had an event of ILD. The median time from first dose to onset of ILD or ILD-like adverse reactions was 57 days in the TAGRISSO arm. The median time from last dose of radiotherapy to onset of ILD or ILD-like adverse reactions was 91 days in the TAGRISSO arm. There was one fatal case reported for ILD or ILD-like adverse reactions in the TAGRISSO arm and no fatal cases in the placebo arm (See 8.2Clinical Trial Adverse Reactions).

For patients treated with TAGRISSO following definitive platinum-based chemoradiation therapy, refer to dose modification instructions (See 4.2 Recommended Dose and Dosage Adjustment):

Radiation pneumonitis: Radiation pneumonitis can be observed for up to a year after patients receive radiation therapy to the lungs. In the LAURA study, following definitive platinum-based chemoradiation therapy, radiation pneumonitis was reported in 48.3% (69 of the143) of patients who received TAGRISSO and 38.4% (28 of the 73) of patients who received placebo. The median time from first dose to onset of radiation pneumonitis was 52 days in the TAGRISSO arm and 54 days in the placebo arm. The median time from last dose of radiotherapy to onset of radiation pneumonitis was 76 days in the TAGRISSO arm and 80 days in the placebo arm. Of the 143 patients in the TAGRISSO arm, 3 (2.1%) had Grade 3 events of radiation pneumonitis, and no Grade 4 or Grade 5 events were reported in either arm (See 8.2Clinical Trial Adverse Reactions).

For patients treated with TAGRISSO following definitive platinum-based chemoradiation therapy, refer to dose modification instructions (See 4.2 Recommended Dose and Dosage Adjustment).

Skeletal Muscles

Case reports of blood CPK increased have been observed with osimertinib therapy in pooled clinical trials (n=1479), including CTCAE Grades ≥ 3 (0.3%), in absence of regular monitoring of blood CPK levels. There were no CTCAE grade 5 adverse events reported. Post-marketing reports of myositis and rhabdomyolysis have also been reported. Consider measuring blood CPK levels if clinically appropriate.

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 15/ 1813 (0.8%) patients, treated with TAGRISSO monotherapy which consisted of dermatitis acneiform in 2/1813 (0.1%) patients, dermatitis in 2/1813 (0.1%) patients, erythema in 3/1813 (0.2%) patients, rash erythematous in 2/1813 (0.1%) patients, rash macular in 1/1813 (0.1%) patients, rash maculo-papular in 3/1813 (0.2%) patients and rash papular in 2/1813 (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 and Toxic epidermal necrolysis: Based on the pooled dataset analysis of the clinical trial data, uncommon cases of erythema multiforme and toxic epidermal necrolysis 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 and toxic epidermal necrolysis. If signs and symptoms suggestive of erythema multiforme develop, close patient monitoring and drug interruption or discontinuation

of TAGRISSO should be considered. If signs and symptoms suggestive of toxic epidermal necrolysis appear, TAGRISSO should be interrupted. TAGRISSO should be discontinued immediately if toxic epidermal necrolysis is diagnosed.

Paronychia: Paronychia was observed in 609/1813 (33.6%) patients who received TAGRISSO 80 mg as monotherapy in the ADAURA, FLAURA, FLAURA2 (monotherapy arm) and AURA trials (n=1813) and was generally mild (380/1813, 21.0%, CTCAE Grade 1) or moderate (221/1813, 12.2%, 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 FLAURA2 trial, paronychia led to dose reduction in 0.4% (1/275) of patients treated with TAGRISSO monotherapy, with no treatment discontinuations. 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, FLAURA2 and AURA trials (TAGRISSO monotherapy; n=1813), 42% of patients were ≥65 years of age, of whom 11% 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% versus 10%). The types of adverse reactions reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (11% versus 9%). No overall differences in efficacy or predicted steady state exposure of osimertinib were observed between these patients and younger patients. See 4.1 Dosing Considerations; 10.3 Pharmacokinetics. Refer to the Product Monographs of pemetrexed and cisplatin/carboplatin when used in combination with TAGRISSO.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The data described below reflect exposure to TAGRISSO as monotherapy (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=338), FLAURA2 (monotherapy arm; n=275) and AURA3 (n=279)] data from 1813 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 FLAURA2, the median duration of study treatment was 22.3 months for patients receiving TAGRISSO with chemotherapy (n=279) and 19.3 months for patients receiving TAGRISSO monotherapy (n=278). 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, where patients were treated with TAGRISSO monotherapy [ADAURA, FLAURA, FLAURA2 (monotherapy arm) and AURA trials (n=1813)], 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 37.2% of patients. Serious Adverse Events (SAEs) were reported in 28.7% of patients. AEs leading to death were reported in 3.8% of patients.

The most commonly reported (in ≥10% of patients, n=1813) adverse drug reactions (ADRs) among patients treated with TAGRISSO monotherapy, by grouped terms include diarrhea (46.6%), rash (46.1%), paronychia (33.6%), dry skin (32.0%), stomatitis (23.8%), pruritus (17.2%), thrombocytopenia (15.9%), leukopenia (13.8%) and neutropenia (12.0%). ADRs by grouped terms with a Grade ≥3 severity (in ≥1% of patients, n=1813) include neutropenia (2.1%), diarrhea (1.4%) and ILD (1.4%) lymphopenia (1.2%), thrombocytopenia (1.2%), QTc interval prolongation (1.0%) and leukopenia (1.0%). ILD (2.0%) was also reported as a serious adverse reaction (SAR).

The safety of TAGRISSO given in combination with pemetrexed and platinum-based chemotherapy is based on data in 276 patients with EGFR mutation-positive NSCLC and was

consistent with TAGRISSO monotherapy and known safety profiles of pemetrexed and platinum-based chemotherapy.

Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from clinical 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, FLAURA2 and AURA trials, the incidence of ILD-like adverse reactions for patients treated with TAGRISSO monotherapy was 11.2% in patients of Japanese ethnicity, 2.3% in patients of non-Japanese Asian ethnicity and 2.7% in non-Asian patients. The median time from first dose to onset of ILD or ILD-like adverse reactions was 2.8 months (see 7 WARNINGS AND PRECAUTIONS, Respiratory; 4.1 Dosing Considerations; 10.3 Pharmacokinetics).

In patients treated with TAGRISSO 80 mg once daily as monotherapy, ADRs that led to dose modification (interruption or reduction) occurred in 11.9% (215/1813) of the patients. Dose reductions due to ADRs occurred in 3.6% (66/1813) of the patients. Discontinuation due to adverse reactions was 4.7% (85/1813). The most frequent adverse drug reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3.4% [61/1813]).

Fatal adverse drug reactions were reported in 0.4% (7/1813) of patients treated with TAGRISSO monotherapy. SARs were reported in 28.7% (521/1813) of patients treated with TAGRISSO monotherapy.

LAURA Trial

The safety of TAGRISSO (80 mg once daily) following platinum-based chemoradiation therapy is based on data from 143 patients with EGFR mutation-positive NSCLC who received TAGRISSO in the LAURA trial. The safety profile of TAGRISSO in this disease setting was manageable and was consistent with TAGRISSO monotherapy and the known safety profile of treatment following platinum-based chemoradiation therapy. Most adverse reactions were Grade 1 or 2 in severity. The median duration of study treatment was 24.0 months for patients receiving TAGRISSO (n=143) and 8.3 months for patients receiving placebo.

The most commonly reported (in ≥10% of patients, n=143) adverse drug reactions in TAGRISSO arm by grouped terms include radiation pneumonitis (48.3%), diarrhea (35.7%), rash (35.7%), paronychia (23.1%), dry skin (17.5%), stomatitis (15.4%) and pruritus (12.6%). Adverse drug reactions by grouped terms with a Grade ≥3 severity (in ≥1% of patients, n=143) in the osimertinib arm include diarrhea (2.1%), radiation pneumonitis (2.1%) and ILD (1.4%).

Serious adverse drug reactions were reported in 13.3% (19/143) of patients treated with TAGRISSO; the most common SARs (≥ 1%) were radiation pneumonitis 10.5% (15/143) and ILD (grouped term) (2.1% [3/143]) (comprising PTs of ILD, 0.7% [1/143], and pneumonitis, 1.4% [2/143])

Adverse drug reactions (ADRs) that led to dose interruption occurred in 42.0% (60/143) of the patients in the TAGRISSO arm. Adverse drug reactions that led to dose reductions occurred in 4.9% (7/143) of the patients in the TAGRISSO arm. Adverse drug reactions that led to discontinuation occurred in 8.4% (12/143) of the patients in the TAGRISSO arm. The most frequent ADR leading to discontinuation of TAGRISSO was radiation pneumonitis (4.9% [7/143]).

Fatal adverse drug reactions were reported in 0.7% (1/143) 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				
Blood creatine phosphokinase increased	11(3.3)		3 (0.9)	
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)
Skin hyperpigmentation	6 (1.8)	0 (0)	0 (0)	0 (0)
Urticaria	5 (1.5)	0 (0)	1 (0.3)	1 (0.3)

Preferred term	TAGRISSO (N=337)		Placebo (N=343)	
Findings based on test results presented as CTCAE grade shifts				
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.

LAURA Trial

Tables below summarize the adverse drug reactions regardless of investigator assessed causality (Table 5) and laboratory abnormalities (Table 5 and Table 9) observed in unresectable locally advanced EGFR mutation positive NSCLC patients treated with 80 mg TAGRISSO in the LAURA Phase III clinical trial.

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

Preferred term	TAGRISSO (N=143)		Placebo (N=73)	
CTCAE Grade[b]	All n (%)	3 or Higher n (%)	All n (%)	3 or Higher n (%)
Eye Disorders				
Keratitis[c]	1 (0.7)	0 (0)	1 (1.4)	0 (0)
Gastrointestinal Disorders				

Preferred term	TAGRISSO (N=143)		Placebo (N=73)	
Diarrhea	51 (35.7)	3 (2.1)	10 (13.7)	0 (0)
Stomatitis[d]	22 (15.4)	0 (0)	3 (4.1)	0 (0)
Investigations				
Blood creatine phosphokinase increased	5 (3.5)	2 (1.4)	0 (0)	0 (0)
Electrocardiogram QT prolonged[e]	1 (0.7)		0 (0)	
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease[f]	11 (7.7)	3 (2.1)[g]	1 (1.4)	0 (0)
Epistaxis	1 (0.7)	0 (0)	0 (0)	0 (0)
Radiation Pneumonitis[h]	69 (48.3)	3 (2.1)	28 (38.4)	0 (0)
Skin disorders				
Rash[i]	51 (35.7)	1 (0.7)	14 (19.2)	0 (0)
Paronychia[j]	33 (23.1)	0 (0)	1 (1.4)	0 (0)
Dry skin[k]	25 (17.5)	1 (0.7)	4 (5.5)	0 (0)
Pruritus[l]	18 (12.6)	0 (0)	5 (6.9)	0 (0)
Alopecia	2 (1.4)	0 (0)	0 (0)	0 (0)
Urticaria	2 (1.4)	0 (0)	1 (1.4)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	0 (0)	0 (0)	0 (0)	0 (0)
Skin hyperpigmentation	0 (0)	0 (0)	0 (0)	0 (0)
Erythema Multiforme	0 (0)	0 (0)	0 (0)	0 (0)
Findings based on test results presented as CTCAE grade shifts				
Lymphocytes decreased[m]	100 (70.4)	5 (3.5)	29 (40.3)	1(1.4)
Leukocytes decreased[m]	94 (66.2)	4 (2.8)	17 (23.6)	0 (0)
Platelet count decreased[m]	73 (51.4)	2 (1.4)	6 (8.3)	1(1.4)
Neutrophils decreased[m]	59 (41.5)	3 (2.1)	11 (15.3)	1(1.4))
Blood creatinine increased[m,n]	27 (19.0)	0 (0)	9 (12.3)	0 (0)

[a] Only events for patients receiving at least one dose of their randomized treatment are summarized.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.
[c] Includes: corneal erosion, corneal epithelium defect, keratitis, punctuate keratitis.
[d] Includes: mouth ulceration, stomatitis.
[e] Represents the incidence of patients who had a QTcF prolongation >500 msec.
[f] Includes: interstitial lung disease, pneumonitis, organizing pneumonia.
[g] One CTCAE Grade 5 event (fatal) was reported.
[h] Includes: radiation pneumonitis and radiation fibrosis-lung

[i] Includes: acne, dermatitis, dermatitis acneiform, drug eruption, erythema, folliculitis, pustule, rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin erosion.
[j] Includes: nail bed disorder, nail bed infection, nail bed inflammation, nail discolouration, nail disorder, nail dystrophy, nail infection, nail pigmentation, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.
[k] Includes: dry skin, eczema, skin fissures, xeroderma, xerosis.
[l] Includes: eyelid pruritus, pruritus.
[m] Represents the incidence of laboratory findings, not of reported adverse events.
[n] A lower baseline blood creatinine clearance (<30 mL/min) was used in the LAURA study compared to other monotherapy TAGRISSO studies (<50 mL/min) so grade shifts were more likely to occur.

FLAURA Trial

Tables below summarize the adverse drug reactions regardless of investigator assessed causality (Table 5) and laboratory abnormalities (Table 5 and Table 9) observed in previously untreated EGFR mutation positive NSCLC patients treated with 80 mg TAGRISSO in the FLAURA Phase III clinical trial.

Table 5 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				
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				
Blood creatine phosphokinase increased	1 (0.4)		1 (0.4)	
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)

Preferred term	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
Palmar-plantar erythrodysesthesia syndrome	4 (1.4)	0 (0)	7 (2.5)	0 (0)
Skin hyperpigmentation	1 (0.4)	0 (0)	3 (1.1)	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.

FLAURA2 Trial

Tables below summarize the adverse drug reactions regardless of investigator assessed causality (Table 6) and laboratory abnormalities (Table 6 and Table 10) observed in previously untreated EGFR mutation- positive NSCLC patients treated with 80 mg TAGRISSO in the FLAURA2 Phase III clinical trial.

Table 6 Adverse drug reactions reported in FLAURA2[a] (Safety analysis set)

Preferred term	TAGRISSO with pemetrexed and platinum-based chemotherapy (N=276)		TAGRISSO (N=275)	
CTCAE Grade[b] n(%)	All	3 or Higher	All	3 or Higher
Eye Disorders				
Keratitis[c]	2 (0.7)	0 (0)	0 (0)	0 (0)
Gastrointestinal Disorders				
Diarrhea[d]	120 (43.5)	8 (2.9)	112 (40.7)	1 (0.4)
Stomatitis[e]	86 (31.2)	1 (0.4)	59 (21.5)	1 (0.4)
Investigations				
Blood creatine phosphokinase increased	9 (3.3)	3 (1.1)	9 (3.3)	0 (0)
Electrocardiogram QT prolonged[f]	5 (1.8)		5 (1.8)	
Respiratory, Thoracic and Mediastinal Disorders				
Epistaxis	20 (7.2)	1 (0.4)	18 (6.5)	0 (0)
Interstitial lung disease[g]	9 (3.3)	2 (0.7)	10 (3.6)	5 (1.8)
Skin disorders				
Rash[h]	135 (48.9)	7 (2.5)	121 (44.0)	4 (1.5)
Paronychia[i]	75 (27.2)	2 (0.7)	87 (31.6)	1 (0.4)
Dry skin[j]	65 (23.6)	0 (0.0)	84 (30.2)	0 (0.0)
Alopecia	24 (8.7)	0 (0)	15 (5.5)	0 (0)
Pruritus[k]	22 (8.0)	0 (0.0)	31 (11.3)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	15 (5.4)	0 (0)	9 (3.3)	0 (0)
Urticaria	4 (1.4)	1 (0.4)	4 (1.5)	0 (0)
Erythema Multiforme	4 (1.4)	2 (0.7)	1 (0.4)	0 (0)
Findings based on test results presented as CTCAE grade shifts				
Leukocytes decreased[l]	241 (87.6)	55 (20.0)	147 (53.5)	9 (3.3)
Platelet count decreased[l]	235 (85.5)	45 (16.4)	121 (44.0)	5 (1.8)
Neutrophils decreased[l]	233 (84.7)	99 (36.0)	111 (40.4)	13 (4.7)
Lymphocytes decreased[l]	214 (77.8)	43 (15.7)	151 (54.9)	18 (6.6)
Blood creatinine increased[l]	60 (21.8)	1 (0.4)	23 (8.4)	0 (0.0)

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

[a] Only events for patients receiving at least one dose of their randomized treatment are summarized. Frequency reported in this table are regardless of causality.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0
[c] Includes: corneal erosion, corneal epithelium defect, keratitis, punctuate keratitis.
[d] 1 CTCAE grade 5 event (fatal) was reported.
[e] Includes: stomatitis, mouth ulceration.
[f] Represents the incidence of patients who had a QTcF prolongation >500 msec.
[g] Includes: interstitial lung disease, pneumonitis, and organizing pneumonia.
[h] Includes: acne, dermatitis, dermatitis acneiform, drug eruption, erythema, folliculitis, pustule, rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin erosion.
[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] Includes: dry skin, skin fissures, xerosis, eczema, xeroderma.
[k] Includes: pruritus, 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 7) and laboratory abnormalities (Table 12) 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 7 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)
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								
Blood creatine phosphokinase increased		2 (0.7)				1 (0.7)		
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								

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
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)
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)
Skin hyperpigmentation	1 (0.4)	1 (0.4)	0 (0)	0 (0)	5 (3.7)	3 (2.2)	2 (1.5)	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, FLAURA2, 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, FLAURA2 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 8 regardless of investigator assessed causality based on adverse event reports in a pooled dataset from the 1813 patients who received TAGRISSO at a dose of 80 mg daily in the ADAURA, FLAURA, FLAURA2 (monotherapy arm) and AURA trials.

Table 8 Adverse drug reactions reported in patients treated with TAGRISSO 80 mg in the ADAURA, FLAURA, FLAURA2 (monotherapy arm) and AURA[a] trials

Preferred term[a]	TAGRISSO 80 mg once daily N=1813	
	All Grades[b] n(%)	Grade 3 and higher n(%)
Blood and lymphatic system disorders		
Aplastic Anemia	1 (0.06)	1 (0.06)
Eye disorders		
Keratitis[c]	10 (0.6)	1 (0.06)
Gastrointestinal disorders		
Diarrhea	845 (46.6)	26(1.4)
Stomatitis[d]	432 (23.8)	8 (0.4)
Investigations		
Blood creatine phosphokinase increased	34 (1.9)	5 (0.3)
QTc interval prolongation[e]	20 (1.1)	
Respiratory, thoracic and mediastinal disorders		
Epistaxis	114 (6.3)	0 (0)
Interstitial lung disease[f]	73 (4.0)	25 (1.4)[g]

Preferred term[a]	TAGRISSO 80 mg once daily N=1813	
	All Grades[b] n(%)	Grade 3 and higher n(%)
Skin and subcutaneous tissue disorders		
Rash[h]	836 (46.1)	15 (0.8)
Paronychia[i]	609 (33.6)	8 (0.4)
Dry skin[j]	580 (32.0)	2 (0.1)
Pruritus[k]	311 (17.2)	1 (0.06)
Alopecia	90 (5.0)	0 (0)
Urticaria	35 (1.9)	2 (0.1)
Palmar-plantar erythrodysesthesia syndrome	38 (2.1)	0 (0)
Skin hyperpigmentation[l]	15 (1.0)	0 (0)
Erythema Multiforme	6 (0.3)	0 (0)
Toxic epidermal necrolysis[m]	3 (0.2)	0 (0)
Cutaneous Vasculitis[m]	3 (0.2)	0 (0)
Findings based on test results presented as CTCAE grade shifts		
Platelet count decreased[n]	953 (53.1)	24 (1.3)
Neutrophils count decreased[n]	635 (35.5)	72 (4.0)
Lymphocytes decreased[n]	1139 (63.8)	147 (8.2)
Leukocytes count decreased[n]	1157 (64.7)	32 (1.8)
Blood creatinine increased[n]	153 (8.5)	3 (0.2)

[a] Data is pooled from Phase III (ADAURA, FLAURA, FLAURA2 (monotherapy arm) 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 5.0.

[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, pneumonitis and organizing pneumonia.

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

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

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

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

[n] 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 1813 patients in the pooled ADAURA (n=337), FLAURA (n=338), FLAURA2 (monotherapy arm; n=278) and AURA Phase I (n=173), II (n=411) and III (n=279) trials treated with TAGRISSO 80 mg, 20 patients (1.1%) were found to have a QTc greater than 500 msec, 79 patients (4.4%) had a QTc greater than 480 msec, 11 patients (0.6%) had an increase from baseline QTc greater than 90 msec, and 78 patients (4.3%) had an increase from baseline QTc greater than 60 msec. No ventricular arrhythmias were reported in any of the above-mentioned trials or the LAURA trial. 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, FLAURA2 (monotherapy arm) 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 4.2% (65/1557) 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): Among patients treated with TAGRISSO monotherapy in the ADAURA, FLAURA, FLAURA2(monotherapy arm) and AURA trials (n=1813), 42% of patients were ≥65 years of age, and 11% 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% versus 10%). The types of adverse reactions reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (11% versus 9%). No overall differences in efficacy 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 9 includes a summary of hematologic findings from the FLAURA trial (see 8 ADVERSE REACTIONS). Table 9 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 9 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)
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

FLAURA2 Trial

Table 10 Clinical chemistry, maximum CTCAE grade shift from baseline during treatment in FLAURA2[a] (Safety analysis set)

Parameter	TAGRISSO with pemetrexed and platinum-based chemotherapy (N=276)					TAGRISSO (N=275)				
CTCAE grade change n (%) of patients	All	1	2	3	4	All	1	2	3	4
ALT (increased) (TAGRISSO + chemo, n=275) (TAGRISSO, n=275)	193 (70.2)	125 (45.5)	41 (14.9)	24 (8.7)	3 (1.1)	113 (41.1)	87 (31.6)	16 (5.8)	9 (3.3)	1 (0.4)
AST (increased) (TAGRISSO + chemo, n=274) (TAGRISSO, n=273)	173 (63.1)	151 (55.1)	14 (5.1)	7 (2.6)	1 (0.4)	71 (26.0)	65 (23.8)	4 (1.5)	1 (0.4)	1 (0.4)
Total bilirubin (TAGRISSO + chemo, n=273) (TAGRISSO, n=275)	79 (28.9)	44 (16.1)	28 (10.3)	7 (2.6)	0	75 (27.3)	42 (15.3)	27 (9.8)	3 (1.1)	3 (1.1)

[a] Includes assessments on or after the date of first dose and up to and including 28 days following discontinuation of randomized treatment. Baseline is defined as the last result obtained prior to the start of study treatment. Percentages have been calculated using the number of patients (n) with a baseline value and at least one on-treatment value. Only worsening shifts in CTCAE grade are included (where the maximum on-treatment CTCAE grade > baseline CTCAE grade).

CTCAE = Common Terminology Criteria for Adverse Events (version 5.0)

LAURA Trial

Table 11 Clinical chemistry, maximum CTCAE grade shift from baseline during treatment in LAURA[a] (Safety analysis set)

Parameter	TAGRISSO (N=143)					Placebo (N=73)				
CTCAE grade change[a] n (%) of patients	All	1	2	3	4	All	1	2	3	4
ALT (increased) (TAGRISSO, n=142) (Placebo, n=72)	39 (27.5)	28 (19.7)	7 (4.9)	3 (2.1)	1 (0.7)	18 (25.0)	18 (25.0)	0	0	0
AST (increased) (TAGRISSO, n=142) (Placebo, n=72)	35 (24.6)	30 (21.1)	2 (1.4)	3 (2.1)	0	13 (18.1)	13 (18.1)	0	0	0
Total bilirubin (TAGRISSO, n=142) (Placebo, n=72))	13 (9.2)	11 (7.7)	1 (0.7)	1 (0.7)	0	7 (9.7)	5 (6.9)	2 (2.8)	0	0

[a] Includes assessments on or after the date of first dose and up to and including the earlier of 28 days following discontinuation of randomized treatment and the day before the start of subsequent anticancer therapy. Baseline is defined as the last result obtained prior to the start of study treatment. If 2 visits are equally eligible to assess patient status at baseline, the average is taken as a baseline value. Percentages have been calculated using the number of patients (n) with a baseline value and at least one on-treatment value. Only worsening shifts in CTCAE grade are included (where the maximum on-treatment CTCAE grade > baseline CTCAE grade).

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 12 below summarizes the shift changes in these hematologic parameters in patients treated with TAGRISSO 80 mg in the AURA3 trial.

Table 12 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	1	2	3	4	All	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 5391 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 1813 patients in the ADAURA, FLAURA, FLAURA2 (monotherapy arm) 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 erythema dyschromicum perstans have been reported.

Cases of cutaneous vasculitis have also been reported.

Hematologic disorders: Aplastic anemia has been reported in patients treated with TAGRISSO in clinical trials and post-marketing. The majority of cases were reported in the post-marketing setting including one case with fatal outcome of aplastic anemia. A frequency of 'rare' has been derived with only one non-fatal case of aplastic anemia reported from clinical studies dataset of 1813 patients.

Skeletal muscles: Myopathy-related events such as myositis and rhabdomyolysis have 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 13.

Table 13 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.

The pharmacokinetics in patients treated with osimertinib in combination with pemetrexed and platinum-based chemotherapy are similar to those in patients treated with osimertinib monotherapy.

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

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

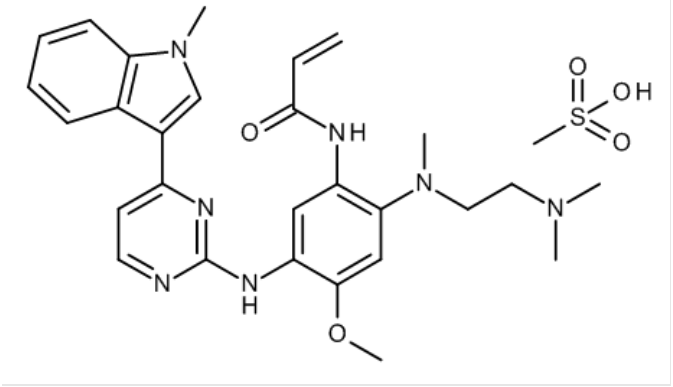
Store at controlled room temperature (15-30°C).

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

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

Trial Design and Study Demographics (ADAURA)

Table 14 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
D5164C 00001 (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 15).

Table 15 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		

	TAGRISSO (N=339)	Placebo (N=343)
Lobectomy	328 (96.8)	322 (93.9)
Sleeve Resection	1 (0.3)	3 (0.9)
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 16, Figure 1, Figure 2 and Figure 3. 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.

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).

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

Table 16 Efficacy results in the overall patient population (stage IB-IIIA) by investigator assessment

Efficacy Parameter	Stage IB-IIIA population	
	TAGRISSO (n=339)	Placebo (n=343)
Disease Free Survival (DFS)		
Number of Events (%)	37 (10.9)	159 (46.4)
Recurrent disease (%)	37 (10.9)	157 (45.8)
Deaths (%)	0	2 (0.6)
Median DFS, months (95% CI)	NC (NC, NC)	27.5 (22.0, 35.0)
HR (99.12% CI)	0.20 (0.14, 0.30)	
P-value [a]	<0.0001	
DFS rate at 12 months, % (95% CI)	97.4 (94.9, 98.7)	68.5 (63.2, 73.2)
DFS rate at 24 months, % (95% CI)	89.1 (84.5, 92.4)	52.4 (46.4, 58.1)
DFS rate at 36 months, % (95% CI) [b]	78.9 (68.7, 86.1)	40.0 (32.1, 47.8)
Overall Survival (OS)		
Number of deaths (18% maturity)	42 (12.4)	82 (23.9)
Median OS, months (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95.03% CI)	0.49 (0.34, 0.70)	
P-value [c]	<0.0001	

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

DFS results based on investigator assessment.

Median follow-up time for DFS was 22.1 months for patients receiving TAGRISSO and 16.6 months for patients receiving placebo.

Median follow-up time for OS in censored patients was 61.5 months in both the TAGRISSO arm and the placebo arm.

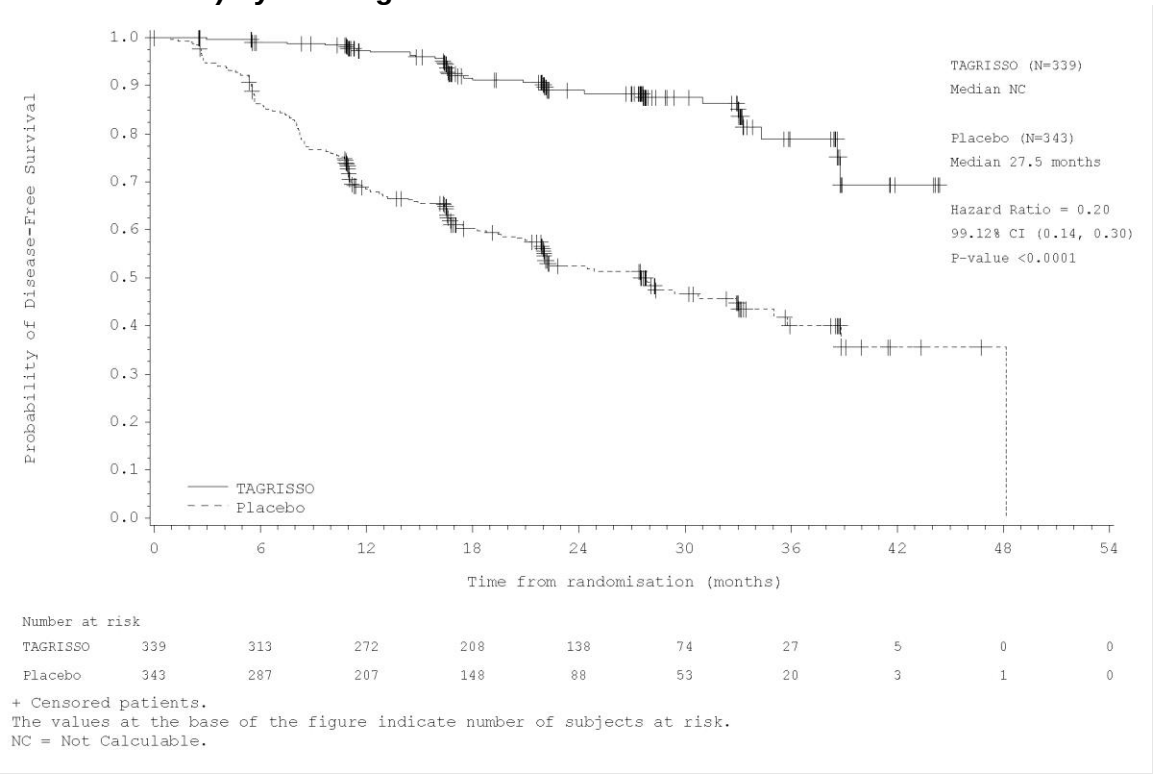
DFS results are from the primary analysis (17 January 2020). OS results are from the final analysis (27 January 2023).

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

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

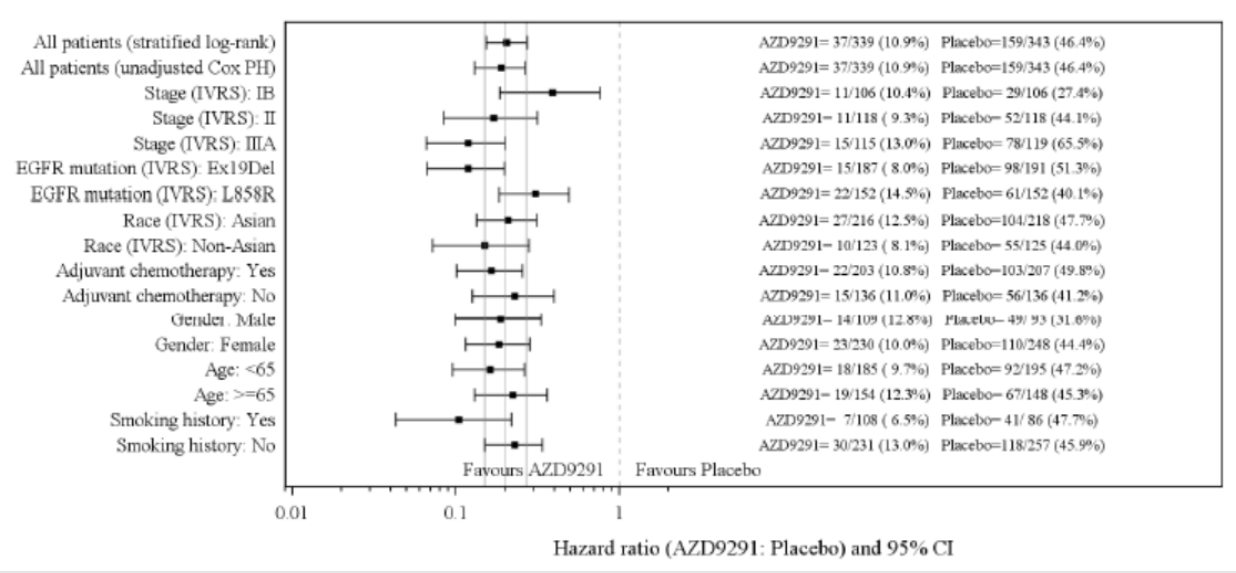
[c] Adjusted for interim analyses a p-value < 0.0497 was required to achieve statistical significance.

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



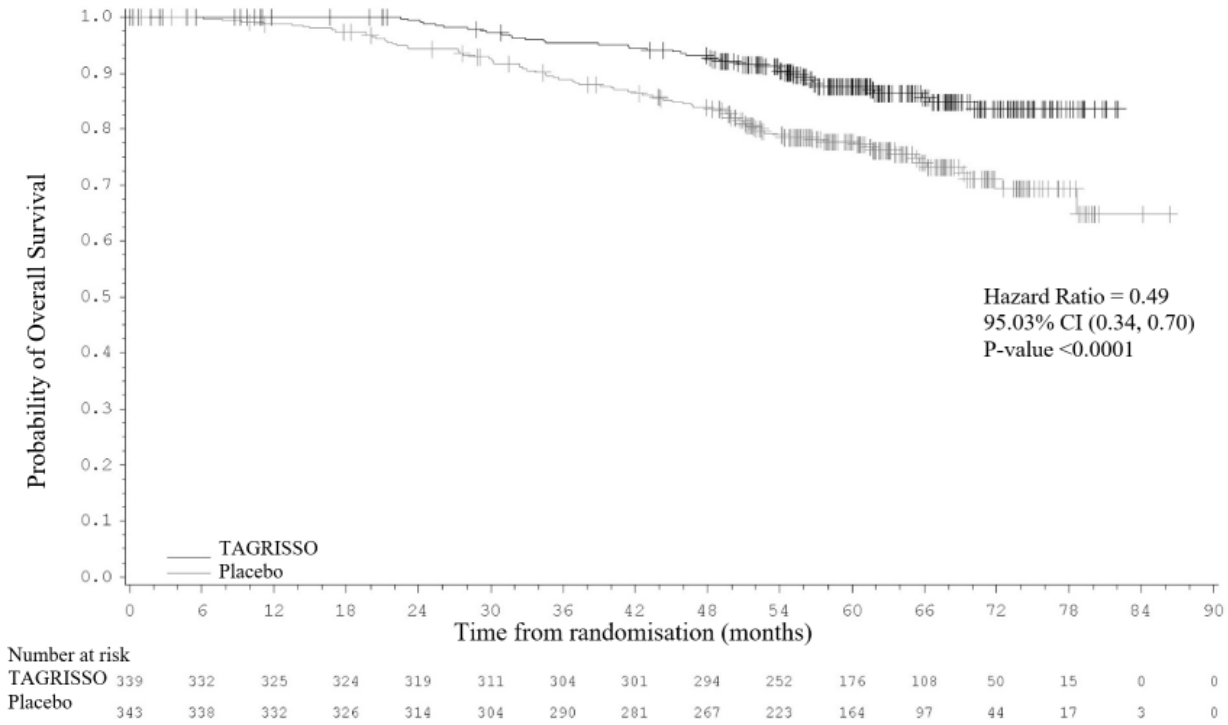
The DFS benefit of TAGRISSO compared to placebo was consistent across all predefined subgroups analysed (see Figure 2). The OS benefit of TAGRISSO compared to placebo was generally consistent across predefined subgroups, which included disease stage, EGFR mutation status, race, adjuvant chemotherapy use, gender, age, and smoking history.

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

Figure 3 Kaplan-Meier Curve of Overall Survival in Overall Population (Stage IB-IIIA patients)



Locally Advanced Unresectable (Stage III) EGFR Mutation-Positive NSCLC, Following Prior Chemoradiation

Trial Design and Study Demographics (LAURA)

Table 17 Summary of patient demographics for LAURA

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D5160C 00048 (LAURA)	Phase III, randomized (2:1), double-blind, placebo-controlled, investigated TAGRISSO 80 mg once daily as treatment for stage III unresectable EGFR mutation positive NSCLC following chemoradiation	80 mg tablets, once daily	TAGRISSO: n=143 Placebo: n=73	TAGRISSO: 60.9 (36-84) Placebo: 62.3 (37-83)	TAGRISSO: Female: n=90 Male: n=53 Placebo: Female: n=42 Male: n=31

The efficacy and safety of TAGRISSO for the treatment of patients with EGFR mutation-positive, locally advanced, unresectable (stage III) NSCLC, who had not progressed during or following definitive platinum based chemoradiation therapy, was demonstrated in a randomised, double-blind, placebo-controlled study (LAURA). Patients were to receive concurrent chemoradiation therapy (CCRT) or sequential chemoradiation therapy (SCRT) regimens, where at least 2 cycles or 5 weekly doses of platinum-based chemotherapy and a total dose of radiation of 60 Gy ±10% (54 Gy to 66 Gy) were to be completed ≤6 weeks prior to randomisation. Patient tumour tissue samples were required to have an EGFR exon 19 deletion or exon 21 L858R mutation, as identified by central or local testing using a certified/approved test.

Patients were randomised (2:1) to receive either TAGRISSO 80 mg orally once daily (n=143) or placebo (n=73). Randomisation was stratified by prior chemoradiation strategy (CCRT vs SCRT), tumour staging prior to chemoradiation (IIIA vs IIIB/IIIC), and by the China cohort. Patients continued to receive study treatment until intolerance to therapy or confirmed disease progression. Post progression, all patients were offered open label TAGRISSO in accordance with local clinical practice if, in the opinion of the treating physician, there was an expected clinical benefit.

The primary efficacy endpoint was PFS as assessed by blinded independent central review (BICR). Key secondary efficacy endpoints were overall survival (OS) and CNS PFS by BICR.

Table 18 Demographics and key baseline disease characteristics in LAURA trial (full analysis set)

	TAGRISSO (N=143)	Placebo (N=73)
Demographics		
Age (years)		
Mean (standard deviation)	60.9 (10.38)	62.3 (12.01)
Median (minimum-maximum)	62.0 (36, 84)	64.0 (37, 83)
Age group (years), n (%)		
<50	24 (16.8)	12 (16.4)
≥50-<65	57 (39.9)	27 (37.0)
≥65-<75	49 (34.3)	20 (27.4)
≥75	13 (9.1)	14 (19.2)
Sex, n (%)		
Male	53 (37.1)	31 (42.5)
Female	90 (62.9)	42 (57.5)
Race, n (%)		
American Indian or Alaska Native	2 (1.4)	1 (1.4)
Asian	116 (81.1)	62 (84.9)
White	20 (14.0)	10 (13.7)
Other	5 (3.5)	0 (0)
Smoking history, n (%)		
Never smokers	102 (71.3)	49 (67.1)
Current smokers	4 (2.8)	1 (1.4)
Former smokers	37 (25.9)	23 (31.5)
WHO performance status		
0 (normal activity)	80 (55.9)	31 (42.5)
1 (restricted activity)	63 (44.1)	42 (57.5)
Disease Stage, n (%) [a]		
Stage IIIA	52 (36.4)	24 (32.9)
Stage IIIB	67 (46.9)	38 (52.1)
Stage IIIC	24 (16.8)	11 (15.1)
Prior CRT		
CCRT	131 (91.6)	62 (84.9)
SCRT	12 (8.4)	11 (15.1)
Prior Chemotherapy		
Carboplatin	75 (52.4)	44 (60.3)
Cisplatin	66 (46.2)	29 (39.7)
Paclitaxel	69 (48.3)	34 (46.6)
Pemetrexed	39 (27.3)	22 (30.1)
Vinorelbine	18 (12.6)	7 (9.6)
Etoposide	15 (10.5)	8 (11.0)
Prior Radiotherapy		
Median Total Dose (Gy)	60.0	60.0
Response to prior CRT		
CR	4 (2.8)	3 (4.1)
PR	67 (46.9)	27 (37.0)
SD	61 (42.7)	37 (50.7)
PD	0	0
Non-evaluable	11 (7.7)	6 (8.2)

	TAGRISSO (N=143)	Placebo (N=73)
Time from end date of radiotherapy to randomization (weeks)		
Mean (standard deviation)	4.22 (1.390)	4.05 (1.514)
Median (minimum-maximum)	4.29 (0.7-6.4)	4.29 (0.4-6.0)
EGFR mutations as used for randomization, n (%)		
Exon 19 deletion	74 (51.7)	43 (58.9)
Exon 21 L858R	68 (47.6)	30 (41.1)
Missing [b]	1 (0.7)	0

[a] Disease stage summarised based on values entered into the eCRF and categorised prior to CRT according to AJCC/UICC 8th Edition.
[b] Patients randomised without an approved local positive EGFR test result or central EGFR test result.
DCO: 05 January 2024

Study Results (LAURA)

At the primary analysis treatment with TAGRISSO following platinum based chemoradiation therapy resulted in a statistically significant and clinically meaningful improvement in PFS compared to placebo (Table 19 and Kaplan-Meier curve Figure 4). A greater proportion of patients treated with TAGRISSO were alive and progression free at 6, 12, 18, 24 and 36 months (84%, 74%, 67%, 65% and 58%, respectively) compared to patients treated with placebo (45%, 22%, 14%, 13% and 10%, respectively).

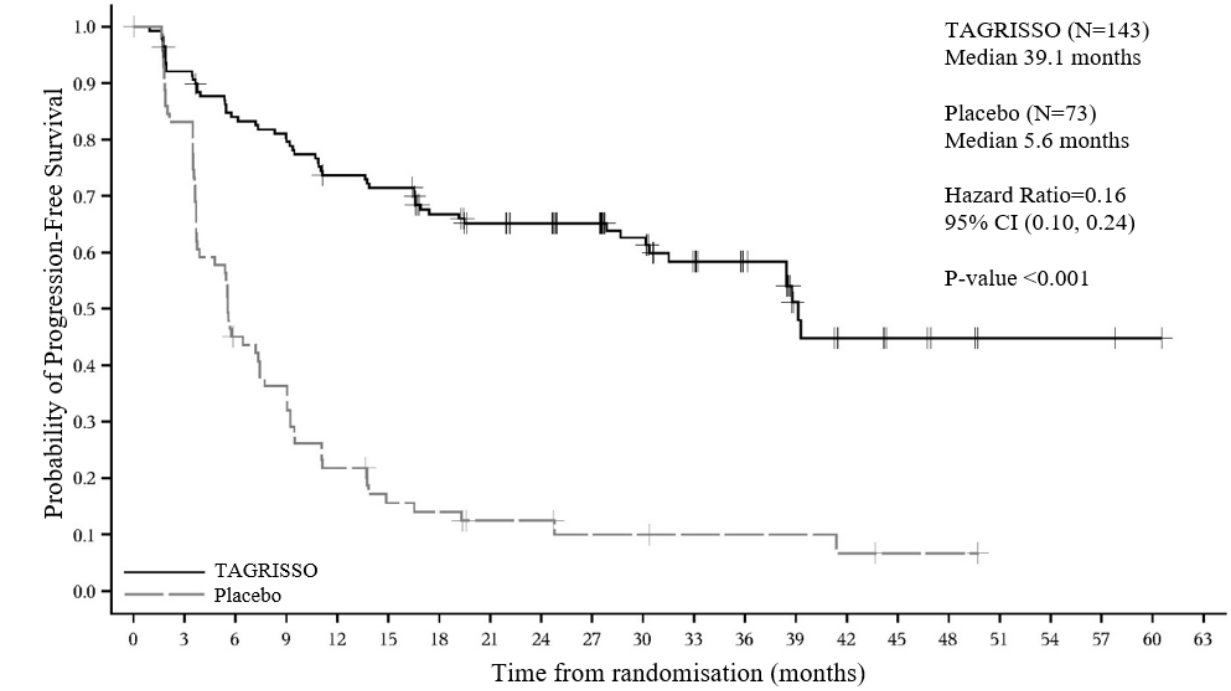
At the interim analysis, overall survival data were immature (20% maturity) (see Table 19).

Table 19 Efficacy results from the LAURA study (Full analysis set)

Efficacy Parameter	TAGRISSO (N=143)	Placebo (N=73)
Progression-Free Survival		
Number of Events (%)	57 (40)	63 (86)
Median, Months (95% CI)	39.1 (31.5, NC)	5.6 (3.7, 7.4)
HR (95% CI); 2-sided P-value	0.16 (0.10, 0.24); P<0.001	
Overall Survival (Interim)		
Number of deaths (%)	28 (20)	15 (21)
Median, Months (95% CI)	54.0 (46.5, NC)	NC (42.1, NC)
HR (95% CI); 2-sided P-value	0.81 (0.42, 1.56); P=0.530 [a]	

HR=Hazard Ratio; CI=Confidence Interval, NC=Not Calculable
PFS results as assessed by BICR.
Median follow-up time for PFS in all patients was 22.0 months in the TAGRISSO arm and 5.6 months in the placebo arm.
A HR <1 favours TAGRISSO, an Odds ratio of >1 favours TAGRISSO.
[a] Adjusted for an interim analysis (20% maturity) a p-value <0.00036 was required to achieve statistical significance.

Figure 4 Kaplan-Meier Curves of Progression-Free Survival as assessed by BICR in LAURA



Number at risk

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

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

CNS metastases efficacy in the LAURA trial

Per protocol, all patients underwent baseline magnetic resonance imaging (MRI) brain scans and all but one patient had scheduled on-treatment MRI brain scans. There was a nominal improvement in CNS PFS (based on neuroradiologist BICR assessment) in patients treated with TAGRISSO compared to placebo. The median CNS PFS was NC for TAGRISSO arm and 14.9 months in Placebo (27% maturity; HR=0.17; 95% CI: 0.09, 0.32). A lower proportion of patients had new CNS lesions in the TAGRISSO arm compared to the placebo arm (17/143 [12%] vs 26/73 [36%], respectively).

EGFR Mutation-Positive NSCLC

Table 20 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
D5169C00001 (FLAURA2)	Phase III, randomized (1:1), open-label, active-controlled, that investigated TAGRISSO 80 mg once daily in combination with pemetrexed and platinum-based chemotherapy as first line-treatment for EGFR mutation positive locally advanced or metastatic NSCLC	TAGRISSO + chemotherapy: TAGRISSO 80 mg tablets, once daily + pemetrexed IV, 500 mg/m^2 Q3W + Either cisplatin, 75 mg/m^2 Q3W or carboplatin, AUC5, Q3W TAGRISSO monotherapy: TAGRISSO 80 mg tablets, once daily	TAGRISSO + chemotherapy: n=279 TAGRISSO monotherapy: n=278	TAGRISSO + chemotherapy: 61.0 (26-83) TAGRISSO monotherapy: 60.7 (30-85)	TAGRISSO + chemotherapy: Female: n=173 Male: n=106 TAGRISSO monotherapy: Female: n=169 Male: n=109

Trial Design and Study Demographics (FLAURA)

The efficacy and safety of TAGRISSO for the treatment of patients with EGFR mutation positive locally advanced or metastatic NSCLC, who had not received previous systemic treatment for advanced disease, was demonstrated in a 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 21): 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 21 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)

	Osimertinib (N=279)	EGFR TKI comparator (gefitinib or erlotinib) (N=277)
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 randomization 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 22, and the Kaplan-Meier curve for PFS is shown in Figure 5. 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 22 and Figure 6).

Table 22 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 PFS, months (95% CI)	18.9 (15.2, 21.4)	10.2 (9.6, 11.1)
HR (95% CI); P-value	0.46 (0.37, 0.57); <0.0001	
Overall Survival		
Number of deaths, (58% maturity)	155 (56)	166 (60)
Median OS, 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); 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); 0.2421	
Duration of Response (DoR)*		
Median DoR, 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 5 Kaplan-Meier Curves of Progression-Free Survival as assessed by investigator in FLAURA

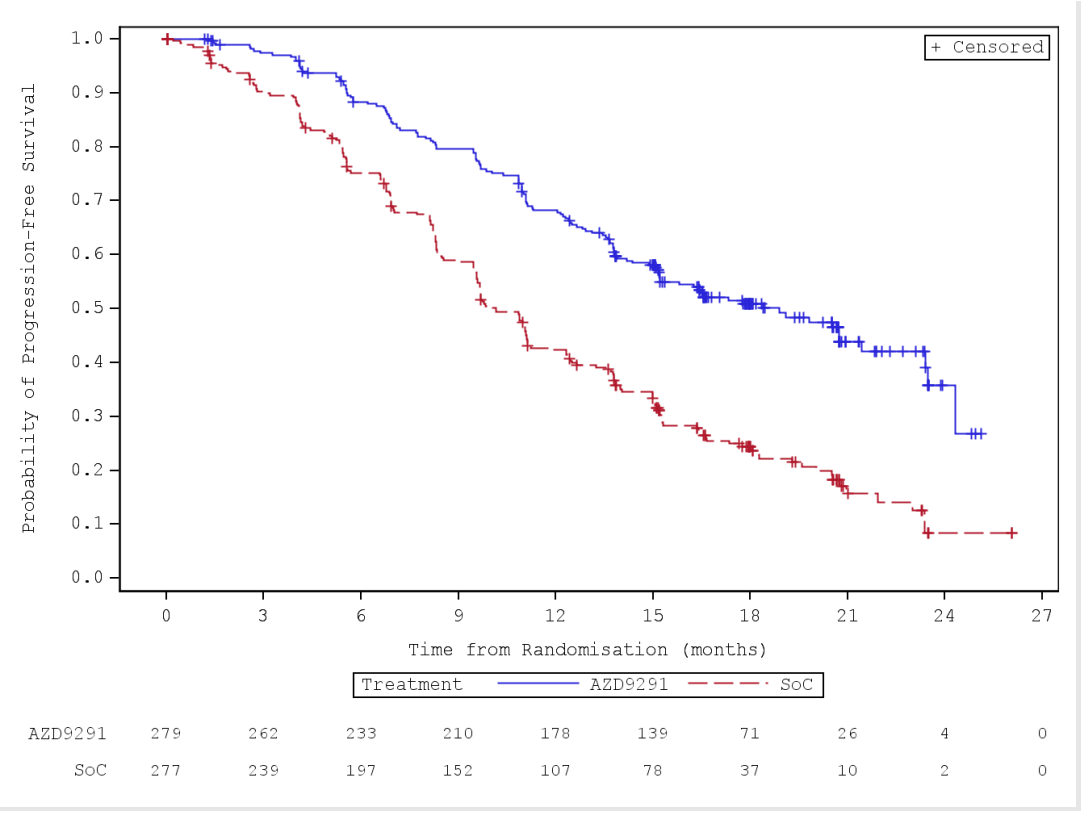
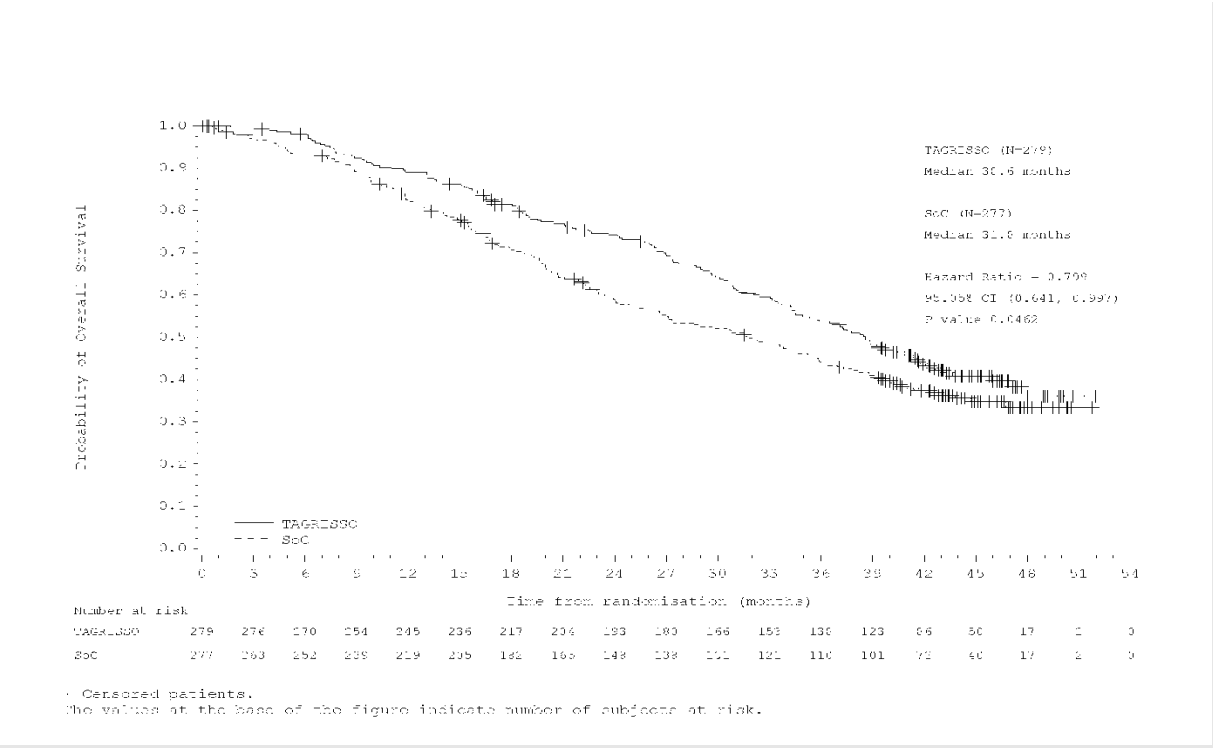


Figure 6 Kaplan-Meier Curves of Overall Survival in FLAURA



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 23. 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 23 CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in FLAURA

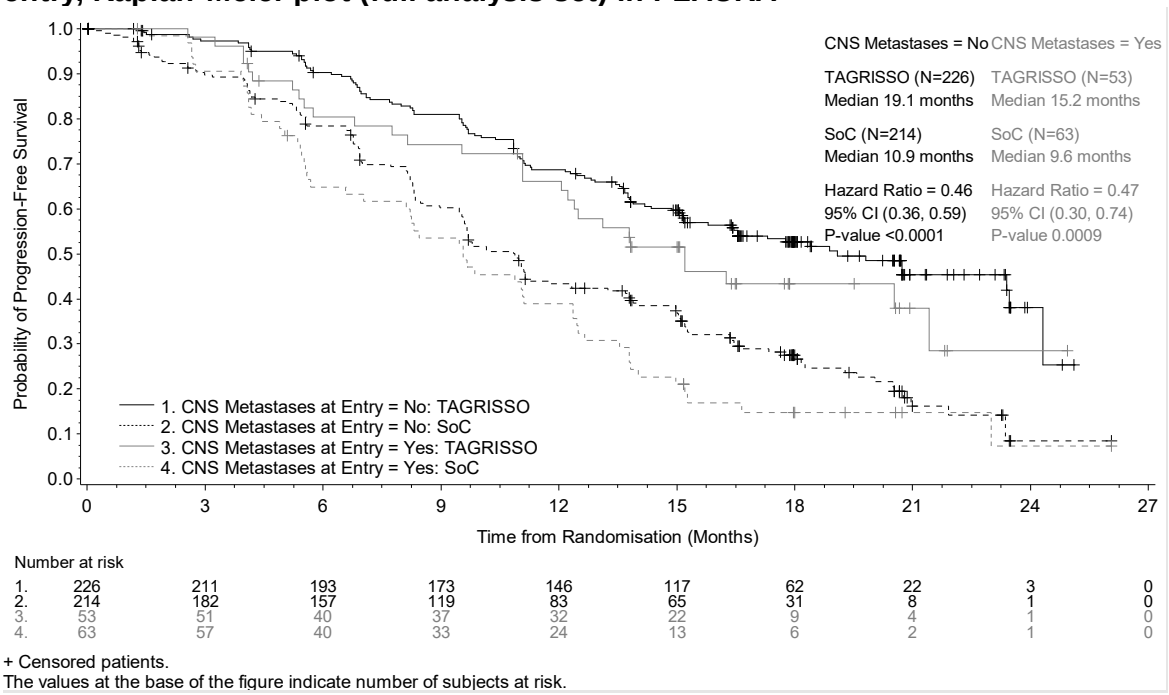
Efficacy Parameter	TAGRISSO (n=61)	EGFR TKI comparator (gefitinib or erlotinib) (n=67)
CNS Progression-Free Survival[a]		
Number of Events (%)	18 (30)	30 (45)
Median CNS PFS, months (95% CI)	NC (16.5, NC)	13.9 (8.3, NC)
HR (95% CI); P-value	0.48 (0.26, 0.86); 0.014	
CNS progression free and alive at 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); 0.011	
CNS Duration of Response[a]		
Median CNS DoR, months (95% CI)	NC (12, NC)	14 (7, 19)
Patients remaining in response at 6 months (%) (95% CI)	86 (70, 94)	76 (55, 89)

Efficacy Parameter	TAGRISSO (n=61)	EGFR TKI comparator (gefitinib or erlotinib) (n=67)
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 7. 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 7 Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in FLAURA



+ 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.

Trial Design and Study Demographics (FLAURA2)

The efficacy and safety of TAGRISSO in combination with pemetrexed and platinum-based chemotherapy for the treatment of patients with EGFR mutation-positive locally advanced or metastatic NSCLC, who had not received prior systemic treatment for advanced disease, was evaluated in a randomized, open-label, active-controlled study (FLAURA2). Patient tumour tissue samples were required to have one of the two common EGFR mutations known to be associated with EGFR TKI sensitivity (Ex19del or L858R), as identified by local or central testing.

Patients were randomized (1:1) to one of the following treatment arms:

- TAGRISSO (80 mg) orally once daily with pemetrexed (500 mg/m2) and the investigator's choice of cisplatin (75 mg/m^2) or carboplatin (AUC5) administered intravenously on Day 1 of 21-day cycles for 4 cycles, followed by TAGRISSO (80 mg) orally once daily and pemetrexed (500 mg/m^2) administered intravenously every 3 weeks (n=279)
- TAGRISSO (80 mg) orally once daily (n=278)

Randomization was stratified by race (Chinese/Asian, non-Chinese/Asian or non-Asian), WHO performance status (0 or 1), and method for tissue testing (central or local). Patients received study therapy until intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit.

The primary efficacy endpoint was PFS as assessed by investigator per RECIST 1.1, a sensitivity analysis for PFS by BICR was conducted. OS was a key secondary endpoint. Additional efficacy endpoints included ORR, DoR, disease control rate (DCR), depth of response, PFS2, TFST and TSST as assessed by investigator. CNS PFS, CNS ORR, CNS DoR, and CNS depth of response as assessed by BICR, and PRO were also assessed.

The baseline demographic and disease characteristics of the overall study population (Table 24) were: median age 61 years (range 26-85 years), ≥75 years old (8%), female (61%), Asian (64%), White (28%), never smokers (66%). All patients had a WHO performance status of 0 or 1; 49% of patients had metastatic bone disease, 53% of patients had extra-thoracic metastases and 20% had liver metastases. Forty-one percent (41%) of patients had CNS metastases (identified by investigator based on CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases).

Table 24 Demographics and key baseline disease characteristics in FLAURA2 trial (full analysis set)

	TAGRISSO with Pemetrexed and Platinum-based Chemotherapy (N=279)	TAGRISSO (N=278)
Demographics		
Age (years) [a]		
Mean (standard deviation)	61.0 (10.03)	60.7 (10.57)
Median (minimum-maximum)	61.0 (26, 83)	61.5 (30, 85)
Age group (years), n (%) [a]		
<50	38 (13.6)	44 (15.8)
≥50-<65	136 (48.7)	122 (43.9)
≥65-<75	82 (29.4)	88 (31.7)
≥75	23 (8.2)	24 (8.6)
Sex, n (%)		
Male	106 (38.0)	109 (39.2)
Female	173 (62.0)	169 (60.8)
Race, n (%)		
Black or African	2 (0.7)	3 (1.1)
Native Hawaiian or other Pacific Islander	0	0
American Indian or Alaska Native	11 (3.9)	6 (2.2)
Asian	179 (64.2)	176 (63.3)
White	74 (26.5)	83 (29.9)
Other	13 (4.7)	10 (3.6)
Smoking history, n (%)		
Never smokers	188 (67.4)	181 (65.1)
Current smokers	4 (1.4)	4 (1.4)
Former smokers	87 (31.2)	93 (33.5)
WHO performance status		
0 (normal activity)	104 (37.3)	102 (36.7)
1 (restricted activity)	174 (62.4)	176 (63.3)
2 [b]	1 (0.4)	0
Overall disease classification at study entry, n(%)		
Metastatic [c]	265 (95.0)	271 (97.5)
Locally-advanced [d]	14 (5.0)	7 (2.5)
CNS metastases [e]	116 (41.6)	110 (39.6)
Extra-thoracic visceral metastases [f]	147 (52.7)	149 (53.6)
Liver metastases [f]	43 (15.4)	66 (23.7)
EGFR mutations as used for randomization, n(%)		
Exon 19 deletion [g]	172 (61.6)	169 (60.8)
Exon 21 L858R	106 (38.0)	107 (38.5)

[a] Age at study entry.

[b] Patient E2805038 had a WHO PS of 1 at the time of randomization but prior to study drug administration on Cycle 1 Day 1 had a record of WHO PS 2 attributed to mobility issues. This was transient with the WHO PS returning to 1 at Cycle 2 Day 1.

[c] Patients had any metastatic site of disease

[d] Patients had only locally advanced sites of disease
[e] CNS lesions as identified by the Investigator and recorded in the eCRF based on CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases.
[f] This is a programmatically derived composite endpoint with a list of contributing eCRF data sources.
[g] Patients with both Exon 19 deletion and L858R are included in the Exon 19 deletion subgroup.
DCO: 03 April 2023

Study Results (FLAURA2)

TAGRISSO in combination with pemetrexed and platinum-based chemotherapy demonstrated a clinically meaningful and statistically significant improvement in PFS compared to TAGRISSO monotherapy (51% maturity; HR=0.62, 95% CI: 0.49, 0.79; P<0.0001; median 25.5 months and 16.7 months, respectively). The second interim analysis of OS (DCO 08 January 2024) demonstrated an HR of 0.75 (95% CI: 0.57, 0.97; P=0.0280, 41% maturity) for TAGRISSO with pemetrexed and platinum-based chemotherapy versus TAGRISSO monotherapy which did not reach statistical significance. Efficacy results by investigator assessment are summarized in Table 25, and the Kaplan-Meier curve for PFS is shown in Figure 8.

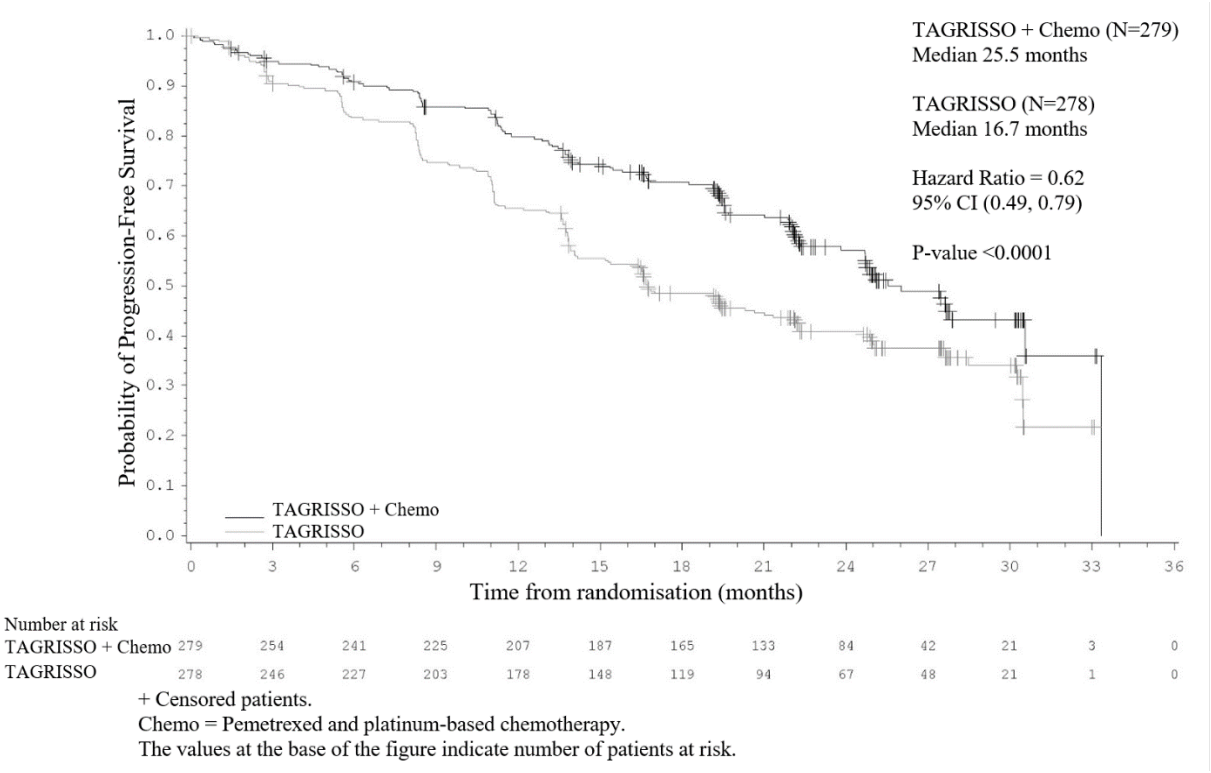
Table 25 Efficacy results from FLAURA2 by investigator assessment (Full analysis set)

Efficacy Parameter	TAGRISSO with Pemetrexed and Platinum-based Chemotherapy (N=279)	TAGRISSO (N=278)
Progression-Free Survival [a]		
Number of Events (51.3% maturity)	120 (43)	166 (60)
Median PFS, months (95% CI)	25.5 (24.7, NC)	16.7 (14.1, 21.3)
HR (95% CI); P-value	0.62 (0.49, 0.79); <0.0001	
Overall Survival		
Number of deaths, (41% maturity)	100 (36)	126 (45)
Median OS in months (95% CI)	NC (38.0, NC)	36.7 (33.2, NC)
HR (95.05% CI); P-value	0.75 (0.57, 0.97); P=0.0280 [b]	
Objective Response Rate [c,d]		
Number of responses	232	210
Response Rate (95% CI)	83 (78, 87)	76 (70, 80)
Odds ratio (95% CI); P-value [e]	1.61 (1.06, 2.44); 0.0261	
Duration of Response (DoR) [c]		
Median, Months (95% CI) [f]	24.0 (20.9, 27.8)	15.3 (12.7, 19.4)

HR=Hazard Ratio; CI=Confidence Interval, NC=Not Calculable
PFS, ORR, and DoR results based on RECIST investigator assessment.
Median follow-up time for PFS in all patients was 19.5 months in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm and 16.5 months in the TAGRISSO monotherapy arm.
PFS, ORR and DoR, results are from DCO 03 April 2023. OS results are from DCO 08 January 2024.
A HR<1 favours TAGRISSO with pemetrexed and platinum-based chemotherapy, an Odds ratio >1 favours TAGRISSO with pemetrexed and platinum-based chemotherapy.
[a] A sensitivity analysis of PFS by blinded independent central review (BICR) was consistent with PFS by investigator assessment.
[b] Based on the second interim analysis (41% maturity) a p-value < 0.00001 was required to achieve statistical significance.
[c] Based on unconfirmed response.
[d] ORR results by BICR were consistent with those reported via investigator assessment; ORR by BICR assessment was 92% (95% CI: 88, 95) for patients in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm and 83% (95% CI: 78, 87) for patients in the TAGRISSO monotherapy arm.

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

Figure 8 Kaplan-Meier Curves of Progression-Free Survival as assessed by investigator in FLAURA2



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

The PFS benefit of TAGRISSO in combination with pemetrexed and platinum-based chemotherapy compared to TAGRISSO monotherapy was consistent across all predefined subgroups analyzed, including ethnicity, age, gender, smoking history, CNS metastases status at study entry and EGFR mutation type (Exon 19 deletion or L858R).

CNS metastases efficacy in FLAURA2

All patients had available baseline brain scans reviewed by BICR using modified RECIST. 78/557 (14%) patients had CNS measurable lesions (cEFR subgroup). Results of pre-specified exploratory analysis of CNS PFS by BICR is summarized in Table 26.

Table 26 CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in FLAURA2

	CNS Measurable Lesions (cEFR)	
Efficacy Parameter	**TAGRISSO with Pemetrexed and Platinum-based Chemotherapy (N=40)**	**TAGRISSO (N=38)**
CNS Progression-Free Survival [a]		
Number (%) of events	11 (28)	18 (47)
Median CNS PFS, months (95% CI)	NC (23.0, NC)	17.3 (13.9, NC)
HR (95% CI); P-value [b]	0.40 (0.19, 0.84); 0.0157	
CNS Objective Response Rate [a]		
Number of CNS responses (n), CNS Response Rate % (95% CI)	35 88 (73, 96)	33 87 (72, 96)
Complete response	19 (48)	6 (16)
Partial response	16 (40)	27 (71)
Odds ratio (95% CI); P-value [b,c]	1.06 (0.28, 4.00); 0.9308	
CNS Duration of Response [a]		
Median CNS DoR, months (95% CI)	NC (21.6, NC)	20.9 (12.6, NC)
Patients remaining in response at 12 months (%) (95% CI)	93 (75, 98)	74 (53, 87)
Patients remaining in response at 24 months (%) (95% CI)	57 (27, 78)	45 (22, 65)

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

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

[a] Based on unconfirmed responses.

[b] Nominal P-value.

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

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

Patient-reported symptoms and 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, physical function or global health status/quality of life (GHS/QoL) were observed between the TAGRISSO with pemetrexed and platinum-based chemotherapy arm and the TAGRISSO monotherapy arm.

Data collected from baseline up to month 19 showed similar improvements for three of the five pre-specified primary PRO symptoms (cough, dyspnoea, and chest pain) in the TAGRISSO with pemetrexed and platinum-based chemotherapy arm compared with the TAGRISSO monotherapy arm, with improvement in cough reaching the established clinically relevant cutoff (change from baseline ≤-10) in both arms. There was a trend towards improvement for appetite loss and fatigue in the TAGRISSO monotherapy arm. In the TAGRISSO with pemetrexed and platinum-based chemotherapy arm, there was a trend towards worsening in fatigue during the first 4 cycles of chemotherapy followed by a trend towards improvement, and a trend towards worsening in appetite loss. Both arms reported no clinically meaningful changes in physical functioning and Global health status/QoL (GHS/QoL).

EGFR T790M Mutation-Positive Advanced NSCLC

Trial Design and Study Demographics (AURA3)

Table 27 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 28.

Table 28 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)

Table 28 Demographic and disease characteristics in Phase III AURA3 trial (Full analysis set)

Characteristic		TAGRISSO 80mg (N=279)	Chemotherapy (N=140)	Total (N=419)
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				
	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 randomized treatment (59.5% in the TAGRISSO arm and 11.8% in the chemotherapy arm).

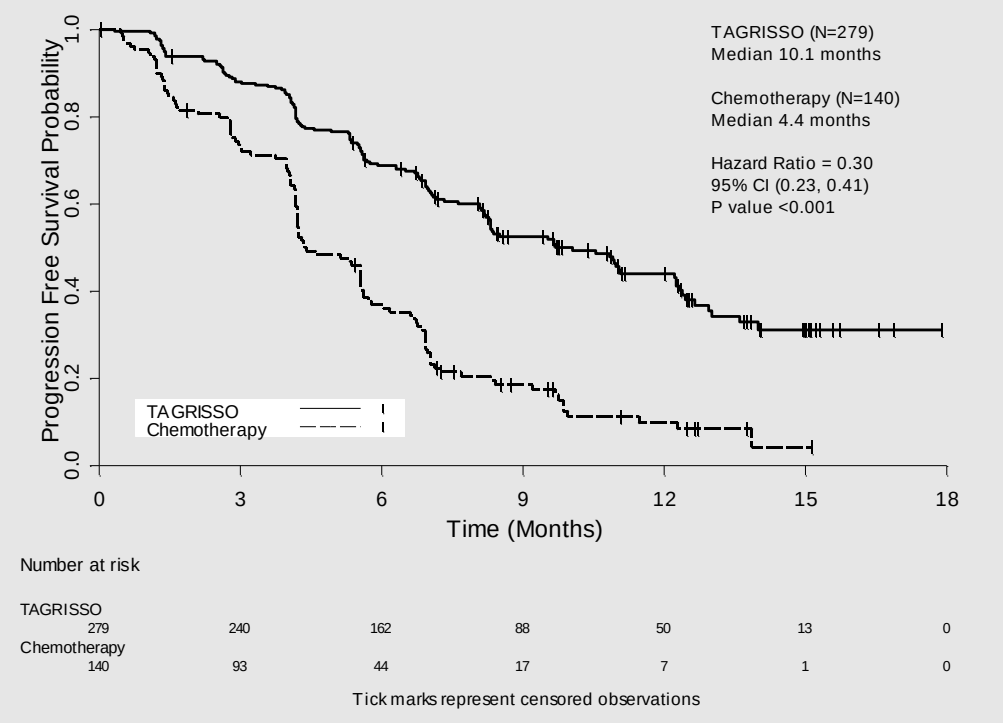
AURA3 demonstrated a clinically meaningful and statistically significant improvement in PFS in the patients treated with TAGRISSO compared to chemotherapy. Efficacy results from AURA3 by investigator assessment are summarized in Table 29, and the Kaplan-Meier curve for PFS is shown in Figure 9.

Table 29 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 PFS, months (95% CI)	10.1 (8.3, 12.3)	4.4 (4.2, 5.6)
HR (95% CI); P-value	0.30 (0.23, 0.41); <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); <0.001	
Duration of Response		
Median DoR, 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 9 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.

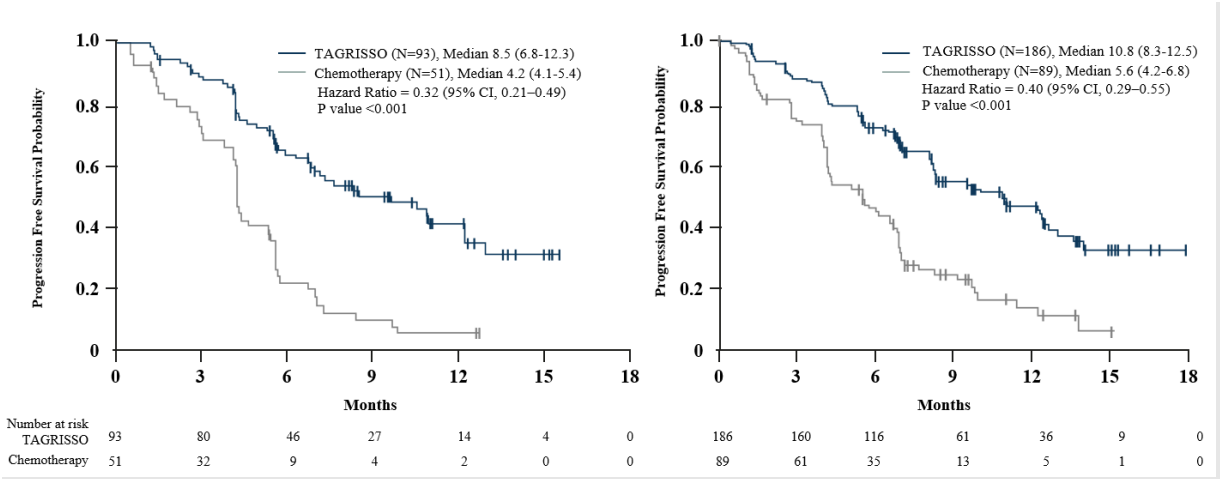
Among the patients in AURA3 treated with TAGRISSO with objective responses, 81.7% (161/279) had documentation of response at 6 weeks, and 94.9% (187/279) had documentation of response at 12 weeks.

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 10). The benefit of TAGRISSO was reported in patients with or without CNS metastases at baseline.

Figure 10 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 30.

Table 30 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); 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); 0.021	
CNS Progression-free survival[c]	N=75	N=41
Number of Events (% maturity)	19 (25)	16 (39)
Median, Months (95% CI)	11.7 (10, NC)	5.6 (4.2, 9.7)
HR (95% CI); P-value	0.32 (0.15, 0.69); 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

PrTAGRISSO®

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**.

Your cancer may be treated with TAGRISSO in combination with other anti-cancer medicines like pemetrexed and platinum-based chemotherapy. Read the Patient Medication Information for the other medications as well as this one.

Serious Warnings and Precautions

TAGRISSO should only be prescribed by a healthcare professional 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).

For the following indication(s) TAGRISSO has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- TAGRISSO is used as a single drug when the tumours cannot be removed by surgery, and are stable after treatment with platinum-containing chemotherapy and radiation, 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 following indication(s) TAGRISSO has been approved without conditions. This means it has passed Health Canada's review and can be bought and sold in Canada.

- TAGRISSO is used as a single drug 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 as a single drug 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.
- TAGRISSO is used with other anti-cancer medicines such as pemetrexed and a platinum-containing chemotherapy. This treatment combination 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.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

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 (hypocalcemia).
- 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.
- are 65 years of age or older.

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.

Aplastic anemia, a condition where the bone marrow stops producing new blood cells, can happen in patients taking TAGRISSO. It can lead to death. Stop taking TAGRISSO and get immediate medical help if you get any symptoms of aplastic anemia: persistent fever, bruising or bleeding more easily, pale skin, increasing tiredness and a decrease in ability to fight infection.

Skin and nail problems can occur. You may get rash, dry skin, acne, 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. Talk to your healthcare professional 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 healthcare professional immediately. Your healthcare professional 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 healthcare professional 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 healthcare professional 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.

Blood tests and monitoring: TAGRISSO can cause abnormal test results. Your healthcare professional 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 healthcare professional will interpret the results.

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 heartbeat 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 healthcare professional has told you. Do not stop taking this medicine - talk to your healthcare professional first.
- It is important to take this medicine **every day**, for as long as your healthcare professional prescribes it for you.
- If you do not take this medicine as prescribed by your healthcare professional, your cancer may grow again. Check with your healthcare professional 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:

<u>When taking TAGRISSO alone, or with pemetrexed and chemotherapy drugs that contain platinum:</u>

- One 80 mg tablet of TAGRISSO every day in a single dose.

Your healthcare professional will monitor your health. They may adjust your dose, interrupt and restart your dose, or stop your dose completely. This may occur based on your current health, if you take certain other medications or if you have certain side effects.

You may also receive treatment with other medicines like pemetrexed and chemotherapy drugs that contain platinum. These medicines will be given to you by your healthcare professional.

Overdose:

If you think you, or a person you are caring for, have taken too much TAGRISSO, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or 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. Some of these side effects may occur when taking TAGRISSO alone or when taking TAGRISSO with pemetrexed and chemotherapy drugs that contain platinum. If you experience any side effects not listed here, tell your healthcare professional. Please also see the Serious Warnings and Precautions Box above.

Side effects may include:

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

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			
Diarrhea that comes and goes, at least 3 loose liquid bowel movements a day.	✓		
Nausea, Constipation	✓		

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**	
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.		✓	
Increased blood creatinine: fluid retention in the lower body, passing low amounts of urine, fatigue, confusion, nausea, shortness of breath, irregular heart rate.		✓	
Common			
Serious Lung problems (interstitial lung disease, pneumonitis, radiation pneumonitis after chest radiation, 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.		✓	
Eye infection (conjunctivitis): itchy, red eyes with discharge, and swelling.		✓	

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 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, fatigue, 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.		✓	
Increased creatine phosphokinase in blood (an enzyme released into the blood when muscle is damaged): muscle aches and pains, muscle stiffness, vision changes, slurred speech, confusion, loss of consciousness.		✓	
Erythema multiforme: skin reaction with target lesions that look like rings.			✓
Skin hyperpigmentation: skin greying or darkening.	✓		
Uncommon			
Pulmonary edema (fluid in the air spaces of the lungs)**:** difficulty breathing that is worse when you lie down. Coughing up blood or blood-tinged froth.		✓	
Reduced kidney function: change in frequency of urination, pain when you urinate, nausea, vomiting, swelling of extremities, fatigue.	✓		
Toxic epidermal necrolysis: severe blistering or peeling of the skin.			✓
Keratitis (red eye with a 'gritty' sensation): eye pain, eye swelling and redness, watery eyes, vision changes, and sensitivity to light.		✓	

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**	
Rare			
Aplastic anemia (when bone marrow stops producing new blood cells): persistent fever, bruising or bleeding more easily, pale skin, increasing tiredness and a decrease in ability to fight infection.			✓
Myositis (muscle inflammation): sore and aching muscles, fatigue, weight loss, night sweats.		✓	
Stevens-Johnson syndrome: severe blistering or peeling of skin.			✓
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.		✓	
Rhabdomyolysis (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea-coloured) urine.		✓	

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 (canada.ca/drug-device-reporting) 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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