Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Tagrisso 40 mg film-coated tablets
Tagrisso 80 mg film-coated tablets

PLGB 17901/0340-0341

(osimertinib)

AstraZeneca UK Limited

LAY SUMMARY

Tagrisso 40 mg film-coated tablets
Tagrisso 80 mg film-coated tablets
(osimertinib)

This is a summary of the Public Assessment Report (PAR) for Tagrisso 40 mg and 80 mg film-coated tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Tagrisso in this lay summary for ease of reading.

For practical information about using Tagrisso, patients should read the package leaflet or contact their doctor or pharmacist.

What is Tagrisso and what is it used for?

These products have been authorised by MHRA for Great Britain (GB, consisting of England, Scotland and Wales). These products were originally European Union (EU) Centrally Authorised Products (CAPs) that have been converted to GB Marketing Authorisations ('grandfathering').

These applications are full-dossier applications. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Tagrisso is used to treat adults with a type of lung cancer called 'non-small cell lung cancer' (NSCLC).

If a test has shown that the patient's cancer has certain changes (mutations) in a gene called 'EGFR' (epidermal growth factor receptor) the cancer is likely to respond to treatment with Tagrisso.

Tagrisso can be prescribed for the patient:
- after complete removal of your cancer as a post-surgical (adjuvant) treatment

or
- as the first medicine you receive for the cancer which has spread to other parts of the body

or
- in certain circumstances if the patient has been treated for the cancer before with other protein kinase inhibitor medicines.

How does Tagrisso work?

Tagrisso contains the active substance osimertinib (as osimertinib mesylate), which belongs to a group of medicines called protein kinase inhibitors which are used to treat cancer. Osimertinib works by blocking EGFR and may help to slow or stop the lung cancer from growing. It may also help to reduce the size of the tumour and prevent the tumour from coming back after removal by surgery.

How is Tagrisso used?

The pharmaceutical form of these medicines is film-coated coats and the route of administration is oral (given by mouth).

How much to take
• The recommended dose is one 80 mg tablet each day.
• If necessary, your doctor may reduce your dose to one 40 mg tablet each day.

How to take
- Tagrisso is taken by mouth. The patient should swallow the tablet whole with water. The patient should not crush, split or chew the tablet.
- The patient should take Tagrisso every day at the same time.
- The patient can take these medicines with or without food.

If the patient has trouble swallowing the tablet, they can mix it in water:
- Put the tablet in a glass.
- Add 50 mL (about two-thirds of a tumblerful) of still (non-fizzy) water – they should 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 straight away.
- To make sure that the patient has taken all of the medicine, they rinse the glass thoroughly with another 50 mL of water and drink it.

For further information on how Tagrisso is used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Tagrisso have been shown in studies?
Tagrisso has been shown to be effective at shrinking tumours in patients with NSCLC when the cancer is advanced or has spread, and at slowing down the worsening of the cancer.

In two studies involving 411 previously treated patients who had T790 mutations, the overall response rates (the proportion of patients whose tumours shrank) with Tagrisso was 66% and the average length of time the response lasted was 12.5 months. In these studies, Tagrisso was not compared with any other treatment.

A third study in 419 previously treated patients with T790 mutations looked mainly at how effective Tagrisso was at preventing the cancer from worsening, comparing it with a platinum-based chemotherapy (the standard treatment for NSCLC). In patients taking Tagrisso, the cancer did not get worse for around 10.1 months compared with 4.4 months in patients on chemotherapy.

In a fourth study of 556 patients with activating mutations, patients taking Tagrisso as a first treatment lived for 18.9 months without their disease getting worse compared with 10.2 months in patients receiving treatment with other medicines (either erlotinib or gefitinib).

Tagrisso has also been shown to be effective in preventing NSCLC coming back after surgery. In a fifth study of 682 patients whose tumours were completely removed by surgery and had defects in the EGFR gene (exon 19 deletions or exon 21 substitution mutations),

97.4% of patients on treatment with Tagrisso were alive and disease-free after 12 months compared with 68.5% of patients on placebo.

What are the possible side effects of Tagrisso?
For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summaries of Product Characteristics (SmPCs) available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Tagrisso approved?
It was concluded that Tagrisso, as monotherapy, has been shown to be effective for:

- the adjuvant treatment after complete tumour resection in adult 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.

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

Furthermore, the side effects observed with use of these products are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that these medicines can be approved for use.

What measures are being taken to ensure the safe and effective use of Tagrisso?
A Risk Management Plan (RMP) has been developed to ensure that Tagrisso is used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Tagrisso
Marketing Authorisations were granted in Great Britain on 1 January 2021.

The full PAR for Tagrisso follows this summary.

This summary was last updated in July 2021.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Tagrisso 40 mg and 80 mg film-coated tablets (PLGB 17901/0340-0341) could be approved.

These products have been authorised by MHRA for Great Britain (GB, consisting of England, Scotland and Wales). Tagrisso 40 mg and 80 mg film coated tablets were originally EU Centrally Authorised Products (CAPs) that have been converted to GB Marketing Authorisations ('grandfathering'). The products were approved centrally via the European Medicines Agency in February 2016.

At the time of centralised authorisation, and conversion to GB Marketing Authorisations, the products were approved for the following indications:
Tagrisso as monotherapy is indicated for:

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

On 6 May 2021, following submission of a national GB variation application, the products were approved for an additional indication:
Tagrisso as monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult 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.

The active substance, osimertinib (as mesylate), is a Tyrosine Kinase Inhibitor (TKI). It is an irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harbouring sensitising mutations (EGFRm) and TKI-resistance mutation T790M.

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

In line with the legal requirements for children's medicines, the applications included a licensing authority decision on the agreement of a full product specific waiver (EMEA-002125- PIP01-17).

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing Authorisations were granted in Great Britain on 1 January 2021.

Summary of key changes after granting of the GB Marketing Authorisations

1. To update sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the Summary of Product Characteristics (SmPC) and sections 1 and 4 of the Patient Information Leaflet (PIL) to include the following indication: 'Tagrisso as a monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult 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
(PLGB 17901/0340-0341_0002, granted 6 May 2021. For the scientific discussion on the variation applications see Annex 1 at the end of this report.)

2. To update section 4.8 of the SmPC and section 4 of PIL for Tagrisso 40 mg film-coated tablets and Tagrisso 80 mg film-coated tablets in line with the company Core Data Sheet (CDS) and Core Patient Information Leaflet (CPIL) to include `urticaria' as an adverse drug reaction (PLGB 17901/0340-0341_0004, granted 7 May 2021. For the scientific discussion on the variation applications see Annex 2 at the end of this report.)

II. ASSESSOR'S COMMENTS ON THE PRODUCT INFORMATION SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPCs are in line with current guidelines and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for these applications is satisfactory.

For the scientific discussion of the quality assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

The grant of Marketing Authorisations are recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for these applications is satisfactory.

For the scientific discussion of the non-clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

The grant of Marketing Authorisations are recommended.

V. CLINICAL ASPECTS

MHRA considered that the clinical data submitted for these applications is satisfactory.

For the scientific discussion of the clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

The grant of Marketing Authorisations are recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the applications in accordance with the requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the products is acceptable. At the time of the GB Marketing Authorisations, the non-clinical and clinical data submitted have shown the positive benefit/risk of these products as monotherapy for:

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

The SmPCs, PIL and labelling are satisfactory.

In accordance with legal requirements, the current approved GB versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of GB licensing are provided below.

Tagrisso 40 mg film-coated tablets


GLUE FLAP CODE
5 000456 053884
TAGRISSO® 40 mg
film-coated tablets
osimertinib
30 x 1 film-coated tablets
Each tablet contains 40 mg osimertinib (as mesylate).
Read the package leaflet before use.
Keep out of the sight and reach of children.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
DATA LINE 1
DATA LINE 2
DATA LINE 3
DATA LINE 4
DATA LINE 5
PC
SN
Lot ▶
EXP ▶
TAGRISSO® 40 mg
film-coated tablets
osimertinib
30 x 1 film-coated tablets
TAGRISSO® 40 mg
film-coated tablets
osimertinib
Oral use
30 x 1 film-coated tablets
AstraZeneca
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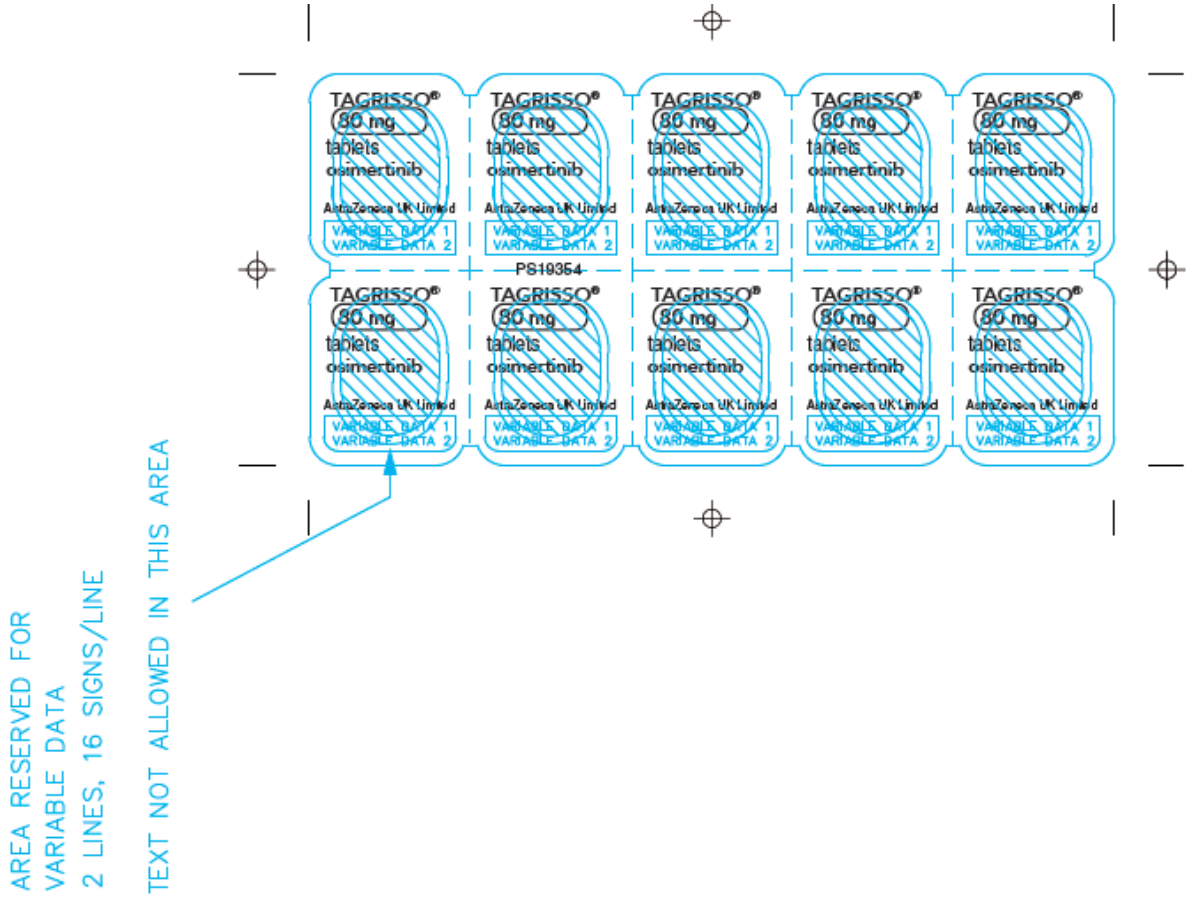
AstraZeneca UK Limited
600 Capability Green,
Luton, LU1 3LU, UK.
PLGB 17901/0340
POM
PS19351

Tagrisso 80 mg film-coated tablets




PS19353
PLGB 17901/0341
POM
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600 Capability Green,
Luton, LU1 3LU, UK
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TAGRISSO is a registered trademark of the
AstraZeneca group of companies.
AstraZeneca
Oral use
30 x 1 film-coated tablets
TAGRISSO® 80 mg
film-coated tablets
osimertinib
30 x 1 film-coated tablets
Lot
EXP
Each tablet contains 80 mg osimertinib
(as mesylate).
Read the package leaflet before use.
Keep out of the sight and reach of children.
Any unused medicinal product or waste
material should be disposed of in accordance
with local requirements.
5 000456 053907
DATA LINE 1
DATA LINE 2
DATA LINE 3
DATA LINE 4
DATA LINE 5
PC
SN
TAGRISSO® 80 mg
film-coated tablets
osimertinib
30 x 1 film-coated tablets
GLUE FLAP CODE

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Steps taken after the initial procedure with an influence on the Public Assessment Report
(non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**
Type II	To update sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC and sections 1 and 4 of the PIL to include the following indication: 'Tagrisso as a monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult 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.'	SmPC PIL	6 May 2021	Approved	Yes (Annex 1)

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N
Type II	To update section 4.8 of the SmPC and section 4 of PIL for Tagrisso 40 mg film-coated tablets and Tagrisso 80 mg film-coated tablets in line with the company Core Data Sheet (CDS) and Core Patient Information Leaflet (CPIL) to include `urticaria' as an adverse drug reaction.	SmPC PIL	7 May 2021	Approved	Yes (Annex 2)

Annex 1

Reference: **PLGB 17901/0340-0002**
PLGB 17901/0341-0002

Product: Tagrisso 40 mg film-coated tablets
Tagrisso 80 mg film-coated tablets

Type of Procedure: National route

Submission category: Type II Variation

These applications were evaluated as part of Project Orbis, which is a programme coordinated by the US Food and Drug Administration (FDA) involving the regulatory authorities of Australia (TGA), Canada (Health Canada), Singapore (HSA), Brazil (ANVISA), Switzerland (Swissmedic) and the UK (MHRA), to review and approve promising cancer treatments. Project Orbis provides a framework for concurrent submission and review of oncology products among international partners. Each regulator made independent decisions regarding approval of the applications.

Reason
To update sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC and sections 1 and 4 of the PIL to include the following indication: 'Tagrisso as a monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult 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.'

Supporting evidence
The Marketing Authorisation Holder (MAH) has submitted updated:
- SmPCs
- PIL

In addition the following studies were submitted to support the applications:

Non-clinical studies
- Pharmacology study reports
  - An *in vitro* inhibition of epidermal growth factor receptor (EGFR), downstream signalling and cell proliferation by AZD9291 in two patient derived tumour cell lines carrying activating, uncommon mutations in EGFR
  - *In vitro* cellular screening assay for AZ13552748 (AZD9291, osimertinib), AZ13575104 (metabolite of osimertinib) and AZ12656575 (afatinib)
  - An *in vivo* Tumour Growth of NSCLC patient-derived xenograft (PDX) harbouring uncommon EGFR mutations at codons G719, S768 and L861
- Analytical method validation reports
- Distribution study report
  - An *in vivo* assessment of brain exposure and regional brain distribution of AZD9291 in cynomolgus monkey using positron emission tomography (PET) microdosing.
- Repeat dose toxicity study reports
  - a 14-day by oral (gavage) dose range finding toxicity study in mice
  - a 42-day oral (gavage) dose range finding toxicity study in mice
  - a six-month oral (gavage) toxicity study in the rat
  - a nine-month oral (gavage) toxicity study in the dog

- 26 week carcinogenicity study report
  - A 26-week Carcinogenicity Study by Oral Gavage in CByB6F1/Tg rasH2 Hemizygous Mice
- Draft audited study report
  - 104 Week Oral (Gavage) Carcinogenicity Study in the Rat
- Reproductive toxicity study report
  - Oral Fertility and Early Embryonic Development Study with Assessment of Recovery in the Female Rat
- AMES study reports
  - Genetic Toxicity Evaluation Using the Bacterial Reverse Mutation Test in Salmonella typhimurium TA98, TA100, TA1535 and TA1537 and Escherichia coli WP2 uvrA (pKM101)

Clinical study:

- An ongoing global Phase III, double-blind, randomised, placebo-controlled multi-centre, study to assess the efficacy and safety of AZD9291 versus placebo, in patients with epidermal growth factor receptor mutation positive Stage IB-IIIA non-small cell lung carcinoma, following complete tumour resection with or without adjuvant chemotherapy (ADAURA, D5164C00001)

Evaluation:

Non-clinical evaluation

The activity of osimertinib to support the additional indication was investigated in the following studies.

Primary pharmacodynamic studies

***In vitro* studies:**

Inhibition of epidermal growth factor receptor (EGFR) phosphorylation in COS7 cells expressing uncommon EGFR mutants

To test the potency of inhibition of EGFR phosphorylation of uncommon EGFR mutations by osimertinib, COS7 cells were transiently transfected to express a variety of uncommon EGFR mutant proteins and treated with osimertinib. EGFR phosphorylation was measured using a homologous time-resolved fluorescence assay.

The data from these experiments are shown in Table 1. The apparent geomean IC_{50} for inhibition of phosphorylation of each of the uncommon mutant variants by osimertinib was <50 nM (range 4.5 nM - 40.7 nM) in all cases tested. In the same assay, the IC_{50} for inhibition of the common Exon 19 deletion and L858R mutants was 8.4 nM and 11.9 nM respectively. The potency of the osimertinib metabolite, AZ5104, against the uncommon mutants was shown to be greater than that of osimertinib (apparent geomean IC_{50} range 1.7 nM – 40.7 nM) representing an average 2.66 fold difference in potency compared to osimertinib ($p<0.05$) (Table 2).

Table 1. Summary of Inhibition of EGFR phosphorylation by osimertinib in COS7 cells expressing uncommon EGFR mutants following a 2 hour pre-incubation (apparent IC_{50} ± SE, µM)

Cell Line, EGFR mutation	Geomean IC_{50} (µM)	± SE	Number of replicates
Cos 7 EGFR L861Q/G719A	0.0370	0.0083	2
Cos 7 EGFR L861Q/G719S	0.0175	0.0054	2
Cos 7 EGFR S768I/G719A	0.0352	0.0070	3
Cos 7 EGFR S768I/G7198S	0.0407	0.0040	3
Cos 7 EGFR G719C	0.0194	0.0081	2

Cell Line, EGFR mutation	Geomean IC_{50} (µM)	± SE	Number of replicates
Cos 7 EGFR G719S	0.0351	0.0144	2
Cos 7 EGFR L816Q	0.0148	0.0047	3
Cos 7 EGFR S768I	0.0240	0.0080	3
Cos 7 EGFR G719A	0.0354	0.0150	2
Cos 7 EGFR G719C/L861Q	0.0112	0.0050	2
Cos 7 EGFR G719C /S768I	0.0045	0.0021	2
Cos 7 L747S	0.0200	0.0059	3
EGFR Ex19del Control Line	0.0084	0.0017	6
L858R Control Line	0.0119	0.0021	7

Table 2. Inhibition of EGFR phosphorylation by AZ5104 in COS7 cells expressing uncommon EGFR mutants following a 2 hour pre-incubation (Apparent IC_{50} geomean, +/- SE, µM)

Cell Line, EGFR mutation	Geomean IC_{50} (µM)	± SE	Number of replicates
Cos 7 EGFR L861Q/G719A	0.0200	0.0023	3
Cos 7 EGFR L861Q/G719S	0.0053	0.0007	2
Cos 7 EGFR S768I/G719A	0.0113	0.0022	3
Cos 7 EGFR S768I/G719S	0.0106	0.0003	2
Cos 7 EGFR/G719C	0.0116	0.0018	3
Cos 7 EGFR /G719S	0.0407	0.0155	3
Cos 7 EGFR/L816Q	0.0064	0.0006	3
Cos 7 EGFR/S768I	0.0102	0.0006	3
Cos 7 EGFR/G719A	0.0141	0.0004	2
Cos 7 EGFR G719C/L861Q	0.0023	0.0009	3
Cos 7 EGFR G719C/S768I	0.0017	0.0002	2
Cos 7 L747S	0.0076	0.0005	3
EGFR Ex19del Control Line	0.0072	0.0007	5
L858R Control Line	0.0087	0.0006	6

Inhibition of EGFR Phosphorylation and downstream signalling in patient derived tumour cell lines, *in vitro*, expressing the EGFR L861Q mutation or the EGFR G719C/S768I mutation

EGFR mutant NSCLC patient-derived cell lines carrying either the EGFR L861Q (YU-1092) or G719C/S768I compound mutation (YU-1099) were used to evaluate inhibition of EGFR and downstream signalling by osimertinib in more disease relevant models, compared to the engineered COS7 model. EGFR phosphorylation (pEGFR) in the YU-1099 was not detected at the lowest concentration of osimertinib (10 nM) but in the YU-1092 cell line the osimertinib concentration required to completely inhibit EGFR phosphorylation was between 30 and 100 nM. In both cell lines osimertinib induced concentration-dependent inhibition of downstream signalling (pAkt, pERK, pS6) and increases in the levels of the pro-apoptotic protein BIM.

Therefore, consistent with engineered COS7 cell data, osimertinib also demonstrates high level of *in vitro* potency against representative uncommon EGFR mutant signalling in more disease relevant cell models.

Inhibition of proliferation and colony formation, in vitro, in patient derived tumour cell lines expressing the EGFR L861Q mutation or the EGFR G719C/S768I mutation
In a colony formation assay in the YU-1099 cell line carrying the compound EGFR G719C/S768I mutation, osimertinib showed potent inhibition of colony formation with an apparent IC_{50} of approximately 30 nM. In the YU-1092 carrying an EGFR L861Q mutation the IC_{50} for inhibition of colony formation was <10 nM.

***In vivo* studies**
***In vivo* activity of osimertinib against tumour models carrying uncommon EGFR mutations involving codons G719, S768 and L861**
In an *in-vivo* study tumour regression was shown in mice treated once daily with 25 mg/kg osimertinib (stated to be similar to human exposure at 80 mg) *In vivo* efficacy data in PDX models that carry 3 of the commonly reported compound mutations involving G719X and either S768I and L861Q (G719A/S768I, G719C/S768I and G719A/L861Q) were determined in mice treated once daily with 25 mg/kg osimertinib (stated to be similar to human exposure at 80 mg) (see Table 3). The LU1901 model which carries a cMET amplification, is not dependent upon EGFR for tumour growth since tumour regression can be achieved by administration of a selective cMET inhibitor. cMET amplification is an established resistance mechanism for EGFR tyrosine kinase inhibitors.

Table 3 *In vivo* activity of osimertinib against tumour models carrying EGFR G719 mutations

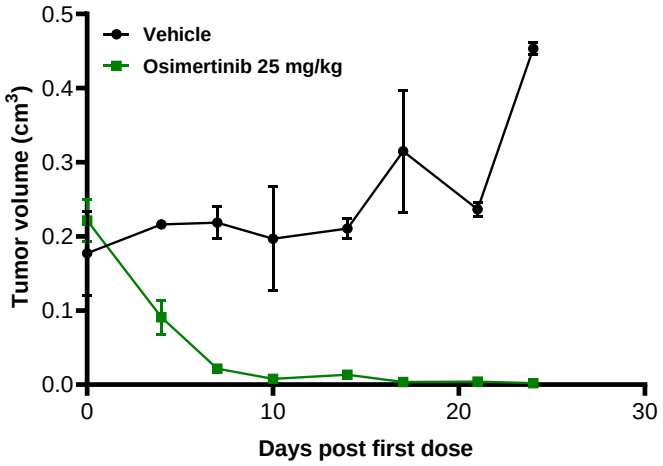
Model (mutation)	Treatment	% Tumour growth inhibition	Regression %	P-value
LU1901 (G719A; c-MET amplification)	osimertinib 25 mg/kg QD	Not detected	Not detected	NA
LC-F-29 (G719A/S768I)	osimertinib 25 mg/kg QD	>100	81%	<0.001
CTG-2534 (G719C/S768I)	osimertinib 25 mg/kg QD	>100	58%	<0.001
CTG-1082 (G719A/L861Q)	osimertinib 25 mg/kg QD	87	Not detected	<0.001
YLR067 (L861Q)	osimertinib	>100	99%	<0.01

NA = not applicable; QD = once daily
Regression was calculated as the percentage reduction in tumour volume from baseline value: % Regression = (1 − RTV) x 100% where RTV = Mean Relative Tumour Volume.

An additional PDX model carrying the L861Q mutation and derived from a patient previously treated with erlotinib was also tested for response to osimertinib (Figure 1).

Whilst the numbers of mice per treatment group were low there is evidence of tumour regression in mice treated once daily with 25 mg/kg osimertinib.

Figure 1 *In vivo* activity of osimertinib against PDX tumour models carrying an EGFR L861Q mutation



The data indicates that osimertinib demonstrated high level of tumour inhibitory activity *in vivo* across multiple representative models of clinically relevant uncommon EGFR mutation types.

Pharmacodynamic Activity of osimertinib in a PDX tumour model carrying the G719A/S768I uncommon compound mutation in EGFR.

A PDX tumour model carrying the G719A/S768I mutation was used to demonstrate time dependent inhibition of EGFR and downstream signalling (pERK, pAkt and pS6) at various time points following a single, oral 25 mg/kg dose of osimertinib. Osimertinib induced time dependent inhibition of EGFR and downstream signalling with a peak inhibition occurring at 6 hours post-dose.

Pharmacokinetics

Additional method development

Additional method development and validation work to improve the analytical methodology with respect to AZ5104 assay variability has been undertaken and while bioanalytical methods were successfully validated, incurred sample reanalysis was not successful for this analyte in rat samples or alternative methods failed to qualify rat samples over an acceptable concentration range. However, one study did identify method improvements that resulted in successful ISR for AZ5104 in dog plasma samples and these changes were incorporated into method 1 to give rise to method 2. Subsequently, method 2, a protein precipitation HPLC/MS/MS assay was partially validated and used to determine osimertinib and metabolites AZ5104 and AZ7550 concentrations in samples from the 9-month dog toxicity study. A validated protein precipitation LC-MS/MS assay was also used to determine osimertinib and metabolites AZ5104 and AZ7550 concentrations in samples from the 6-month mouse carcinogenicity study.

Distribution

Assessment of brain exposure and regional brain distribution of AZD9291 in cynomolgus monkey using positron emission tomography (PET) microdosing.

A study was conducted to assess brain exposure and regional brain distribution of osimertinib in cynomolgus monkey using PET microdosing to assess the blood-brain barrier penetration potential of osimertinib and compare to the active metabolite AZ5104. Osimertinib and AZ5104 were labelled with carbon-11 to enable microdosing studies with PET. Three monkeys were used for brain uptake experiments of microdoses of [^{11}C]-osimertinib (n=3) and [^{11}C]-AZ5104 (n=2). No adverse effects related to the administration of microdoses of [^{11}C]-osimertinib or [^{11}C]-AZ5104 were observed.

The distribution of [^{11}C]-osimertinib to brain was rapid and within 10 min of dosing reached a plateau of 1.29% ± 0.42% (n=3) of injected radioactivity. In contrast, distribution of the active metabolite [^{11}C]--AZ5104 was lower corresponding to 0.17% (n=2)of injected radioactivity. The ratio of the area under the brain radioactivity concentration-time curve (corrected for radioactivity in cerebral blood; $AUC_{0\text{-}90\ min}$) to that in blood for [^{11}C]-osimertinib was 2.62 ± 1.42 with the corresponding value of 0.35 for [^{11}C]--AZ5104.

In conclusion, this PET microdosing study demonstrated that [^{11}C]-osimertinib distributed across the blood--brain barrier of the cynomolgus monkey brain and that a microdose of [^{11}C]-osimertinib exhibited a higher level of brain exposure to that of the active metabolite [^{11}C]-AZ5104.

Toxicology

Repeat dose toxicity

14-day Oral (Gavage) Dose Range Finding Toxicity

The objectives of this study were to determine the potential toxicity of osimertinib when given orally once daily for 14 days to mice and to help establish dose levels for a subsequent carcinogenicity study in the Tg.ras H2 mouse. In addition, the toxicokinetic characteristics of osimertinib and metabolites (AZ7550 and AZ5104) were determined. Three groups of CByB6F1 (non-transgenic littermates) hybrid mice, each consisting of 3 males and 3 females, were dosed with osimertinib via oral gavage at dose levels of 25, 75, or 100 mg/kg/day once daily for 14 days.

There were no deaths during the study. Osimertinib administration resulted in clinical signs of slight dehydration, decreased activity, and body weight loss at ≥75 mg/kg/day in both sexes. Histopathological findings at ≥25 mg/kg/day included reduced lymphoid cellularity in the spleen and thymus, with associated decreases in organ weights. Osimertinib administration also resulted in decreased uterine weights for all females. The microscopic finding of a shift from the pro-oestrus stage for all control females to the dioestrus stage for all 100 mg/kg/day-dosed females accounted partially for this observation. There was no histopathologic correlate for the uterine weight decrease in the females dosed at 25 or 75 mg/kg/day.

Osimertinib-related microscopic findings were observed in epithelial and cutaneous tissues and included epithelial atrophy in the cornea and oesophagus, and/or mixed cell infiltration in the dermis of eyelid of both sexes for all osimertinib-treated animals.

In conclusion, oral administration of osimertinib was poorly tolerated in CByB6F1 mice when dosed at 100 mg/kg/day over 14 days due to marked body weight loss. Microscopic findings consistent with EGFR inhibition were observed in the eye, eyelid and oesophagus.

42-day Oral (Gavage) Dose Range Finding Toxicity Study in Mice

The objectives of this study were to determine the potential toxicity of osimertinib when given orally for 42 days to mice and to help establish dose levels for a subsequent 6-month carcinogenicity study in the Tg.ras H2 hybrid mouse. In addition, the toxicokinetic characteristics of osimertinib and the metabolites (AZ7550 and AZ5104) were determined.

Three groups of CByB6F1 (non-transgenic littermates) hybrid mice, each consisting of 10 males and 10 females, were dosed with osimertinib via oral gavage at dose levels of 10, 45, and 75 mg/kg/day. A control group of 10 males and 10 females was dosed with vehicle (methane sulfonic acid in reverse osmosis deionised [RODI] water). An additional 24 males and 24 females per group (osimertinib-treated groups) or 12 males and 12 females per group (controls) were included to evaluate the toxicokinetics on Days 1 and 42.

There were no osimertinib-related deaths but there were overt signs of toxicity at ≥10 mg/kg/day in males and ≥45 mg/kg/day in females. There was a reduction in body weight gain at 45 mg/kg/day in males and body weight losses at 75 mg/kg/day in males and females with corresponding reductions in food consumption at 75 mg/kg/day in females only (with corresponding decreases in ALP and triglycerides).

There were gross pathology findings, organ weight changes, and/or histopathology changes at ≥10 mg/kg/day with adversity noted in pathology at ≥45 mg/kg/day based on the severity of the changes. Microscopic findings stated to be consistent with EGFR inhibition were observed in the skin, eyelid, eye, oesophagus, stomach, tongue, and ileum. The inflammatory changes present in particular epithelial tissues (skin, eyelid and eye) correlated with increases in neutrophils and decreases in albumin, increases in globulin, and decreased albumin/globulin ratio. Increased lymph node (axillary, cervical and mandibular) cellularity and increased bone marrow myelopoiesis were considered reactive responses to the osimertinib-induced inflammation in epithelial tissues. Other target organs included pituitary and adrenal gland (with corresponding organ weight decreases), sublingual salivary gland, and exocrine pancreas. Target organs where stress was considered a contributory factor included thymus and spleen (decreased lymphoid cellularity and organ weight changes for both with a corresponding decrease in lymphocytes), and cervix, vagina, ovary, and uterus (including histological appearance of all female reproductive tract tissues consistent with dioestrus or anoestrus and decreased organ weights for uterus and ovary).

Six Month Oral (Gavage) Toxicity Study in the Rat

Four groups of Han Wistar rats, each consisting of 15 males and 15 females, were given osimertinib orally, once daily at doses of 0, 1, 5 or 20 mg/kg/day for 6 months. Additional animals were included for toxicokinetic evaluation.

Overt signs of toxicity were evident at ≥ 5 mg/kg/day and a decrease in bodyweight gain in males at 20 mg/kg/day. Compound-related histopathological changes were present in the skin, cornea, oesophagus, tongue, Harderian gland, lacrimal gland, spleen and lymph nodes at ≥ 5 mg/kg/day and also in the non-glandular stomach, kidney, male mammary gland, eyelid tarsal gland, prostate gland, seminal vesicles, uterus, vagina, adrenal gland, bone marrow, lung and thymus at 20 mg/kg/day. There were histopathological findings in the Harderian gland of one female at 1 mg/kg/day, however these were considered to be non-adverse given the minimal severity and lack of any other histopathology or ophthalmology findings in the eye. The low dose of 1 mg/kg/day is therefore considered to be the no observed adverse effect level (NOAEL).

Nine Month Oral (Gavage) Toxicity Study in the Dog

Four groups of beagle dogs, each consisting of 4 males and 4 females, were given vehicle or osimertinib orally, once daily, for at least 273 days at dose levels of 0, 0.5, 1.5 or 6 mg/kg/day.

Doses of 0.5, 1.5 or 6 mg/kg/day were tolerated for 9 months in both sexes. The main clinical signs associated with administration of osimertinib at 6 mg/kg/day were changes in the eye (conjunctival reddening, discharge and eyes partially closed). On ophthalmology examination, an increased incidence/severity of corneal translucency/opacity was seen at 1.5 mg/kg/day and 6 mg/kg/day, with some of these lesions showing evidence of corneal epithelial ulceration/erosion (areas of the cornea that stained positively with fluorescein dye). The severity of these ocular findings resulted in two high dose females being taken off-dose for a short period during Week 11 or Week 34. Following 4 to 5 days off-dose these findings recovered and the dogs resumed dosing at 6 mg/kg/day.

Compound-related histopathological changes were present in the testes at all dose levels, in the kidney at ≥1.5 mg/kg/day and in the adrenal gland, liver and eyelid (tarsal gland) at 6 mg/kg/day. As histology findings were present at the low dose a NOAEL was not identified in this study.

Conclusion of repeat toxicity studies
Repeated administration of osimertinib resulted in adverse effects in the eye in all three species tested that is the mouse, the rat and the dog. In the dog nine month study these effects were reported as being reversible upon cessation of dosing.

Overall, the results from the new repeat dose toxicity studies do not indicate a reason to preclude the proposed extension of indication.

Carcinogenicity
A 26-week Carcinogenicity Study by Oral Gavage in CByB6F1/Tg rasH2 Hemizygous Mice
The objective of this study was to determine the potential carcinogenicity of osimertinib when given orally for a minimum of 26 weeks to CByB6F1/Tg rasH2 Hemizygous mice. In addition, the toxicokinetic characteristics of osimertinib and the metabolites (AZ7550 and AZ5104) were determined.

Three groups of CByB6F1/Tg rasH2 Hemizygous (transgenic littermates) mice, each consisting of 25 males and 25 females, were dosed with osimertinib via oral gavage at dose levels of 1, 3 or 10 mg/kg/day once daily, for 26 weeks. Two control groups consisting of 25 males and 25 females each were dosed with vehicle (methane sulfonic acid in ultra-pure water) or water (ultra-pure water). An additional group consisting of 15 males and 15 females was dosed with a known carcinogen as a positive control. In addition, 5 groups of CByB6F1 hybrid (non-transgenic littermates) mice, each consisting of 24 males and 24 females per group (osimertinib-dosed groups) or 12 males and 12 females per group (control groups), were included to evaluate the toxicokinetics on Days 1 and 180.

All animals dosed with osimertinib were exposed to osimertinib, AZ7550 and AZ5104. Plasma concentrations at 24 hours were below the limit of quantification in most of the profiles, therefore, a partial area up to 6 hour post dose, $AUC_{(0-6)}$, was calculated for all profiles to allow exposure comparison across the different dose levels and sampling occasions. Based on C_{max} and $AUC_{(0-6)}$ values, from 1 to 10 mg/kg/day, systemic exposure to osimertinib, AZ7550 and AZ5104, increased in proportion to the dose of osimertinib following a single dose and after repeated dosing for 180 days. Following 180 repeat daily doses of osimertinib, there were no obvious differences in the C_{max} and $AUC_{(0-6)}$ values of osimertinib, AZ7550 and AZ5104, compared to those for a single daily dose. The data suggested there is no sex difference in the exposure of osimertinib, AZ7550 or AZ5104 in mice. The parent osimertinib toxicokinetic values were greater than its metabolites AZ7550 and AZ5104.

There were no osimertinib-related effects on survival. There were no osimertinib-related gross pathology or neoplastic histopathological findings at any dose. However, there was one osimertinib-related, non-neoplastic histopathology finding: minimal epithelial atrophy of the cornea in both sexes at 10 mg/kg/day. This finding was only observed during histopathological evaluation and was not observed during in-life ophthalmology examinations conducted during Week 13 or Week 26 (prior to study termination). Given the low severity of the corneal epithelial atrophy, and lack of associated inflammation and ulceration, this finding was considered non-adverse by the applicant.

In conclusion, there was one osimertinib-related, non-neoplastic histopathology finding observed (minimal epithelial atrophy of the cornea in both sexes at 10 mg/kg/day). Based on these results, there was no carcinogenic effect related to osimertinib administration at any dose in this study.

Reproduction toxicity
Osimertinib: Oral Fertility and Early Embryonic Development Study with Assessment of Recovery in the Female Rat
A female rat fertility study was conducted to investigate the effects of osimertinib on fertility and early embryonic development in the female rat following oral gavage administration of osimertinib (0, 1 and 20 mg/kg/day) 14 days prior to pairing, through pairing and until Day 8

of gestation inclusive.

Once daily oral administration at 20 mg/kg/day was associated with transient clinical observations, body weight loss and reductions in food consumption during the pre-pairing dosing period. Administration at 20 mg/kg/day resulted in a decrease in the number of live implants together with an associated increased incidence of early embryonic deaths. After administration at 20 mg/kg/day for 21 days followed by a one-month recovery period prior to pairing for mating, there were no compound-related effects on mating or pregnancy indices. The incidence of early embryonic deaths was slightly higher than the concurrent control group but was within the historical control background ranges. The NOAEL for maternal toxicity, reproductive performance, embryonic survival and development was 1 mg/kg/day.

Other toxicity studies

Impurities

Two osimertinib impurities were tested for mutagenicity in four Salmonella typhimurium strains (TA98, TA100, TA1535 and TA1537) and in Escherichia coli. WP2 uvrA (pKM101) in the presence and absence of a rat liver metabolic activation system (S9)] using the Ames test. The impurities tested negative in the Ames test.

Changes to the Product Information

As a result of this variation, section 5.3 of the SmPC has been updated to reflect the results of the 26-week carcinogenicity study by oral gavage in CByB6F1/Tg rasH2 hemizygous mice.

Discussion on non-clinical aspects

In vitro, osimertinib and its metabolite AZ5104 inhibited EGFR phosphorylation in COS7 cells expressing uncommon EGFR mutants. In PDX tumour cell lines, osimertinib induced concentration-dependent inhibition of downstream signalling (pAkt, pERK, pS6) and increased in the levels of the pro-apoptotic protein BIM. Osimertinib inhibited the cell proliferation in these models.

In vivo, tumour regression was shown in mice treated once daily with 25 mg/kg osimertinib (similar to human exposure of the 80 mg therapeutic dose).

A distribution study showed that osimertinib was able to cross the blood-brain barrier in cynomolgus monkeys.

The main findings observed in previous repeat dose toxicity studies up to 3 months in rats and dogs comprised atrophic, inflammatory and/or degenerative changes affecting the epithelia of the cornea (accompanied by corneal translucencies and opacities in dogs at ophthalmology examination), GI tract (including tongue), skin, and male and female reproductive tracts with secondary changes in spleen. These findings were generally reversible but occurred at exposure levels below those seen in patients at the 80 mg therapeutic dose.

Additional findings in the newly reported 6 month rat, 9 month dog and 6 week mouse studies were considered consistent with findings observed in the previous reported studies or were secondary to osimertinib-induced inflammatory changes or were considered to be related to stress/effects on food consumption and body weight. With the exception of corneal opacity which was only partial reversible within a 1-month recovery period, other findings observed in repeat dose toxicity studies were reversible.

No tumorigenic findings were reported following oral administration of osimertinib to CByB6F1/Tg rasH2 Hemizygous (transgenic) mice for 26 weeks.

In an oral fertility and early embryonic development study a decrease in the number of live implants together with an associated increased incidence of early embryonic deaths was observed.

Conclusion on the non-clinical aspects
Overall, the results from the newly reported studies do not provide any reason to preclude this extension of indication.

Clinical evaluation
Introduction
The data to support the efficacy and safety in the new indication are derived from a single Phase III, double-blind, randomised, placebo controlled study designed to assess the efficacy and safety of osimertinib versus placebo in patients with EGFRm stage IB-IIIA NSCLC following complete tumour resection with or without prior adjuvant chemotherapy, measured by disease free survival (DFS) (ADAURA D5164C00001). The Applicant has provided a statement regarding Good Clinical Practice (GCP) compliance. No GCP issues were identified during the assessment of this application.

Pharmacokinetics
Introduction
Bioanalytical methods for the determination of osimertinib (AZD9291) and its metabolites AZ7550 and AZ5104 in human K_2EDTA plasma were and have been previously assessed in (EMA) assessment reports.

The clinical pharmacology data provided in this submission is an addendum to the previous submissions that have comprehensively described the PK and absorption, distribution, metabolism and elimination (ADME) characteristics of osimertinib and its metabolites (AZ5104 and AZ7550).

In the previous submissions, population PK and exposure-response analysis was performed using data from AURA Phase I, AURA extension, AURA2, AURA3 and FLAURA studies. In this submission, external validation of this population PK model was performed to demonstrate that available population PK model characterises the pharmacokinetic profile of osimertinib in adjuvant EGFRm NSCLC patient population.

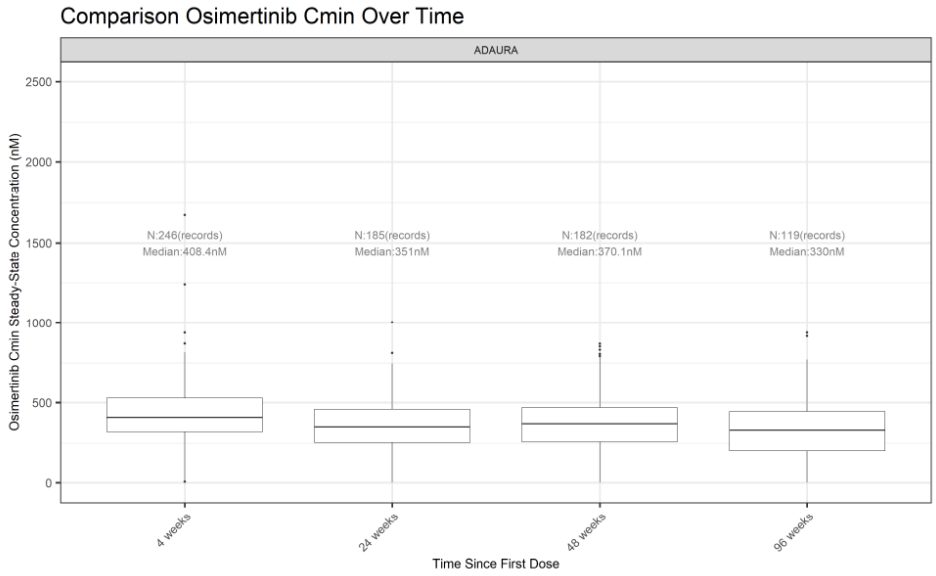
Pharmacokinetics
The Phase III study, ADAURA (D5164C00001) utilised sparse PK samples, the objective was to characterise the pharmacokinetics (PK) of osimertinib and its metabolites (AZ5104 and AZ7550) in patients receiving osimertinib treatment.

PK samples were obtained at pre-dose, 0.5 to 1.5 hours, and 2 to 4 hours at Week 4, Week 24, Week 48 and Week 96 from all patients; however, only osimertinib treated patients were analysed and the concentrations were determined using validated bioanalytical methods and reported. Of 337 patients treated with osimertinib, there were 12 patients who did not have at least one PK concentration measured and hence, were excluded from the PK analysis set. Patients who had a dose interruption or dose reduction within seven days of the PK sampling day or who had below lower limit of quantification concentrations at or after Week 4 were excluded from summary statistics and were only listed. Furthermore, PK samples with unknown sampling time and PK samples that were analysed beyond the established bioanalytical stability period were listed and excluded from the summary tables and figures. It should be noted that during the study, based on a comprehensive review of the osimertinib PK-PD relationships, it was determined that AZ7550 does not contribute to efficacy and safety after osimertinib administration and hence, was removed from bioanalytical assays. So, only plasma concentration data from subjects who had AZ7550 bioanalysis completed prior to this change are reported.

Median plasma concentrations of osimertinib and metabolites, AZ5104 and AZ7550, appear to be maintained at Week 4, Week 24, Week 48 and Week 96. After multiple dosing with osimertinib, the inter-patient variability (% coefficient of variation) for osimertinib exposure was ranging from 56.3 % to

182 %, across Week 4 to Week 96 at different time points. The metabolites AZ5104 and AZ7550 also reached steady state by Week 4 and their concentrations were maintained across the dosing interval. Observed C_{min} values over the first 96 weeks of treatment in the ADAURA study did not suggest changes over time (Figure 1).

Figure 1 Comparison Osimertinib C_{min} Over Time



Note: The ends of the box represent the 25th and 75th percentiles of the concentration distribution and the black middle line is showing the median of the distribution. Data above the 95th percentile are shown as black dots.
Source: osimertinib-pk-eda.rmd

Pharmacodynamics

The mechanism of action is described in previous assessment reports and the current SmPC. In brief, osimertinib is described as an irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harbouring sensitising-mutations (EGFRm) and TKI-resistance mutation T790M and *in vitro* studies have demonstrated that osimertinib has high potency and inhibitory activity against EGFR across a range of all clinically relevant EGFR sensitising-mutant and T790M mutant NSCLC cell lines.

Population PK modelling

An external validation of the existing population PK model was conducted to analyse the exposure of osimertinib when given as adjuvant therapy. The currently available population PK model characterises the pharmacokinetic profile of osimertinib in Phase I, II and III studies in pre-treated (second line and above) and treatment-naïve (first line) EGFRm NSCLC patient populations.

Patients from the ADAURA study with at least one post-dose PK sample were used for this validation analysis. Model validation was performed using a non-linear mixed effects modelling approach. The adequacy of the existing model and parameter estimates for ADAURA patients were assessed based on goodness of fit plots and predictive check method.

The previously developed population PK model adequately describes the totality of the data (AURA, AURA2, AURA3, FLAURA and ADAURA). A linear one-compartmental disposition model for both osimertinib and AZ5104, with first order oral absorption of osimertinib into the central compartment and the formation of AZ5104 from osimertinib described the data in an adequate manner. In the validated population PK model, the typical values of CL/F (apparent clearance of the parent drug), CLM/F (apparent clearance of the metabolite), V/F (apparent volume of distribution of the parent drug) and VM/F (apparent volume of distribution of the metabolite) are 14.3 L/hour, 31.3 L/hour, 918 L and 143 L, respectively. This confirmed that PK profiles for patients in the adjuvant setting from ADAURA are similar to the previously studied profiles for patients with locally advanced and metastatic EGFRm NSCLC. Therefore, as established in the previous population PK analysis, dose adjustment on the basis

of patients' age, gender, bodyweight, renal or hepatic impairment, smoking status and ethnicity or line of therapy is not required.

Figure 2. Osimertinib population predictions vs. observed concentration left), and weighted residuals vs. population predictions (middle) or time after first dose (right).

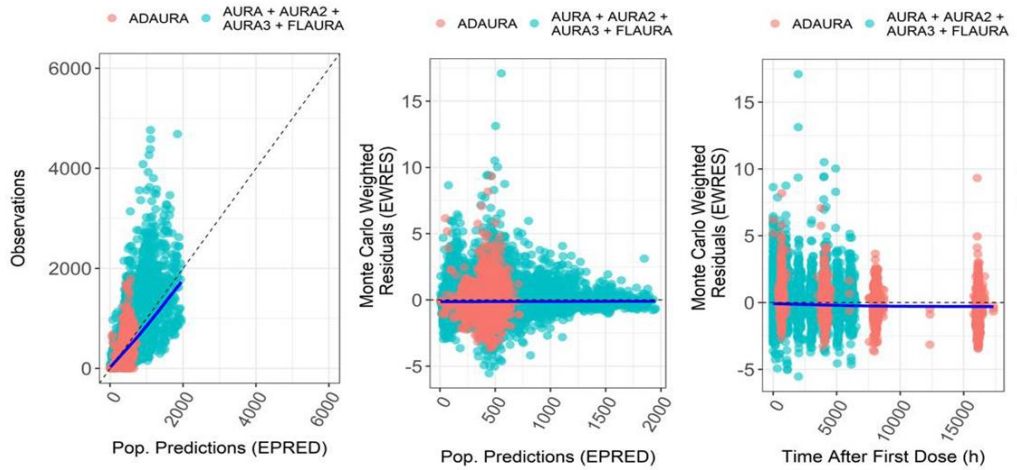
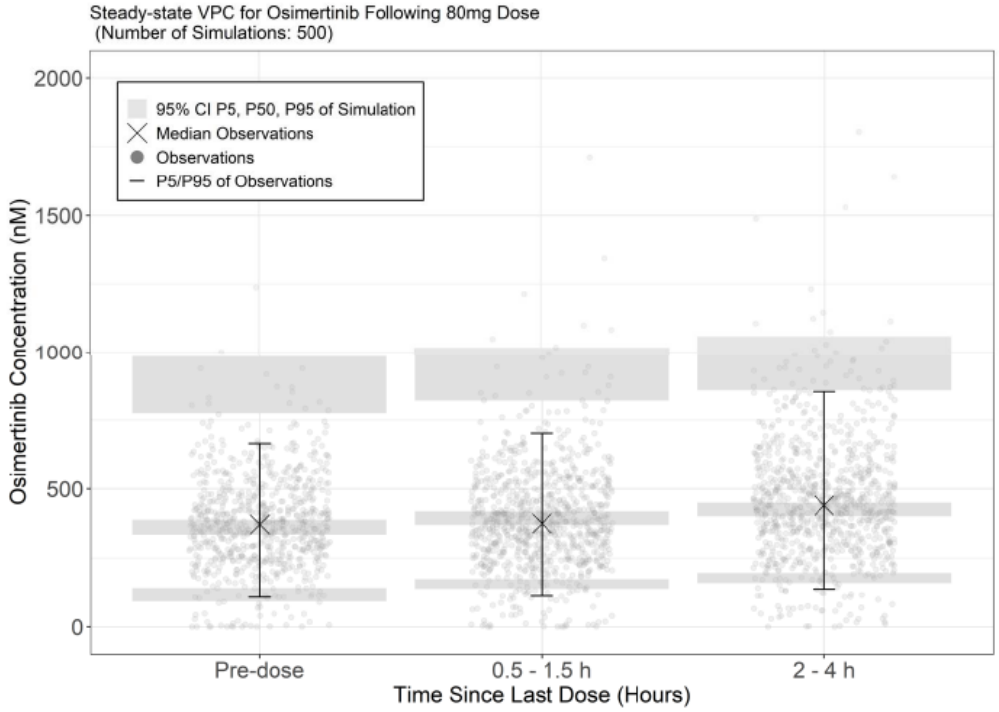
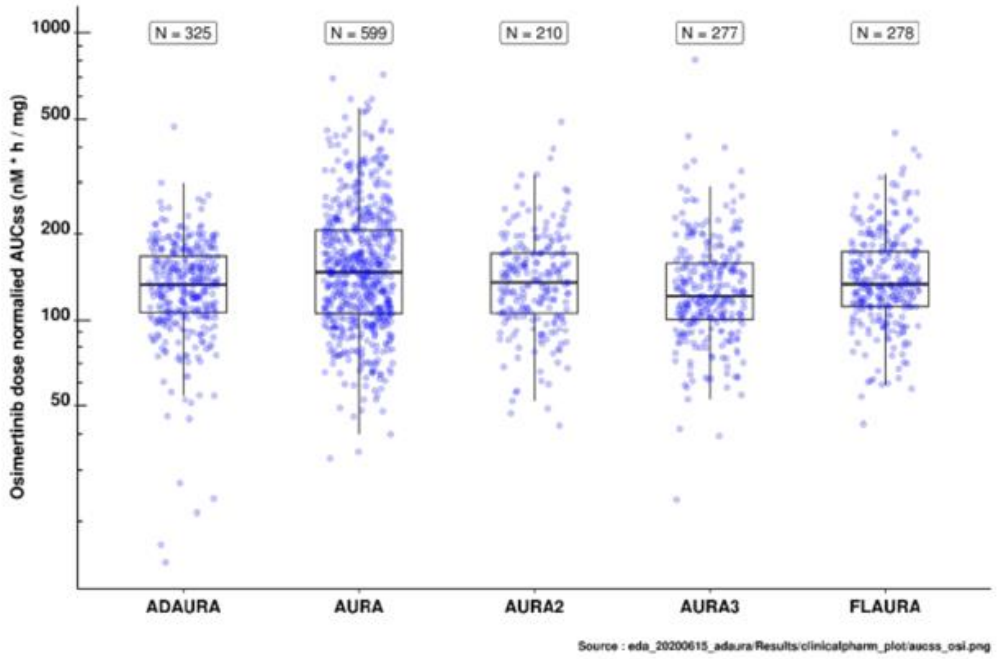


Figure 3. Steady state visual prediction check (VPC) for osimertinib following 80 mg dose according to the planned sampling time point intervals.



Note: All data-points considered in this VPC have been sampled in steady-state conditions, meaning that at least 10 doses of 80 mg had been given in the last 250 hours before sampling of concentrations.
Source: osimertinib-pk-vpc.rmd

Figure 4. Box plot (with individual data overlaid) dose normalised osimertinib AUCss



Source : eda_20200615_adaura/Results/clinicalpharm_plot/aucssosi.png
Where: Symbols represent individual AUCss values.

PK/PD modelling

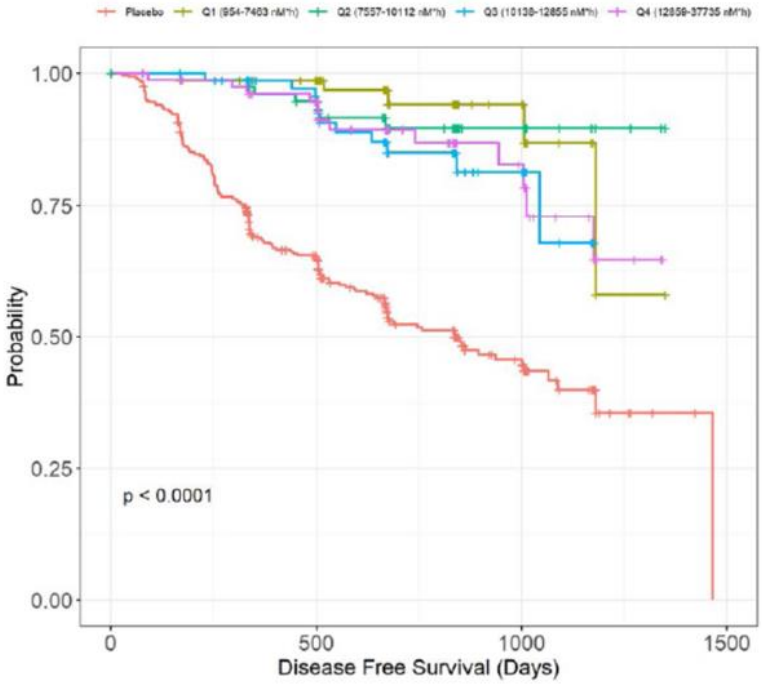
Individual AUCss (area under the concentration-time curve at steady state) values calculated using the final population PK model were used to assess PK/PD relationships for efficacy and safety.

Exposure response analysis relating efficacy events and osimertinib exposure based on clinical data from ADAURA (D5164C00001)

Systemic exposure to osimertinib and AZ5104 was considered as AUCss. Individual AUCss values obtained from the population PK model for osimertinib and AZ5104 were used to assess the relationship between osimertinib and /or AZ5104 exposure and DFS. Graphical assessments were used to explore the relationship between AUCss and DFS. The individual AUCss values were divided into four quartiles and DFS of patients in each quartiles were compared.

The exposure-DFS analysis indicated overlapping DFS across the four AUCss quartiles of osimertinib and/or AZ5104. Most importantly, the Kaplan Meier (KM) plot of DFS stratified by quartiles of osimertinib AUCss indicates that the DFS effect was significantly greater for osimertinib than the placebo treatment across all exposure quartiles. This analysis suggested that treatment of osimertinib is associated with longer DFS compared to the placebo treatment. There is no apparent relationship between increasing plasma exposure of osimertinib and/or AZ5104 and increase in the magnitude of DFS in patients with EGFRm NSCLC.

Figure 5 Kaplan-Meier representative of DFS stratified by quartiles of osimertinib AUCss and Placebo



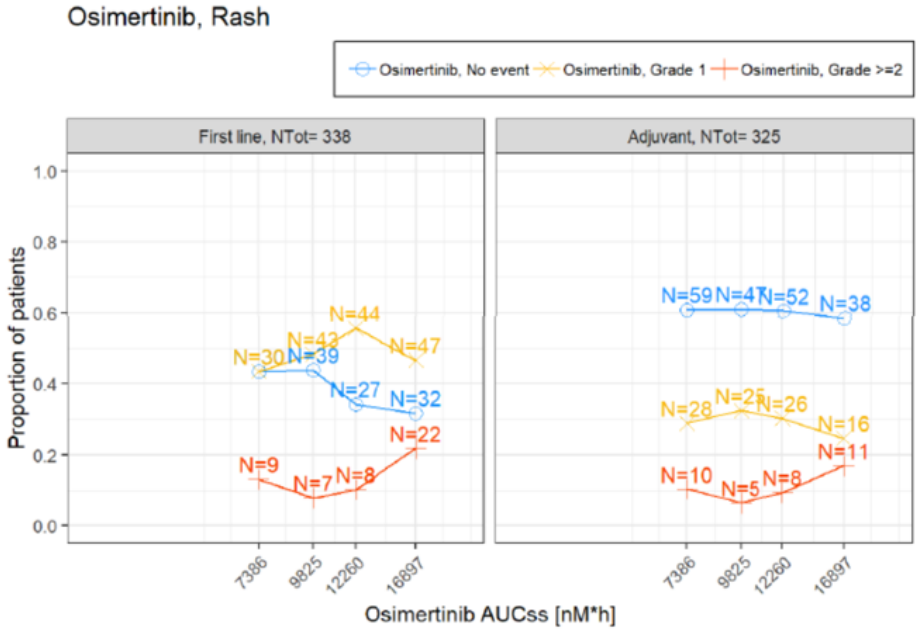
Rash and diarrhoea

Graphical and descriptive analyses were conducted to investigate the relationships between osimertinib exposure and the maximum (at any study day Common Terminology Criteria for Adverse Events (CTCAE)) severity levels for rash and diarrhoea in first-line and adjuvant treated patients.

Figure 6 and Figure 7 show comparison of exposure response relationship for rash and diarrhoea, respectively. For diarrhoea and rash events, a higher proportion of patients with no diarrhoea events was observed in the adjuvant population, compared with first line population.

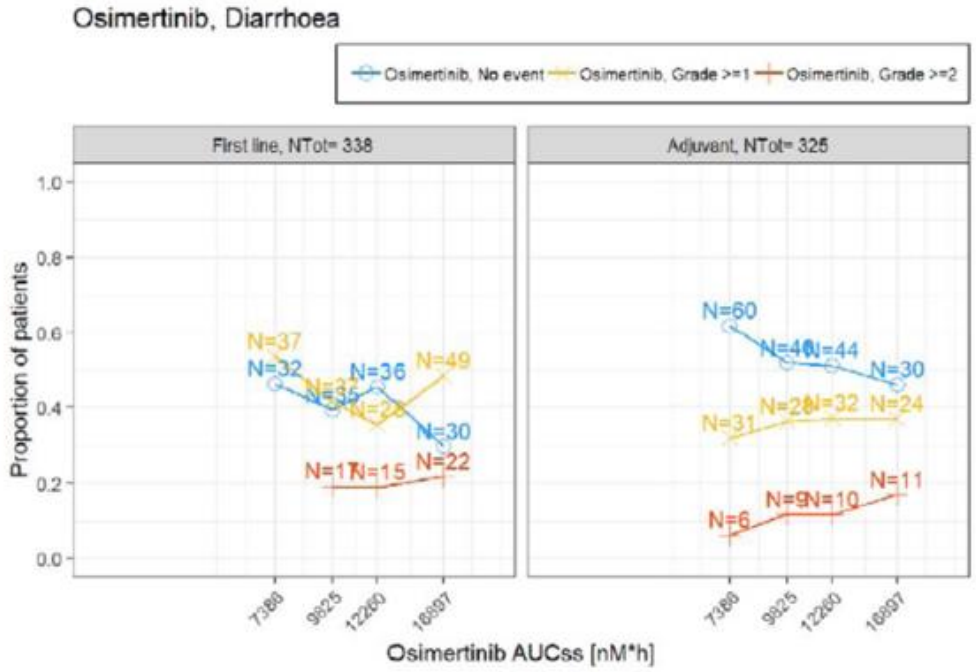
Proportions of moderate to severe events look overall similar between type of treatment across exposure quartiles. Moreover, the incidence and severity of rash or diarrhoea was confirmed to increase with increasing exposure (AUCss) of osimertinib. These findings are in agreement with the observation of a dose-related increase in the incidence and severity of rash and diarrhoea at doses of 160 mg and above and supports selection of an 80 mg dose as the recommended dose of osimertinib.

Figure 6 Proportion of patients with CTCAE grade of rash and quartiles of osimertinib AUCss stratified by line of treatment



Source: Figure 23 , PK-PD exposure-response report, Module 5.3.4.2.
Abbreviations: NTot: number of total patients in each of the treatment populations. The values on the x-axis correspond to the median AUCss values in each quartile. "Grade >=2" refers to the pooled population of patients with a maximum CTCAE grade of 2 or 3. Symbols and colors distinguish the grade levels of the rash events.

Figure 7 Proportion of patients with Diarrhoea and quartiles of osimertinib AUCss stratified by line of treatment

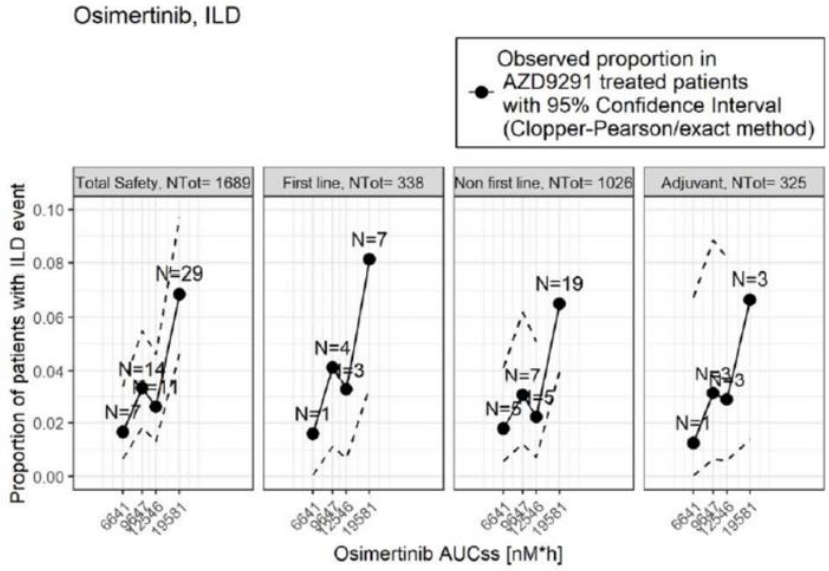


Source: Figure 27 , PK-PD exposure-response report, Module 5.3.4.2.
Abbreviations: NTot: number of total patients in each of the treatment populations. The values on the x-axis correspond to the median AUCss values in each quartile. "Grade >=2" refers to the pooled population of patients with a maximum CTCAE grade of 2 or 3. Symbols and colors distinguish the grade levels of the diarrhoea events.

Interstitial lung disease (ILD)

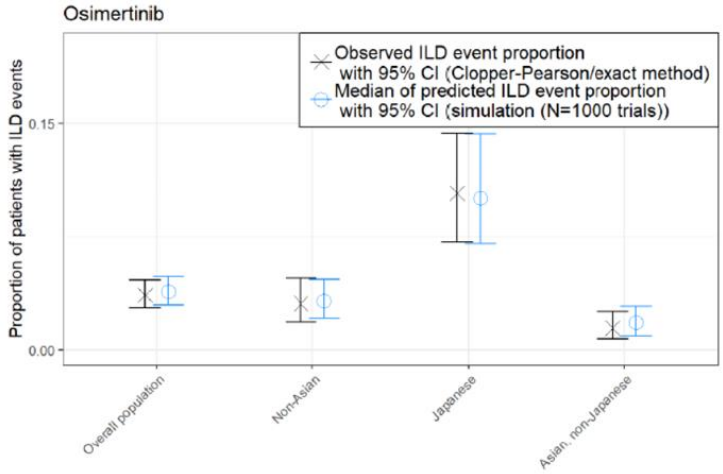
Distribution of AUCss between ILD vs no-ILD was similar across different lines of treatment and adjuvant treatment. The proportion of patients experienced ILD events at different osimertinib AUCss quartiles is presented in Figure 8 and compared across adjuvant and metastatic patients. The data indicates that a probability of patient experiencing ILD events are likely to increase with increasing osimertinib exposure across different lines of treatment and adjuvant treatment. A penalised logistic regression model based evaluation of exposure and ILD relationship, as applied in previous analysis, was applied to the extended dataset including ADAURA study. Visual predictive checks suggested that the model (for osimertinib and AZ5104) was able to well describe the observed occurrence of ILD observed in the extended available dataset. This model included AUCss (for osimertinib or AZ5104), Japanese and Asian non-Japanese as predictive variables which described the observed occurrence of ILD across various subpopulations. Figure 10 indicates that at a similar AUCss of osimertinib, patients of Japanese ethnicity tend to have higher incidence of ILD compared to Non-Asian and Asian (non-Japanese) patients. Although the reason for the difference in incidence of ILD between Japanese and non-Japanese Asians and non-Asians is unknown, it may relate to constitutional and environment factors specific to Japan, or Japanese patients. A similar graphical and model-based analyses using AZ5104 AUCss were conducted and which also led to the same conclusions.

Figure 8 Proportion of patients with ILD events over osimertinib AUCss quartiles by line of treatment



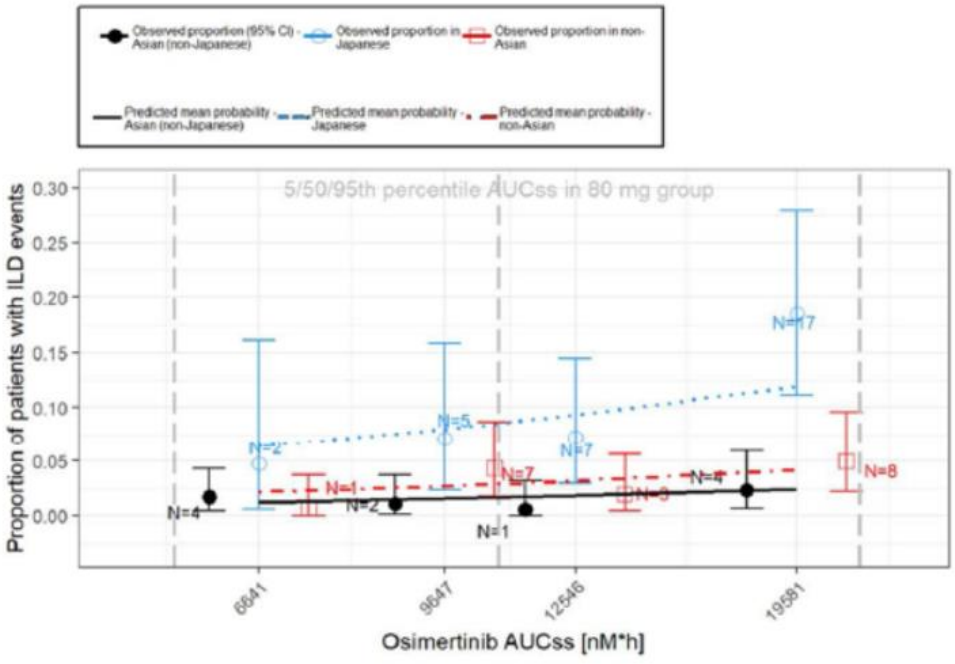
Source : Figure 31 , PK-PD exposure-response report, Module 5.3.4.2.
Where: Circles represent individual AUCss values.
Abbreviations: NTot, Number of total patients in each of the treatment populations. Note: Overall observed probability was calculated for each quartile of AUCss. The values on the x-axis correspond to the median AUCss values in each quartile. The Clopper-Pearson interval ('exact' method) is based on the cumulative probabilities of the binomial distribution. The true coverage rate of a 95% Clopper-Pearson interval may be wider than it needs to be to achieve 95% confidence.

Figure 9 VPCs for the frequency of ILD events- for the osimertinib ILD model



Source : Figure 33 , PK-PD exposure-response report, Module 5.3.4.2.
Black crosses: Means of observed probability of ILD events in AURA, AURA2, AURA3, FLAURA and ADAURA. Black error bars: 95% CIs for the observed probability of ILD events (Clopper-Pearson/exact method) Blue circles: Median of model predicted probability of ILD events. Blue error bars: 95% Cis of ILD events predicted by the final model.

Figure 10 Predicted mean probability of ILD in different ethnic groups



Source : Figure 35 , PK-PD exposure-response report, Module 5.3.4.2. Abbreviations: A-NJ = Asian (Non-Japanese) population; CI: Confidence Interval (CP/exact method). JAP = Japanese population; N = number of patients; N-A = Non-Asian population. Results based on osimertinib model.
The values on the x-axis correspond to the median AUCss osimertinib values in each quartile. The observed proportion and 95% CI of patients with ILD events for the different populations have been computed based on the exposure (AUCss) quartiles for the total safety population. The predicted mean probabilities over AUCss osimertinib are computed from the parameter estimates for the final osimertinib model. Error bars for the model simulations are not shown. The dashed vertical lines represent the 5/50/95th percentile of osimertinib AUCss exposure in (first dose) 80 mg treated patients.

Discussion on clinical pharmacology

Dose justification and recommended daily dose

In a potentially curative setting such as adjuvant, selection of a dose with a maximum potential for tumour cell kill whilst maintaining acceptable tolerability profile and enabling long term treatment duration represents a widely accepted approach across different solid tumour types and targeted agents. The recommended daily dose of osimertinib 80 mg, administered orally once daily is well supported by the exposure-efficacy and exposure-safety analyses. Exposure and efficacy analysis of the ADAURA data suggests that across the exposure (AUCss) range investigated, exposure (AUCss) of osimertinib is not associated with increased efficacy with respect to DFS and hence, dosing above 80 mg is not likely to provide increased benefit. Exposure and safety response analysis indicated an increased probability of rash, diarrhoea and ILD events with increasing osimertinib exposure and hence, long term treatment at a higher dose (e.g. 160 mg) may not be optimal and might lead to frequent dose interruptions.

At a dose of 80 mg once a day, osimertinib demonstrated central nervous system (CNS) efficacy for patients with measurable and non-measurable CNS metastases at baseline in other Phase II and Phase III studies. Based on preclinical models, 80 mg dose is likely to provide higher CNS activity than the 40 mg dose. In the ADAURA study, around 20% of the recurrences on placebo arm involved CNS which is associated with poor prognosis and quality of life. The selection of 80 mg dose likely provides greater CNS penetration and may minimize the risk of disease spread into the CNS.

Across the clinical program, patients with the lowest osimertinib exposure at 80 mg once daily have osimertinib exposures that are approximately 2-fold the geometric mean AUC observed at steady-state for the 20 mg once-daily dose. Thus, the 80 mg dose ensures patients will attain exposures above 20 mg (the lowest dose evaluated in the clinical trials which demonstrated clinical activity in metastatic settings) whilst still allowing prescribers the option to dose reduce in response to toxicity. Moreover, taking into consideration the PK variability in exposure, the 40 mg dose would result in some patients with similar exposure to the lowest dose studied (20 mg) and lower CNS exposure, which would provide limited ability to reduce dose to maintain efficacy. As such, decreasing the dose below 80 mg might result in some patients having lower exposure levels that may impact maximum tumour cell kill.

The recommended daily dose of 80 mg has demonstrated a positive benefit/risk profile that maximises clinical activity after complete tumour resection in patients with EGFR mutation positive NSCLC, while simultaneously minimising the incidence and severity of adverse reactions as well as dose modifications. The dose has been evaluated across multiple studies and line of treatments including in patients with T790M mutation (AURA3), for first line treatment in EGFRm (FLAURA) and currently, as adjuvant treatment (ADAURA). Importantly, this dose ensures that patients will receive a clinically active dose regardless of inter-patient variability and allows prescribers to reduce the dose to 40 mg, should this be necessary.

Conclusions on clinical pharmacology

An external validation of existing population PK model demonstrated that the available population PK model characterises the PK profile of osimertinib and AZ5104 in the adjuvant EGFRm NSCLC patient population. The MAH has provided standard goodness-of-fit plots for the updated model, stratified by adjuvant setting and $\geq 1^{st}$ line setting. It is agreed that these plots do not indicate major differences. A visual predictive check (VPC) has been presented to compare the previous model predictions with the observed data in adjuvant patients, the VPC indicates that the central tendency is adequately predicted, while the variability is under-predicted.

Exposure response analysis was conducted to understand the relationship between systemic exposure (AUCss) and efficacy/ safety variables. Overall, these exposure-response relationships for efficacy and safety justify the 80 mg once daily as the recommended dose of osimertinib to treat the adjuvant as well as advanced NSCLC population. The relationship between osimertinib exposure and the incidence and severity of rash and diarrhoea in the adjuvant setting seems similar to other lines of therapy across the

limited AUCss range investigated. These analyses are quite simplistic and additional analysis would have been helpful to fully investigate E-R. Alternative exposure parameters e.g. initial AUC, or as a continuous variable, could have allowed an improved understanding however this would not impact significantly on the conclusions.

Clinical Efficacy

Dose response study

No clinical dose response trials have been provided within this submission. The proposed dose for osimertinib is the same as currently authorised in the advanced setting. The recommended dose is 80 mg osimertinib once a day until disease progression or unacceptable toxicity.

Main study overview

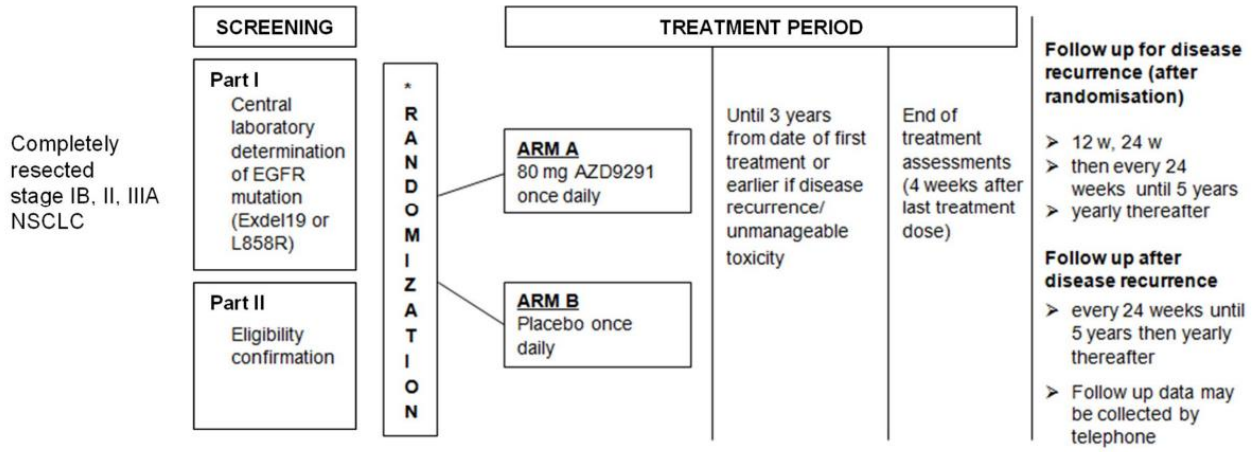
Study ADAURA

ADAURA is an ongoing Phase III, double-blind, randomised, placebo-controlled study to assess the efficacy and safety of osimertinib versus placebo in patients with stage IB, II, IIIA EGFRm (Ex19del or L858R) NSCLC, who have undergone complete tumour resection, with or without adjuvant chemotherapy.

Table 1 Tabular overview of the clinical study is below

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	Healthy subjects or diagnosis of patients	Duration of treatment	Study status
Efficacy safety and PK	D5164C00001 ADAURA	To assess the efficacy of Osimertinib (AZD9291) compared to placebo as measured by disease free survival (DFS)	Phase III, double-blind, randomised, placebo-controlled study	AZD9291 40 mg and 80 mg tablets, or matching placebo, administered orally once daily	Adult patients with stage IB-IIIA NSCLC with a centrally confirmed EGFR mutation (EX19del and L858R), who had complete tumour resection, with or without post-operative adjuvant chemotherapy.	Patients received either AZD9291 or placebo for a planned treatment duration of 3 years or until disease recurrence or a treatment criterion was met.	Ongoing; Data cut-off (17 January 2020)

Flow chart of study design



Comments

The study design is acceptable for the objective of demonstrating improvements in disease free survival in the adjuvant setting. The choice of placebo as comparator is appropriate, as the standard care after surgery (and adjuvant chemotherapy, if utilised) is a wait-and-watch. It is noted that overall survival data are likely to be confounded as patients in the placebo arm were able to receive osimertinib following recurrence.

Study participants

Subjects were those that harboured EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), had stage IB, II or IIIA NSCLC and had undergone prior complete surgical resection. EGFR status was confirmed by the central laboratory on tissue samples. Performance status was 0-1. Post-operative adjuvant platinum-based chemotherapy was allowed as per clinical practice. Overall, the inclusion and exclusion criteria are considered acceptable and representative of a clinical population in the real-world setting.

Main inclusion criteria

1. Male or female, aged at least 18 years. Patients from Japan/Taiwan aged at least 20 years.
2. Histologically confirmed diagnosis of primary NSCLC, of predominantly non-squamous histology.
3. MRI or CT scan of the brain must have been done prior to surgery (as it is considered standard of care). Patients in whom this was not done prior to surgery may still have been be enrolled if appropriate imaging was performed prior to randomisation, i.e., MRI or CT of brain.
4. Patients must have been classified post-operatively as Stage IB, II or IIIA on the basis of pathologic criteria. Staging was conducted in accordance with the TNM staging system for lung cancer (7th edition).
5. Confirmation by the central laboratory that the tumour harboured one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations including T790M.
6. Complete surgical resection of the primary NSCLC was mandatory. All gross disease must have been removed at the end of surgery. All surgical margins of resection must have been negative for tumour. Resection may have been accomplished by open or Video Associated Thoracic Surgery (VATS) techniques.
7. Complete recovery from surgery and standard post-operative therapy (if applicable) at the time of randomisation. Treatment could not commence within 4 weeks following surgery. No more than 10 weeks must have elapsed between surgery and randomisation for patients who did not received

adjuvant chemotherapy; and no more than 26 weeks may have elapsed between surgery and randomisation for patients who received adjuvant chemotherapy. Additionally:

- Complete post-operative wound healing must have occurred following any surgery;
- For patients who received post-operative adjuvant platinum-based chemotherapy, a minimum of 2 weeks must have elapsed (but no more than 10 weeks) from the last administered dose of chemotherapy to the date of randomisation;
- Patients must have recovered from all toxicities of prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2 prior platinum therapy related neuropathy.

8. World Health Organization Performance Status of 0 to 1.

Main exclusion criteria

1. Previous randomisation and treatment in the present study.
2. Treatment with any of the following:
   - Pre-operative or post-operative or planned radiation therapy for the current lung cancer;
   - Pre-operative (neo-adjuvant) platinum-based or other chemotherapy;
   - Any prior anticancer therapy, including investigational therapy, for treatment of NSCLC other than standard platinum-based doublet post-operative adjuvant chemotherapy;
   - Prior treatment with neoadjuvant or adjuvant EGFR-TKI;
   - Major surgery (including primary tumour surgery, excluding placement of vascular access) within 4 weeks of the first dose of study drug;
   - Patients who were currently receiving (or were unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inducers of CYP3A4 (at least 3 weeks prior);
   - Treatment with an investigational drug within five half-lives of the compound or any of its related material, if known.
3. Patients who had only segmentectomies or wedge resections.
4. History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated in-situ cancer, or other solid tumours curatively treated with no evidence of disease for > 5 years following the end of treatment and which, in the opinion of the treating physician, did not have a substantial risk of recurrence of the prior malignancy.
5. Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum therapy related neuropathy (CSP Amendment 1 [reflected in Revised CSP Version 2.0]).
6. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion made it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol; or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Active infection included any patient receiving intravenous treatment for infection; active hepatitis B infection, at a minimum, included all patients who were hepatitis B surface antigen positive (HbsAg positive) based on serology assessment. Screening for chronic conditions was not required.

7. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would have precluded adequate absorption of osimertinib.
8. Any of the following cardiac criteria:
    - Mean resting corrected QT interval (QTc) > 470 msec, obtained from 3 ECGs, using the screening clinic ECG machine-derived QTcF value;
    - Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG, e.g., complete left bundle branch block, third-degree heart block, second degree heart block;
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic event such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives, or any concomitant medication known to prolong the QT interval.
9. Past medical history of ILD, drug induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.
10. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
    - Absolute neutrophil count < 1.5 x 109/L;
    - Platelet count < 100 x 109/L;
    - Haemoglobin < 90 g/L;
    - Alanine aminotransferase (ALT) > 2.5x the upper limit of normal (ULN);
    - Aspartate aminotransferase (AST) > 2.5 x ULN;
    - Total bilirubin > 1.5 x ULN or > 3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia);
    - Creatinine > 1.5 x ULN concurrent with creatinine clearance < 50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is > 1.5 x ULN.
11. Women who were breast feeding.

Treatments

Patients were randomised 1:1 to receive either osimertinib 80 mg once daily or matching placebo. All patients receive randomised treatment until recurrence of disease, a treatment discontinuation criterion was met, or until completing the 3-year treatment period. Patients in the placebo arm were allowed to receive osimertinib open label after recurrence. Dose modifications were allowed during the study. Dose reduction to 40 mg once daily was permitted due to the occurrence of a clinically significant adverse event or unacceptable toxicity. Due to the double-blind nature of the study, a matching 40 mg placebo tablet for dose reduction was available to maintain study integrity. Dose interruptions were also permitted.

Objectives

The primary objective was to assess the efficacy of osimertinib compared to placebo as measured by disease free survival (DFS). Secondary objectives included further assessment of efficacy using a variety of endpoints, PK analysis and to determine the safety and tolerability.

Primary endpoint

Disease free survival (DFS)	DFS (as determined by the Investigator), defined as the time (in days) from the date of randomisation until the date of disease recurrence or death (by any cause in the absence of recurrence). Disease recurrence is defined as evidence of disease recurrence on CT or MRI scan and/or pathological disease on biopsy by investigational site assessment.

Secondary efficacy endpoints

The following secondary endpoints were selected to measure.

DFS rate at 2, 3, 4 and 5 years
Overall survival (OS), defined as the time from randomisation to the date of death (from any cause), or to the date the patient was last known to be alive
OS rate at 2, 3, 4, and 5 years
Patient reported outcome measures: Health-related Quality of Life (HRQoL). HRQoL is assessed using the SF-36 questionnaire. Time to deterioration of HRQoL is defined as time from date of randomisation to the date of first clinically important worsening confirmed at the subsequent assessment, or death (by any cause) in the absence of a clinically important worsening, provided death occurs within 2 assessment visits of the last assessment where HRQoL could be evaluated, and regardless of whether the patient withdrew from randomised therapy or received another anticancer therapy prior to symptom deterioration
PK plasma concentrations of osimertinib, and metabolites AZ5104 and AZ7550; and ratio of metabolite to osimertinib for each PK sample(included in this clinical study report)
Safety endpoints: Adverse events (graded by Common Terminology Criteria for Adverse Events version 4 (CTCAE v4)), Clinical chemistry, Haematology and urinalysis, Vital signs, Physical Examination, Weight, Digital electrocardiogram (ECG), Left ventricular ejection fraction (LVEF), World Health Organisation (WHO) Performance Status, Ophthalmologic assessment

Exploratory endpoints

To compare the effects of osimertinib with placebo on post recurrence outcomes	Time to next treatment(s), Type of recurrence (local/regional or distant), Site(s) of relapse, Type of next treatment(s) (including procedures, radiotherapy and anticancer agents), PFS, as determined by investigator assessment
To further assess the efficacy of osimertinib compared with placebo	Estimated approximately one year post primary analysis data cut-off date: OS, OS rate at 2, 3, 4, and 5 years

Comments

DFS is recognised as an acceptable primary endpoint in the adjuvant setting and the OS results will be reported. The OS results are likely to be confounded due to crossover from the placebo arm to osimertinib. However, prolonged DFS itself is a positive outcome for patients. The primary and secondary endpoints are agreed. The study was double blinded which provides some reassurance to the robustness of the dataset. However, a sample of independent versus investigator assessed DFS would have been preferred.

Sample size

The study was sized to characterise DFS (based on investigator assessment), assessed primarily in a subset of patients with stage II-IIIA cancer, and additionally in the overall population (additional comprising patients with stage IB disease). Approximately 700 patients were to be randomised in a 1:1

ratio (osimertinib: placebo) to obtain approximately 247 disease recurrence events in approximately 490 stage II-IIIA patients (non-IB) in the FAS at the planned time of the primary analysis (50% maturity).

Randomisation
Eligible patients were centrally randomised in a 1:1 ratio (to receive either osimertinib or matching placebo) using the IVRS/IWRS system. Patients were stratified at randomisation based on disease stage (IB vs. II vs. IIIA), EGFR mutation status (Ex19del or L858R), and race (Asian or Non-Asian).

Blinding
The study was double-blind. Active drug and placebo tablets were identical and presented in the same packaging to ensure blinding of the medication. The study drug was labelled using a unique material pack code, which was linked to the randomisation code.

Statistical methods

Main efficacy evaluations
Disease-free survival (as determined by the Investigator) was defined as the time from the date of randomisation until the date of disease recurrence or death (by any cause in the absence of recurrence). Patients who were disease-free and alive at the time of analysis were censored at the date of their last assessment for disease recurrence. However, if the patient had a recurrence event or died immediately after 2 or more consecutive missed visits, the patient was censored at the time of the latest evaluable assessment for disease recurrence prior to the two missed visits. Sensitivity analyses of DFS were performed to assess the presence of quantitative interactions, possible evaluation-time bias, and possible attrition bias. DFS in the subset of patients with stage II-IIIA cancer and in the overall population (equivalent to the Full Analysis Set [FAS]) was analysed using a log rank test stratified by stage, mutation type, and race for the generation of the p-value. The effect of osimertinib versus placebo was estimated by the hazard ratio (HR) together with its 95% and (1-alpha) confidence intervals (CIs) and p-value. Subgroup analyses were conducted by comparing DFS between treatments in the following planned groups: Stage (IB, II, IIIA), EGFR mutation type (Ex19del, L858R), Race (Asian, Non-Asian), Adjuvant chemotherapy (Yes, No), Gender (Male, Female), Age at screening (<65, ≥65), and Smoking history (Never, Ever).

Interim analyses
An Independent Data Monitoring Committee (IDMC) met every 6 months for the first 2 years and yearly thereafter in order to review safety and efficacy data. A pre-planned futility analysis was conducted in February 2019 (IDMC-6 meeting) in which data from 655 randomised patients were reviewed. The IDMC reviewed futility outcomes and provided a recommendation that the study should continue unchanged. An ad hoc request was made by the IDMC to review key efficacy data at their next scheduled meeting (IDMC-7 meeting; April 2020), which concerned data from 682 randomised patients. Following this review, the IDMC recommendation was a full analysis of efficacy and safety should be performed by Sponsor as soon as possible for public disclosure due to the overwhelming benefit observed. Consequently, the alpha allocation required revision to account for this unplanned interim analysis, which is based on a smaller number of disease recurrence events than originally planned for the primary analysis.

Two unplanned interim analyses of DFS in the stage II/IIIA population were conducted at the time of observing 86 DFS events and 156 DFS events respectively. The corresponding information fractions were 0.35 and 0.63 where the final number of events would have been 247. The Lan DeMets approach that approximates the O'Brien and Fleming spending function will be used to maintain an overall 2-sided 5% type I error.

As there had been no provision in the protocol or statistical analysis plan to conduct an interim analysis for superiority, an alpha-spending function was applied based on the information fraction. This is a

sensible approach and was devised in collaboration with regulators. The alpha-spending is shown in the table below.

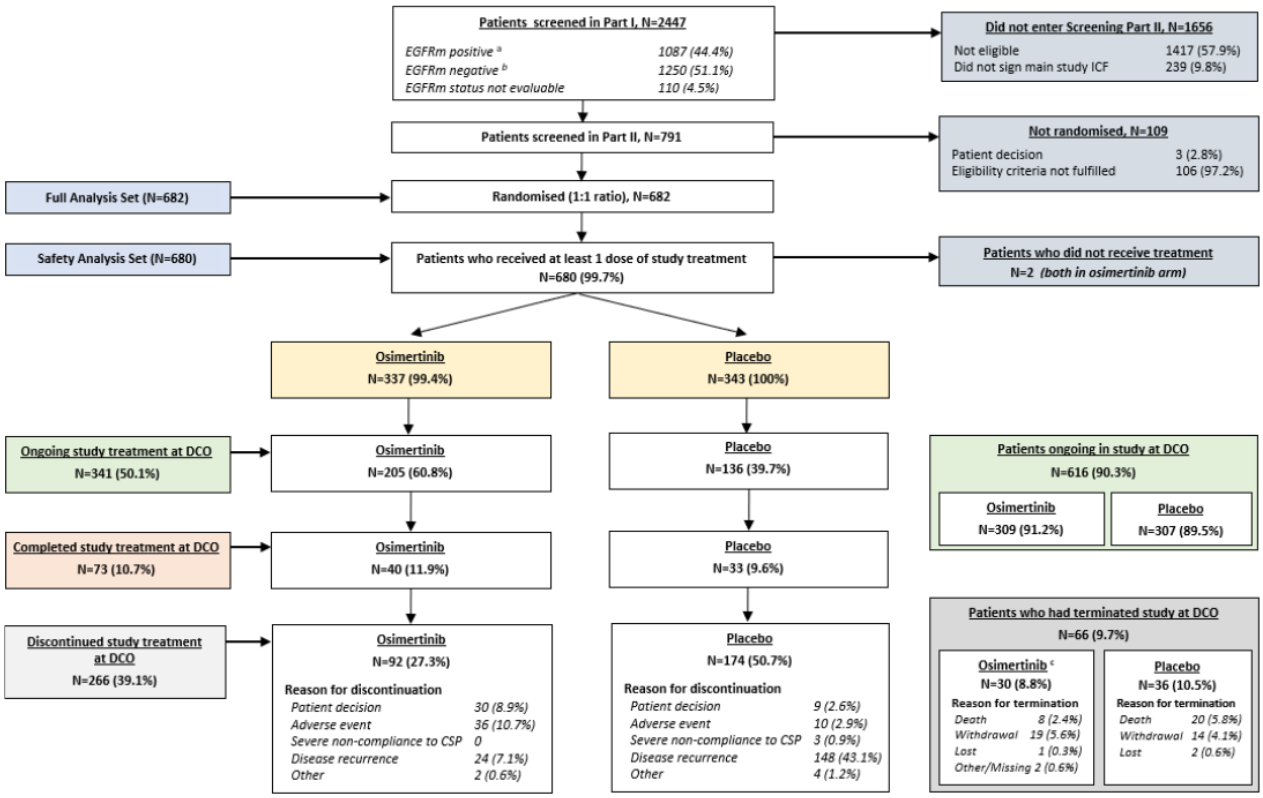
Table 2 Alpha allocation under Lan-De-Mets with O'Brien-Fleming type spending function, stage II/IIIA population

Timepoint	Number of events/ information fraction/maturity	Critical value (HR)	2-sided p-value
IDMC6 (April 2019) - safety and futility review	86/0.35/18%	0.4590	0.00030
IDMC7 (April 2020) - safety review	156/0.63/33%	0.6588	0.009384
Primary planned analysis per protocol (expected Q1 2022)	247/1.0/53%	0.7763	0.04701

Results

Participant flow

Patient disposition (all patients)



a EGFRm positive: Includes any EGFR mutation detected by the cobas test, not limited to Exon 19 deletions and L858R mutations.
b EGFRm negative: No EGFR mutation detected in targeted EGFR regions by the cobas test.
c One patient in the osimertinib arm [redacted] did not have an exact date of death recorded and had discontinuation status marked as "not answered". This patients' reason for terminating the study is classed as missing and the death is not included in this figure.
Note: The definitions of EGFRm positive and EGFRm negative above are only applicable to the classification of patients in Screening Part I.

1030 patients had an eligible EGFR mutation Ex19del or L858R mutation (either alone or in combination with other EGFR mutations) out of 2447 screened. Following screening and application of inclusion and exclusion criteria, a total of 682 eligible patients were randomised to receive study treatment at 185 study centres in 24 countries. 680 received at least one dose, 337 patients in the osimertinib arm (99.4% of all randomised) and 343 patients in the placebo arm (100% of all

randomised). In the osimertinib arm, two patients were randomised in error and therefore did not receive any study treatment.

At the data cut off (17 January 2020)

- 341 patients (50.1%) were ongoing on their randomised treatment
  - 205 patients (60.8%) in the osimertinib arm
  - 136 patients (39.7%) in the placebo arm
- 266 patients had discontinued their randomised study treatment prior to the planned 3-year treatment duration
  - 92 patients (27.3%) in the osimertinib arm
  - 174 patients (50.7%) in the placebo arm
  - 73 patients (10.7%) had completed study treatment

Recruitment

The ADAURA was a global study with 185 study centres in 24 countries across Europe (78 study sites), Asia-Pacific (89 study sites), North America (12 study sites) and South America (6 study sites in Brazil). The first subject was enrolled on 21 October 2015. The analyses provided are based on a data cut-off date of 17 January 2020 and database lock date of 24 June 2020.

Conduct of the study - data quality assurance

Protocol amendments

The original study protocol (Version 1.0, dated 04 June 2015) was amended twice prior to the data cut-off. None of the amendments were implemented for safety concerns and recruitment was not held between amendments. The changes to the statistical analysis plan in versions 3 and 4 were to do with the multiple testing procedure and are acceptable.

Protocol deviations

Protocol deviations were not substantial and are not considered likely to have affected the efficacy analysis or conclusions. Similarly, the number and nature of the protocol deviations do not raise concerns regarding the conduct of the study.

Baseline data

The majority of patients randomised in the study were female, and Asian, with a median age of 63.0 years (range 30 to 86 years). Overall, demographics and patient characteristics were similar between treatment arms, with no notable discrepancies evident. Approximately one third of patients randomised in the study had stage IB disease, approximately one third had stage II disease, and approximately one third had stage IIIA disease at the time of diagnosis. All patients enrolled in the study had a WHO performance status (PS) of 0 or 1, with the majority of patients (63.6%; 434/682) classified as PS 0 at baseline. 60.1% of patients had received a prior anti-cancer therapy, of which usage was well balanced across treatment arms. The most frequently used adjuvant platinum chemotherapy agents were cisplatin (40.3% of patients) and carboplatin (20.4% of patients), with the most commonly used secondary agents being vinorelbine (13.5% of patients) / vinorelbine tartrate (14.8% of patients), and pemetrexed (12.0% of patients).

Overall, baseline characteristics were well balanced between treatment arms and the enrolled patients reflect the inclusion exclusion criteria of the study protocol.

Table 3 Key demographic and patient characteristics (Full Analysis Set)

Characteristic	Osimertinib (N=339)	Placebo (N=343)	Total (N=682)
Age (years)			
Mean (sd)	62.5 (10.27)	61.6 (10.46)	62.1 (10.37)
Median	64.0	62.0	63.0
Min, Max	30, 86	31, 82	30, 86
Sex, n (%)			
Male	109 (32.2%)	95 (27.7%)	204 (29.9%)
Female	230 (67.8%)	248 (72.3%)	478 (70.1%)
Race, n (%)			
White	122 (36.0%)	122 (35.6%)	244 (35.8%)
Asian	216 (63.7%)	218 (63.6%)	434 (63.6%)
Other	1 (0.3%)	2 (0.6%)	3 (0.4%)
Missing [a]	0	1 (0.3%)	1 (0.1%)
Ethnic group, n (%)			
Hispanic or Latino	12 (3.5%)	9 (2.6%)	21 (3.1%)
Asian (other than Chinese and Japanese)	78 (23.0%)	67 (19.5%)	145 (21.3%)
Chinese	95 (28.0%)	100 (29.2%)	195 (28.6%)
Japanese	46 (13.6%)	51 (14.9%)	97 (14.2%)
Other	108 (31.9%)	116 (33.8%)	224 (32.8%)
Body mass index (kg/m^2) [b]			
Mean (sd)	24.8 (4.29)	24.9 (4.36)	24.9 (4.32)
Median	24.4	24.1	24.2
Min, Max	15.1, 41.8	16.6, 42.0	15.1, 42.0

Characteristic	Number (%) of patients		
	Osimertinib (N=339)	Placebo (N=343)	Total (N=682)
WHO performance status			
0	216 (63.7)	218 (63.6)	434 (63.6)
1	123 (36.3)	125 (36.4)	248 (36.4)
AJCC stage at diagnosis [a, b]			
IB	107 (31.6)	109 (31.8)	216 (31.7)
IIA	86 (25.4)	90 (26.2)	176 (25.8)
IIB	29 (8.6)	26 (7.6)	55 (8.1)
IIIA	117 (34.5)	118 (34.4)	235 (34.5)
EGFR mutations by central cobas test [c]			
Exon 19 deletions	185 (54.6)	188 (54.8)	373 (54.7)
L858R	153 (45.1) [d]	155 (45.2)	308 (45.2)
Histology type			
Adenocarcinoma: acinar	85 (25.1)	82 (23.9)	167 (24.5)
Adenocarcinoma: papillary, malignant	43 (12.7)	44 (12.8)	87 (12.8)
Adenocarcinoma: malignant	183 (54.0)	188 (54.8)	371 (54.4)
Adenocarcinoma: bronchiolo-alveolar	11 (3.2)	13 (3.8)	24 (3.5)
Adenocarcinoma: solid with mucous formation	4 (1.2)	5 (1.5)	9 (1.3)
Bronchial gland carcinoma (NOS)	1 (0.3)	2 (0.6)	3 (0.4)
Carcinoma, adenosquamous, malignant	4 (1.2)	5 (1.5)	9 (1.3)
Other	8 (2.4)	4 (1.2)	12 (1.8)
Lung cancer resection type			
Lobectomy	328 (96.8)	322 (93.9)	650 (95.3)
Sleeve Resection	1 (0.3)	3 (0.9)	4 (0.6)
Bilobectomy	7 (2.1)	8 (2.3)	15 (2.2)
Pneumonectomy	3 (0.9)	10 (2.9)	13 (1.9)

AJCC Stage [a]	Number (%) of patients		
	Osimertinib (N=339)	Placebo (N=343)	Total (N=682)
Number of patients with adjuvant platinum-based chemotherapy [b]	202 (59.6)	207 (60.3)	409 (60.0)
IB [c]	27 (25.2)	30 (27.5)	57 (26.4)
Non-IB [c]	175 (75.4)	177 (75.6)	352 (75.5)
IIA [c]	60 (69.8)	65 (72.2)	125 (71.0)
IIB [c]	20 (69.0)	20 (76.9)	40 (72.7)
IIIA [c]	95 (81.2)	92 (78.0)	187 (79.6)

Numbers analysed

The full analysis set was all randomised patients. The analysis sets and the number of patients in each analysis set are summarised in the table below.

Table 4 Analysis sets and number of patients in each analysis set

	Number of patients		
	Osimertinib	Placebo	Total
Patients included in Full Analysis Set	339	343	682
Patients included in the FAS with Stage II-IIIA disease *	233	237	470
Patients included in Safety Analysis Set	337	343	680
Patients excluded from Safety Analysis Set	2	0	2
Did not receive treatment	0	0	0
Randomised in error	2	0	2
Patients included in Pharmacokinetic Analysis Set	325	0	325
Patients excluded from Pharmacokinetic Analysis Set	14	343	357
Patient did not take osimertinib	0	343	343
Patient has no PK data	12	0	12
Patient not in safety population	2	0	2

Outcomes and estimation

Primary endpoint

The efficacy data are based on an unplanned interim analysis. DFS by investigator assessment was first tested in the stage II-IIIA population, and if statistically significant, DFS would be tested in the overall population (patients with stage IB-IIIA disease). At the time of cut-off 98.7% of patients had at least 1-year of follow-up, 61.1% at least 2 years of follow-up and 18.3% at least 3-years.

DFS in the stage II-IIIA population

A statistically significant and clinically meaningful improvement was observed in the stage II-IIIA population, hazard ratio (HR): 0.17; 99.06% confidence interval (CI): 0.11, 0.26; p-value < 0.0001, (log rank test). 156 DFS events were recorded in 470 evaluable patients (33.2% maturity of data), 26 patients (11.2%) in the osimertinib arm and 130 patients (54.9%) in the placebo arm experienced a DFS event [adjusted CI is computed at the 2-sided 99.06% level, considering a 2-sided significance level of 0.0094 for the interim analysis, based on the O Brien and Fleming spending function, assuming 247 DFS events would have been observed for the final analysis]. The KM plot curves showed an early separation (after the first scan at 12 weeks post-randomisation) and maintained separation. The KM estimate of median duration of DFS was not reached for patients in the osimertinib arm (95% CI: 38.8, NC) compared to 19.6 months (95% CI: 16.6, 24.5) for patients in the placebo arm. The majority of the censored patients were censored within 26 weeks prior to the cut off.

Table 5 Disease free survival (Full Analysis Set: Stage II-IIIA patients)

	Osimertinib (N=233)	Placebo (N=237)
Recurrence or death, n (%)		
Number (%) of patients with recurrence events [a]	26 (11.2)	130 (54.9)
Disease recurrence	26 (11.2)	129 (54.4)
Local/regional only	17 (7.3)	48 (20.3)
Distant only	8 (3.4)	67 (28.3)
Local/regional and Distant	1 (0.4)	14 (5.9)
Death [b]	0	1 (0.4)
Comparison between groups [c]		
Hazard ratio (95% CI)	0.17 (0.12, 0.23)	
Adjusted 99.06% CI [d]	0.11, 0.26	
2-sided p-value	< 0.0001	
Median disease-free survival		
Median disease-free survival (months) [e]	NC	19.6
95% CI for median disease-free survival	38.8, NC	16.6, 24.5
Disease-free survival rate at 6 months (%) (95% CI)	99.1 (96.5, 99.8)	83.1 (77.6, 87.3)
Disease-free survival rate at 12 months (%) (95% CI)	97.2 (93.9, 98.7)	60.8 (54.1, 66.8)
Disease-free survival rate at 18 months (%) (95% CI)	90.9 (85.7, 94.3)	51.7 (44.8, 58.2)
Disease-free survival rate at 24 months (%) (95% CI)	89.5 (84.0, 93.2)	43.6 (36.5, 50.6)
Disease-free survival rate at 36 months (%) (95% CI) [f]	78.3 (64.5, 87.3)	27.9 (18.9, 37.6)
Median follow-up for disease-free survival in all patients (months) [g]	22.1	14.9
Median follow-up for disease-free survival in censored patients (months) [h]	22.1	21.9
No recurrence or death, n (%)		
Total	207 (88.8)	107 (45.1)
Censored due to alive and disease recurrence free [i]	196 (84.1)	100 (42.2)
Censored due to no evaluable assessments or no baseline data [j]	3 (1.3)	4 (1.7)
Censored due to 2 or more missed visits before recurrence or death [k]	0	1 (0.4)
Censored due to lost to follow-up [i]	0	1 (0.4)
Censored due to withdrawn consent [i]	8 (3.4)	0
Censored due to evidence of disease at study entry [l]	0	1 (0.4)

[a] Disease-free survival events are type of disease recorded as local/regional or distant, or death. Disease-free survival events that do not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events.

[b] Death in the absence of disease recurrence, or death occurring within 2 visits of baseline where the patient has no evaluable assessments or no baseline data.

[c] Patients who had evidence of disease at study entry have been censored at day 1. The analysis was performed using a log rank test stratified by stage (II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). Stratification factors are as recorded in IVRS. A hazard ratio < 1 favours osimertinib. The HR and CI are obtained directly from the U and V statistics (Berry et al 1991; Selke and Siegmund 1983).

[d] The adjusted CI is computed at the 2-sided 99.06% level, considering a 2-sided significance level of 0.0094 for the interim analysis, based on the O Brien and Fleming spending function, assuming 247 DFS events would have been observed for the final analysis.

[e] Calculated using the KM method.

[f] The number of patients at risk at 36 months was 18 patients in the osimertinib arm, and 9 patients in the placebo arm.

[g] Calculated as the median time from randomisation to date of disease recurrence events or to date of censoring in all patients.

[h] Calculated as the median time from randomization to date of censoring (date last known to have not recurred) in censored (not recurred) patients only.

[i] Patients censored at last evaluable assessment for disease recurrence.

[j] Patients censored at day 1.

[k] Patients censored at last evaluable assessment for disease recurrence prior to the two missed visits.

[l] Patients who had evidence of disease at study entry have been censored at day 1.

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Figure 11 Kaplan-Meier plot of disease-free survival (Full Analysis Set: Stage II-IIIA patients)

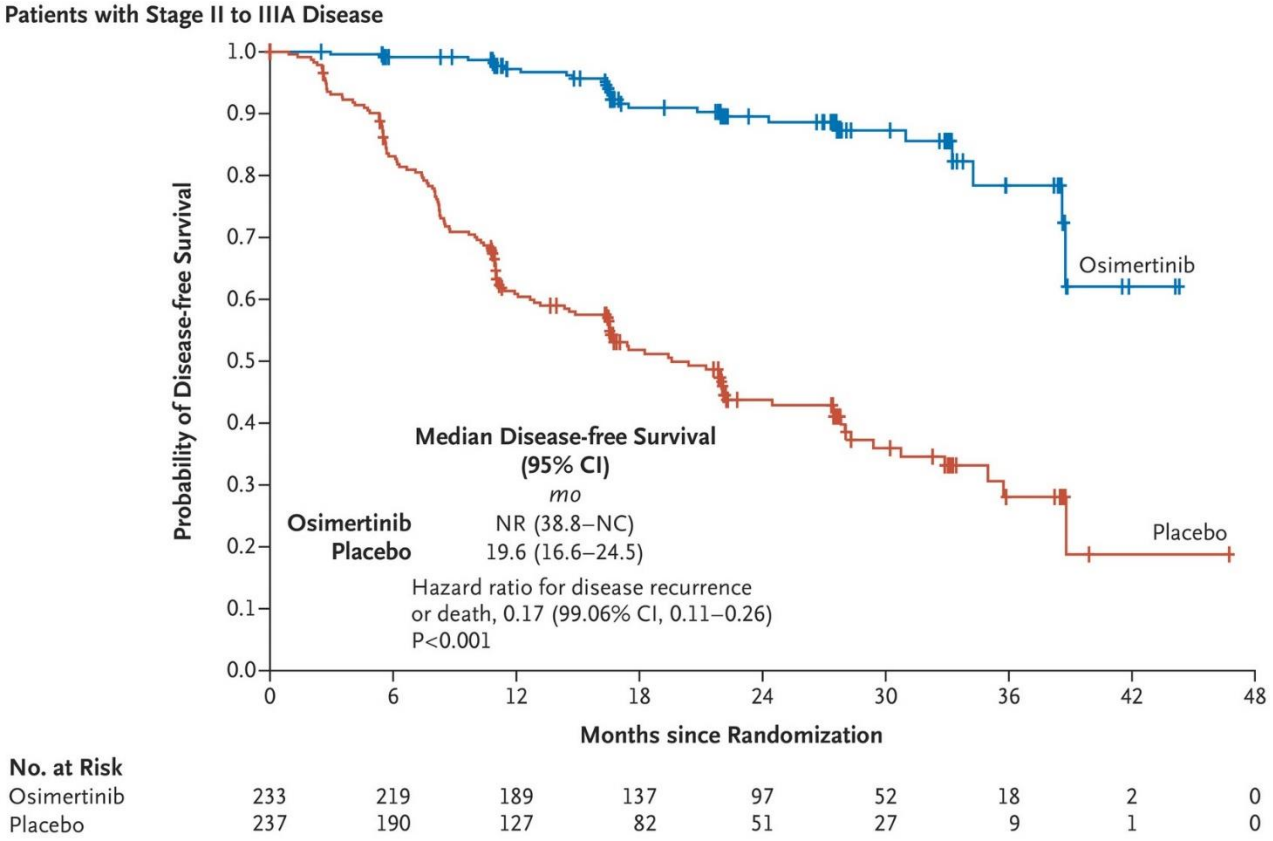

Table 6 Treatment status at disease recurrence or death (Full Analysis Set: Stage II-IIIA patients)

	Number (%) of patients [a]	
	AZD9291 (N=233)	Placebo (N=237)
Patients who have had disease recurrence or died		
n	26	130
On treatment at time of disease recurrence	15 (57.7)	122 (93.8)
Died on treatment	0	1 (0.8)
Discontinued treatment prior to disease recurrence	11 (42.3)	7 (5.4)
Died following discontinuation of treatment	0	0
Completed treatment prior to disease recurrence	0	0
Died after completing treatment	0	0
Did not receive treatment	0	0
Patients who have not had disease recurrence and did not die (censored)		
n	207	107
On treatment	170 (82.1)	98 (91.6)
Discontinued treatment	23 (11.1)	2 (1.9)
Completed treatment	13 (6.3)	7 (6.5)
Did not receive treatment	1 (0.5)	0

[a] Percentages are calculated from the number of patients who have/have not had disease-free survival event.
A window of 28 days is used to assess if patients were still on treatment at date of disease recurrence, death or date of censoring.
Patients who had evidence of disease at study entry have been censored at day 1.

Sensitivity analyses

Sensitivity analyses were conducted to assess the impact of potential biases on DFS, including the possibility of evaluation time bias and attrition bias. Evaluation-time bias affecting DFS (which could occur if scans were not performed at the protocol-scheduled time intervals) was assessed by the analysis of the midpoint between the time of recurrence and the previous evaluable assessment, using a log rank test stratified by disease stage, mutation status and race. There was no evidence of evaluation-time bias; the HR of 0.17 (95% CI: 0.12, 0.23; p-value < 0.0001) was consistent with the primary analysis.

Disease-free survival in the overall population - Stage IB-IIIA patients

In the overall study population of IB-IIA patients, a statistically significant and clinically meaningful improvement in DFS was observed for patients randomised to receive osimertinib compared to placebo (HR: 0.20; 99.12% CI: 0.14, 0.30; p-value < 0.0001), based on 196 DFS events having been recorded in 682 evaluable patients (28.7% maturity of data, 37 patients (10.9%) osimertinib arm, 159 patients (46.6%) placebo arm). The majority of the censored patients were censored within 26 weeks prior to the data cut, and the proportion was similar in both arms (osimertinib: 268/302 [88.7%]; placebo: 167/184 [90.8%]):

- In the osimertinib arm, 35 patients (94.6% of the patients with disease recurrence) had recurrence within the protocol-specified 36 months of study treatment, with the remaining 2 patients (5.4%) having recurrence after the protocol-specified 36 months of study treatment

- In the placebo arm, 157 patients (98.7% of the patients with disease recurrence) had recurrence within the protocol-specified 36 months of study treatment, with the remaining 2 patients (1.3%) having recurrence after the protocol-specified 36 months of study treatment.

The KM estimate of median duration of DFS was not reached in the osimertinib arm (95% CI: NC, NC) compared to 27.5 months (95% CI: 22.0, 35.0) in the placebo arm, with a greater proportion of osimertinib arm patients alive and disease-free at all assessed timepoints. Separation in the curves of the KM plot was observed early and was maintained.

Table 7 Disease free survival (Full Analysis Set: Overall population)

	Number (%) of patients	
	Osimertinib (N=339)	Placebo (N=343)
Recurrence or death		
Number (%) of patients with events [a]	37 (10.9)	159 (46.4)
Disease recurrence	37 (10.9)	157 (45.8)
Local/regional only	23 (6.8)	61 (17.8)
Distant only	10 (2.9)	78 (22.7)
Local/regional and Distant	4 (1.2)	18 (5.2)
Death [b]	0	2 (0.6)
Comparison between groups [c]		
Hazard ratio (95% CI)	0.20 (0.15, 0.27)	
99.12% CI [d]	0.14, 0.30	
2-sided p-value	< 0.0001	
Median disease-free survival		
Median disease-free survival (months) [e]	NC	27.5
95% CI for median disease-free survival	NC, NC	22.0, 35.0
Disease-free survival rate at 6 months (%) (95% CI)	99.1 (97.2, 99.7)	86.3 (82.1, 89.5)
Disease-free survival rate at 12 months (%) (95% CI)	97.4 (94.9, 98.7)	68.5 (63.2, 73.2)
Disease-free survival rate at 18 months (%) (95% CI)	91.6 (87.6, 94.4)	60.2 (54.6, 65.4)
Disease-free survival rate at 24 months (%) (95% CI)	89.1 (84.5, 92.4)	52.4 (46.4, 58.1)
Disease-free survival rate at 36 months (%) (95% CI) [f]	78.9 (68.7, 86.1)	40.0 (32.1, 47.8)
Median follow-up for disease-free survival in all patients (months) [g]	22.1	16.6
Median follow-up for disease-free survival in censored patients (months) [h]	22.1	22.1
No recurrence or death, n (%)		
Total	302 (89.1)	184 (53.6)
Censored due to alive and disease recurrence free [i]	279 (82.3)	175 (51.0)
Censored due to no evaluable assessments or no baseline data [j]	8 (2.4)	4 (1.2)
Censored due to 2 or more missed visits before recurrence or death [k]	0	1 (0.3)
Censored due to lost to follow-up [i]	0	1 (0.3)
Censored due to withdrawn consent [i,]	14 (4.1) [l]	0
Censored due to evidence of disease at study entry [m]	1 (0.3)	3 (0.9)

[a] Disease-free survival events are type of disease recorded as local/regional or distant, or death. Disease-free survival events that do not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events.

[b] Death in the absence of disease recurrence, or death occurring within 2 visits of baseline where the patient has no evaluable assessments or no baseline data.

[c] Patients who had evidence of disease at study entry have been censored at day 1. The analysis was performed using a log rank test stratified by stage (II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). Stratification factors are as recorded in IVRS. A hazard ratio < 1 favours osimertinib. The HR and CI are obtained directly from the U and V statistics (Berry et al 1991; Selke and Siegmund 1983).

[d] The adjusted CI is computed at the 2-sided 99.06% level, considering a 2-sided significance level of 0.0094 for the interim analysis, based on the O Brien and Fleming spending function, assuming 247 DFS events would have been observed for the final analysis.

[e] Calculated using the Kaplan-Meier method.

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

[g] Calculated as the median time from randomisation to date of disease recurrence events or to date of censoring in all patients.

[h] Calculated as the median time from randomization to date of censoring (date last known to have not recurred) in censored (not recurred) patients only.

[i] Patients censored at last evaluable assessment for disease recurrence.

[j] Patients censored at day 1.

[k] Patients censored at last evaluable assessment for disease recurrence prior to the two missed visits.

[l] Given the observed imbalance in this reason for censoring, further review of these data were performed. Upon review, no pattern of the reasons for withdrawal of consent were noted for patients in the osimertinib treatment arm.

[m] Patients who had evidence of disease at study entry have been censored at day 1.

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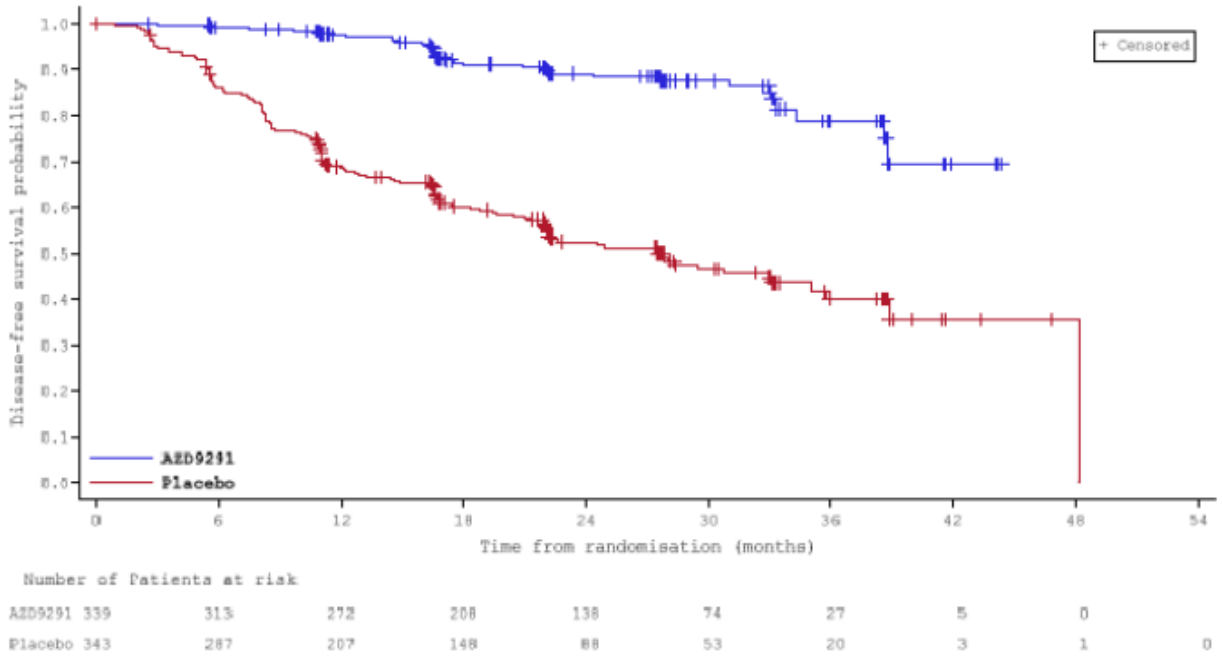
Figure 12 Kaplan-Meier plot of disease-free survival (Full Analysis Set: Overall population)



The values at the base of the figure indicate number of patients at risk.
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Table 8 Treatment status at disease recurrence or death (Full analysis set: overall population)

	Number (%) of patients [a]	
	AZD9291 (N=339)	Placebo (N=343)
Patients who have had disease recurrence or died		
n	37	159
On treatment at time of disease recurrence	24 (64.9)	149 (93.7)
Died on treatment	0	1 (0.6)
Discontinued treatment prior to disease recurrence	13 (35.1)	8 (5.0)
Died following discontinuation of treatment	0	1 (0.6)
Completed treatment prior to disease recurrence	0	0
Died after completing treatment	0	0
Did not receive treatment	0	0
Patients who have not had disease recurrence and did not die (censored)		
n	302	184
On treatment	244 (80.8)	162 (88.0)
Discontinued treatment	36 (11.9)	5 (2.7)
Completed treatment	20 (6.6)	17 (9.2)
Did not receive treatment	2 (0.7)	0

[a] Percentages are calculated from the number of patients who have/have not had disease-free survival event.
A window of 28 days is used to assess if patients were still on treatment at date of disease recurrence, death or date of censoring.
Patients who had evidence of disease at study entry have been censored at day 1.

Sensitivity analyses

Evaluation-time bias: There was no evidence of evaluation-time bias; the hazard ratio (HR) of 0.20 (95% CI: 0.15, 0.27; p-value < 0.0001) was consistent with the primary analysis. Attrition bias: There was no evidence of attrition bias; the HR was 0.20 (95% CI: 0.15, 0.27; p < 0.0001).

Comments

At the time of the data cut-off, a total of 156 events were observed, 26 [11.2%] in the osimertinib arm and 130 [54.9%] in the placebo arm in stage II-IIIA subjects. A statistically significant improvement in DFS was observed in the stage II-IIIA population; HR 0.17; 99.06% CI: 0.11, 0.26, and in the overall population which also includes stage IB, HR 0.20; 99.12%CI: 0.14, 0.30. Median DFS was not reached in the osimertinib arm and the majority of events were reported within 36 months. Several sensitivity analyses were consistent with the primary analysis for both the stage II-IIIA population and for the overall population.

Secondary endpoints

Overall survival (OS)

OS data are immature as only 29 events had been reported in the overall population (4.3% maturity of data). The majority of patients were still in survival follow up (616 patients [90.3%) overall: 309 patients [91.2%] in the osimertinib arm, and 307 patients [89.5%] in the placebo arm).

Median follow-up for OS was 26.1 months in the osimertinib arm and 24.6 months in the placebo arm. A final analysis of OS will be conducted when approximately 94 deaths have been observed in the stage II-IIIA (approximately 20% maturity). This data cut is currently estimated to occur Q1 2023. The MAH has committed to providing updated survival to the Agency when these are available.

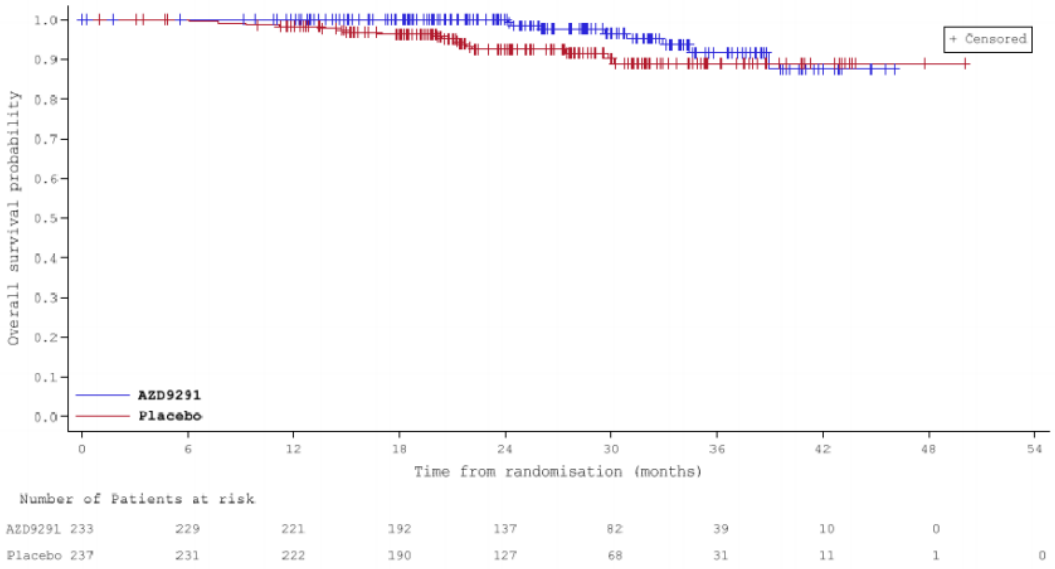
Table 9 Overall survival analysis

Stage II-IIIA patients	Osimertinib (N=233)	Placebo (N=237)
Number (%) of patients with events [a]	8 (3.4)	17 (7.2)
Hazard ratio (95% CI) [b]	0.40 (0.18, 0.89)	
99.98% CI [c]	0.09, 1.83	
2-sided p-value	0.0244	
Median OS (months) (95% CI) [d]	NC (NC, NC)	NC (NC, NC)
OS rate at 2 years(%) (95% CI) [d]	100 (100, 100)	92.6 (87.6, 95.6)
OS rate at 3 years(%) (95% CI) [d]	91.7 (82.4, 96.2)	89.0 (82.1, 93.3)
Median follow-up for OS in all patients (months) [e]	26.1	24.6
Median follow-up for OS in censored patients (months) [f]	26.1	25.2

Overall population	Osimertinib (N=339)	Placebo (N=343)
Number (%) of patients with events [a]	9 (2.7)	20 (5.8)
Hazard ratio (95% CI) [b]	0.48 (0.23, 1.02)	
99.98% CI [c]	0.12, 1.98	
2-sided p-value	0.0553	
Median OS (months) (95% CI) [d]	NC (NC, NC)	48.2 (48.2, NC)
OS rate at 2 years(%) (95% CI) [d]	99.6 (96.9, 99.9)	94.7 (91.4, 96.8)
OS rate at 3 years(%) (95% CI) [d]	93.9 (87.4, 97.1)	91.8 (87.1, 94.9)
Median follow-up for OS in all patients (months) [e]	26.1	25.9
Median follow-up for OS in censored patients (months) [f]	26.1	26.5

[a] Overall survival events that do not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events.
[b] The analysis was performed using a log rank test stratified by stage (II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). Stratification factors are as recorded in IVRS. A Hazard ratio < 1 favours AZD9291. The HR and CI are obtained directly from the U and V statistics (Berry et al 1991; Selke and Siegmund 1983).
[c] The adjusted CI is computed at the 2-sided 99.98% level, considering a 2-sided significance level of 0.0002 for the interim analysis, based on the Haybittle-Peto spending function.
[d] Calculated using the KM method.
[e] Time from randomisation to date of death or to date of censoring for censored patients.
[f] Time from randomisation to date of censoring (date last known to be alive) for patients who have not died at the time of analysis.

Figure 13 Kaplan-Meier plot of overall survival (Full Analysis Set: Stage II-IIIA patients)



The values at the base of the figure indicate number of patients at risk.
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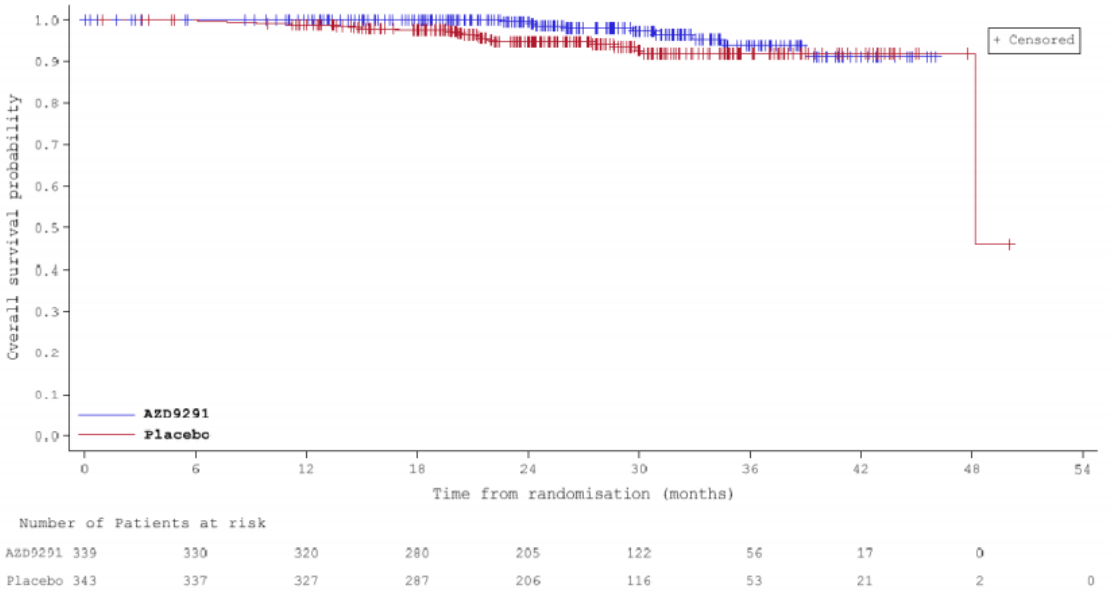
Figure 14 Kaplan-Meier plot of overall survival (Full Analysis Set: Overall population)



The values at the base of the figure indicate number of patients at risk.
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Patient reported outcomes/Health-related quality of life (HRQL)
HRQL was assessed with the SF-36 questionnaire.

Compliance rates for SF-36 were high (> 90%) , however due to the earlier discontinuation in completing SF-36 in the placebo arm, these data are considered descriptive and only until Week 96. The primary outcome regarding HRQL was time to deterioration in the two summary scores: The Physical Component Summary (PCS) and Mental Component Summary (MCS).With regard to PCS, time to deterioration might be shorter in the osimertinib arm compared with the placebo arm, although statistical significance was not reached (HR 1.43 [97.5% CI: 0.90, 2.25). Time to deterioration in MCS appears similar between treatment arms (HR 0.90 [97.5% CI: 0.58, 1.40].

Table 10 Summary of SF-36 - Time to deterioration (Full Analysis Set: Stage II-IIIA patients)

	Osimertinib (N=233)	Placebo (N=237)
Physical Component Summary		
Total number of patients with confirmed deterioration or death	58 (24.9)	39 (16.5)
Deterioration	57 (24.5)	37 (15.6)
Death	1 (0.4)	2 (0.8)
Median deterioration free survival (95% CI)	NC (NC, NC)	NC (NC, NC)
Proportion of patients who are deterioration free (95% CI)		
6 months	78.5 (72.4, 83.5)	89.4 (84.4, 92.8)
12 months	76.4 (70.0, 81.6)	82.1 (75.5, 87.1)
18 months	74.4 (67.8, 79.9)	77.4 (69.8, 83.4)
24 months	72.5 (65.5, 78.4)	75.9 (67.7, 82.3)
30 months	70.0 (62.2, 76.4)	75.9 (67.7, 82.3)
Comparison between groups [a]		
Hazard ratio (95% CI)	1.43 (0.96, 2.13)	
Adjusted 97.5% CI [b]	0.90, 2.25	
2-sided p-value	0.0817	
Mental Component Summary		
Total number of patients with confirmed deterioration or death	52 (22.3)	52 (21.9)
Deterioration	51 (21.9)	49 (20.7)
Death	1 (0.4)	3 (1.3)
Median deterioration free survival (95% CI)	39.0 (NC, NC)	NC (NC, NC)
Proportion of patients who are deterioration free (95% CI)		
6 months	83.6 (77.9, 88.0)	81.1 (75.2, 85.8)
12 months	80.9 (74.8, 85.6)	77.1 (70.4, 82.4)
18 months	77.3 (70.6, 82.7)	73.4 (66.1, 79.4)
24 months	74.5 (67.3, 80.4)	70.7 (62.5, 77.4)
30 months	70.2 (60.9, 77.8)	70.7 (62.5, 77.4)
Comparison between groups [a]		
Hazard ratio (95% CI)	0.90 (0.61, 1.33)	
Adjusted 97.5% CI [b]	0.58, 1.40	
2-sided p-value	0.5949	

[a] The analysis was performed using a log rank test stratified by stage (II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). A hazard ratio < 1 favours AZD9291. The HR and CI are obtained directly from the U and V statistics (Berry et al 1991; Selke and Siegmund 1983). Calculated using the Kaplan-Meier method.

[b] Adjusted confidence interval. This analysis is not included in multiple testing procedure.

Time to deterioration of HRQoL is defined as time from date of randomization to the date of first clinically important worsening confirmed at the subsequent assessment, or death (by any cause) in the absence of a clinically important worsening, provided death occurs within two assessment visits of the last assessment where HRQoL could be evaluated and regardless of whether the patients withdraws from randomized therapy or receives another anticancer therapy prior to symptom deterioration. Summary statistics are calculated using the Kaplan-Meier method. Patients with two missed visits prior to confirmed deterioration were censored at last evaluable assessment prior to the two missed visits.

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Exploratory endpoints

Type and site of recurrence

More subjects in the placebo arm experienced a recurrence event, 157 versus 37.

Of 37 patients with recurrence events in the osimertinib arm

- 23 patients had local/regional recurrence only
- 10 patients had distant only recurrence
- 4 patients had both local/regional and distant recurrence.

Of 157 patients with recurrence in the placebo arm

- 78 patients had distant recurrence only
- 61 patients had local/regional only recurrence
- 18 patients had local/regional and distant recurrence

A variety of sites of tumour recurrence were reported in both treatment arms. The most commonly reported sites of disease recurrence in both treatment arms were lung (osimertinib: 19 patients; placebo: 61 patients) and lymph nodes (osimertinib: 10 patients; placebo: 48 patients). A post-hoc exploratory analysis of disease recurrence in the CNS suggests that patients receiving osimertinib experienced fewer CNS events compared to placebo in the stage II-IIIA population (1.3% vs. 11.4%).

Progression free survival (PFS) and Time to first subsequent therapy or death (TFST)
Exploratory endpoints Progression free survival (PFS) and Time to first subsequent therapy or death (TFST) are based on immature data. However, they tend to favour the osimertinib arm and are considered supportive. In the osimertinib arm 31 (9.1%) patients received first subsequent treatment compared with 125 (36.4%) in the placebo arm. The MAH has committed to providing any updates and final analysis for all endpoints, once these are available.

Progression free survival (PFS)
Due to the immaturity of the data on patients who experienced a disease recurrence event, data are of limited value at this time.

Table 11 Progression status at time of progression analysis (Full analysis set: overall population)

		Number (%) of patients	
Progression status	Type of Event	AZD9291 (N=339)	Placebo (N=343)
Progression	Total	13 (3.8)	46 (13.4)
	Radiological progression	6 (1.8)	25 (7.3)
	Symptomatic progression	0	5 (1.5)
	Other progression	1 (0.3)	3 (0.9)
	Death [a]	6 (1.8)	13 (3.8)
No progression	Total	326 (96.2)	297 (86.6)
	Progression free at time of analysis [b]	281 (82.9)	179 (52.2)
	Patient with recurrence [c]	24 (7.1)	113 (32.9)
	Lost to follow-up	1 (0.3)	1 (0.3)
	Withdrawn consent	20 (5.9)	4 (1.2)
	Other	0	0

[a] Death in the absence of progression.

Table 12 Median progression-free survival (Full analysis set: overall population)

	AZD9291 (N=339)	Placebo (N=343)
Total number of events	13	46
Median progression-free survival (months) [a]	NC	48.2
95% CI for median progression-free survival [a]	NC , NC	NC , NC

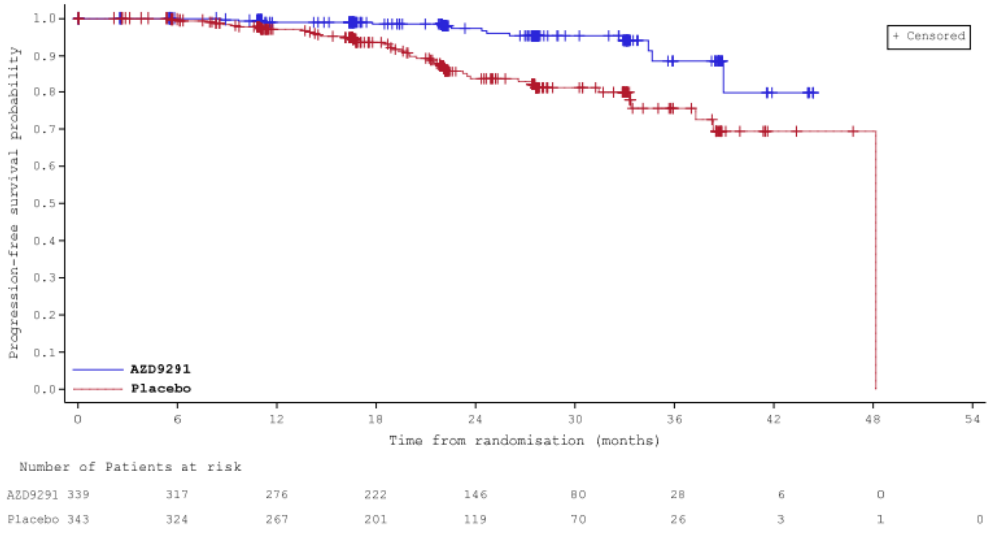
[a] Calculated using the Kaplan-Meier method.
NC = not calculable.

Table 13 Analysis of progression-free survival (Full analysis set: overall population)

			Comparison between groups		
Group	N	Number (%) of patients with events [a]	Hazard ratio	95% CI	2-sided p-value
AZD9291	339	13 (3.8)	0.24	0.14, 0.41	<0.0001
Placebo	343	46 (13.4)			

The analysis was performed using a log rank test stratified by stage (IB versus II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). Stratification factors are as recorded in IVRS. A hazard ratio <1 favours AZD9291. The HR and CI are obtained directly from the U and V statistics (Berry, et al., 1991; Selke & Siegnumd, 1983).
[a] PFS events are type of disease progression after disease recurrence or death.
Patients will be censored at the latest progression assessment date or disease recurrence assessment date if the patient has not had a recurrence, progression or death.

Figure 15 Kaplan-Meier plot of progression free survival (Full analysis set: overall population)



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

Time to first subsequent therapy or death (TFST)

Table 14 Median time to first subsequent anti-cancer therapy or death (Full analysis set: overall population)

	AZD9291 (N=339)	Placebo (N=343)
Total number of patients with events	31	134
Median TFST (months) [a]	NC	39.8
95% CI for median TFST [a]	NC , NC	30.8, NC
TFST rate at 2 years (%) [a]	92.5	60.8
95% CI for TFST rate at 2 years (%) [a]	88.7, 95.1	55.1, 66.1
TFST rate at 3 years (%) [a]	85.8	56.3
95% CI for TFST rate at 3 years (%) [a]	78.7, 90.7	50.0, 62.1

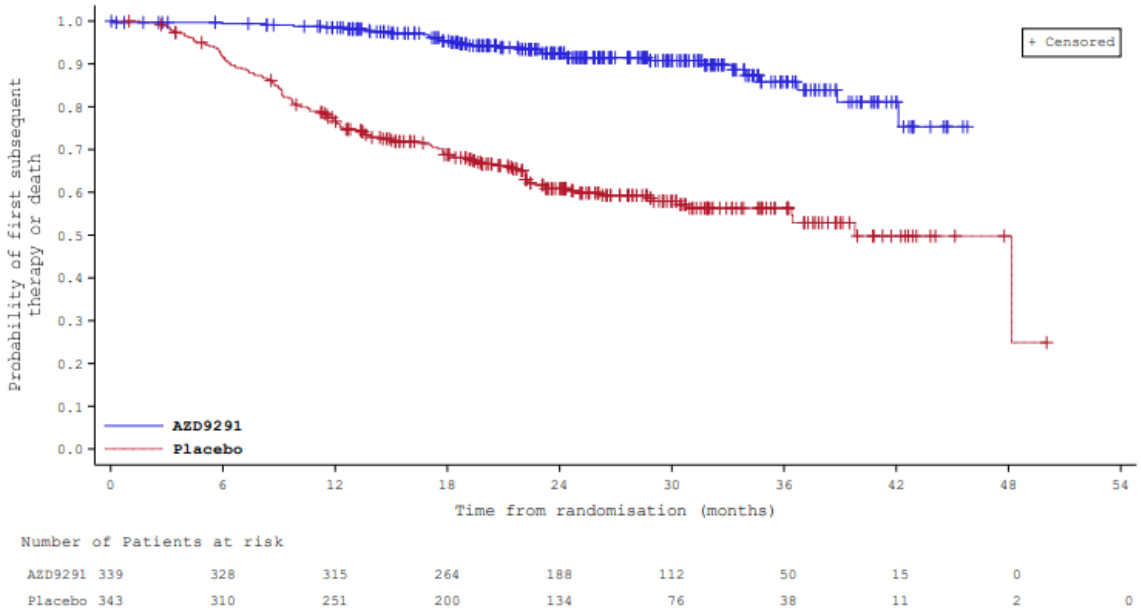
TFST = Time to first subsequent anti-cancer therapy or death.
[a] Calculated using the Kaplan-Meier method.
NC = not calculable.

Table 15 Analysis of time to first subsequent anti-cancer therapy or death (Full analysis set: overall population)

	AZD9291 (N=339)	Placebo (N=343)
Number (%) of patients with events	31 (9.1)	134 (39.1)
Death	1 (3.2)	9 (6.7)
First subsequent cancer therapy	30 (96.8)	125 (93.3)
Comparison between arms		
Median TFST (months), 95% CI	NC (NC , NC)	39.8 (30.8, NC)
Hazard ratio (95% CI)	0.20 (0.14, 0.27)	
2-sided p-value	<0.0001	

The analysis was performed using a log rank test stratified by stage (IB versus II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). Stratification factors are as recorded in IVRS. A hazard ratio <1 favours AZD9291. The HR and CI are obtained directly from the U and V statistics (Berry, et al., 1991; Selke & Siegnumd, 1983).
NC = not calculable.

Figure 16 Kaplan-Meier Plot of time to first subsequent anti-cancer therapy or death (Full analysis set: overall population)



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

Comment

Exploratory endpoints PFS and TFST are based on immature data. However, they tend to favour the osimertinib arm and are considered supportive. In the osimertinib arm 31 (9.1%) patients received first subsequent treatment compared with 125 (36.4%) in the placebo arm. The applicant has committed to provided updates and final analysis for all endpoints when they are available.

Subgroup analyses

Analysis of DFS by specific demographic and patient/disease characteristic subgroups was conducted using a Cox proportional-hazards model that contained a term for treatment, the subgroup covariate of interest, and the treatment-by-subgroup interaction term to assess the consistency of treatment effect across expected prognostic factors. A benefit with osimertinib was consistently observed in all pre-specified subgroups with sufficient events for analysis (subgroups with < 20 events were excluded from the analysis), with a HR of below 0.4 for all subgroups.

Subgroup analyses showed a clear benefit of osimertinib in terms of DFS in all pre-specified subgroups.

Table 16 Subgroup analyses of disease-free survival (Full Analysis Set: Overall population)

Subgroup	Category	Treatment	N	Number (%) of patients with events	Comparison between groups	
					Hazard ratio	95% CI
All patients (stratified log-rank)		Osimertinib	339	37 (10.9)	0.20	0.15, 0.27
		Placebo	343	159 (46.4)		
All patients (unadjusted Cox PH)		Osimertinib	339	37 (10.9)	0.19	0.13, 0.27
		Placebo	343	159 (46.4)		
Stage (IVRS)[a]	IB	Osimertinib	106	11 (10.4)	0.39	0.18, 0.76
		Placebo	106	29 (27.4)		
	II	Osimertinib	118	11 (9.3)	0.17	0.08, 0.31
		Placebo	118	52 (44.1)		
	IIIA	Osimertinib	115	15 (13.0)	0.12	0.07, 0.20
		Placebo	119	78 (65.5)		
EGFR mutation type (IVRS)[b]	Ex19del	Osimertinib	187	15 (8.0)	0.12	0.07, 0.20
		Placebo	191	98 (51.3)		
	L858R	Osimertinib	152	22 (14.5)	0.31	0.18, 0.49
		Placebo	152	61 (40.1)		
Race (IVRS)	Asian	Osimertinib	216	27 (12.5)	0.21	0.13, 0.31
		Placebo	218	104 (47.7)		
	Non-Asian	Osimertinib	123	10 (8.1)	0.15	0.07, 0.28
		Placebo	125	55 (44.0)		
Adjuvant chemotherapy	Yes	Osimertinib	203	22 (10.8)	0.16	0.10, 0.26
		Placebo	207	103 (49.8)		
	No	Osimertinib	136	15 (11.0)	0.23	0.13, 0.40
		Placebo	136	56 (41.2)		
Gender	Male	Osimertinib	109	14 (12.8)	0.19	0.10, 0.33
		Placebo	95	49 (51.6)		
	Female	Osimertinib	230	23 (10.0)	0.18	0.11, 0.28
		Placebo	248	110 (44.4)		
Age	< 65	Osimertinib	185	18 (9.7)	0.16	0.09, 0.26
		Placebo	195	92 (47.2)		
	≥ 65	Osimertinib	154	19 (12.3)	0.22	0.13, 0.36
		Placebo	148	67 (45.3)		
Smoking history	Yes	Osimertinib	108	7 (6.5)	0.10	0.04, 0.22
		Placebo	86	41 (47.7)		
	No	Osimertinib	231	30 (13.0)	0.23	0.15, 0.34
		Placebo	257	118 (45.9)		

[a] AJCC TNM lung cancer staging 7th edition.

[b] Note: 10 patients were mis-stratified because the EGFR mutation status entered in IVRS differed from the confirmed status resulting from central prospective EGFR testing.

DCO: 17 January 2020

Figure 17 Disease-free survival, forest plot, by subgroup (Full Analysis Set: Overall population)

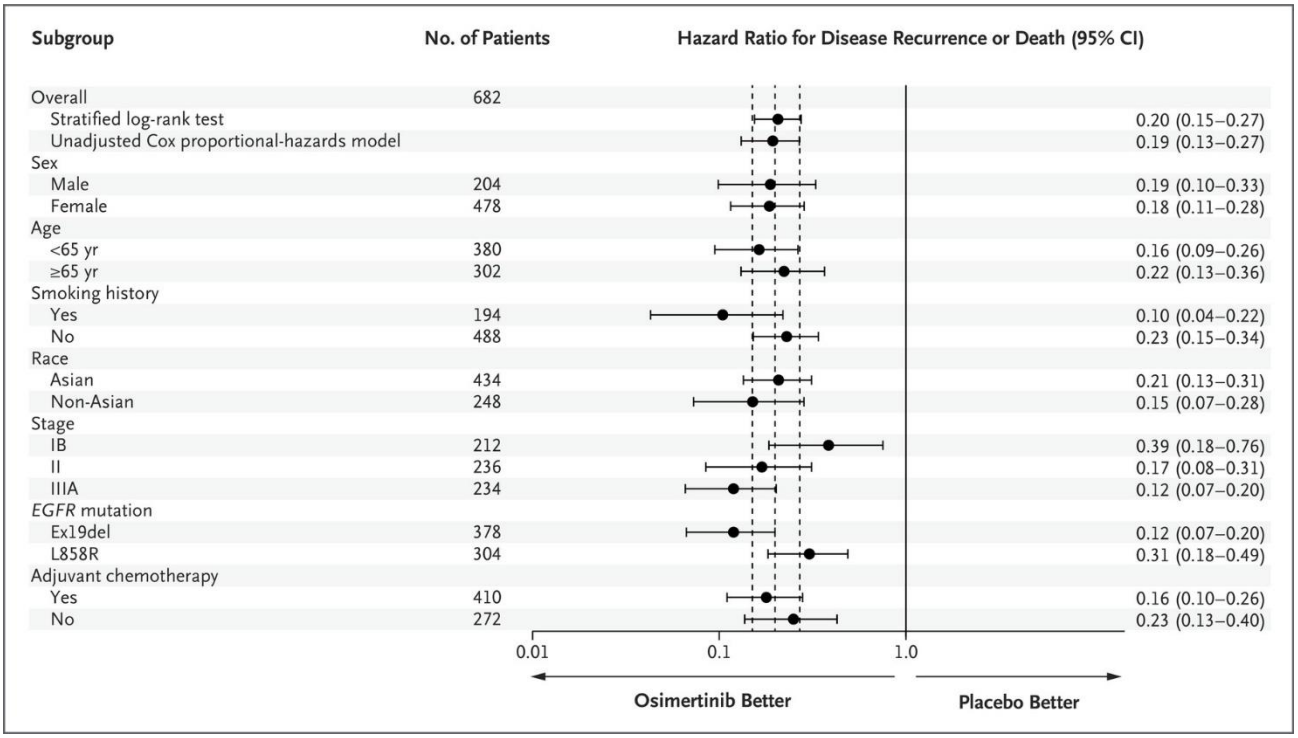


Table 17 Summary of main study - ADAURA trial

Title: A Phase III, Double-blind, Randomized, Placebo-Controlled Multi-centre, Study to Assess the Efficacy and Safety of AZD9291 versus Placebo, in Patients with Epidermal Growth Factor Receptor Mutation Positive Stage IB-IIIA Non-small Cell Lung Carcinoma, following Complete Tumour Resection With or Without Adjuvant Chemotherapy (ADAURA)			
Study identifier	D5164C00001 *EudraCT Number*: 2015-000662-65 *NCT Number*: NCT02511106		
Design	Ongoing, phase 3, double-blind, randomised, placebo-controlled study		
	Duration of main phase:		21-Oct-2015 (FSI) to 17-Jan-2020 (DCO)
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Superiority		
Treatment groups	Osimertinib		Osimertinib 80 mg orally once daily; 3 years, n=339
	Placebo		Placebo orally once daily; 3 years, n=343
Endpoints and definitions	Primary endpoint	DFS	Time from the date of randomisation until the date of disease recurrence or death (by any cause in the absence of recurrence).
	Secondary endpoint	OS	Time from randomisation to the date of death (from any cause), or to the date the patient was last known to be alive.
Database lock	24-Jun-2020		

<table>
<tr><td colspan="4">Results and Analysis</td></tr>
<tr><td>Analysis description</td><td colspan="3">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">All efficacy analyses were conducted on the ITT population (defined as the FAS) at the DCO of 17-Jan-2020. The 2 efficacy analysis populations were:
• Stage II-IIIA patients (subset of the FAS): Osimertinib (n=233); Placebo (n=237)
• Overall population (FAS): Osimertinib (n=339); Placebo (n=343)</td></tr>
<tr><td rowspan="10">Descriptive statistics and estimate variability</td><td colspan="3">Stage II-IIIA patients</td></tr>
<tr><td>Treatment group</td><td>Osimertinib</td><td>Placebo</td></tr>
<tr><td>Number of subjects</td><td>233</td><td>237</td></tr>
<tr><td>DFS (median, months)</td><td>NC</td><td>19.6</td></tr>
<tr><td>95% CI</td><td>38.8, NC</td><td>16.6, 24.5</td></tr>
<tr><td colspan="3">Overall population</td></tr>
<tr><td>Treatment group</td><td>Osimertinib</td><td>Placebo</td></tr>
<tr><td>Number of subjects</td><td>339</td><td>343</td></tr>
<tr><td>DFS (median, months)</td><td>NC</td><td>27.5</td></tr>
<tr><td>95% CI</td><td>NC, NC</td><td>22.0, 35.0</td></tr>
<tr><td rowspan="10">Effect estimate per comparison</td><td rowspan="10">DFS</td><td colspan="2">Stage II-IIIA patients</td></tr>
<tr><td>Comparison groups</td><td>Osimertinib vs. Placebo</td></tr>
<tr><td>HR</td><td>0.17</td></tr>
<tr><td>Adjusted 99.06% CI *</td><td>0.11, 0.26</td></tr>
<tr><td>2-sided p-value</td><td>< 0.0001</td></tr>
<tr><td colspan="2">Overall population</td></tr>
<tr><td>Comparison groups</td><td>Osimertinib vs. Placebo</td></tr>
<tr><td>HR</td><td>0.20</td></tr>
<tr><td>Adjusted 99.12% CI **</td><td>0.14, 0.30</td></tr>
<tr><td>2-sided p-value</td><td>< 0.0001</td></tr>
<tr><td>Notes</td><td colspan="3">* The adjusted CI is computed at the 2-sided 99.06% level, considering a 2-sided significance level of 0.0094 for the interim analysis, based on the O Brien and Fleming spending function, assuming 247 DFS events would have been observed for the final analysis.
** The adjusted CI is computed at the 2-sided 99.12% level, considering a 2-sided significance level of 0.0088 for the interim analysis, based on the O'Brien and Fleming spending function, assuming 317 DFS events for the final analysis.</td></tr>
<tr><td>Analysis description</td><td colspan="3">Secondary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">OS was analysed at the DCO of 17-Jan-2020, in the following populations:
• Stage II-IIIA patients (subset of the FAS): Osimertinib (n=233); Placebo (n=237)
• Overall population (FAS): Osimertinib (n=339); Placebo (n=343)</td></tr>
<tr><td></td><td colspan="3">Stage II-IIIA patients</td></tr>
</table>

Descriptive statistics and estimate variability	Treatment group	Osimertinib	Placebo
	Number of subjects	233	237
	OS (median, months)	NC	NC
	95% CI	NC, NC	NC, NC
	Overall population		
	Treatment group	Osimertinib	Placebo
	Number of subjects	339	343
	OS (median, months)	NC	48.2
	95% CI	NC, NC	48.2, NC

Effect estimate per comparison	OS	**Stage II-IIIA patients**	
		Comparison groups	Osimertinib vs. Placebo
		HR	0.40
		Adjusted 99.98% CI *	0.09, 1.83
		2-sided p-value	0.0244 **
		Overall population	
		Comparison groups	Osimertinib vs. Placebo
		HR	0.48
		Adjusted 99.98% CI *	0.12, 1.98
		2-sided p-value	0.0553 **
Notes	* The adjusted CI is computed at the 2-sided 99.98% level, considering a 2-sided significance level of 0.0002 for the interim analysis, based on the Haybittle-Peto spending function. ** A 2-sided p-value < 0.0002 was required for statistical significance		

Discussion on clinical efficacy

Osimertinib is authorised for the treatment of adult patients with advanced or metastatic NSCLC, in patients with T790M mutation and in the first-line setting, in patients with activating EGFR mutations. With this variation application the MAH is seeking the extension of the indications to include the adjuvant setting. To support the proposed extension of indication, the MAH submitted efficacy data from one single clinical study (ADAURA). The study was unblinded following the recommendation by the IDMC that had performed an unplanned interim analysis of efficacy after seeing results of the planned futility analysis.

ADAURA is an ongoing global, Phase III, double-blind, randomised, placebo controlled, multi-centre study designed to assess the efficacy and safety of osimertinib versus placebo in patients with EGFRm stage IB-IIIA NSCLC following complete tumour resection, with or without prior adjuvant chemotherapy. The proportion of patients randomised with stage IB disease and stages II-IIIA disease was to be 30% and 70%, respectively. The patient population comprised centrally confirmed EGFR mutations (Ex19del and L858R) either alone or in combination with other EGFR mutations including T790M. The inclusion and exclusion criteria are acceptable. The dosing is 80 mg once a day which is the currently authorised posology in the advanced disease. Patients were randomised 1:1 to the study arms and received randomised treatment until recurrence of disease, a treatment discontinuation criterion was met, or the 3-year treatment period was completed. With the possibility to reduce the dose to 40 mg if necessary. The treatment duration of 3 years is based on the observations that the highest rate of

recurrence is typically in the first two to three years post-surgery. DFS by investigator assessment was the primary endpoint. The secondary endpoints included OS, DFS rates, changes in HRQL, PK analyses and safety assessment. Following recurrence, patients in the placebo arm were allowed to receive osimertinib. This will confound the OS data. The overall study design is considered adequate.

The number of patients with ongoing treatment is higher in the osimertinib arm (60.8%) than the placebo arm (39.7%), mostly due to fewer patients discontinuing due to disease recurrence. A total of 682 eligible patients were randomised to receive study treatment at 185 study centres in 24 countries. 680 received at least one dose, 337 patients in the osimertinib arm (99.4% of all randomised) and 343 patients in the placebo arm. The majority of subjects were female, Asian and non-smoking patients, the baseline demographic and patient characteristics in the study were representative of the intended patient population. Demographic and patient characteristics were well balanced between the treatment arms. In line with standard therapeutics for NSCLC, 60.1% of the patients received platinum-based doublet chemotherapy prior to randomisation, with a higher percentage in stage II-IIIA than IB disease.

The primary endpoint of the ADAURA study was met, demonstrating a statistically significant difference in DFS in favour of osimertinib both for the stage II-IIIA disease and the overall population (includes stage IB patients). The DFS HR for patients with stage II-IIIA disease was 0.17 (99.06% CI: 0.11, 0.23, $p < 0.0001$) and for the overall population was 0.20 (99.12% CI: 0.14, 0.30, $p < 0.0001$). DFS KM curves separation occurred at around 12 weeks and was maintained. The main secondary endpoint was OS. At the time of data cut off, the OS data were immature (5.3% maturity) but indicate a trend in favour of osimertinib. OS was formally tested in stage II-IIIA disease patients giving a HR of 0.40 (99.98% CI: 0.09, 1.83; $p = 0.0244$). Subgroup analyses showed a clear benefit of osimertinib in terms of DFS in all pre-specified subgroups, including all disease stages and in the presence or absence of prior adjuvant chemotherapy.

Conclusions on the clinical efficacy
Adjuvant treatment with osimertinib after complete tumour resection showed a clinically meaningful and statistically significant benefit in terms of DFS over placebo. The improvement in the primary endpoint was supported by the secondary endpoints, subgroup and sensitivity analyses. The data are considered robust and clearly demonstrate a benefit of treatment in the patient population. The data supports the proposed indication ‘Tagrisso as monotherapy for the adjuvant treatment after complete tumour resection in adult 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.’

The MAH has committed to providing any updates and final analysis for all endpoints, once these are available.

Analysis performed across trials (pooled analyses and meta-analysis)
None

Clinical safety
ADAURA study
These applications focus on safety and tolerability of osimertinib in adjuvant monotherapy after complete tumour resection in lung cancer patients. Many osimertinib adverse drug reactions (ADRs) are class effects associated with the inhibition of wild-type EGFR signalling. The primary source of safety data is the pivotal Phase III study ADAURA. In the ADAURA study all safety analyses were conducted based on the Safety Analysis Set, which comprised 680 patients overall, of which 337 patients received at least one dose of osimertinib treatment, and 343 patients received at least one dose of placebo. Safety data from ADAURA were pooled with a previously submitted dataset of 1142 patients (AURA, AURA extension, AURA2, AURA3, and FLAURA studies) with advanced/metastatic EGFRm NSCLC that is included in the current label.

Patient exposure

337 patients received at least one dose of osimertinib in ADAURA and 343 patients received at least one dose of placebo. Median exposure is shorter than planned because of the early analysis of the study data. The median total osimertinib exposure was 22.5 months, with 43.9% and 26.1% patients having an exposure of ≥ 24 months and ≥ 30 months, respectively. The actual median exposure in the osimertinib arm was similar to the total median exposure, indicating that the frequency of dosing interruptions for any reason and their median duration had almost no impact on osimertinib exposure.

The MAH commits to providing updated safety data to the Agency when available and will continue to review all safety data collected after this exploratory DFS analysis for those patients who did not complete three years treatment at DFS exploratory analysis, in line with routine surveillance practice and the ADAURA clinical study protocol.

The number of patients exposed and the duration of exposure to osimertinib treatment in the ADAURA study is considered adequate to characterise the safety profile in the adjuvant setting. The duration of treatment of TKIs in the adjuvant setting remains uncertain. The placebo arm provides for comparative analysis.

Adverse events

The majority of patients (97.6%) treated with osimertinib reported an adverse event (AE), mainly non -serious, mild or moderate in severity, and did not lead to treatment discontinuation. The majority of patients (89.2%) in the placebo arm also experienced at least one AE.

Table 18 Adverse events in any category

AE Category	Number (%) of patients [a]				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Any AE	329 (97.6)	306 (89.2)	303 (98.1)	823 (98.8)	1455 (98.4)
Any AE causally related to treatment [b]	305 (90.5)	192 (56.0)	282 (91.3)	727 (87.3)	1314 (88.8)
Any AE of CTCAE Grade 3 or higher	68 (20.2)	46 (13.4)	108 (35.0)	313 (37.6)	489 (33.1)
Any AE of CTCAE Grade 3 or higher, causally related to treatment [b]	32 (9.5)	8 (2.3)	53 (17.2)	108 (13.0)	193 (13.0)
Any AE with outcome of death	0	1 (0.3)	6 (1.9)	35 (4.2)	41 (2.8)
Any AE with outcome of death, causally related to treatment [b]	0	0	0	5 (0.6)	5 (0.3)
Any SAE (including those with an outcome of death)	54 (16.0)	42 (12.2)	71 (23.0)	244 (29.3)	369 (24.9)
Any SAE (including those with an outcome of death), causally related to treatment [b]	8 (2.4)	2 (0.6)	26 (8.4)	44 (5.3)	78 (5.3)
Any AE leading to discontinuation of treatment	37 (11.0)	10 (2.9)	40 (12.9)	69 (8.3)	146 (9.9)
Any AE leading to discontinuation of osimertinib, causally related to treatment [b]	31 (9.2)	5 (1.5)	29 (9.4)	35 (4.2)	95 (6.4)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] As assessed by the investigator, and programmatically derived from individual causality assessments.

Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy.

MedDRA version 22.1. CTCAE version 4.03.

Sources: Table 14.3.2.1.1, ADAURA CSR (Module 5.3.5.1), and Table 2.7.4.2.1.1

Common Adverse Events

The most common AEs reported in the ADAURA study were diarrhoea, paronychia and dry skin. The AEs diarrhoea, paronychia, dry skin, pruritus, and stomatitis all had an incidence at least 10 % higher in the osimertinib arm than the placebo arm, consistent with the osimertinib ADR safety profile. Diarrhoea, rashes and acne and stomatitis occurred early in treatment, with no apparent increased risk with long-term osimertinib treatment.

Table 19 Most common AEs, by PT (reported in ≥ 10% osimertinib-treated patients in the ADAURA study)

MedDRA Preferred Term	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Patients with any AEs	329 (97.6)	306 (89.2)	303 (98.1)	823 (98.8)	1455 (98.4)
Diarrhoea	156 (46.3)	68 (19.8)	178 (57.6)	364 (43.7)	698 (47.2)
Paronychia	85 (25.2)	5 (1.5)	92 (29.8)	184 (22.1)	361 (24.4)
Dry skin	79 (23.4)	22 (6.4)	99 (32.0)	194 (23.3)	372 (25.2)
Pruritus	65 (19.3)	30 (8.7)	55 (17.8)	136 (16.3)	256 (17.3)
Cough	62 (18.4)	57 (16.6)	53 (17.2)	161 (19.3)	276 (18.7)
Stomatitis	59 (17.5)	14 (4.1)	92 (29.8)	130 (15.6)	281 (19.0)
Nasopharyngitis	47 (13.9)	35 (10.2)	28 (9.1)	95 (11.4)	170 (11.5)
Upper respiratory tract infection	45 (13.4)	35 (10.2)	35 (11.3)	107 (12.8)	187 (12.6)
Decreased appetite	44 (13.1)	13 (3.8)	60 (19.4)	175 (21.0)	279 (18.9)
Mouth ulceration	39 (11.6)	8 (2.3)	15 (4.9)	25 (3.0)	79 (5.3)
Dermatitis acneiform	37 (11.0)	16 (4.7)	76 (24.6)	88 (10.6)	201 (13.6)

Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy.
MedDRA version 22.1
Sources: Table 14.3.2.6, ADAURA CSR, Module 5.3.5.1; Table 2.7.4.2.1.2

1 Grouped term, comprising PTs of: Acne, Acne Pustular, Dermatitis, Dermatitis Acneiform, Drug Eruption, Erythema, Eyelid Folliculitis, Folliculitis, Rash, Rash Erythematous, Rash Follicular, Rash Macular, Rash Maculo-Papular, Rash Maculovesicular, Rash Papular, Rash Pruritic, Rash Pustular, Rash Vesicular, and Skin Erosion.

Adverse events by severity

The majority of AEs were mild or moderate in severity (Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2), with only a small proportion of patients reporting an AE that was CTCAE ≥ Grade 3. In the ADAURA study, a total of 32 patients (9.5%) had AEs of CTCAE ≥ Grade 3 considered by the investigator to be causally related to osimertinib treatment, with preferred terms (PTs) of paronychia, stomatitis, diarrhoea, electrocardiogram QT prolonged, and decreased appetite being reported as causally related in ≥ 2 patients. These AEs are not unexpected. CTCAE Grade 4 AEs (irrespective of causality) were reported in 3 patients (0.9%) in the osimertinib arm (AEs of appendicitis, blood uric acid increased, and hypokalaemia), and 1 patient (0.3%) in the placebo arm (AE of neutropenia).

Table 20 AEs of CTCAE Grade 3 or higher (reported in ≥ 2 osimertinib-treated patients in the ADAURA study

MedDRA Preferred Term	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Patients with any CTCAE ≥ Grade 3 AE	68 (20.2)	46 (13.4)	108 (35.0)	313 (37.6)	489 (33.1)
Diarrhoea	8 (2.4)	1 (0.3)	6 (1.9)	7 (0.8)	21 (1.4)
Stomatitis	6 (1.8)	-	1 (0.3)	-	7 (0.5)
Pneumonia	4 (1.2)	4 (1.2)	7 (2.3)	29 (3.5)	40 (2.7)
Paronychia	3 (0.9)	-	1 (0.3)	2 (0.2)	6 (0.4)
Hypertension	3 (0.9)	4 (1.2)	1 (0.3)	3 (0.4)	7 (0.5)
ECG QT prolonged	3 (0.9)	1 (0.3)	6 (1.9)	7 (0.8)	16 (1.1)
Gastroenteritis	2 (0.6)	-	1 (0.3)	2 (0.2)	5 (0.3)
Upper respiratory tract infection	2 (0.6)	-	-	1 (0.1)	3 (0.2)
Viral upper respiratory tract infection	2 (0.6)	-	-	-	2 (0.1)
Decreased appetite	2 (0.6)	-	7 (2.3)	8 (1.0)	17 (1.1)
Cataract	2 (0.6)	-	2 (0.6)	3 (0.4)	7 (0.5)
Femur fracture	2 (0.6)	1 (0.3)	-	-	2 (0.1)

Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy.

MedDRA version 22.1

Serious adverse event/deaths/other significant events

Serious Adverse Events (SAEs)

Despite the longer exposure to study treatment in the osimertinib arm of the ADAURA study, SAEs were reported in a similar proportion of patients in both treatment arms (osimertinib: 54 patients [16%]; placebo: 42 patients [12.2%]). In the ADAURA study, pneumonia was the most frequently reported SAE, (osimertinib: 1.5%; placebo: 1.2%). Aside from diarrhoea, the majority of the other events in the osimertinib arm represent medical conditions that may occur over a prolonged period of evaluation.

Table 21 SAEs, by PT (reported in ≥2 osimertinib-treated patients in the ADAURA study)

MedDRA Preferred Term	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Patients with any SAE	54 (16.0)	42 (12.2)	71 (23.0)	244 (29.3)	369 (24.9)
Pneumonia	5 (1.5)	4 (1.2)	8 (2.6)	28 (3.4)	41 (2.8)
Cataract	3 (0.9)	-	-	-	3 (0.2)
Diarrhoea	2 (0.6)	-	2 (0.6)	2 (0.2)	6 (0.4)
Acute kidney injury	2 (0.6)	-	1 (0.3)	1 (0.1)	4 (0.3)
Ureterolithiasis	2 (0.6)	-	-	-	2 (0.1)
Femur fracture	2 (0.6)	1 (0.3)	-	-	2 (0.1)

Includes AEs with onset date on or after the date of first dose up to and including 28 days following discontinuation of study treatment and before starting subsequent cancer therapy. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
MedDRA version 22.1
Sources: Table 14.3.4.1.1, ADAURA CSR, Module 5.3.5.1; Table 2.7.4.2.1.8.

Deaths

A small proportion of study participants had died at the data cut-off date. 29 patients overall, osimertinib: 9 patients [2.7%]; 20 placebo patients [5.8%]. None of the patients in the osimertinib arm were reported to have died from an AE.

Table 22 Summary of Deaths

Category	Number (%) of patients				
	ADAURA Study (Adjuvant)		Advanced / metastatic NSCLC Studies		Overall osimertinib safety pool (N=1479)
	Osimertinib (N=337)	Placebo (N=343)	Osimertinib First-line (N=309)	Osimertinib ≥Second-line (N=833)	
Total number of deaths	9 (2.7)	20 (5.8)	58 (18.8)	252 (30.3)	319 (21.6)
Death related to disease under investigation only	9 (2.7)	18 (5.2)	51 (16.5)	212 (25.5)	272 (18.4)
AE with outcome of death only	-	-	6 (1.9)	18 (2.2)	24 (1.6)
Number of patients with death related to disease and an AE with outcome of death	-	1 (0.3)	-	17 (2.0)	17 (1.1)
Other deaths *	-	1 (0.3)	1 (0.3)	5 (0.6)	6 (0.4)

* Patients who died and are not captured in the earlier categories.
Death related to disease under investigation are determined by the investigator. Rows are mutually exclusive; patients are only reported in one category.
Sources: Table 14.3.3.1, ADAURA CSR, Module 5.3.5.1; Table 2.7.4.2.1.13

Adverse Events of Special Interest (AESI)
A number of AEs were prospectively identified as being topics of interest in the ADAURA study before database lock, based on the understanding of the osimertinib safety profile to date. Cardiac failure is an important potential risk of osimertinib and Interstitial Lung Disease (ILD) is an important identified risk.

Interstitial Lung Disease (ILD)
In the ADAURA study, AEs in the ILD grouped term were reported for 10 patients (3%) in the osimertinib arm (1 SAE [due to hospitalisation]), and no patients in the placebo arm. 60% were reported as mild (6/10 patient with an event of ILD). Overall, the frequency of ILD in the ADAURA study was consistent with the advanced/metastatic population.

Cardiac Failure
Changes in left ventricular ejection fraction (LVEF) have previously been observed for patients treated with osimertinib. In the ADAURA study, there was no difference between treatment arms in the number of patients who experienced LVEF decreases ≥ 10 pp and a drop to < 50%, despite the longer treatment duration in the osimertinib arm. No differences in the severity of AEs indicative of cardiac failure was noted between treatment arms, with the majority of AEs in the cardiac failure grouped term mild or moderate in severity.

Adverse Drug Reactions (ADRs)
Osimertinib ADRs have previously been identified based on an evaluation of data from the entire osimertinib clinical development programme and from routine reviews of post-marketing data and are reflected in current labelling documents. Alopecia, epistaxis, Palmar-plantar erythrodysaesthesia syndrome (PPES), and blood creatinine increased have been added as ADRs. In the ADAURA study, ADRs were more common in the osimertinib arm than the placebo arm:

- Alopecia [PT]: 5.6% vs 2% of patients
- Epistaxis [PT]: 5.6% vs 0.9%
- PPES [PT]: 1.8% vs 0
- Blood creatinine increased [worsening CTCAE grade shift from baseline]: 9.8% vs 4.5%
- Mouth ulceration [PT]: 11.6% vs 2.3%.

Laboratory findings
No clinically significant changes from baseline or trends in haemoglobin values over time were observed. Median counts in the osimertinib arm were within the normal range for neutrophil, platelet, lymphocyte and leukocyte counts. No clinically significant changes in median values of albumin, calcium, glucose, magnesium, potassium or sodium were observed. Median creatinine in both treatment arms was within the normal range for the duration of the on-treatment period. No clinically important changes from baseline in AST, ALT or total bilirubin were observed.

Safety related to drug-drug interactions and other interactions
There is no new information relating to drug interactions, use in pregnancy or lactation overdose and drug abuse withdrawal and rebound, or ability to drive or operate machinery.

Discontinuation/dose modification due to adverse events
A total of 266 patients had discontinued their randomised study treatment prior to the planned 3-year treatment duration: 92 patients (27.3% of those who received treatment) in the osimertinib arm, and 174 patients (50.7%) in the placebo arm. In the osimertinib arm, the most frequently reported reason for study treatment discontinuation was AE (36 patients). In the placebo arm, the most frequently reported reason for study treatment discontinuation was disease recurrence (148 patients). Three patients in the placebo arm (0 patients in the osimertinib arm) discontinued due to severe non-compliance to the protocol. The number and reasons for discontinuations from treatment do not raise any concerns about the conduct of the study.

The overall incidence of discontinuation AEs in osimertinib-treated patients in the adjuvant population (11 %) was consistent with the incidence of discontinuation AEs in the advanced/metastatic population (in which 12.9% of first-line patients, and 8.3% of second-line or greater patients had an adverse event leading to permanent discontinuation of randomised treatment), with comparable incidences of individual discontinuation AEs reported across treatment settings. The incidence of patients with AEs leading to dose modifications (defined as a treatment interruption and/or a dose reduction) was 28.8% in the osimertinib arm and 11.4% in the placebo arm. Adverse events leading to dose interruption were reported for 23.7% of patients in the osimertinib arm and 10.8% of patients in the placebo arm (most common were diarrhoea and stomatitis).

Post marketing data

The AstraZeneca Core Data Sheet (CDS) and Core Patient Information Leaflet (CPIL) for Tagrisso 40mg Film-Coated Tablets and Tagrisso 80mg Film-Coated Tablets have been updated to include urticaria as an adverse drug reaction following an internal Safety Information Review Committee meeting.

A literature article constitutes the source for the signal of urticaria, emerging from the regular pharmacovigilance surveillance activities. The authors suggested the possibility of a causal association between the urticaria and osimertinib.

According to the Applicant's submission, there were 31 urticaria AEs reported in 28 patients in the clinical data summary and from post marketing data, 192 cases (197 events). The frequency category is considered as 'Common' (1.9%). There appears to be a sufficiently strong association between administration of osimertinib and urticaria as an ADR. The proposed changes to the SmPC and PIL are accepted.

AstraZeneca's global Patient Safety database contains all adverse events reports, from spontaneous sources. A search of the safety database was undertaken on 20 July 2020 for adverse event reports of urticaria in association with the use of osimertinib. The search identified 192 case reports containing 197 adverse events. A detailed assessment of case reports was performed to identify the aetiology behind the reported terms. The evaluation was based on time to onset, specific risk factors present, circumstances leading to event, clinical course, any associated signs and symptoms, treatment given, comorbidities, concomitant drugs, information on de-challenge and re-challenge. Among the 192 cases, there were 3 case reports seemingly without any alternate aetiology.

Discussion on clinical safety

The main safety data set comprises 680 ADAURA study patients (337 osimertinib/343 placebo), supported by previous analysis of safety data for 1,142 patients that received at least one dose of osimertinib 80 mg in studies of osimertinib in advanced/metastatic EGFRm NSCLC (AURA, AURA extension, AURA2, AURA3, and FLAURA studies). In the ADAURA study, median exposure to osimertinib was 22.5 months. The median exposure is shorter than planned due to the early analysis of the study.

There is a debate around the optimal duration of treatment of TKIs in the adjuvant setting. There is currently limited data from ADAURA beyond 24 months exposure and few patients received osimertinib for the planned 3-year treatment duration. Data on time to onset for ADRs show that ADRs generally occur early in treatment, with no observed significant risk with long-term treatment. The MAH commits to providing updated safety data to the MHRA when available and will continue to review all safety data collected for those patients who did not complete three years treatment at DFS exploratory analysis, in line with routine surveillance practice and the ADAURA clinical study protocol.

Many of the osimertinib ADRs are associated with the inhibition of wild-type EGFR signalling and the ADAURA study safety data is consistent with the known safety profile of osimertinib. The following events and grouped terms have previously been identified as ADRs and are already in the core label of osimertinib: ILD, diarrhoea, stomatitis, keratitis, rash, dry skin, paronychia, pruritus, erythema multiforme, Stevens-Johnson syndrome, cutaneous vasculitis, QTc interval prolongation, platelet count decreased, leucocytes decreased, lymphocytes decreased, and neutrophils decreased. Throughout the current ADAURA study, five new ADRs have been identified: alopecia, epistaxis, PPES, mouth ulceration (a grouped term under 'stomatitis'), and increased blood creatinine. All of the newly identified ADRs have been added to the SmPC and are mainly related to the mechanism of action of osimertinib.

In the ADAURA study nearly all patients reported at least one adverse event (AE), the most frequently reported being (≥20%) diarrhoea (46.3% osimertinib vs. 19.8% placebo), paronychia (25.2% vs. 1.5%) and dry skin (23.4% vs. 6.4%). Of these, 20.1% of patients in the osimertinib arm and 13.4% in the placebo arm, reported AEs of Grade ≥3. In general terms, the most frequently observed AEs were those expected with osimertinib, and most of them were of mild or moderate severity.

Conclusions on clinical safety

Osimertinib treatment was generally well tolerated by most patients. Adverse events leading to discontinuation of treatment were low and most of these adverse events were mild or moderate in severity. Overall, the safety data from ADAURA are consistent with the known safety profile of osimertinib and no major safety concerns are observed.

Benefit-Risk Balance

Disease or condition

Lung cancer is the most common cancer in the world and the leading cause of cancer related death. Advances in the knowledge of tumour-specific genomic abnormalities have enabled the identification of specific molecular targets for NSCLC treatment. EGFR tyrosine kinase inhibitors (TKIs) are established effective therapies in patients who have activating and sensitising mutations.

Available therapies and unmet medical need

The primary treatment option for patients with stage IB-IIIA NSCLC is complete tumour resection. Adjuvant platinum-based chemotherapy is offered to patients with resected stage II and III NSCLC. Despite surgical resection, recurrence remains an issue. No treatment options are currently approved for EGFRm resectable NSCLC after surgery and standard adjuvant chemotherapy

Main clinical study

The ADAURA trial was a randomised, double-blind, Phase III study comparing osimertinib versus placebo in patients with stage IB, II, IIIA EGFRm (Ex19del or L858R) NSCLC, who have undergone complete tumour resection. A total of 682 patients were randomised in a 1:1 ratio to receive either osimertinib 80 mg once daily (n=339) or matching placebo (n=343). Treatment was continued until recurrence of disease, a treatment discontinuation criterion was met, or up to a maximum of 3 years. Stratification factors included disease stage (IB vs. II vs. IIIA), EGFR mutation status (Ex19del or L858R), and race (Asian or Non-Asian). The primary endpoint of the study was disease free survival (DFS), as determined by the investigator. Overall survival (OS) and health related quality of life (HRQL) were included as secondary endpoints. The design of the study is appropriate for the objective of demonstrating improved outcomes in the patient group.

Favourable effects

An unplanned interim analysis, at the cut-off date of 17 January 2020 demonstrated a statistically and clinically significant improvement in DFS (HR 0.17; 99.06% CI: 0.11, 0.26) in the stage II-IIIA population. Median DFS had not been reached in the osimertinib arm. In the overall population

including stage IB, DFS results were consistent with the primary efficacy population (HR 0.20; 99.12% CI: 0.14, 0.30). The results are supported by sensitivity and subgroup analyses. OS data at the time of the data cut-off were immature, although a positive trend was noted.

Uncertainties and limitations about favourable effects
The data are from an unplanned interim analysis. An ad hoc request was made by the IDMC to review key efficacy data. This resulted in a recommendation to report the results of the trial due to overwhelming efficacy. As there had been no provision in the protocol or statistical analysis plan to conduct an interim analysis for efficacy, an alpha-spending function was applied based on the information fraction.

Positive DFS data of the magnitude presented are considered beneficial in their own right. However, the immaturity of the OS data means it is not possible to determine if the delay in the time to recurrence translates into a survival benefit. Cross over of placebo patients to osimertinib will confound the future longer-term analysis.

No firm conclusions can be drawn on the proposed treatment duration as only 11.9% of patients in the osimertinib arm completed the 3-year study treatment period.

Unfavourable effects
In the ADAURA study nearly all patients (97.6%) reported at least one adverse event (AE). The majority of AEs were non-serious, or mild or moderate in severity. The most frequently reported (≥20%) were diarrhoea (46.3% osimertinib vs. 19.8% placebo), paronychia (25.2% vs. 1.5%) and dry skin (23.4% vs. 6.4%). Of these, 20.1% of patients in the osimertinib arm and 13.4% in the placebo arm, reported AEs of Grade ≥3. The frequency and severity of AEs was higher in the active osimertinib arm than in the placebo arm. The median total exposure was longer in the osimertinib arm (22.5 months) than in the placebo arm (18.7 months). Overall, osimertinib was well tolerated, with a low frequency of dose modifications and discontinuations. The reported safety data for osimertinib are broadly consistent with the known safety profile.

There is shorter follow-up for safety in the context of adjuvant treatment proposed for up to 3 years.

Table 23 Effects Table

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
DFS	Disease free survival (by investigator) – Stage II-IIIA population	Median months (95% CI)	NC (38.8, NC)	19.6 (16.6, 24.5)	IA with 11.2% events in the osimertinib arm and 59.9% events in the placebo arm HR 0.17 (95%CI: 0.12, 0.23) (99.06CI[a]: 0.11, 0.26)	
	Disease free survival (by investigator)– Overall population	Median Months (95% CI)	NC (NC, NC)	27.5 (22.0, 35.0)	IA with 10.9% events in the osimertinib arm and 46.4% in the placebo arm	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					HR 0.20 (95%CI: 0.15, 0.27) (99.12%CI[b]: 0.14, 0.30)	
OS	Overall survival – Stage II-IIIA population	Median Months (95% CI)	NC (NC, NC)	NC (NC, NC)	IA with 3.4% events in the osimertinib arm and 7.2% in the placebo arm HR 0.40 (95%CI: 0.18, 0.89) (99.98%CI[c]: 0.09, 1.83)	
Unfavourable Effects						
Diarrhoea		N (%)	156 (46.3)	68 (19.8)	Prevalence of diarrhoea was at its greatest during the first month of treatment; after this initial increase, prevalence decreased, with a sharp drop between 3 and 7 months and a continuing decreasing trend over the remaining duration of treatment. Diarrhoea primarily occurs early in treatment, with no increased risk with longer treatment exposure durations.	
Paronychia			85 (25.2)	5 (1.5)		
Dry skin			79 (23.4)	22 (6.4)		
Pruritus			65 (19.3)	30 (8.7)		
Cough			62 (18.4)	57 (16.6)		
Stomatitis			59 (17.5)	14 (4.1)	After an initial increase during the first month of treatment, prevalence remained relatively constant	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					over the remaining duration of treatment	
Nasopharyngitis			47 (13.9)	35 (10.2)		
Upper respiratory tract infection			45 (13.4)	35 (10.2)		
Decreased appetite			44 (13.3)	13 (3.8)		
Mouth ulceration			39 (11.6)	8 (2.3)		
Dermatitis acneiform			37 (11.0)	16 (4.7)		
ILD:	-Interstitial Lung disease -Pneumonitis -Acute interstitial pneumonitis -Alveolitis - Diffuse alveolar damage -Idiopathic pulmonary fibrosis -Lung disorder -Pulmonary toxicity -Pulmonary fibrosis	N (%)	10 (0.3)	0	Uncommon but well documented EGFR-related toxicity. The median time to onset for events of ILD (grouped term) was 81.5 days (range 55 to 950 days)	
Cardiac failure			16 (4.7)	10 (2.9)	Only 1 AE (pulmonary oedema in osimertinib arm) was reported as an SAE (due to hospitalization). This SAE was reported 22 days after the patient had stopped study treatment (due to a prior AE of diarrhoea) and was considered unrelated to study treatment. The median time to onset for events indicative of cardiac failure (grouped term)	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					was 418.5 days in the osimertinib arm (range 52 to 1021 days), and 126.0 days in the placebo arm (range 82 to 832 days). Six patients overall (3 patients in each treatment arm; 0.9%) discontinued study treatment due to an AE in the cardiac failure grouped term	
Death	Deaths due to adverse events		0	1 (0.3%)	Disease recurrence (as assessed by the Investigator) was the only reported reason for death in the osimertinib arm (9 [2.7%]), and was the most common reason for death in the placebo arm (18 [5.2%]).	

Skin reactions, diarrhoea, and stomatitis have previously been confirmed as commonly reported osimertinib ADRs based on evaluations of data across the entire clinical program

Abbreviations: ILD: Interstitial lung disease Notes: [a] The adjusted CI is computed at the 2-sided 99.06% level, considering a 2-sided significance level of 0.0094 for the interim analysis, based on the O Brien and Fleming spending function, assuming 247 DFS events would have been observed for the final analysis. [b] The adjusted CI is computed at the 2-sided 99.12% level, considering a 2-sided significance level of 0.0088 for the interim analysis, based on the O'Brien and Fleming spending function, assuming 317 DFS events for the final analysis. [c] The adjusted CI is computed at the 2-sided 99.98% level, considering a 2-sided significance level of 0.0002 for the interim analysis, based on the Haybittle-Peto spending function.

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

Results from the ADAURA study have shown a statistically significant and clinically meaningful advantage in terms of DFS. The safety profile of osimertinib appears consistent with the known safety profile and osimertinib was generally well tolerated.

Balance of benefits and risks

Osimertinib in the adjuvant setting is well tolerated and the substantial delay of disease recurrence is clinically meaningful. The benefits outweigh the risks.

Additional considerations on the benefit-risk balance

Not applicable

Conclusions
The overall benefit/risk of Tagrisso 40 mg and 80 mg film-coated tablets is positive for the applied indication:

‘Tagrisso as a monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult 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.’

The proposed changes are acceptable.

In accordance with legal requirements, the current approved GB versions of the SmPCs and PIL for these products are available on the MHRA website.

Decision: Grant

Date: 6 May 2021

Annex 2

Reference: PLGB 17901/0340-0004
PLGB 17901/0341-0004

Product: Tagrisso 40 mg film-coated tablets
Tagrisso 80 mg film-coated tablets

Type of Procedure: National route

Submission category: Type II Variation

Reason
To update section 4.8 of the SmPC and section 4 of PIL for Tagrisso 40 mg Film-coated tablets and Tagrisso 80 mg Film-coated tablets in line with the company Core Data Sheet (CDS) and Core Patient Information Leaflet (CPIL) to include `urticaria' as an adverse drug reaction.

Supporting evidence
The Marketing Authorisation Holder (MAH) has submitted:
- Updated SmPCs
- Updated PIL

Evaluation
The updated documents are satisfactory.

Conclusion
The proposed changes are acceptable.

In accordance with legal requirements, the current approved GB versions of the SmPCs and PIL for these products are available on the MHRA website.

Decision: Grant

Date: 7 May 2021