Observational Study Report

Study Code	D5160R00021
Version	1.0
Date	26-Nov-2020

NOBLE

An observational study to evaluate AZD9291 treatment in patients with EGFR T790M positive locally advanced or metastatic non-small cell lung cancer following progression on at least one prior EGFR TKI treatment

Sponsor: AstraZeneca Taiwan

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AEs	Adverse Event(s)
ARMS	Amplification Refractory Mutation System
BEAMing	Beads, Emulsions, Amplification and Magnetics Digital PCR Assay
CEA	Carcinoembryonic Antigen
cfDNA	Cell Free Deoxyribonucleic Acid
CI	Confidence Interval
CL/F	Total body clearance of drug from plasma after an oral dose
C_{max}	Maximum of plasma concentration
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRF	Case Report Form
CSP	Clinical Study Protocol
dPCR	Digital Polymerase Chain Reaction
ddPCR	Droplet Digital Polymerase Chain Reaction
EAP	Early Access Program
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EGFRm	Epidermal Growth Factor Receptor Sensitizing Mutation
FAS	Full Analysis Set
G719X	An in-frame amino acid, glycine (G), deletion at position 719 in EGFR
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
L858R	An amino acid substitution at position 858 in EGFR, from a Leucine (L) to a Arginine (R)

Abbreviation or special term	Explanation
LDT	Lab Developed Test
L/h	Liters per hour
MassARRAY	MassARRAY Genotyping
mg	milligrams
N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NE	Not Evaluable
NGS	Next Generation Sequencing
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PFS	Progression-free Survival
PR	Partial Response
S768I	An amino acid substitution at position 768 in EGFR, from a Serine (S) to a Isoleucine (I)
SAP	Statistical Analysis Plan
SD	Stable Disease
T790M	An amino acid substitution at position 790 in EGFR, from a Threonine (T) to a Methionine (M)
TFDA	Taiwan Food and Drug Administration
TKI	Tyrosine Kinase Inhibitor
TTD	Time to Treatment Discontinuation

RESPONSIBLE PARTIES

Name	Professional Title	Role in Study	Affiliation	Email Address
Judy Yeh	Medical Evidence Delivery Manager	Local Study Leader	AstraZeneca Taiwan	judy.yeh@astrazeneca.com
Nina Yeh	Oncology Medical Advisor-Lung Cancer	Medical Advisor	AstraZeneca Taiwan	nina.yeh@astrazeneca.com
Sandy Wei	Senior MSL-Lung Cancer	Medical Advisor	AstraZeneca Taiwan	sandy.wei@astrazeneca.com
Irene Lee	Project Manager	Project Manager	QPS	irene.lee@qps-taiwan.com

OBSERVATIONAL STUDY REPORT SYNOPSIS

NOBLE

An observational study to evaluate AZD9291 treatment in patients with EGFR T790M positive locally advanced or metastatic non-small cell lung cancer following progression on at least one prior EGFR TKI treatment

Milestones:	Study initiation	21-Jun-2018
	End of data collection	16-Mar-2020
Phase of development:	Not applicable – Observational study	
Sponsor:	AstraZeneca Taiwan	

This study was performed in compliance with Good Clinical Practice and Good Pharmacoepidemiology Practice, including the archiving of essential documents.

Background/Rationale:

Advanced or metastatic non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor sensitizing mutation (EGFRm) are initially responsive to EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib, and afatinib. However, approximately 50-60% of NSCLC patients who have been treated with frontline EGFR TKIs develop resistance to these TKIs due to acquired EGFR T790M mutation. Osimertinib (AZD9291) is a highly potent, irreversible TKI to target both EGFR sensitizing and T790M resistance mutation. AZD9291 has been approved by Taiwan Food and Drug Administration (TFDA) on 10th November 2016 under the priority review and accelerated approval for the patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressive disease (PD) under or after other EGFR TKI therapy. Due to the limited treatment options for patients who had PD following early lines of treatments for locally advanced or metastatic NSCLC, the AZD9291 Early Access Program (EAP) was available in Taiwan during October 2015 to September 2016. AZD9291 EAP was able to supply the unlicensed AZD9291 for NSCLC patients who had received at least one EGFR TKI therapy. This observational study aimed to evaluate the effectiveness of AZD9291 treatment in the real world for locally advanced or metastatic NSCLC patients with EGFRm who had participated in the EAP in Taiwan.

Objectives:

Primary objective

To evaluate the investigator assessed real world progression in locally advanced or metastatic NSCLC subjects with EGFRm who have been treated with AZD9291

Secondary objectives

1. To analyzed the overall survival (OS) of AZD9291 treatment
2. To analyze the time to treatment discontinuation (TTD) of AZD9291 treatment
3. To summarize the last therapy for locally advanced or metastatic NSCLC with EGFRm and the clinical outcome just before the first dose of AZD9291 if available
4. To summarize the rationale for the use of AZD9291 over other NSCLC treatments at EAP enrollment
5. To summarize the type of test performed for the confirmation of acquired EGFR T790M mutation if available
6. To summarize the subsequent line(s) of systemic NSCLC treatment on AZD9291 monotherapy
7. To summarize the reasons that the investigators prescribed other NSCLC therapy as an add-on to AZD9291 monotherapy [e.g., NSCLC progression, adverse events (AEs) related to the use of AZD9291, or AEs unrelated to the use of AZD9291]

Study design:

This observational study aimed to investigate the effectiveness of AZD9291 treatment in subjects with locally advanced or metastatic NSCLC with EGFRm who had participated in the EAP in the real world practice in Taiwan.

Clinical benefits were evaluated by real world progression, OS, and TTD.

Data source:

All data were retrieved from the medical charts per local institutional review board (IRB)/independent ethics committee (IEC) regulations.

Data required for determining the study objectives were captured from the medical charts of the eligible subjects who had participated in the AZD9291 EAP and met the eligibility criteria of this study.

Data from subjects who were deceased before study initiation were collected from the first date of confirmed diagnosis of NSCLC to the date of death.

Data from subjects who were alive at study initiation were collected from the first date of confirmed diagnosis of NSCLC to the date of signing informed consent form (ICF).

The data collection for subjects who were alive at study initiation and enrolled under clinical study protocol (CSP) version 1.1 was stopped immediately when the CSP version 2.5 and the waiver of signing amended ICF for CSP version 2.5 were approved by the IRB/IEC.

Per local IRB regulations, data from subjects with unknown date of death or unknown living status (i.e. lost to follow up longer than 6 months) were collected from the first date of confirmed diagnosis of NSCLC to the last date of clinical assessment or the last date of contact, whenever came the last.

The duration of data collection for this study was from 21-Jun-2018 to 16-Mar-2020.

Study population:

All the available subjects who had participated in the AZD9291 EAP for locally advanced or metastatic NSCLC with EGFRm were screened for the eligibility of data collection in this observational study. NSCLC patients in the EAP had the following characteristics:

- NSCLC with EGFRm patients who used AZD9291 as the second or third line treatment were enrolled in the EAP
- NSCLC with EGFRm patients who used AZD9291 as the first line treatment option were not included in the EAP

A total of 423 subjects were enrolled in this study.

Inclusion criteria:

- At least 20 years of age
- Subjects who had participated the AZD9291 EAP
- Subjects who had received at least one dose of AZD9291 monotherapy
- Subjects agreed to provide the written informed consent or the informed consent was waived by IRB (e.g. deceased patients or patients who lost to follow up longer than 6 months after the last day of assessment/contact per local IRB/IEC approval)

Exclusion criterion:

- Subjects who received AZD9291 as the first line therapy for NSCLC

Statistical methods:

The Full Analysis Set (FAS) population was defined as all enrolled subjects who had received at least one dose of AZD9291 in the EAP. The FAS population was applied for all analyses.

Descriptive statistics were used to analyze all objectives in this study. Categorical measures (e.g., gender) were presented as count and percentages. Continuous measures (e.g., age) were presented as mean, median, standard deviation, minimum, and maximum. Additionally, Kaplan-Meier curves as well as median and 95% confidence interval (CI) of median were presented for time-to-event outcomes such as progression-free survival (PFS), OS, and TTD.

To analyze the PFS, the data from subjects who survived without PD (without event) during the study period were censored on the last day of the tumor assessment. The data from subjects with unknown date of death or unknown living status (i.e. lost to follow up longer than 6 months after the last day of assessment/contact) were censored on the last day of clinical assessment or the last day of contact, whenever came the last. The number and

percentage of subjects survived without PD (without event) at the 12th and 18th month after the first dose of AZD9291 were analyzed using Kaplan-Meier method, and the frequency table was provided.

To analyze the OS, the data from subjects with unknown date of death or unknown living status (i.e. lost to follow up longer than 6 months after the last day of assessment/contact) were censored on the last day of clinical assessment or the last day of contact, whenever came the last. The number and percentage of subjects survived (without event) at the 18th and 24th month after the first dose of AZD9291 were analyzed using Kaplan-Meier method, and the frequency table was provided.

To analyze the TTD, the data from subjects who were still receiving the monotherapy of AZD9291 at the end of data collection were censored on the date when the last known dose of AZD9291 monotherapy was taken. For analyzing TTD in subjects with unknown ending of treatment date, the data were censored on the last known dose date of AZD9291 monotherapy.

Results:

Of 423 subjects enrolled, 422 subjects completed the study and 1 subject was withdrawn due to loss to follow-up. All 423 subjects enrolled were included in the FAS population.

Primary endpoint

The primary endpoint was to determine the PFS. Of the 419 subjects who had PFS data available after receiving the first dose of AZD9291, 363 subjects (86.63%) had PD or died during the study period. The median PFS was 10.5 months (95% CI: 8.95, 11.41) and was approximately equivalent to 320.0 days (95% CI: 273.00, 348.00).

Secondary endpoints

1. PFS at the 12th and 18th month after the first dose of AZD9291

   Of the 419 subjects who had PFS data available after receiving the first dose of AZD9291, 172 subjects (41.05%) had a progression event and 52 subjects (12.41%) had a death event by the 12th month; and 195 subjects (46.54%) were progression-free. The Kaplan-Meier estimated of PFS rate at the 12th month was 42.58% (95% CI: 37.59, 47.48). Of the 419 subjects, 214 subjects (51.07%) had a progression event and 69 subjects (16.47%) had a death event by the 18th month; and 136 subjects (32.46%) were progression-free. The Kaplan-Meier estimated of PFS rate at the 18th month was 26.50% (95% CI: 22.14, 31.05).

2. OS and OS at the 18th and 24th month after the first dose of AZD9291

   Of the 422 subjects who had OS data available after receiving the first dose of AZD9291, 296 subjects (70.14%) had death events during the study period and 126 subjects were censored. The Kaplan-Meier estimated median OS was 19.0 months (95% CI: 16.30, 20.95) and was approximately equivalent to 579.0 days (95% CI: 497.00, 639.00).

   By the 18th month, of the 422 subjects, 199 subjects (47.16%) had death events and 223 subjects (52.84%) were censored. The Kaplan-Meier estimated OS rate at the 18th month was 51.51% (95% CI: 46.54, 56.24).

By the 24th month, of the 422 subjects, 239 subjects (56.64%) had death events and 183 subjects (43.36%) were censored. The Kaplan-Meier estimated OS rate at the 24th month was 40.90% (95% CI: 36.04, 45.70).

3. Time to treatment discontinuation (TTD)

   Of the 399 subjects who had TTD data available after receiving the first dose of AZD9291, 326 subjects (81.70%) discontinued from AZD9291 monotherapy during the study period and 73 subjects (18.30%) were censored. The Kaplan-Meier estimated median TTD was 11.9 months (95% CI: 10.49, 13.11) and was approximately equivalent to 363.0 days (95% CI: 320.00, 400.00).

4. Last NSCLC therapy and the clinical outcome just before receiving the first dose of AZD9291
   - Last NSCLC therapy

   If analyzed by EGFR TKI therapy, the most common (> 10%) therapies in the FAS population were erlotinib (22.46%), followed by afatinib (13%), and gefitinib (12.29%).

   If analyzed by chemotherapy, 36.41% of the FAS population had received other chemotherapy and 29.79% of the FAS population had received platinum- or taxane-based therapy, as the last NSCLC treatment just before receiving the first dose of AZD9291.

   If analyzed by other systemic therapy, the most common (> 1%) therapies were bevacizumab (4.02%) and nivolumab (1.65%).

   If analyzed by radiation therapy for brain metastasis, 17.02% of the FAS population received radiation alone, 7.33% of the FAS population received radiation combined with systemic therapy, as the last NSCLC treatment just before receiving the first dose of AZD9291.

   If analyzed by combined therapy, 3.31% of the FAS population received chemotherapy combined with other systemic therapy, 2.60% of the FAS population received EGFR TKI combined with other systemic therapy, and 2.36% of the FAS population received EGFR TKI combined with chemotherapy, as the last NSCLC treatment just before receiving the first dose of AZD9291.

   - Clinical outcome

   Of the 396 subjects with clinical outcome data available, the most common (> 10%) response assessments of the last NSCLC therapy were stable disease (12.88%) and PD (77.27%).

5. Rationale for the use of AZD9291 over other NSCLC treatments at EAP enrollment

   Of the 423 subjects enrolled, the main reason (94.80%) for subjects participated in the EAP was due to lack of efficacy for the last NSCLC therapy.

6. Type of test performed for the confirmation of acquired EGFR T790M mutation

   Of the 421 EGFR T790M mutation tests collected in this study, the most common (> 10%) test results were from tissue biopsy (44.42%), followed by plasma-based samples (36.34%) and cytological samples (12.59%).

The most common (>100 test results) test platforms used for detecting EGFR T790M mutation were MassARRAY genotyping (MassARRAY; 31.61% in all forms) and COBAS EGFR mutation test (30.17%).

7. The subsequent line(s) of systemic NSCLC treatment on AZD9291 monotherapy

   Of the 348 subsequent systemic treatments, the most common treatments (> 5%) were combined therapy with AZD9291 (59.20%), followed by single chemotherapy (27.87%) and combined therapy without AZD9291 (9.20%).

   Regarding the combined therapy with AZD9291, the most common (> 5%) therapies were paclitaxel (8.91%), followed by pemetrexed (6.32%), vinorelbine (6.03%), and gemcitabine (5.46%).

8. The reasons that the investigators prescribed other therapy for NSCLC with EGFRm as an add-on to AZD9291 monotherapy

   Of the 113 subjects who had received other therapies for NSCLC with EGFRm as an add-on to AZD9291 monotherapy, the main reason (78.76%) that the investigators prescribed other therapies as an add-on to AZD9291 monotherapy was due to progression of NSCLC.

Conclusions:

In this study, a total of 423 subjects were enrolled. The effectiveness of AZD9291 was evaluated by the analyses of real world progression, OS, and TTD.

Of the 419 subjects who had PFS data available after receiving the first dose of AZD9291, PD or death was observed in 363 subjects (86.63%) during the study period, with median PFS of 10.5 months (95% CI: 8.95, 11.41) and was approximately equivalent to 320.0 days (95% CI: 273.00, 348.00). After receiving the first dose of AZD9291, approximately 42.58% (95% CI: 37.59, 47.48) of them survived without PD at the 12^{th} month and 26.50% (95% CI: 22.14, 31.05) of them survived without PD at the 18^{th} month.

Of the 422 subjects who had OS data available after receiving the first dose of AZD9291, death was observed in 296 subjects (70.14%) during the study period, with median OS of 19.0 months (95% CI: 16.30, 20.95) and was approximately equivalent to 579.0 days (95% CI: 497.00, 639.00). After receiving the first dose of AZD9291, approximately 51.51% (95% CI: 46.54, 56.24) of them survived at the 18^{th} month and 40.90% (95% CI: 36.04, 45.70) of them survived at the 24^{th} month.

Of the 399 subjects who had TTD data available after receiving the first dose of AZD9291, 326 subjects (81.70%) discontinued from AZD9291 monotherapy during the study, with median TTD of 11.9 months (95% CI: 10.49, 13.11) and was approximately equivalent to 363.0 days (95% CI: 320.00, 400.00).

Overall, the clinical benefits of AZD9291 monotherapy were demonstrated in locally advanced or metastatic, EGFR T790M positive NSCLC subjects.

Publications:

Not available.

AMENDMENT HISTORY

Date	Section of study protocol	Amendment or update	Reason
15-Jul-2019	All	Amended from version 1.1, dated 27-Mar-2018 to dv 2.5, dated 15-Jul-2019	Revised the endpoints, timeline, sample size, and clarification for the study population.
27-Mar-2018	All	Amended from version 1.0, dated 01-Dec-2017 to version 1.1, dated 27-Mar-2018	Revised the timeline for data analysis and sample size. Clarification for the study population.

MILESTONES

Milestone	Date
Study initiation	21-Jun-2018
End of data collection	16-Mar-2020

1. BACKGROUND AND RATIONALE

1.1 Background

Advanced molecular profiling for patients with advanced-stage non-small-cell lung cancer (NSCLC) has been well established to direct the use of targeted therapy, such as tyrosine kinase inhibitors (TKIs). However, acquired resistance to TKIs inevitably occurs, which means patients develop progressive disease (PD) after initial benefits from the targeted therapies. Approximately 50-60% of patients with NSCLC who are treated with frontline epidermal growth factor receptor (EGFR) TKIs (e.g. gefitinib or erlotinib) have acquired resistance due to EGFR T790M mutation [1].

Current standard of care among patients with PD under or after EGFR-TKI therapy is platinum-based doublet chemotherapy (e.g. pemetrexed + cisplatin/ carboplatin). Response rates reported for this treatment are within the range of 20-30% [2–4]. In preclinical models, the irreversible EGFR inhibitors, such as afatinib and dacomitinib, have also shown to be effective in EGFR TKI resistant mutants [5,6]. However, in clinical studies, the response rates of these TKIs are limited. Nonetheless, increased skin and gastrointestinal toxic effects are also reported [7,8].

1.2 Rationale

AZD9291, known as osimertinib, is a highly potent, irreversible TKI to target both EGFR TKI sensitizing and EGFR T790M resistance mutations [9]. The efficacy and safety of AZD9291 have been demonstrated in the AURA and AURA2 studies with objective response rate of 51% in the AURA and 66.1% in the AURA phase II pooled analysis, respectively [10,11]. The most common all-cause adverse events (AEs) were diarrhea, rash, nausea, and decreased appetite. Skin and gastrointestinal AEs were noted but limited [10].

A confirmatory, randomized, open label, international, phase III trial (AURA3) was conducted to show the superiority of AZD9291 over platinum-based therapy plus pemetrexed that followed by optional pemetrexed maintenance. Platinum-based therapy plus pemetrexed is a standard of care for patients with centrally confirmed EGFR T790M mutation positive advanced NSCLC after the first line EGFR-TKI therapy [12]. In the AURA3 study, the median duration of progression-free survival (PFS) was significantly longer with AZD9291 than that with platinum-based therapy plus pemetrexed (10.1 months *vs* 4.4 months). The objective response rate was significantly better with AZD9291 than that with platinum-based therapy plus pemetrexed (71% *vs* 31%). The percentage of patients with AEs of grade 3 or higher was lower with AZD9291 than with platinum-based therapy plus pemetrexed (23% *vs* 47%) [10,11].

AZD9291 has been approved by Taiwan Food and Drug Administration (TFDA) for patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have PD under or after EGFR TKI therapy [13]. This indication was approved by TFDA on 10th November 2016 as accelerated approval based on tumor response rate and duration of response in the AURA and the AURA2 studies.

The AZD9291 Early Access Program (EAP) was available for EGFR T790M mutated NSCLC patients who had PD following early lines of treatments for locally advanced or

metastatic NSCLC from October 2015 to September 2016. This option was available to NSCLC patients before the regulatory approval of AZD9291 in Taiwan. The objective of EAP was to provide an unlicensed investigative drug to patients who could not be adequately treated as there were no other comparable or satisfactory therapies and/or all currently available therapies, including participating in ongoing relevant clinical trials, had been exhausted. With the AZD9291 EAP, patients who had received at least one EGFR TKI therapy with confirmed EGFR T790M mutation NSCLC were eligible for the program.

In summary, AZD9291 has demonstrated the efficacy and safety in the clinical development program and may shed light on poorly treated NSCLC patients with EGFR T790M mutation. This observational study aimed to investigate the effectiveness of AZD9291 in NSCLC patients with epidermal growth factor receptor sensitizing mutation (EGFRm) in EAP as in the real world practice in Taiwan.

2. OBJECTIVES AND HYPOTHESES

The objective of this observational study was to analyze the effectiveness of AZD9291 in locally advanced or metastatic NSCLC subjects with EGFRm who had participated in the EAP in Taiwan.

2.1 Primary Objective(s) & Hypothesis(es)

To evaluate the investigator assessed real world progression in locally advanced or metastatic NSCLC subjects with EGFRm who have been treated with AZD9291.

2.2 Secondary Objective(s) & Hypothesis(es)

1. To analyze the overall survival (OS) of AZD9291 treatment
2. To analyze the time to treatment discontinuation (TTD) of AZD9291 treatment
3. To summarize the last therapy for locally advanced or metastatic NSCLC with EGFRm and the clinical outcome just before the first dose of AZD9291
4. To summarize the rationale for the use of AZD9291 over other NSCLC treatments at EAP enrollment
5. To summarize the type of test performed for the confirmation of acquired EGFR T790M mutation
6. To summarize the subsequent line(s) of systemic NSCLC treatment on AZD9291 monotherapy
7. To summarize the reasons that the investigators prescribed other NSCLC therapy as an add-on to AZD9291 monotherapy (e.g. NSCLC progression, AEs related to the use of AZD9291, or AEs unrelated to the use of AZD9291)

2.3 Exploratory Objective(s) & Hypothesis(es)

Not applicable.

3. METHODOLOGY

3.1 Study Design – General Aspects

This observational study aimed to investigate the effectiveness of AZD9291 treatment in subjects with locally advanced or metastatic NSCLC with EGFRm who had participated in the EAP in the real world practice in Taiwan.

Data required for determining the study objectives were captured from the medical charts of the eligible subjects who had participated in the AZD9291 EAP and met the eligibility criteria of this study.

Clinical benefits were evaluated by real world progression, OS, and TTD.

3.1.1 Data Source

All data were retrieved from the medical charts per local institutional review board (IRB)/independent ethics committee (IEC) regulations.

Data from subjects who were deceased before study initiation were collected from the first date of confirmed diagnosis of NSCLC to the date of death.

Data from subjects who were alive at study initiation were collected from the first date of confirmed diagnosis of NSCLC to the date of signing informed consent form (ICF).

The data collection for subjects who were alive and enrolled under clinical study protocol (CSP) version 1.1 was stopped immediately when the CSP version 2.5 and waiver of signing amended ICF for CSP version 2.5 were approved by the IRB/IEC.

Per local IRB regulations, data from subjects with unknown date of death or unknown living status were collected from the first date of confirmed diagnosis of NSCLC to the last date of clinical assessment or the last date of contact, whenever came the last.

All data required to address study objectives were collected in the case report form (CRF). The principal investigator at each site was responsible for ensuring that the required data from the medical charts were accurately extracted and documented in the CRFs.

3.2 Study Population

All the available subjects who had participated in the AZD9291 EAP for locally advanced or metastatic NSCLC with EGFRm were screened for the eligibility for data collection in this observational study. NSCLC patients in the EAP had the following characteristics:

- NSCLC with EGFRm patients who used AZD9291 as the second or third line treatment were enrolled in the EAP.
- NSCLC with EGFRm patients who used AZD9291 as the first line treatment option were not included in the EAP.

The specific study inclusion and exclusion criteria are described in the sections below.

3.3 Inclusion Criteria

All eligible subjects in the study should meet all the following inclusion criteria:

- At least 20 years of age
- Subjects who had participated in the AZD9291 EAP
- Subjects who had received at least one dose of AZD9291 monotherapy
- Subjects agreed to provide the written informed consent or the informed consent was waived by IRB (e.g. deceased patients or patients who lost to follow up longer than 6 months after the last day of assessment/contact per local IRB/IEC approval)

3.4 Exclusion Criterion

Subjects were excluded from this study if they met the following criterion:

- Subjects who received AZD9291 (osimertinib) as the first line therapy for NSCLC

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Exposure

This observational study aimed to investigate the effectiveness in the real world of AZD9291 in locally advanced or metastatic NSCLC subjects with EGFRm in the EAP in Taiwan. The prescribing of AZD9291 and other medication managements was determined by the investigators based on the disease status of each subject.

4.1.1 Definition of Primary Drug Exposure

AZD9291, known as osimertinib, is a TKI of the EGFR, which binds irreversibly to the EGFR kinase domain of certain mutant forms (e.g., T790M, L858R, and exon 19 deletion). The affinity of AZD9291 to mutant forms is 99 times higher than the wild type. AZD9291 exhibited anti-tumor activity against NSCLC subtypes harboring EGFR-mutations (e.g., T790M/L858R, L858R, T790M/exon 19 deletion, and exon 19 deletion) [13]. However, AZD9291 also affects wild-type EGFR amplifications to a lesser extent [13]. The median time to C_{max} of AZD9291 is 6 hours (range 3-24 hours). A population estimated mean half-life of AZD9291 is 48 hours. Oral clearance (CL/F) of AZD9291 is 14.2 (L/h) [13].

AZD9291 has been approved by TFDA for patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC, who have PD under or after EGFR TKI therapy [13].

The recommended dosage and administration route of AZD9291 is 80 mg by oral once daily [13]. The use of AZD9291 was determined by the investigators based on the disease status of each subject.

4.1.2 Definition of Comparison Drug Exposure

No comparison of effectiveness between the treatment of AZD9291 and other NSCLC therapy was planned in the present study.

4.2 Outcomes

Primary endpoint of this study was to determine the PFS. PFS is considered as an appropriate surrogate marker for assessing the efficacy of cancer therapy in NSCLC populations [12,14]. Secondary endpoints of this study included determining the OS and TTD, summarizing the last therapy targeted for locally advanced or metastatic NSCLC with EGFRm just before receiving the first dose of AZD9291, the rationale for the use of AZD9291 over other NSCLC treatments at EAP enrollment, the type of test performed for the confirmation of acquired EGFR T790M mutation, the subsequent line(s) of systemic NSCLC treatment on AZD9291 monotherapy, and the reasons that the investigators prescribed other therapy for NSCLC with EGFRm as an add-on to AZD9291 monotherapy. All tumor responses, including complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE) were collected based on the investigators' assessments.

Primary endpoint

- PFS was defined as the time interval (in days and months) from the date of the first dose of AZD9291 to the date of PD by the investigators' assessments or to the date of death from any cause, whenever came the first.

Secondary endpoints

- To determine the number and percentage of subjects survived without PD (without event) at the 12^{th} and 18^{th} month after the first dose of AZD9291 using Kaplan-Meier method.
- OS was defined as the time interval (in days and months) from the date of the first dose of AZD9291 until the date of death due to any cause. The number and percentage of subjects survived (without event) at the 18^{th} and 24^{th} month after the first dose of AZD9291 were analyzed using Kaplan-Meier method.
- TTD was defined as the time interval (in days and months) from the date of the first dose of AZD9291 monotherapy until the date of the discontinuation of AZD9291 monotherapy for any reason including disease progression, AEs resulting from AZD9291, death, or other reason as recorded in the medical chart.
- To summarize the last therapy targeted for locally advanced or metastatic NSCLC with EGFRm just before the first dose of AZD9291 (e.g., EGFR TKI therapy, chemotherapy, other systemic therapy, or radiation therapy for brain metastasis of NSCLC with EGFRm) and the clinical outcomes, i.e., PR, SD, PD, or NE.
- To summarize the rationale for the use of AZD9291 over other NSCLC treatments at EAP enrollment.
- To summarize the type of test performed for the confirmation of acquired EGFR T790M mutation. The sample type (e.g., plasma-based test, tissue biopsy, or cytology) and test platform [e.g., cobas EGFR Mutation Test, Therascreen test, BEAMing digital polymerase chain reaction (dPCR) assay, lab developed tests (LDT), or next generation sequencing (NGS)] used to confirm EGFR T790M mutation status were analyzed.

- To summarize the subsequent line(s) of systemic NSCLC treatment on AZD9291 monotherapy. Number and treatment types of the subsequent line(s) of systemic NSCLC treatment other than the monotherapy of AZD9291 were summarized.
- To summarize the reasons that the investigators prescribed other therapy for NSCLC with EGFRm as an add-on to AZD9291 monotherapy (e.g., NSCLC progression, AEs related to the use of AZD9291, or AEs unrelated to the use of AZD9291).

4.3 Other Variables and Covariates

The medical records containing the following information were collected in the CRF as baseline characteristics.

- To document the demographic characteristics, including age, gender, smoking status, body weight, height, and Eastern Cooperative Oncology Group (ECOG) performance status score just before the first dose of AZD9291 in the EAP for all subjects.
- To document the clinical characteristics of NSCLC with EGFRm for all subjects, including:
  - ✓ Details of the primary diagnosis of tumor: tumor stage and histology, tumor site including metastasis and presence of other malignancy
  - ✓ Details of tumor stage and tumor site including metastasis just before receiving the first NSCLC systemic therapy
  - ✓ Details of tumor stage and tumor site including metastasis just before the first dose of AZD9291 in the EAP
  - ✓ Comorbidity burden
- To document the EGFR mutation status other than T790M, including but not limited to exon 19 deletion, exon 21 L858R, G719X, S768I, or exon 20 insertion.
- To document the NSCLC treatment history prior to the first dosing of AZD9291 if available in the medical charts, including detailed regimens and treatment period of first-line systemic therapy, detailed regimens and treatment period of subsequent line of systemic therapy, and details of radiation therapy for brain metastasis of NSCLC with EGFRm.
- To document the tumor response assessed by the investigator in the listed time points below for all subjects.
  1. Tumor assessment at the initiation of the first dose of AZD9291.
  2. The period of collecting the best tumor response assessment was from the date when the first dose of AZD9291 administered to the date of disease progression, the date of death, or the date when discontinued the monotherapy of AZD9291, whenever came the first. In case the date of death was unknown, it was the last date of clinical assessment or the last date of contact, whenever came the last. For subjects who survived without PD (without event), the period of collecting the best tumor response assessment was from the date when the first dose of AZD9291 administered to the last

tumor assessment prior to the ICF date. If the same results of "the best tumor response" were judged in several assessments during the study period, the result date and result of the last assessment were collected.

3. Tumor assessment at the time of the first disease progression on AZD9291 treatment.
4. Tumor assessment at the time of discontinuation of AZD9291 treatment.

5. STATISTICAL ANALYSIS

5.1 Statistical Methods – General Aspects

Baseline characteristics, including demographic characteristics, clinical characteristics of NSCLC, EGFR mutation status other than T790M, and NSCLC treatment history prior to the first dose of AZD9291 were collected and summarized for all subjects.

Descriptive statistics were used to analyze all objectives and baseline characteristics in this study. Categorical measures (e.g. gender) were presented as count and percentage. Continuous measures (e.g. age) were presented as mean, median, standard deviation, minimum, and maximum. Additionally, Kaplan-Meier curves as well as median and 95% confidence interval (CI) of median were presented for time-to-event outcomes such as PFS, OS, and TTD.

The detailed statistical analyses in this study were described in the statistical analysis plan (SAP) (Version 1.0, dated 05-Mar-2020).

Population for analysis

The full analysis set (FAS) population was defined as all enrolled subjects who have received at least one dose of AZD9291 in the EAP. The FAS population was applied for all analyses.

No interim analysis was performed in this study.

5.1.1 Primary Objective(s):

The primary objective was to evaluate the investigator assessed real world progression in locally advanced or metastatic NSCLC subjects with EGFRm who had been treated with AZD9291.

PFS was evaluated as the time interval (in days and months) from the date of the first dose of AZD9291 to the date of PD by the investigators' assessments or the date of death from any cause, whenever came the first.

To analyze the primary objective, the data from subjects who survived without PD (without event) during the study period were censored on the last day of tumor assessment. If the subject's date of death or current status was unknown (i.e. lost to follow up longer than 6 months after the last day of assessment/contact), the data was censored on the last day of assessment or contact, whenever came the last.

Kaplan-Meier method was used to estimate the PFS. The Kaplan-Meier curves as well as median and 95% CI of median were included for PFS assessment. Kaplan-Meier curves was

plotted to estimate the changes in probability of PFS over time (in days and months). Censored observations were presented by vertical ticks on the graph.

5.1.2 Secondary Objective(s):

The following secondary objectives were analyzed:

- To determine the number and percentage of subjects survived without PD (without event) at the 12th and 18th month after the first dose of AZD9291 using Kaplan-Meier method.

  The data from subjects who survived without PD (without event) during the study period were censored on the last day of tumor assessment. The data from subjects with unknown date of death or unknown living status (i.e. lost to follow up longer than 6 months after the last day of assessment/contact) were censored on the last day of clinical assessment or the last day of contact, whenever came the last.

  Frequency table was provided to indicate the number and percentage of subjects survived without PD (without event) at the 12th and 18th month after the first dose of AZD9291 using Kaplan-Meier method.

- OS was evaluated as the time interval (in days and months) from the date of the first dose of AZD9291 until the date of death due to any cause.

  To analyze the OS, the data from subjects with unknown date of death or unknown living status (i.e. lost to follow up longer than 6 months after the last day of assessment/ contact) were censored on the last day of clinical assessment or the last day of contact, whenever came the last.

  Kaplan-Meier method was used to estimate the OS by generating the Kaplan-Meier curves as well as median and 95% CI of median. Kaplan-Meier curves were plotted to estimate the survival probability changes over time (in days and months). Censored observations were represented by vertical ticks on the graph.

  Frequency table was provided to indicate the percentage of subjects survived (without event) at the 18th and 24th month after the first dose of AZD9291 using Kaplan-Meier method.

- To analyze the TTD, the data from subjects who were still receiving the monotherapy of AZD9291 at the end of study were censored on the day when the last known dose of AZD9291 monotherapy was taken.

  For analyzing TTD in subjects with unknown ending of treatment date, the data were censored on the last known dose date of AZD9291 monotherapy.

  Kaplan-Meier method was used to estimate the TTD by presenting the Kaplan-Meier curves as well as median and 95% CI of median. Kaplan-Meier curves were plotted to estimate the probability changes of treatment continuation over time (in days and months). Censored observations were represented by vertical ticks on the graph.

- To summarize the last NSCLC therapy and the clinical outcome just before the first dose of AZD9291, the categorical variables of the last therapy targeted for locally

advanced or metastatic NSCLC with EGFRm (e.g., EGFR TKI therapy, chemotherapy, other systemic therapy, or radiation therapy for brain metastasis of NSCLC with EGFRm) just before the first dose of AZD9291 and the clinical outcomes (i.e., PR, SD, PD, or NE) were described as count and percentage.

- To summarize the rationale for the use of AZD9291 over other NSCLC treatments at EAP enrollment, this categorical variable was listed and described as count and percentage.
- To summarize the type of test performed for the confirmation of acquired EGFR T790M mutation, the sample type (e.g., plasma-based test, tissue biopsy, or cytology) and test platform (e.g., cobas EGFR Mutation Test, Therascreen test, BEAMing dPCR assay, LDT, or NGS) used to confirm EGFR T790M mutation status were described as count and percentage.
- To summarize the subsequent line(s) of systemic NSCLC treatment on AZD9291 monotherapy, the number and treatment types (e.g., single chemotherapy, single target therapy, combined therapies with AZD9291, or combined therapies without AZD9291) of the subsequent line(s) systemic NSCLC treatment on AZD9291 monotherapy was listed and described as count and percentage.
- To summarize the reasons that investigators prescribed other NSCLC therapy as an add-on therapy to the AZD9291 monotherapy (e.g., NSCLC progression, AEs related to the use of AZD9291, or AEs unrelated to the use of AZD9291), the results were listed and presented as count and percentage.

5.1.3 Exploratory Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

Not applicable.

5.2 Bias

5.2.1 Methods to Minimize Bias

Due to the individual IRB regulations, some IRBs may not allow the data collection from the subjects who were deceased before study initiation. In order to prevent the bias introduced by the unbalanced subject distribution between subjects who were deceased before study initiation and subjects who were alive at study initiation, this study was conducted in the study centers which allowed medical data collection from subjects who were deceased before study initiation.

5.2.2 Adjustment for Multiple Comparisons

Not applicable.

5.2.3 Strengths and Limitations

- This was an observational study. All data were collected from the medical charts based on the actual clinical practice; therefore, missing data problem may be an issue in effectiveness analysis.
- Data of tumor response were collected from medical charts. The evaluation of tumor response was based on the investigators' assessments in real word practice, which may not be standardized. Thus, bias may be introduced in tumor measurement-based outcomes.

5.3 Sample Size and Power Calculations

All patients in the EAP received the first dose of AZD9291 prior to October 2016; therefore, they had the potential for at least 2 years of follow-up. Approximately 600 subjects previously participated in the AZD9291 EAP and met the eligibility criteria were enrolled in this observational study. No sample size estimation was performed.

5.4 Data Quality

No imputations were performed for handling missing data. Standard operating procedures and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) were followed for data collection, management, monitoring, and analyses.

6. RESULTS

6.1 Study Participation

Of 423 subjects enrolled, 422 subjects completed the study and 1 subject was withdrawn due to loss to follow-up. All 423 enrolled subjects were included in the FAS population.

At study initiation, 102 subjects (24.11%) were alive and 297 subjects (70.21%) were dead. The survival status of 24 subjects (5.67%) was unknown.

The summary of subject disposition is presented in Table 1. Detailed listing of subject disposition is provided in Appendices 16.2.1.1, 16.2.1.2, and 16.2.3.

Table 1: Summary of Subject Disposition

Variable/ Status	Total (N=423)
Enrolled	
Yes	423 (100 %)
Completed Study	
Yes	422 (99.76 %)
No	1 (0.24 %)

Variable/ Status	Total (N=423)
Primary Withdraw Reason*	
Other: lost follow-up	1 (100 %)
Survival Status	
Alive	102 (24.11 %)
Death	297 (70.21 %)
Unknown	24 (5.67 %)
FAS Population	
FAS Population	423 (100 %)

Note:
Reason for discontinuation = 100%[The number of subject(s) in the category / The number of subject(s) who did not complete study in the treatment group]
[Full analysis set (FAS) population was defined as all enrolled subjects who have received at least one dose of AZD9291 in the EAP.]
Source: Appendices 16.2.1.1, 16.2.1.2, and 16.2.3

6.2 Main Results

6.2.1 Protocol Deviation

No protocol deviation was reported in the present study.

6.2.2 Demographic and Other Baseline Characteristics before the First Dose of AZD9291

Gender and age

Of 423 subjects enrolled, 284 subjects (67.14%) were females and 139 subjects (32.86%) were males. The average age (mean±SD) of all subjects was 63.3±11.90 years old.

Body weight and height

One hundred and two (102) subjects did not have body weight data. The mean body weight (mean±SD) of the remaining 321 subjects was 56.16±11.603 kg.

One hundred and twelve (112) subjects did not have height data. The mean height (mean±SD) of the remaining 311 subjects was 158.12±8.320 cm.

ECOG performance status

Of 423 subjects enrolled, the ECOG performance status in 210 subjects was missing. Of the remaining 213 subjects, there were 43 subjects (20.19%) with Grade 0, 127 subjects (59.62%) with Grade 1, 29 subjects (13.62%) with Grade 2, 12 subjects (5.63%) with Grade 3, and 2 subjects (0.94%) with Grade 4 before receiving the first dose of AZD9291.

TNM classification

Of 423 subjects enrolled, more than 60% (290) of the enrolled subjects did not have the data of TNM classification available or were unknown. Details of TNM classification can be referred Table 2.

Location of tumor site (including NSCLC metastasis)

Of 423 subjects enrolled, 213 subjects (50.35%) had tumors in lung, followed by bone (26.24%), lymph node (21.99%), brain (18.91%), pleura effusion/seeding (12.06%), liver (7.57%), adrenal (1.65%), skin (0.24%), and head and neck (0.24%). Ten subjects (2.36%) had tumors in others sites including leptomeningeal, pericardium, pericardial effusion, ascites, kidney, right supraclavicular fossa nodal, left cervical lymph node, pericardial, spine, and spleen. The sum of tumor site location is more than 100% because multiple counting in one subject was applied (including NSCLC metastasis).

Comorbidity burden by system

Of 423 subjects enrolled, 132 subjects (31.21%) had comorbidity in cardiovascular system, followed by gastrointestinal system in 59 subjects (13.95%), endocrine system in 59 subjects (13.95%), respiratory system in 31 subjects (7.33%), malignancy in 21 subjects (4.96%), renal system in 13 subjects (3.07%), body weight in 11 subjects (2.60%), rheumatologic in 10 subjects (2.36%), neurological system in 5 subjects (1.18%), and immunological system in 2 subjects (0.47%).

In those 31 subjects with comorbidity in respiratory system, the most common (≥ 2 subjects) diseases were chronic obstructive pulmonary disease (COPD) (14/423, 3.31%), followed by asthma (6/423, 1.42%), and tuberculosis (2/423, 0.47%).

The demographics and baseline characteristic of subjects are summarized in Table 2. Individual subject's smoking status is listed in Appendix 16.2.4.2.

Detailed listing of demographics and baseline characteristic is provided in Appendices 16.2.4.1, 16.2.4.3.1-16.2.4.3.3, 16.2.4.4, and 16.2.4.7.

Table 2: Summary of Subject Demographics and Baseline Characteristics (FAS Population)

	Variable/ Status	Total (N=423)
Age (years)		
	n	423
	Mean (SD)	63.3 (11.90)
	Median (min, max)	63.0 (32, 95)
Gender		
	Female	284 (67.14 %)
	Male	139 (32.86 %)
TNM Staging		
	T0N3M1b	1 (0.24 %)
	T1N0M1	2 (0.47 %)
	T1N1M1	1 (0.24 %)
	T1N2M1	1 (0.24 %)
	T1aN3M1b	1 (0.24 %)
	T1bN0M1b	1 (0.24 %)
	T1bN1M1b	2 (0.47 %)

	Variable/ Status	Total (N=423)
	T1bN2M1b	1 (0.24 %)
	T1bN3M1b	1 (0.24 %)
	T1bNUnknownMUnknown	1 (0.24 %)
	T2N0M1a	2 (0.47 %)
	T2N0M1b	2 (0.47 %)
	T2N1M1	1 (0.24 %)
	T2N1M1a	1 (0.24 %)
	T2N2M1	1 (0.24 %)
	T2N3M0	1 (0.24 %)
	T2N3M1a	2 (0.47 %)
	T2N3M1b	3 (0.71 %)
	T2aN2M1b	3 (0.71 %)
	T2aN3M1a	1 (0.24 %)
	T2aN3M1b	2 (0.47 %)
	T2bN2M1a	1 (0.24 %)
	T2bN3M1b	2 (0.47 %)
	T3N0M1b	2 (0.47 %)
	T3N2M1	1 (0.24 %)
	T3N2M1a	1 (0.24 %)
	T3N2M1b	2 (0.47 %)
	T3N2Mx	1 (0.24 %)
	T3N3M1	2 (0.47 %)
	T3N3M1b	6 (1.42 %)
	T4N0M1	1 (0.24 %)
	T4N0M1a	2 (0.47 %)
	T4N0M1b	3 (0.71 %)
	T4N1M1	4 (0.95 %)
	T4N1M1a	1 (0.24 %)
	T4N1M1b	1 (0.24 %)
	T4N2M0	1 (0.24 %)
	T4N2M1	7 (1.65 %)
	T4N2M1a	6 (1.42 %)
	T4N2M1b	4 (0.95 %)
	T4N3M0	2 (0.47 %)
	T4N3M1	8 (1.89 %)
	T4N3M1a	7 (1.65 %)
	T4N3M1b	22 (5.20 %)
	T4NUnknownM1a	1 (0.24 %)
	T4NxM1b	1 (0.24 %)
	TUnknownN1M0	1 (0.24 %)
	TUnknownNUnknownM1	4 (0.95 %)
	TUnknownNUnknownM1a	2 (0.47 %)
	TUnknownNUnknownM1b	6 (1.42 %)
	TUnknownNUnknownMUnknown	92 (21.75 %)
	Not Done	198 (46.81 %)
Tumor Sites*		
	Lung	213 (50.35 %)
	Liver	32 (7.57 %)
	Lymph node	93 (21.99 %)
	Skin	1 (0.24 %)
	Bone	111 (26.24 %)
	Head and Neck	1 (0.24 %)

	Variable/ Status	Total (N=423)
	Adrenal	7 (1.65 %)
	Brain	80 (18.91 %)
	Pleura effusion/seeding	51 (12.06 %)
	Other**	10 (2.36 %)
Comorbidity Burden by System		
	Cardiovascular System	
	Yes	132 (31.21 %)
	No	291 (68.79 %)
	Respiratory System	
	Yes	31 (7.33 %)
	No	392 (92.67 %)
	Gastrointestinal System	
	Yes	59 (13.95 %)
	No	364 (86.05 %)
	Renal System	
	Yes	13 (3.07 %)
	No	410 (96.93 %)
	Endocrine System	
	Yes	59 (13.95 %)
	No	364 (86.05 %)
	Neurological System	
	Yes	5 (1.18 %)
	No	418 (98.82 %)
	Rheumatologic	
	Yes	10 (2.36 %)
	No	413 (97.64 %)
	Immunological System	
	Yes	2 (0.47 %)
	No	421 (99.53 %)
	Malignancy	
	Yes	21 (4.96 %)
	No	402 (95.04 %)
	Body Weight	
	Yes	11 (2.60 %)
	No	412 (97.40 %)
Comorbidity Burden by Sub-Item in Each System		
	Cardiovascular System	
	Coronary Artery Disease (CAD)	11 (2.60 %)
	Congestive Heart Failure (CHF)	2 (0.47 %)
	Arrhythmias	5 (1.18 %)
	Hypertension	120 (28.37 %)
	Cardiomegaly	1 (0.24 %)
	Hypertensive Heart Disease	1 (0.24 %)
	Incomplete right bundle branch block	1 (0.24 %)
	Mitral valve regurgitation	1 (0.24 %)
	Other forms of angina pectoris	1 (0.24 %)
	Paroxysmal Atrial fibrillation	1 (0.24 %)
	Paroxysmal atrial fibrillation	1 (0.24 %)
	Subclavian vein thrombosis	1 (0.24 %)
	Unspecified Atrial fibillation	1 (0.24 %)
	Valvular heart disease	1 (0.24 %)

Variable/ Status	Total (N=423)
atrial fibrillation	1 (0.24 %)
Respiratory System	
Chronic Obstructive Pulmonary Disease (COPD)	14 (3.31 %)
Asthma	6 (1.42 %)
Tuberculosis	2 (0.47 %)
Bronchiectasis	1 (0.24 %)
Bronchitis, Allergic rhinitis	1 (0.24 %)
Chronic Sinusitis	1 (0.24 %)
Community acquired pneumonia	1 (0.24 %)
Other Pneumonia, unspecified organism	1 (0.24 %)
Pneumoconiosis	1 (0.24 %)
Upper respiratory infection	1 (0.24 %)
pneumonia	1 (0.24 %)
pulmonary embolism	1 (0.24 %)
Allergic Rhinitis	2 (0.47 %)
Gastrointestinal System	
Hepatitis B	30 (7.09 %)
Hepatitis C	5 (1.18 %)
Anti-viral agent	4 (0.95 %)
Alcoholic fatty liver	1 (0.24 %)
Alcoholic fatty liver disease	1 (0.24 %)
Chronic Gastric Ulcer without hemorrhage	1 (0.24 %)
Chronic Peptic Ulcer	1 (0.24 %)
Chronic hepatitis	1 (0.24 %)
Duodenitis without Bleeding	1 (0.24 %)
Fatty liver	1 (0.24 %)
Gastric ulcer	1 (0.24 %)
Gastro-Esophageal Reflux	1 (0.24 %)
Gastro-Esophageal Reflux disease	1 (0.24 %)
Gastro-Esophageal Reflux disease with Esophagitis	1 (0.24 %)
Hepatic hemangioma	1 (0.24 %)
Hepatitis C virus carrier	1 (0.24 %)
Liver function impairment	1 (0.24 %)
Peptic ulcer	1 (0.24 %)
colon perforation	1 (0.24 %)
gastric ulcer	1 (0.24 %)
Gastroesophageal reflux disease	3 (0.71 %)
Hepatitis B virus carrier	3 (0.71 %)
Renal System	
Chronic kidney disease	1 (0.24 %)
Chronic kidney disease stage IV	1 (0.24 %)
Hydronephrosis	1 (0.24 %)
Iatrogenic ureteral injury with ureteral stricture, lower third, right s/p Percutaneous Nephrostomy	1 (0.24 %)
Right renal angiomyolipoma	1 (0.24 %)
Urinary tract infection	1 (0.24 %)
chronic kidney disease stage III-IV	1 (0.24 %)
Chronic Renal Insufficiency	6 (1.42 %)
Endocrine System	
Diabetes Mellitus	47 (11.11 %)
Goiter	1 (0.24 %)
Hypercholesterolemia	1 (0.24 %)
Hyperthyroidism	1 (0.24 %)

	Variable/ Status	Total (N=423)
	Hypokalemia	1 (0.24 %)
	Iron deficiency anemia	1 (0.24 %)
	hypothyroidism	1 (0.24 %)
	Thyroid goiter	3 (0.71 %)
	Hyperlipidemia	8 (1.89 %)
	Neurological System	
	Stroke	1 (0.24 %)
	Dizziness	1 (0.24 %)
	Parkinsonism	1 (0.24 %)
	Parkinsonism senile tremor	1 (0.24 %)
	Trigeminal neuralgia	1 (0.24 %)
	Rheumatologic	
	Rheumatoid Arthritis	3 (0.71 %)
	Gout	1 (0.24 %)
	Gouty arthritis	1 (0.24 %)
	Multinodular goiter	1 (0.24 %)
	gouty arthritis	1 (0.24 %)
	Osteoarthritis	3 (0.71 %)
	Immunological System	
	Antiphospholipid syndrome	1 (0.24 %)
	herpes zoster	1 (0.24 %)
	Malignancy	
	Adenocarcinoma of sigmoid colon, T3N0M0, stage II, Dukes' B s/p op (93/4/14)	1 (0.24 %)
	Cervix cancer	1 (0.24 %)
	Invasive ductal carcinoma of left breast	1 (0.24 %)
	Non-Hodgkin Lymphoma, unspecified	1 (0.24 %)
	Oral cancer	1 (0.24 %)
	Prostate cancer	1 (0.24 %)
	Squamous cell carcinoma of cervix, stage pT1aN0M0 s/p radical hysterectomy	1 (0.24 %)
	Thyroid cancer	1 (0.24 %)
	Thyroid cancer(rT4aN1bMx stage IVa)	1 (0.24 %)
	Thyroid papillary microcarcinoma	1 (0.24 %)
	breast cancer	1 (0.24 %)
	Breast cancer	2 (0.47 %)
	Cervical cancer	2 (0.47 %)
	Hepatocellular carcinoma	2 (0.47 %)
	Nasopharyngeal carcinoma	2 (0.47 %)
	thyroid cancer	2 (0.47 %)
	Body Weight	
	Obesity	10 (2.36 %)
	Cachexia	1 (0.24 %)
Body Weight (kg)		
	n	321
	Mean (SD)	56.16 (11.603)
	Median (min, max)	54.60 (30, 103)
	Number of Missing	102
Body Height (cm)		
	n	311
	Mean (SD)	158.12 (8.320)

	Variable/ Status	Total (N=423)
	Median (min, max)	158.00 (134, 185)
	Number of Missing	112
ECOG Performance Status		
	0 - Normal activity	43 (20.19 %)
	1 - Symptoms, but ambulatory	127 (59.62 %)
	2 - In bed <50% of the time	29 (13.62 %)
	3 - In bed >50% of the time	12 (5.63 %)
	4 - 100% bedridden	2 (0.94 %)
	Number of Missing	210

Note:
*Sum of the percentage for tumor sites is over 100% due to multiple choices.
**Other tumor sites include leptomeningeal metastasis, pericardium, pericardial effusion, ascites, kidney, right supraclavicular fossa nodal metastasis, left cervical lymph node, pericardial, spine, and spleen.
[Baseline characteristic was defined as data collection when AZD9291 initiated.]
[Age in baseline table was calculated as the year of AZD9291 initiated minus the year of birth.]
["Other" was summarized with the actual terms in the table for comorbidity burden by sub-item in each system.]
[0 - Normal activity: fully active, able to carry on all pre-disease performance without restriction]
[1 - Symptoms, but ambulatory: restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)]
[2 - In bed < 50% of the time: ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours]
[3 - In bed > 50% of the time: capable of only limited self-care, confined to bed or chair more than 50% of waking hours]
[4 - 100% bedridden: completely disabled. Cannot carry on any self-care. Totally confined to bed or chair]
Source: Appendices 16.2.4.1, 16.2.4.3.1, 16.2.4.3.2, 16.2.4.3.3, 16.2.4.4, and 16.2.4.7

6.2.3 Primary Endpoint Analysis

The primary endpoint was to determine the PFS. Of 423 subjects enrolled, 4 subjects (T01-010, T02-068, T09-022, and T09-046) were excluded from the analysis of PFS for the reasons listed below.

For subject T01-010, the survival status was unknown at study initiation. Because neither the record of tumor assessment after the initiation of AZD9291 treatment nor the date of last contact was available, this subject was then excluded from the analysis of PFS.

For subjects T02-068, T09-022, and T09-046, they were alive at study initiation. However, because there were no records of tumor assessment after the initiation of AZD9291 treatment, these subjects were then excluded from the analysis of PFS.

Of the remaining 419 subjects who had PFS data available after receiving the first dose of AZD9291, 363 subjects (86.63%) had PD or died during the study period. The median PFS was 10.5 months (95% CI: 8.95, 11.41) and was approximately equivalent to 320.0 days (95% CI: 273.00, 348.00).

The summary results of PFS can be referred to Table 3. The plot of PFS by months is presented in Figure 1.

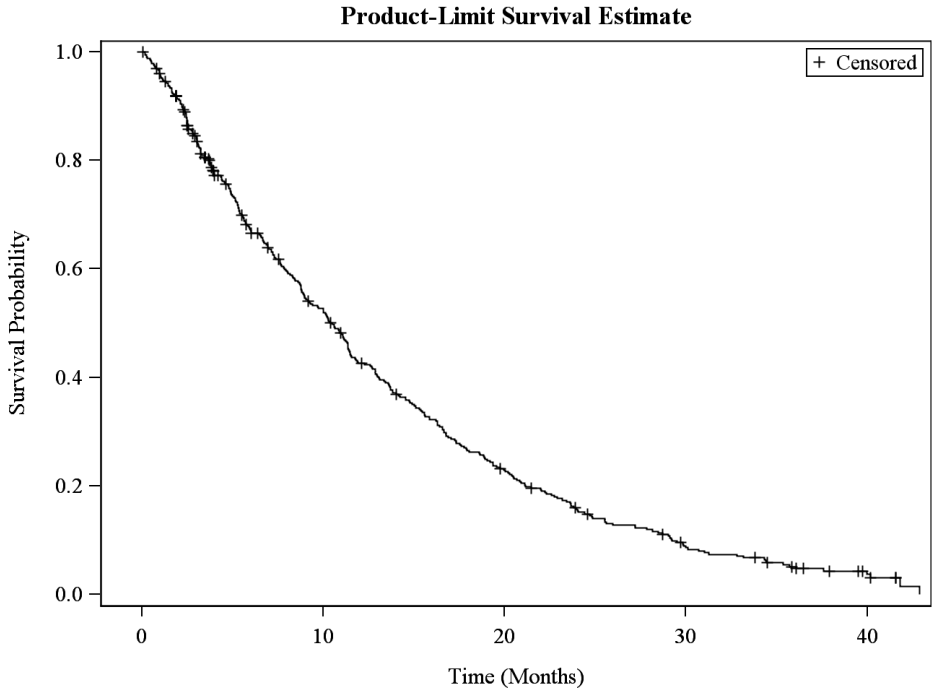
Detailed listing of survival status and AZD9291 administration record can be referred to Appendices 16.2.1.1 and 16.2.5, respectively. Detailed listing of tumor assessment can be referred to Appendix 16.2.6.4.3.

Table 3: Summary of Progression Free Survival to Date of Progressive Disease or Death (FAS Population)

Variable/ Status	FAS Population (N=423)
Progression Free Survival (PFS)	
Total Number	419
Event Number (%)	363 (86.63 %)
Median Time (95% CI) (Months)	10.5 (8.95, 11.41)
Median Time (95% CI) (Days)	320.0 (273.00, 348.00)

Note:
[Progression free survival (PFS) was defined as the time interval (in days and in months) from the date of the first dose of AZD9291 to the date of PD by the investigators' assessments or to the date of death from any cause.]
[Event was defined as PD or death, whenever came the first.]
[4 subjects with missing data for PFS: T01-010, T02-068, T09-022, and T09-046.]
Source: Appendices 16.2.1.1, 16.2.5, and 16.2.6.4.3

Figure 1: Progressive Free Survival over Time (by Months)



Note:
[Progression-free survival (PFS) was defined as the time interval from the date of the first dose of AZD9291 to the date of PD by the investigators' assessments or to the date of death from any cause, whenever came the first.]

6.2.4 Secondary Endpoints Analyses

6.2.4.1 Progressive Free Survival

Of 423 subjects enrolled, 4 subjects (T01-010, T02-068, T09-022, and T09-046) were excluded from the analysis of PFS as mentioned in the primary endpoint (Section 6.2.3). The remaining 419 subjects were included in the analysis of this endpoint.

Of the 419 subjects, 172 subjects (41.05%) had a progression event and 52 subjects (12.41%) had a death event by the 12th month; 195 subjects (46.54%) were progression-free. The Kaplan-Meier estimated of PFS rate at the 12th month was 42.58% (95% CI: 37.59, 47.48).

Of the 419 subjects, 214 subjects (51.07%) had a progression event and 69 subjects (16.47%) had a death event by the 18th month; 136 subjects (32.46%) were progression-free. The Kaplan-Meier estimated of PFS rate at the 18th month was 26.50% (95% CI: 22.14, 31.05).

The summary results of PFS at the 12th and 18th month after receiving the first dose of AZD9291 are presented in Table 4.

Detailed listing of survival status and study drug administration can be referred to Appendices 16.2.1.1 and 16.2.5, respectively. Detailed listing of tumor assessment can be referred to Appendix 16.2.6.4.3.

Table 4: Summary of Progression Free Survival (FAS Population)

FAS Population (N=423)								
			Event Details					
Treatment Population	Number of Subjects	Event N (%)	Progression N (%)	Death N (%)	Proportion event-free N (%)	Median (95% CI) (Months)	Median (95% CI) (Days)	PFS Rate (95% CI) (%)
12th Month After the First Dose of AZD9291	419	224 (53.46)	172 (41.05)	52 (12.41)	195 (46.54)	10.5 (8.95, 11.41)	320.0 (273.00, 348.00)	42.58 (37.59, 47.48)
18th Month After the First Dose of AZD9291	419	283 (67.54)	214 (51.07)	69 (16.47)	136 (32.46)	10.5 (8.95, 11.41)	320.0 (273.00, 348.00)	26.50 (22.14, 31.05)

Note:
[Progression free survival (PFS) was defined as the time interval (in days and in months) from the date of the first dose of AZD9291 to the date of PD by the investigators' assessments or to the date of death from any cause.]
[Event was defined as PD or death, whenever comes first.]
[4 subjects with missing data for PFS: T01-010, T02-068, T09-022, and T09-046.]
Source: Appendices 16.2.1.1, 16.2.5, and 16.2.6.4.3

6.2.4.2 Overall Survival

Of the 422 subjects included for OS analysis, 296 subjects (70.14%) had death events during the study period and 126 subjects were censored. The Kaplan-Meier estimated median OS was 19.0 months (95% CI: 16.30, 20.95) and was approximately equivalent to 579.0 days (95% CI: 497.00, 639.00).

Notably, subject T01-010 was excluded from the analysis of OS. The survival status of subject T01-010 was unknown at study initiation. Because neither the record of tumor assessment after the initiation of AZD9291 treatment nor the date of the last contact was available, this subject was then excluded from the analysis of OS. Thus, only 422 subjects were included in the analysis of this endpoint.

The summary results of OS can be referred to Table 5. The plot of OS presented by months can be referred to Figure 2.

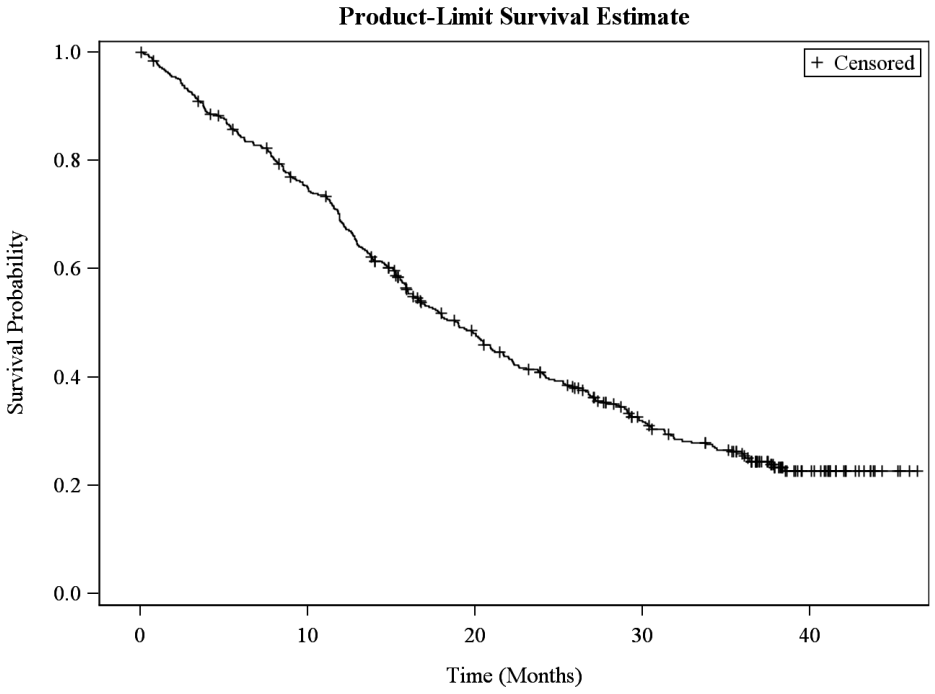
Detailed listing of survival status and study drug administration can be referred to Appendices 16.2.1.1 and 16.2.5, respectively.

Table 5: Summary of Overall Survival (FAS Population)

	Variable/ Status	FAS Population (N=423)
Overall Survival (OS)		
	Total Number	422
	Number of Deaths (%)	296 (70.14 %)
	Median Time (95% CI) (Months)	19.0 (16.30, 20.95)
	Median Time (95% CI) (Days)	579.0 (497.00, 639.00)

Note:
[Overall survival (OS) was defined as the time interval (in days and in months) from the date of the first dose of AZD9291 until the date of death due to any cause.]
[Event was defined as death.]
[1 subject with missing data for OS: T01-010.]
Source: Appendices 16.2.1.1 and 16.2.5

Figure 2: Overall Survival over Time (by Months)



Note:
[Overall survival (OS) was defined as the tine interval from the date of the first dose of AZD9291 until the date of death due to any cause.]

Of the 422 subjects, 199 subjects (47.16%) had death events by the 18th month and 223 subjects (52.84%) were censored. The Kaplan-Meier estimated OS rate at the 18th month was 51.51% (95% CI: 46.54, 56.24).

Of the 422 subjects, 239 subjects (56.64%) had death events by the 24th month and 183 subjects (43.36%) were censored. The Kaplan-Meier estimated OS rate at the 24th month was 40.90% (95% CI: 36.04, 45.70).

The summary results of OS at the 18th and 24th month after receiving the first dose of AZD9291 are presented in Table 6. Detailed listing of survival status and study drug administration can be referred to Appendices 16.2.1.1 and 16.2.5, respectively.

Table 6: Summary of Overall Survival (FAS Population)

FAS Population (N=423)						
Treatment Population	**Number of Subjects**	**Event (Death) N (%)**	**Without Event N (%)**	**Median (95% CI) (Months)**	**Median (95% CI) (Days)**	**OS Rate (95% CI) (%)**
OS at 18 Months	422	199 (47.16)	223 (52.84)	- (16.30, -)	- (497.00, -)	51.51 (46.54, 56.24)
OS at 24 Months	422	239 (56.64)	183 (43.36)	19.0 (16.30, 20.95)	579.0 (497.00, 639.00)	40.90 (36.04, 45.70)

Note:
[Overall survival (OS) was defined as the time interval (in days and in months) from the date of the first dose of AZD9291 until the date of death due to any cause.]
[Event was defined as death.]
[1 subject with missing data for OS: T01-010.]
Source: Appendices 16.2.1.1 and 16.2.5

6.2.4.3 Time to Treatment Discontinuation

Of the 399 subjects included in TTD analysis, 326 subjects (81.70%) discontinued from AZD9291 monotherapy during the study period and 73 subjects (18.30%) were censored. The Kaplan-Meier estimated median TTD was 11.9 months (95% CI: 10.49, 13.11) and was approximately equivalent to 363.0 days (95% CI: 320.00, 400.00).

Notably, of 423 subjects enrolled, 24 subjects (T01-016, T01-029, T01-032, T01-035, T01-065, T01-074, T02-024, T02-025, T02-026, T02-027, T02-028, T02-029, T02-030, T02-031, T02-074, T02-082, T02-085, T03-004, T04-037, T06-028, T09-015, T09-016, T09-043, and T09-048) were excluded from the analysis of TTD for the reasons listed below.

Subject T03-004 was excluded because the date of receiving the first dose of AZD9291 monotherapy was the same as the date of initiating the other treatment (vinorelbine on 22-Nov-2016). Thus, no record of receiving AZD9291 as monotherapy was available for this subject. The other 23 subjects were excluded because no ending date of receiving AZD9291 treatment was available resulted from unknown date of death or unknown living status. The remaining 399 subjects were included in the analysis of this endpoint.

The summary results of time to AZD9291 monotherapy discontinuation are presented in Table 7. The plot of time to AZD9291 monotherapy discontinuation presented by months is in Figure 3.

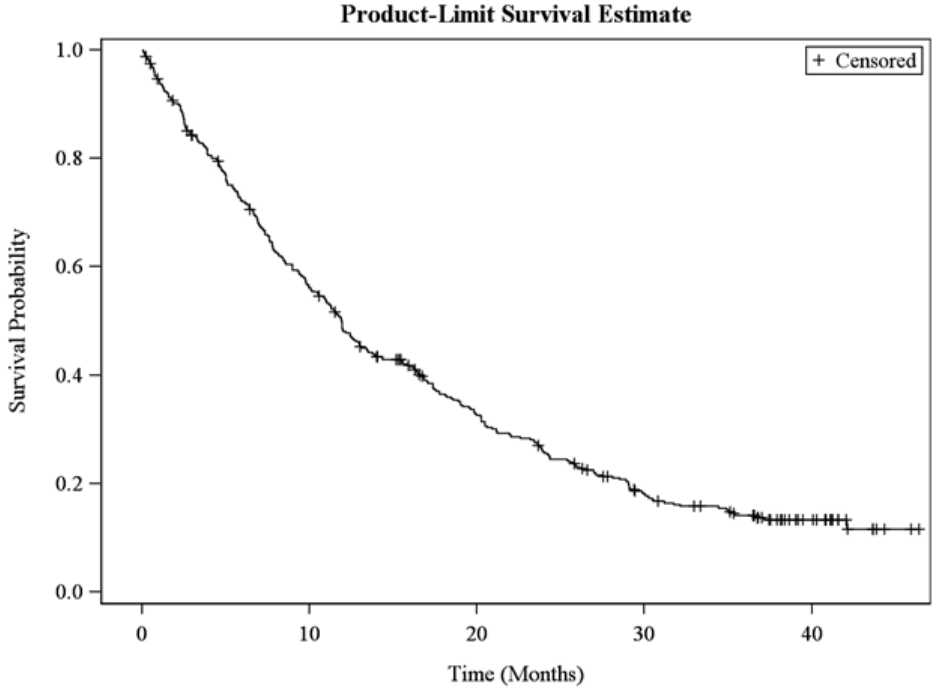
Detailed listing of study drug administration and systemic regimens received after the first dose of AZD9291 can be referred to Appendices 16.2.5 and 16.2.6.3.2, respectively.

Table 7: Summary of Time to AZD9291 Monotherapy Discontinuation (FAS Population)

Variable/ Status	FAS Population (N=423)
Time to AZD9291 Monotherapy Discontinuation	
Total Number	399
Event Number (%)	326 (81.70 %)
Censored Number (%)	73 (18.30 %)
Median Time (95% CI) (Months)	11.9 (10.49, 13.11)
Median Time (95% CI) (Days)	363.0 (320.00, 400.00)

Note:
[Time to AZD9291 monotherapy discontinuation was defined as the time interval (in days and months) from the date of the first dose of AZD9291 monotherapy until the date of the discontinuation of AZD9291 monotherapy for any reason.]
[Event was defined as AZD9291 monotherapy discontinuation for any reason.]
[24 subjects with missing data for time to AZD9291 monotherapy discontinuation: T01-016, T01-029, T01-032, T01-035, T01-065, T01-074, T02-024, T02-025, T02-026, T02-027, T02-028, T02-029, T02-030, T02-031, T02-074, T02-082, T02-085, T03-004, T04-037, T06-028, T09-015, T09-016, T09-043, and T09-048.]
Source: Appendices 16.2.5 and 16.2.6.3.2

Figure 3: Time to AZD9291 Monotherapy Discontinuation over Time (by Months)



Note:
[Time to AZD9291 monotherapy discontinuation was defined as the time interval (in days and months) from the date of the first dose of AZD9291 monotherapy until the date of the discontinuation of AZD9291 monotherapy for any reason.]

6.2.4.4 Last NSCLC Therapy and the Clinical Outcome just before the First Dose of AZD9291

The last NSCLC therapies (excluding those administered as temporary treatment, adjuvant therapy, or add-on therapy) prior to receiving the first dose of AZD9291 were categorized into EGFR TKI therapy, chemotherapy, other systemic therapy, radiation therapy for brain metastasis, and combined therapy. The sum of last NSCLC therapies is more than 100% because multiple counting in one subject was applied for this analysis.

Last NSCLC therapy just before receiving the first dose of AZD9291

- EGFR TKI therapy

Of 423 subjects enrolled, 95 subjects (22.46%) received erlotinib, 55 subjects (13%) received afatinib, 52 subjects (12.29%) received gefitinib, 8 subjects (1.89%) received other EGFR TKI therapy, and 5 subjects (1.18%) received other 3rd generation EGFR TKI therapy (including nazartinib/EGFR816, olmutinib/HM61713, naquotinib, and rociletinib), as the last NSCLC treatment just before receiving the first dose of AZD9291.

- Chemotherapy

Carboplatin or cisplatin were grouped as platinum-based therapies. Docetaxel, nab-paclitaxel, and paclitaxel were grouped as taxane-based therapies. In addition, the combination of platinum- or taxane-based therapy with other chemotherapy was included in the category of "platinum or taxanes based therapy".

Of 423 subjects enrolled, 126 subjects (29.79%) received platinum- or taxane-based therapy, and 154 subjects (36.41%) received other chemotherapy as the last NSCLC treatment just before receiving the first dose of AZD9291.

- Other systemic therapy

Of 423 subjects enrolled, 17 subjects (4.02%) received bevacizumab, 7 subjects (1.65%) received nivolumab, and 4 subjects (0.95%) received pembrolizumab as the last NSCLC treatment just before receiving the first dose of AZD9291.

In addition, 1 or 2 subjects had received each of the following systemic therapies as the last NSCLC treatment just before receiving the first dose of AZD9291: crizotinib, capmatinib (INC280), selumetinib, AUY922, bavituximab, biotherapy, ramucirumab, and sunitinib.

Notably, there was 1 subject (0.24%) participating in other clinical trial to receive other systemic therapy without specified name just before receiving the first dose of AZD9291.

- Radiation therapy for brain metastasis

Of 423 subjects enrolled, 72 subjects (17.02%) with brain metastasis received radiation alone, and 31 subjects (7.33%) with brain metastasis received radiation combined with systemic therapy as the last NSCLC treatment just before receiving the first dose of AZD9291.

- Combined therapy

Of 423 subjects enrolled, 10 subjects (2.36%) received EGFR TKI combined with chemotherapy, 11 subjects (2.60%) received EGFR TKI combined with other systemic therapy, and 14 subjects (3.31%) received chemotherapy combined with other systemic therapy as the last NSCLC treatment just before receiving the first dose of AZD9291.

Clinical outcome of the last NSCLC therapy before the first dose of AZD9291

Of 423 subjects enrolled, the data of clinical outcome were missing in 27 subjects. Of the remaining 396 subjects, the response assessment of the last NSCLC therapy were PR in 1 subject (0.25%), SD in 51 subjects (12.88%), PD in 306 subjects (77.27%), NE in 26 subjects (6.57%), and not applicable (N/A) in 12 subjects (3.03%) just before receiving the first dose of AZD9291.

The summary results of the last NSCLC therapy and the clinical outcome just before receiving the first dose of AZD9291 are presented in Table 8.

Detailed listing can be referred to Appendix 16.2.4.6 for radiation therapy for brain metastasis of NSCLC received prior to receiving the first dose of AZD9291; and Appendix 16.2.6.3.1 for systemic regimens received prior to receiving the first dose of AZD9291. Detailed listing for the tumor assessment at the initiation of AZD9291 can be referred to Appendix 16.2.6.4.1.

Table 8: Summary of Last NSCLC Therapy and the Clinical Outcome just before the First Dose of AZD9291 (FAS Population)

Variable/ Status	FAS Population (N=423)
Last NSCLC Therapy Before the First Dose of AZD9291 Administration	
EGFR TKI therapy	
Afatinib	55 (13 %)
Erlotinib	95 (22.46 %)
Gefitinib	52 (12.29 %)
Other EGFR TKI therapy	8 (1.89 %)
Other 3G EGFR TKI therapy [1]	5 (1.18 %)
Chemotherapy	
Platinum or taxanes based therapy [2]	126 (29.79 %)
Other chemotherapy	154 (36.41 %)
Other systemic therapy [3]	
Bevacizumab	17 (4.02 %)
Nivolumab	7 (1.65 %)
Pembrolizumab	4 (0.95 %)

Variable/ Status	FAS Population (N=423)
Crizotinib	1 (0.24 %)
Capmatinib (INC280)	1 (0.24 %)
Selumetinib	1 (0.24 %)
AUY922	1 (0.24 %)
Bavituximab	1 (0.24 %)
Biotherapy	1 (0.24 %)
Ramucirumab	1 (0.24 %)
Selumetinib	1 (0.24 %)
Sunitinib	1 (0.24 %)
Clinical Trial	1 (0.24 %)
Radiation therapy for brain metastasis [4]	
Radiation alone	72 (17.02 %)
Radiation combined with systemic therapy [5]	31 (7.33 %)
Combined therapy	
EGFR TKI combined with chemotherapy	10 (2.36 %)
EGFR TKI combined with other systemic therapy	11 (2.60 %)
Chemotherapy combined with other systemic therapy	14 (3.31 %)
Clinical Outcome Before the First Dose of AZD9291 Administration	
Partial Response (PR)	1 (0.25 %)
Stable Disease (SD)	51 (12.88 %)
Progression Disease (PD)	306 (77.27 %)
Not Evaluable (NE)	26 (6.57 %)
N/A	12 (3.03 %)
Number of Missing	27

Note:
[1] Other 3G EGFR TKI therapy = other third generation EGFR TKI therapy. Other 3G EGFR TKI therapy includes nazartinib/EGF816, olmutinib/HM61713, naquotinib and rociletinib.
[2] Platinum-based therapies include carboplatin and cisplatin. Taxanes-based therapies include docetaxel, nab-paclitaxel, and paclitaxel. The combination of platinum- or taxane-based therapy with other chemotherapy was included in this category.
[3] Other systemic therapies entered in the database were summarized in the table.
[4] Sponsor requested to summarize the usage of radiation therapy for brain metastasis.
[5] Radiation therapy for brain metastasis combined with EGFR TKI, chemotherapy, or other systemic therapy were included in this category.
[Excluded therapies of temporary, adjuvant or add-on and selected the last number line of therapy for analysis]
Source: Appendices 16.2.4.6, 16.2.6.3.1, and 16.2.6.4.1

6.2.4.5 Rationale for the Use of AZD9291 over Other NSCLC Treatments at EAP Enrollment

Of 423 subjects enrolled, 401 subjects (94.80%) participated in the EAP due to lack of efficacy for the last NSCLC therapy, 16 subjects (3.78%) participated in the EAP because of the incidence of AE resulting from existing treatment, and 6 subjects (1.42%) participated in the EAP because of other reasons [including general weakness, EGFR T790M positive, available of AZD9291, subject was too weak (performance status was 3), from study change to EAP, and cost-free].

The summary results of rationale for the use of AZD9291 over other NSCLC treatments at EAP enrollment are presented in Table 9. Detailed listing of rationale for the use of AZD9291 can be referred to Appendix 16.2.6.2.

Table 9: Summary of Rationale for the Use of AZD9291 over Other NSCLC Treatments at EAP Enrollment (FAS Population)

	Variable/ Status	FAS Population (N=423)
Rationale for the Use of AZD9291		
	Lack of efficacy	401 (94.80 %)
	Adverse event of existing treatment	16 (3.78 %)
	Other	6 (1.42 %)

Source: Appendix 16.2.6.2

6.2.4.6 Type of Test Performed for the Confirmation of Acquired EGFR T790M Mutation

Of 423 subjects enrolled, the data of EGFR T790M mutation were missing in 6 subjects, including subjects T01-074, T01-076, T01-078, T01-084, T01-088, and T01-094. Of the remaining 417 subjects, 413 subjects had one EGFR T790M mutation test result and 4 subjects (T01-053, T03-014, T09-045, and T09-050) had two EGFR T790M mutation test results. Therefore, a total of 421 EGFR T790M mutation test results from 417 subjects were included in this analysis.

Sample type

Of the 421 EGFR T790M mutation test results collected in this study, 153 test results (36.34%) were from plasma-based samples, 187 test results (44.42%) were from tissue biopsy, and 53 test results (12.59%) were from cytological samples. The sample types from 28 test results (6.65%) were unknown.

Test platform

Of the 421 EGFR T790M mutation test results collected in this study, the test platforms in 49 test results (11.64%) were unknown. Of the remaining 372 test results, the test platforms included COBAS EGFR mutation test, Therascreen test [including Scorpions & ARMS (Amplification Refractory Mutation System) and EGFR RGQ PCR], BEAMing digital PCR assay (BEAMing), LDT, NGS, MassARRAY genotyping (MassARRAY), competitive allele-specific TaqMan polymerase chain reaction, dPCR, PCR based method, real-time PCR mutation analysis, and cell-free DNA (cfDNA).

The most common (>100 test results) test platforms used for detecting EGFR T790M mutation were MassARRAY (31.61% in all forms) and COBAS EGFR mutation test (30.17%).

The summary results of sample type and type of test performed for the confirmation of acquired EGFR T790M mutation are presented in Table 10. Detailed listing of EGFR T790M positive mutation can be referred to Appendix 16.2.6.1.

Table 10: Summary of Type of Test Performed for the Confirmation of Acquired EGFR T790M Mutation (FAS Population)

	Variable/ Status	FAS Population (N=423/E=421)
Sample Type		
	Plasma-based test	153 (36.34 %)
	Tissue biopsy	187 (44.42 %)
	Cytology	53 (12.59 %)
	Unknown	28 (6.65 %)
	Dissection	0 (0 %)
	Serum	0 (0 %)
	Number of Missing	6
Test Platform		
	cobas EGFR Mutation Test	127 (30.17 %)
	Therascreen test	1 (0.24 %)
	BEAMing dPCR assay	25 (5.94 %)
	Lab developed tests	21 (4.99 %)
	Next generation sequencing	4 (0.95 %)
	Unknown	49 (11.64 %)
	Competitive allele-Specific TaqMan ploymerase chain reaction	1 (0.24 %)
	Competitive allele-specific TaqMan Polymerase Chain reaction	1 (0.24 %)
	Competitive allele-specific TaqMan polymerase chain reaction	4 (0.95 %)
	Digital PCR	1 (0.24 %)
	EGFR RGQ PCR	1 (0.24 %)
	EGFR RGQ PCR kit (Qiagene)	1 (0.24 %)
	MassARRAY	21 (4.99 %)
	MassARRAY genotyping (SEQUENOM)	1 (0.24 %)
	MassARRAY genotyping (SEQUENOM)	29 (6.89 %)
	MassARRAY genotyping(	1 (0.24 %)
	MassARRAY genotyping(SEQUENOM	6 (1.43 %)
	MassARRAY genotyping(SEQUENOM)	5 (1.19 %)
	MassARRY genotyping (SEQUENOM)	4 (0.95 %)
	Massarray	66 (15.68 %)
	PCR-based method	16 (3.80 %)
	QIAGEN EGFR RGO PCR KIT	12 (2.85 %)
	Real-Time PCR Mutation analysis	1 (0.24 %)
	Real-Time PCR mutation analysis	4 (0.95 %)
	Scorpions & ARMS	1 (0.24 %)
	Scorpions & ARMS (Amplification Refractory Mutation System)	7 (1.66 %)
	Scorpions & ARMS(Amplification Refractory Mutation System)	5 (1.19 %)
	Scorpions&ARMS(Amplification Refractory Mutation System)	3 (0.71 %)
	cfDNA	1 (0.24 %)
	digital PCR(Bio-rad)	1 (0.24 %)
	Qiagen	1 (0.24 %)
	Number of Missing	6

	Variable/ Status	FAS Population (N=423/E=421)
Note:		
["Other" was summarized with the actual terms in the table.]		
[Percentage = 100%*[The number of event(s) in the category / The number of event(s) which overall testing time in the study (E)]]		
[No EGFR T790M mutation data for subjects T01-074, T01-076, T01-078, T01-084, T01-088 and T01-094.]		
[According to NTF dated on 2020-07-29, sample type for subject T04-013 should be corrected from 'Other: dissection' to 'Tissue biopsy'.]		
[According to NTF dated on 2020-08-04, sample type for subject T10-001 should be corrected from 'Other: serum' to 'Unknown'.]		
[Based on above NTF, the actual count and percentage for tissue biopsy and unknown should be 187 (44.42 %) and 28 (6.65 %), respectively.]		
[The actual count and percentage for dissection and serum should be 0 (0 %).]		
Source: Appendix 16.2.6.1		

Test platform summarized by category A

The types of test performed to confirm the acquired EGFR T790M mutation were re-categorized using category A (by real-time PCR, MassARRAY, NGS, BEAMing / ddPCR, and others / unknown).

Of the 421 EGFR T790M mutation test results collected in this study, 186 test results (44.18%) were from real-time PCR, 133 test results (31.59%) were from MassARRAY, 27 test results (6.41%) were from BEAMing / ddPCR, and 4 test results (0.95%) were from NGS. In addition, 71 test results (16.86%) were from other platforms or the test platforms used were unknown.

The summary results of sample and types of test to confirm the acquired EGFR T790M mutation by new category A are presented in Table 11. Detailed listing of EGFR T790M positive mutation can be referred to Appendix 16.2.6.1.

Table 11: Summary of Type of Test Performed for the Confirmation of Acquired EGFR T790M Mutation by New Category A (FAS Population)

Variable/ Status	FAS Population (N=423/E=421)
Sample Type	
Plasma-based test	153 (36.34 %)
Tissue biopsy	187 (44.42 %)
Cytology	53 (12.59 %)
Unknown	28 (6.65 %)
Dissection	0 (0 %)
Serum	0 (0 %)
Number of Missing	6
Test Platform	
real-time PCR	186 (44.18 %)
MassARRAY	133 (31.59 %)
NGS	4 (0.95 %)
BEAMing / ddPCR	27 (6.41 %)
others / unknown	71 (16.86 %)
Number of Missing	6

Note:
["Other" was summarized with the actual terms in the table for Sample Type.]
[Percentage = 100%*[The number of event(s) in the category / The number of event(s) which overall testing time in the study (E)]]
[No EGFR T790M mutation data for subjects T01-074, T01-076, T01-078, T01-084, T01-088 and T01-094.]
[Test platform was summarized with test category A on the excel file 'TM_GP_Testing_v2.xls' which was provided by sponsor.]
[According to NTF dated on 2020-07-29, sample type for subject T04-013 should be corrected from 'Other: dissection' to 'Tissue biopsy'.]
[According to NTF dated on 2020-08-04, sample type for subject T10-001 should be corrected from 'Other: serum' to 'Unknown'.]
[Based on above NTF, the actual count and percentage for tissue biopsy and unknown should be 187 (44.42 %) and 28 (6.65 %), respectively.]
[The actual count and percentage for dissection and serum should be 0 (0 %).]
Source: Appendix 16.2.6.1

Test platform summarized by category B

The types of test performed to confirm the acquired EGFR T790M mutation were re-categorized using category B (by real-time PCR, LDT, and others).

Of the 421 EGFR T790M mutation test results collected in this study, 186 test results (44.18%) were from real-time PCR, 164 test results (38.95%) were from LDT, and 71 test results (16.86%) were from other platforms or the test platforms used were unknown.

The summary results of sample and types of test to confirm the acquired EGFR T790M mutation by new category B are presented in Table 12. Detailed listing of EGFR T790M positive mutation can be referred to Appendix 16.2.6.1.

Table 12: Summary of Type of Test Performed for the Confirmation of Acquired EGFR T790M Mutation by New Category B (FAS Population)

Variable/ Status	FAS Population (N=423/E=421)
Sample Type	
Plasma-based test	153 (36.34 %)
Tissue biopsy	187 (44.42 %)
Cytology	53 (12.59 %)
Unknown	28 (6.65 %)
Dissection	0 (0 %)
Serum	0 (0 %)
Number of Missing	6
Test Platform	
real-time PCR	186 (44.18 %)
LDT	164 (38.95 %)
Others	71 (16.86 %)
Number of Missing	6

Note:
["Other" was summarized with the actual terms in the table for Sample Type.]
[Percentage = 100%*[The number of event(s) in the category / The number of event(s) which overall testing time in the study (E)]]
[No EGFR T790M mutation data for subjects T01-074, T01-076, T01-078, T01-084, T01-088 and T01-094]
[Test platform was summarized with test category B on the excel file 'TM_GP_Testing_v2.xls' which provided by sponsor.]
[According to NTF dated on 2020-07-29, sample type for subject T04-013 should be corrected from 'Other: dissection' to 'Tissue biopsy'.]
[According to NTF dated on 2020-08-04, sample type for subject T10-001 should be corrected from 'Other: serum' to 'Unknown'.]
[Based on above NTF, the actual count and percentage for tissue biopsy and unknown should be 187 (44.42 %) and 28 (6.65 %), respectively.]
[The actual count and percentage for dissection and serum should be 0 (0 %).]
Source: Appendix 16.2.6.1

6.2.4.7 The Subsequent Line(s) of Systemic NSCLC Treatment on AZD9291 Monotherapy

All subsequent line(s) of systemic NSCLC treatment received after AZD9291 monotherapy were included in this analysis and categorized into with continuation of AZD9291 (combined therapy with AZD9291) and without continuation of AZD9291 treatment (including single chemotherapy, single target therapy, combined therapy without AZD9291, and others). The sum of subsequent line(s) of systemic NSCLC treatment is more than 100% because multiple counting in one subject was applied for this analysis.

The single use of afatinib, erlotinib, or gefitinib was excluded from this analysis because they were not considered as systemic treatment for NSCLC based on the National Comprehensive Cancer Network (NCCN) guidelines [15].

Of 423 subjects, only 175 subjects had received subsequent systemic treatments after discontinuation of AZD9291 monotherapy. The sum of subsequent systemic treatments is more than 100% because multiple counting in one subject applied. As a result, a total of

348 subsequent systemic treatments after discontinuation of AZD9291 monotherapy in 175 subjects were included in this analysis.

Of these 348 subsequent systemic treatments, 206 treatments (59.20%) were combined therapy with AZD9291 treatment, 97 treatments (27.87%) were single chemotherapy, 32 treatments (9.20%) were combined therapy without AZD9291 treatment, and 8 treatments (2.30%) were single target therapy. In addition, 5 treatments were other therapies without AZD9291.

Combined therapy with AZD9291

Of the 206 treatments as combined therapy with AZD9291, 31 (8.91%) were paclitaxel, 22 (6.32%) were pemetrexed, 21 (6.03%) were vinorelbine, 19 (5.46%) were gemcitabine, 16 (4.60%) were bevacizumab, 13 (3.74%) were docetaxel, 8 (2.30%) were crizotinib, 6 (1.72%) were carboplatin combined with pemetrexed, 6 (1.72%) were cisplatin combined with pemetrexed, 6 (1.72%) were cetuximab, and 6 (1.72%) were etoposide.

The frequency of the following treatments was less than 3:

- carboplatin combined with (a) cisplatin and pemetrexed, (b) gemcitabine, (c) gemcitabine and nivolumab, (d) etoposide, (e) campto, (f) paclitaxel, or (g) pemetrexed and bevacizumab;
- cisplatin combined with (a) atezolizumab and etoposide, (b) gemcitabine, (c) etoposide, (d) paclitaxel, (e) pembrolizumab, or (f) pemetrexed and bevacizumab;
- docetaxel combined with bevacizumab or ramucirumab;
- erlotinib combined with bevacizumab;
- gemcitabine combined with bevacizumab or nivolumab;
- paclitaxel combined with bevacizumab, nivolumab, or ramucirumab;
- pembrolizumab or pembrolizumab combined with etoposide
- pemetrexed combined with bevacizumab and atezolizumab;
- vinorelbine combined with bevacizumab or nivolumab;
- nivolumab, brigatinib, campto, DS1205, erbitux, methotrexate sodium, savolitinib, tegafur, topotecan, or kisqali

The remaining 142 treatment types were either single chemotherapy (27.87%) or other combined chemotherapies without AZD9291 (9.20%), or single target therapy (2.30%). In addition, 5 treatment types were immunotherapies without AZD9291.

The summary results of subsequent systemic treatment after discontinuation of AZD9291 monotherapy are presented in Table 13. Detailed listing of systemic regimens received after the first dose of AZD9291 can be referred to Appendix 16.2.6.3.2.

Table 13: Summary of Subsequent Systemic Treatment after Discontinuation of AZD9291 Monotherapy (FAS Population)

Variable/ Status	FAS Population (N=175/E=348)
Treatment Types Other than the Single Use of AZD9291	
With continuation of AZD9291	
Combined therapy with AZD9291	206 (59.20 %)
Bevacizumab	16 (4.60 %)
Carboplatin (Paraplatin), Cisplatin (Platinol), Pemetrexed (Alimta)	2 (0.57 %)
Carboplatin (Paraplatin), Gemcitabine (Gemzar)	2 (0.57 %)
Carboplatin (Paraplatin), Gemcitabine (Gemzar), Nivolumab	1 (0.29 %)
Carboplatin (Paraplatin), Other: Etoposide	3 (0.86 %)
Carboplatin (Paraplatin), Other: campto	2 (0.57 %)
Carboplatin (Paraplatin), Paclitaxel (Taxol)	2 (0.57 %)
Carboplatin (Paraplatin), Pemetrexed (Alimta)	6 (1.72 %)
Carboplatin (Paraplatin), Pemetrexed (Alimta), Bevacizumab	1 (0.29 %)
Cisplatin (Platinol), Atezolizumab, Other: Etoposide	1 (0.29 %)
Cisplatin (Platinol), Gemcitabine (Gemzar)	2 (0.57 %)
Cisplatin (Platinol), Other: Etoposide	1 (0.29 %)
Cisplatin (Platinol), Paclitaxel (Taxol)	1 (0.29 %)
Cisplatin (Platinol), Pembrolizumab	1 (0.29 %)
Cisplatin (Platinol), Pemetrexed (Alimta)	6 (1.72 %)
Cisplatin (Platinol), Pemetrexed (Alimta), Bevacizumab	1 (0.29 %)
Crizotinib	8 (2.30 %)
Docetaxel (Docefrez, Taxotere)	13 (3.74 %)
Docetaxel (Docefrez, Taxotere), Bevacizumab	1 (0.29 %)
Docetaxel (Docefrez, Taxotere), Other: Ramucirumab	1 (0.29 %)
Erlotinib, Bevacizumab	1 (0.29 %)
Gemcitabine (Gemzar)	19 (5.46 %)
Gemcitabine (Gemzar), Bevacizumab	1 (0.29 %)
Gemcitabine (Gemzar), Nivolumab	1 (0.29 %)
Nivolumab	1 (0.29 %)
Other: Brigatinib	1 (0.29 %)
Other: Campto	2 (0.57 %)
Other: Cetuximab	6 (1.72 %)
Other: DS1205,AZD9291	1 (0.29 %)
Other: Erbitux	2 (0.57 %)
Other: Etoposide	6 (1.72 %)
Other: Methotrexate Sodium	2 (0.57 %)
Other: Savolitinib	1 (0.29 %)
Other: Savolitinib (AZD6094)	1 (0.29 %)
Other: Tegafur	1 (0.29 %)
Other: Topotecan	2 (0.57 %)
Other: campto	1 (0.29 %)
Other: kisqali	1 (0.29 %)
Paclitaxel (Taxol)	31 (8.91 %)
Paclitaxel (Taxol), Bevacizumab	2 (0.57 %)
Paclitaxel (Taxol), Nivolumab	2 (0.57 %)
Paclitaxel (Taxol), Other: Ramucirumab	1 (0.29 %)
Pembrolizumab	2 (0.57 %)
Pembrolizumab, Other: Etoposide	1 (0.29 %)
Pemetrexed (Alimta)	22 (6.32 %)

Variable/ Status	FAS Population (N=175/E=348)
Pemetrexed (Alimta), Bevacizumab, Atezolizumab	1 (0.29 %)
Vinorelbine (Navelbine)	21 (6.03 %)
Vinorelbine (Navelbine), Bevacizumab	1 (0.29 %)
Vinorelbine (Navelbine), Nivolumab	1 (0.29 %)
Without continuation of AZD9291	
Single chemotherapy	97 (27.87 %)
Single target therapy	8 (2.30 %)
Combined therapy without AZD9291	32 (9.20 %)
Afatinib, Other: Cetuximab	1 (0.29 %)
Bevacizumab	1 (0.29 %)
Carboplatin (Paraplatin), Bevacizumab, Other: Etoposide	1 (0.29 %)
Carboplatin (Paraplatin), Other: Etoposide	1 (0.29 %)
Carboplatin (Paraplatin), Pemetrexed (Alimta), Bevacizumab	1 (0.29 %)
Cisplatin (Platinol), Docetaxel (Docefrez, Taxotere)	1 (0.29 %)
Cisplatin (Platinol), Other: Etoposide	1 (0.29 %)
Cisplatin (Platinol), Pemetrexed (Alimta)	2 (0.57 %)
Cisplatin (Platinol), Pemetrexed (Alimta), Bevacizumab	1 (0.29 %)
Docetaxel (Docefrez, Taxotere), Atezolizumab	1 (0.29 %)
Docetaxel (Docefrez, Taxotere), Bevacizumab	2 (0.57 %)
Docetaxel (Docefrez, Taxotere), Other: Ramucirumab	1 (0.29 %)
Docetaxel (Docefrez, Taxotere), Other: cetuximab	1 (0.29 %)
Erlotinib, Bevacizumab	1 (0.29 %)
Gemcitabine (Gemzar)	1 (0.29 %)
Gemcitabine (Gemzar), Bevacizumab	1 (0.29 %)
Gemcitabine (Gemzar), Bevacizumab, Pembrolizumab	1 (0.29 %)
Gemcitabine (Gemzar), Other: Cetuximab	1 (0.29 %)
Other: Brigatinib, Cetuximab	1 (0.29 %)
Other: Cetuximab	2 (0.57 %)
Paclitaxel (Taxol), Bevacizumab	2 (0.57 %)
Paclitaxel (Taxol), Bevacizumab, Nivolumab	1 (0.29 %)
Paclitaxel (Taxol), Other: Cetuximab	1 (0.29 %)
Paclitaxel (Taxol), Other: Ramucirumab	1 (0.29 %)
Pemetrexed (Alimta), Bevacizumab	1 (0.29 %)
Vinorelbine (Navelbine), Bevacizumab, Atezolizumab	1 (0.29 %)
Vinorelbine (Navelbine), Bevacizumab, Pembrolizumab	1 (0.29 %)
Vinorelbine (Navelbine), Other: cetuximab	1 (0.29 %)
Other: immunotherapy	2 (0.57 %)
Nivolumab	1 (0.29 %)
Pembrolizumab	1 (0.29 %)
Other: single immunotherapy	1 (0.29 %)
Atezolizumab	1 (0.29 %)
Other: single Immunotherapy	1 (0.29 %)
Atezolizumab	1 (0.29 %)
Other: single immunotherapy	1 (0.29 %)
Pembrolizumab	1 (0.29 %)

	Variable/ Status	FAS Population (N=175/E=348)

Note:
["Combined therapy" and "Other" were summarized by the detailed regimens and the actual terms, respectively, in the final report.]
[Percentage = 100%*[The number of event(s) in the category / The number of event(s) which overall subsequent systemic treatment in the study (E)]]
[The records for the single use of afatinib, erlotinib or gefitinib were not the systemic treatment for NSCLC and have been excluded from analysis.]
[According to NTF dated on 2020-03-25, Subject T02-013 used systemic regimens carboplatin (paraplatin), paclitaxel (taxol) from 2017-02-20 to 2017-09-06 should be corrected from single chemotherapy to combined therapy with AZD9291.]
[According to NTF dated on 2020-03-25, Subject T02-058 used systemic regimens cisplatin (platinol), gemcitabine (gemzar) from 2018-07-02 to ongoing should be corrected from single chemotherapy to combined therapy with AZD9291.]
[According to NTF dated on 2020-03-31, Subject T09-025 used systemic regimens paclitaxel (taxol) from 2017-11-23 to 2017-11-24 should be corrected from single chemotherapy to combined therapy with AZD9291.]
[Based on above NTF dated on 2020-03-25 and 2020-03-31, the actual count and percentage for single chemotherapy under without continuation of AZD9291 should be 97 (27.87 %) and the combined therapy with AZD9291 under with continuation of AZD9291 should be 206 (59.20 %).]
[The actual count and percentage for 'Carboplatin (Paraplatin), Paclitaxel (Taxol)', 'Cisplatin (Platinol), Gemcitabine (Gemzar)' and 'Paclitaxel (Taxol)' under combined therapy with AZD9291 should be 2 (0.57 %), 2 (0.57 %), and 31 (8.91 %), respectively.]
Source: Appendix 16.2.3.2

6.2.4.8 The Reasons that the Investigators Prescribed Other Therapy for NSCLC with EGFRm as an Add-on to AZD9291 Monotherapy

Of 423 subjects enrolled, 113 subjects had received other therapies for NSCLC with EGFRm as an add-on to AZD9291 monotherapy. Of the 113 subjects, 89 subjects (78.76%) received other therapies as an add-on to AZD9291 monotherapy because of NSCLC progression and 24 subjects received AZD9291 treatments (21.24%) because of other reasons (including small cell lung cancer transformation, MET amplification positive, patient ask, clinical benefit, clinical progression, investigator judgment, carcinoembryonic antigen (CEA) increase, elevated tumor markers, or increase tumor index).

The summary results of reasons that the investigators prescribed other NSCLC therapy as an add-on therapy to AZD9291 monotherapy are presented in Table 14. Detailed listing of reasons that the investigators prescribed other NSCLC therapy as an add-on therapy to AZD9291 monotherapy can be referred to Appendix 16.2.6.3.2.

Table 14: Summary of Reasons that Investigators Prescribed Other NSCLC Therapy as an Add-on Therapy to the AZD9291 Monotherapy (FAS Population)

	Variable/ Status	FAS Population (N=113/E=113)
Reason		
	NSCLC progression	89 (78.76 %)
	Other	24 (21.24 %)

Note:
[Percentage = 100%*[The number of event(s) in the category / The number of event(s) which overall other therapy as an add-on to AZD9291 monotherapy in the study (E)]]
Source: Appendix 16.2.6.3.2

7. SAFETY EVALUATION

Not applicable for this study.

8. CONCLUSION & DISCUSSION

8.1 Discussion

This was an observational study to analyse the effectiveness of AZD9291 in locally advanced or metastatic NSCLC subjects with EGFRm who had participated in the EAP in Taiwan. A total of 423 subjects were enrolled and included in the FAS population for analyses.

Conclusion

Primary endpoint

The primary endpoint was to determine the PFS. Of the 419 subjects who had PFS data available after receiving the first dose of AZD9291, 363 subjects (86.63%) had PD or died during the study period. The median PFS was 10.5 months (95% CI: 8.95, 11.41) and was approximately equivalent to 320.0 days (95% CI: 273.00, 348.00).

Secondary endpoints

1. PFS at the 12th and 18th month after the first dose of AZD9291

   Of the 419 subjects who had PFS data available after receiving the first dose of AZD9291, 172 subjects (41.05%) had a progression event and 52 subjects (12.41%) had a death event by the 12th month; and 195 subjects (46.54%) were progression-free. The Kaplan-Meier estimated of PFS rate at the 12th month was 42.58% (95% CI: 37.59, 47.48). Of the 419 subjects, 214 subjects (51.07%) had a progression event and 69 subjects (16.47%) had a death event by the 18th month; and 136 subjects (32.46%) were progression-free. The Kaplan-Meier estimated of PFS rate at the 18th month was 26.50% (95% CI: 22.14, 31.05).

2. OS and OS at the 18th and 24th month after the first dose of AZD9291

   Of the 422 subjects who had OS data available after receiving the first dose of AZD9291, 296 subjects (70.14%) had death events during the study period and 126 subjects were censored. The Kaplan-Meier estimated median OS was 19.0 months (95% CI: 16.30, 20.95) and was approximately equivalent to 579.0 days (95% CI: 497.00, 639.00).

   By the 18th month, of the 422 subjects, 199 subjects (47.16%) had death events and 223 subjects (52.84%) were censored. The Kaplan-Meier estimated OS rate at the 18th month was 51.51% (95% CI: 46.54, 56.24).

   By the 24th month, of the 422 subjects, 239 subjects (56.64%) had death events and 183 subjects (43.36%) were censored. The Kaplan-Meier estimated OS rate at the 24th month was 40.90% (95% CI: 36.04, 45.70).

3. Time to treatment discontinuation (TTD)

Of the 399 subjects who had TTD data available after receiving the first dose of AZD9291, 326 subjects (81.70%) discontinued from AZD9291 monotherapy during the study period and 73 subjects (18.30%) were censored. The Kaplan-Meier estimated median TTD was 11.9 months (95% CI: 10.49, 13.11) and was approximately equivalent to 363.0 days (95% CI: 320.00, 400.00).

4. Last NSCLC therapy and the clinical outcome just before receiving the first dose of AZD9291
   - Last NSCLC therapy

   If analyzed by EGFR TKI therapy, the most common (> 10%) therapies in the FAS population were erlotinib (22.46%), followed by afatinib (13%) and gefitinib (12.29%).

   If analyzed by chemotherapy, 36.41% of the FAS population had received other chemotherapy and 29.79% of the FAS population had received platinum- or taxane-based therapy, as the last NSCLC treatment just before receiving the first dose of AZD9291.

   If analyzed by other systemic therapy, the most common (> 1%) therapies were bevacizumab (4.02%) and nivolumab (1.65%).

   If analyzed by radiation therapy for brain metastasis, 17.02% of the FAS population received radiation alone, 7.33% of the FAS population received radiation combined with systemic therapy, as the last NSCLC treatment just before receiving the first dose of AZD9291.

   If analyzed by combined therapy, 3.31% of the FAS population received chemotherapy combined with other systemic therapy, 2.60% of the FAS population received EGFR TKI combined with other systemic therapy, and 2.36% of the FAS population received EGFR TKI combined with chemotherapy, as the last NSCLC treatment just before receiving the first dose of AZD9291.

   - Clinical outcome

   Of the 396 subjects with clinical outcome data available, the most common (> 10%) response assessments of the last NSCLC therapy were SD (12.88%) and PD (77.27%).

5. Rationale for the use of AZD9291 over other NSCLC treatments at EAP enrollment

   Of the 423 subjects enrolled, the main reason (94.80%) for subjects participated in the EAP was due to lack of efficacy for the last NSCLC therapy.

6. Type of test performed for the confirmation of acquired EGFR T790M mutation

   Of the 421 EGFR T790M mutation tests collected in this study, the most common (> 10%) test results were from tissue biopsy (44.42%), followed by plasma-based samples (36.34%) and cytological samples (12.59%).

   The most common (>100 test results) test platforms used for detecting EGFR T790M mutation were MassARRAY genotyping (MassARRAY; 31.61% in all forms) and COBAS EGFR mutation test (30.17%).

7. The subsequent line(s) of systemic NSCLC treatment on AZD9291 monotherapy

Of the 348 subsequent systemic treatments, the most common treatments (> 5%) were combined therapy with AZD9291 (59.20%), followed by single chemotherapy (27.87%) and combined therapy without AZD9291 (9.20%).

Regarding the combined therapy with AZD9291, the most common (> 5%) therapies were paclitaxel (8.91%), followed by pemetrexed (6.32%), vinorelbine (6.03%), and gemcitabine (5.46%).

8. The reasons that the investigators prescribed other therapy for NSCLC with EGFRm as an add-on to AZD9291 monotherapy
   Of the 113 subjects who had received other therapies for NSCLC with EGFRm as an add-on to AZD9291 monotherapy, the main reason (78.76%) that the investigators prescribed other therapies as an add-on to AZD9291 monotherapy was due to progression of NSCLC.

Discussion

This retrospective study was conducted to obtain the effectiveness of AZD9291 in EAP patients as in a real-world practice. This study collected clinical data based on routine clinical practice and data collection was able to proceed in a shorter duration than the prospective study design. Nonetheless, because of the limitation as an observational study, the evaluation of tumor response was based on the individual investigator's assessments without standardization. Thus, bias may be introduced in tumor measurement-based outcomes such as PFS. In addition, missing data issue may also affect the analyses of effectiveness (PFS, OS, and TTD) of AZD9291 treatment. To reduce the impact of missing data, the following assumptions were made:

- for the analyses of PFS and OS, the data of subjects with unknown date of death or unknown living status (i.e. lost to follow-up longer than 6 months after the last day of assessment/contact) were censored on the last day of clinical assessment or the last day of contact, whenever came the last;
- for the analysis of TTD, the data of subjects with unknown ending of treatment date, the data were censored on the last known dose date of AZD9291 monotherapy

With the above assumptions applied, there were still some missing data observed when analyzed PFS (4 missing data), OS (1 missing data), and TTD (24 missing data). However, because the number of missing data was relatively small (less than 6%) when compared to the FAS population (423 subjects), the impact was considered as minimal.

Regarding the data of PFS and OS at specific time points after receiving the first dose of AZD9291, it is observed that the percentage of subjects without event was slightly higher than the rates estimated by Kaplan-Meier method. Further investigation by comparing with the results of other studies will be needed to confirm whether there is an overestimation.

Recently, the results of two studies (AURA3 and ASTRIS) of AZD9291 in patients with EGFR T790M positive NSCLC were available [12,16]. AURA3 was a randomized, open-label, international, phase III trial aimed to compare AZD9291 with platinum-based doublet therapy in patients with EGFR T790M positive advanced NSCLC, whose disease had progressed on first-line EGFR TKI therapy. ASTRIS was a global, open-label, single-arm, real-world

treatment study aimed to assess the effectiveness and safety of AZD9291 in adults with EGFR T790M positive advanced NSCLC, who had received prior EGFR-TKI therapy. The study population was similar in NOBLE, AURA3, and ASTRIS except that only Taiwanese population was enrolled in NOBLE.

To understand whether the effectiveness of AZD9291 in patients with EGFR T790M positive advanced NSCLC observed in the present study (NOBLE; observational study in Taiwan) would be different from the other two studies (AURA3 and ASTRIS; both were multi-national, prospective studies), the results of PFS, OS, and TTD between studies are summarized in Table 15.

Table 15: Summary of PFS, OS, and TTD from Different Studies

Study name		**NOBLE**		**AURA3**[12]		**ASTRIS**[16]	
Study population		423		419; 279 in the AZD9291 (osimertinib) group		3015	
Region		Taiwan		International (including Taiwan)		International (including Taiwan)	
Median by months (95% CI)	**PFS**	n=419	10.5 (8.95, 11.41)	n=279	10.1 (8.3, 12.3)	n=3015	11.1 (11.0, 12.0)
	OS	n=422	19.0 (16.30, 20.95)	-*		-*	
	TTD	n=399	11.9 (10.49, 13.11)	-		n=3015	13.5 (12.6, 13.9)

Note:
n=Number of subjects included in the analysis
* Immature at the time of publication.

TTD was not assessed in AURA3 but in NOBLE and ASTRIS. The median TTD was 11.9 months in NOBLE and was 13.5 months in ASTRIS. In both studies, the main reason for the discontinuation of AZD9291 monotherapy was due to PD. An approximately 48-day difference was observed between the two studies. The difference in size of study population between studies may be one of the reasons.

For PFS, the median time observed in the three studies was ranging from 10.1 to 11.1 months (10.5 months in NOBEL *vs* 10.1 months in AURA3 *vs* 11.1 months in ASTRIS). There was a difference of median PFS between studies ranging from approximately 12 to 30 days. The reasons for such a difference may be due to:

(1) differences in size of study population between studies; or

(2) differences in TTD (AZD9291 monotherapy discontinuation) between studies as above mentioned; or

(3) inclusion of patients who had treated with chemotherapy before receiving the first dose of AZD9291 in NOBLE and ASTRIS but not in AURA3; or

(4) the prescription of medication management other than AZD9291 due to the acquired other EGFR mutations before the judgment of PD per investigator's discretion

Notably, with the inclusion of patients who had received chemotherapy before receiving the first dose of AZD9291 (a more diverse population in terms of prior treatment which was closer to the real world practice) in NOBLE and ASTRIS, a longer median PFS was observed in the two studies when compared to AURA3. This result suggested that prior chemotherapy before AZD9291 treatment may not affect the effectiveness of AZD9291 in advanced NSCLC patients with EGFR T790M positive mutation.

Interestingly, a longer median TTD in ASTRIS concurrent with a longer median PFS was observed in ASTRIS when compared with the results in NOBLE. Further investigation will be needed to understand whether subjects treated with AZD9291 monotherapy for a longer period would prolong the disease free interval after receiving the first dose of AZD9291.

For OS, because of data immature at the time of publication of AURA3 and ASTRIS studies, no median OS in these two studies was available for comparison. In ASTRIS, approximately 74% (estimated by Kaplan-Meier method) of subjects survived at the 12th month after receiving the first dose of AZD9291. However, as the OS rate at the 12th month was not evaluated in NOBLE, further investigation will be needed to confirm whether there is a difference between studies.

It should be noted that in NOBLE, OS was defined as the time interval from the date of first dose of AZD9291 until the date of death due to any cause. As a result, the OS results in the present study not only demonstrated the effectiveness of AZD9291 monotherapy but also included the effectiveness of combined treatment of AZD9291 with subsequent therapies after PD. Thus, the following issues would need to be further investigated:

(1) whether a longer treatment duration with AZD9291 may prolong patient's OS; or

(2) if the early onset of combined treatment with AZD9291 may prolong patient's OS; or

(3) what will be the preferred subsequent therapy to be combined with AZD9291 that may prolong patient's OS

Taken together, regardless the minor differences in PFS and TTD between studies as discussed above, the clinical benefits of AZD9291 monotherapy were demonstrated in patients with EGFR T790M positive NSCLC.

8.2 Conclusion

In this study, a total of 423 subjects were enrolled. The effectiveness of AZD9291 was evaluated by the analyses of real world progression, OS, and TTD.

Of the 419 subjects who had PFS data available after receiving the first dose of AZD9291, PD or death was observed in 363 subjects (86.63%) during the study period, with median PFS of 10.5 months (95% CI: 8.95, 11.41) and was approximately equivalent to 320.0 days (95% CI: 273.00, 348.00). After receiving the first dose of AZD9291, approximately 42.58% (95% CI: 37.59, 47.48) of them survived without PD at the 12th month and 26.50% (95% CI: 22.14, 31.05) of them survived without PD at the 18th month.

Of the 422 subjects who had OS data available after receiving the first dose of AZD9291, death was observed in 296 subjects (70.14%) during the study period, with median OS of 19.0 months (95% CI: 16.30, 20.95) and was approximately equivalent to 579.0 days (95% CI: 497.00, 639.00). After receiving the first dose of AZD9291, approximately 51.51% (95% CI: 46.54, 56.24) of them survived at the 18th month and 40.90% (95% CI: 36.04, 45.70) of them survived at the 24th month.

Of the 399 subjects who had TTD data available after receiving the first dose of AZD9291, 326 subjects (81.70%) discontinued from AZD9291 monotherapy during the study, with median TTD of 11.9 months (95% CI: 10.49, 13.11) and was approximately equivalent to 363.0 days (95% CI: 320.00, 400.00).

Overall, the clinical benefits of AZD9291 monotherapy were demonstrated in locally advanced or metastatic, EGFR T790M mutation NSCLC subjects.

9. LIST OF REFERENCES

1. Camidge, D. R., Pao, W. &Sequist, L.V. Acquired resistance to TKIs in solid tumours: Learning from lung cancer. *Nat. Rev. Clin. Oncol.* **11**, 473–481 (2014).
2. Gridelli, C. *et al.* First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: The TORCH randomized trial. *J. Clin. Oncol.* **30**, 3002–3011 (2012).
3. Masuda, T. *et al.* Efficacy of platinum combination chemotherapy after first-line gefitinib treatment in non-small cell lung cancer patients harboring sensitive EGFR mutations. *Clin. Transl. Oncol.* **17**, 702–709 (2015).
4. Park, S. *et al.* Pemetrexed singlet versus nonpemetrexed-based platinum doublet as second-line chemotherapy after first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor failure in non-small cell lung cancer patients with EGFR Mutations. *Cancer Res. Treat.* **47**, 630–7 (2015).
5. Li, D. *et al.* BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene* **27**, 4702–4711 (2008).
6. Engelman, J. A. *et al.* PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to gefitinib. *Cancer Res.* **67**, 11924–11932 (2007).
7. Miller, V. A. *et al.* Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): A phase 2b/3 randomised trial. *Lancet Oncol.* **13**, 528–538 (2012).
8. Yap, T. A. *et al.* Phase I trial of the irreversible EGFR and HER2 kinase inhibitor BIBW 2992 in patients with advanced solid tumors. *J. Clin. Oncol.* **28**, 3965–3972 (2010).
9. Cross, D. A. E. *et al.* AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov.* **4**, 1046–1061 (2014).
10. Jänne, P. A. *et al.* AZD9291 in EGFR inhibitor–resistant non–small-cell lung cancer. *N. Engl. J. Med.* **372**, 1689–1699 (2015).
11. Goss, G., Yang, J. C.-H., Ahn, M.-J. &Tsai, C. AZD9291 in pre-treated patients with T790M positive advanced non-small cell lung cancer (NSCLC): pooled analysis from two Phase II studies (poster presentation). *Eur. J. Cancer* **51**, S640 (2015).
12. Mok, T. S. *et al.* Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N. Engl. J. Med.* **376**, 629–640 (2017).
13. AstraZeneca Taiwan Ltd. Package of Tagrisso. 2018.
14. AstraZeneca Ltd. Tagrisso package label. (2018).
15. Non-small Cell Lung Cancer. *NCCN Guidel. version 3.2020* (2020) doi:10.1016/j.thorsurg.2020.01.007.
16. DeMarinis, F. *et al.* ASTRIS: A global real-world study of osimertinib in >3000 patients with EGFR T790M positive non-small-cell lung cancer. *Futur. Oncol.* **15**, 3003–3014 (2019).

10. APPENDICES

Appendix 16.2.1.1 Subjects Disposition

Appendix 16.2.1.2 Subjects Eligibility

Appendix 16.2.2 Protocol Deviations

Appendix 16.2.3 Subjects Excluded from the Analysis

Appendix 16.2.4.1 Individual Subject Demographics

Appendix 16.2.4.2 Individual Subject Smoking Status at Primary Diagnosis of NSCLC

Appendix 16.2.4.3.1 Clinical Characteristics of NSCLC: The Primary Diagnosis

Appendix 16.2.4.3.2 Clinical Characteristics of NSCLC: Just Before Receiving the First Anti-NSCLC Systemic Therapy

Appendix 16.2.4.3.3 Clinical Characteristics of NSCLC: When Administered the Frist Dose of AZD9291

Appendix 16.2.4.4 Comorbidity Burden

Appendix 16.2.4.5 Other Types of EGFR Positive Mutation

Appendix 16.2.4.6 Radiation Therapy for Brain Metastasis of NSCLC: Prior to the First Dose of AZD9291

Appendix 16.2.4.7 ECOG at AZD9291 Initiation

Appendix 16.2.5 Study Drug Administration

Appendix 16.2.6.1 T790M Positive Mutation

Appendix 16.2.6.2 Rationale for the Use of AZD9291

Appendix 16.2.6.3.1 Systemic Regimens: Prior to the First Dose of AZD9291

Appendix 16.2.6.3.2 Systemic Regimens: After the First Dose of AZD9291

Appendix 16.2.6.4.1 Tumor Assessment: At the Initiation of AZD9291

Appendix 16.2.6.4.2 Tumor Assessment: The Best Tumor Response from the First Dose of AZD9291 to PD, Death or Stop the Single Use (v1.1)/ the Monotherapy (v2.0) of AZD9291

Appendix 16.2.6.4.3 Tumor Assessment: At the First Disease Progression on AZD9291 Treatment

Appendix 16.2.6.4.4 Tumor Assessment: At the Discontinuation of AZD9291 Treatment

11. ATTACHMENTS

Not applicable.