The APPLE Trial: Feasibility and Activity of AZD9291 (Osimertinib) Treatment on Positive PLasma *T790M* in *EGFR*-mutant NSCLC Patients. EORTC 1613

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Abstract

The AZD9291 (Osimertinib) Treatment on Positive PLasma T790M in EGFR-mutant NSCLC Patients (APPLE) trial is a randomized, open-label, multicenter, 3-arm, phase II study in advanced, epidermal growth factor receptor (*EGFR*)-mutant and EGFR tyrosine kinase inhibitor (TKI)-naive non–small-cell lung cancer (NSCLC) patients, to evaluate the best strategy for sequencing gefitinib and osimertinib treatment. Advanced *EGFR*-mutant NSCLC patients, with World Health Organization performance status 0-2 who are EGFR TKI treatment-naive and eligible to receive first-line treatment with EGFR TKI will be randomized to:

- Arm A: osimertinib until disease progression according to Response Evaluation Criteria In Solid Tumors 1.1 (RECIST);
- Arm B: gefitinib until emergence of circulating tumor DNA (ctDNA) substitution of threonine with methionine at amino acid position 790 (*T790M*)-positive status and then switch to osimertinib until disease progression according to RECIST; or
- Arm C: gefitinib until disease progression according to RECIST and then switch to osimertinib until second radiologic disease progression.

In all arms, a plasmatic ctDNA T790M test will be performed by a central laboratory at the Medical University of Gdansk (Poland) but will be applied as a predictive marker for making treatment decisions only in arm B. The primary objective is to evaluate the best strategy for sequencing of treatment with gefitinib and osimertinib in advanced NSCLC patients with common *EGFR* mutations, and to understand the value of liquid biopsy for the decision-making process. The progression-free survival rate at 18 months is the primary end point of the trial. The activity of osimertinib versus gefitinib to prevent brain metastases will be evaluated.

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Introduction

The activating epidermal growth factor receptor (*EGFR*) mutation is present in almost 50% of patients with advanced non–small-cell lung cancer (NSCLC), who are of Asian ethnicity[1] compared with only 12% in the Caucasian population.[2] These molecular alterations predict sensitivity to first- and second-generation EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, afatinib, or icotinib (only available in China). Response rate and

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progression-free survival (PFS) with EGFR TKIs are superior to standard first-line platinum doublet chemotherapy, making them the standard of care.[3] However, tumors invariably develop acquired resistance in approximately 9 to 13 months after treatment initiation.

The substitution of threonine with methionine at amino acid position 790 (T790M) in exon 20 of the *EGFR* gene reduces first-generation EGFR inhibitor binding, and accounts for more than half of acquired resistance mechanisms.[4-6] Osimertinib (AZD9291)[7] is an orally available, mutant-selective, third-generation EGFR TKI covalent inhibitor of commonly mutated and resistant (T790M) forms of the protein, sparing EGFR wild type, so inducing less frequent and less severe gastrointestinal and skin toxicity compared with first- or second-generation EGFR TKIs. In various animal models of *EGFR*-mutant NSCLC with brain metastases, osimertinib has also shown greater penetration of the mouse blood-brain barrier than other EGFR TKIs.[8] Preliminary antitumor activity of osimertinib in the brain has been reported in the phase I BLOOM trial.[9] In the phase I AURA trial, osimertinib was tested in 253 advanced NSCLC patients who had radiologically documented disease progression after previous treatment with a first-generation EGFR TKI. Among patients with centrally confirmed *T790M* mutation in the tumor, osimertinib was reported to reach a response rate (RR) of 61% and median PFS of 9.6 months.[10] Activity of osimertinib has also been reported in *T790M*-negative tumors but of lower magnitude (RR of 26% and PFS of 3.4 months).[11] The US Food and Drug Administration (FDA) approved osimertinib in November 2015 for treatment of NSCLC patients with acquired *T790M* mutation, on the basis of data from the 2 AURA phase II studies (AURA extension[12] and AURA2[13]), which showed efficacy in 411 T790M-mutant NSCLC patients whose disease had progressed during or after an EGFR TKI with a RR equal to 59%. On the basis of these results, in April 2016, the European Medicines Agency (EMA) approved osimertinib in the same population. Osimertinib efficacy has recently been validated in the phase III AURA3 study, which compared osimertinib with platinum-pemetrexed chemotherapy in 419 patients with *T790M* tissue biopsy-positive advanced NSCLC, in whom first-line EGFR TKIs therapy had failed. A significant improvement in response rate (71% vs. 31%; $P < .001$) and PFS (10.1 months vs. 4.4 months; hazard ratio, 0.30; $P < .001$) were reported.[14] Recently, the FDA as well as the EMA approved osimertinib in patients with acquired EGFR T790M mutations tested in a tumor biopsy or in plasma.[15,16] Osimertinib efficacy has not been prospectively established in patients with *T790M* mutation determined in the plasma, and having unknown EGFR status in the tissue. Moreover, there is no evidence that switching treatment according to molecular progression (ie, circulating tumor DNA [ctDNA] T790M mutation positivity without disease progression according to Response Evaluation Criteria In Solid Tumors [RECIST]) could have an effect on treatment outcomes.

The ongoing phase III first-line FLAURA trial (NCT02296125), which is comparing osimertinib with erlotinib or gefitinib as first-line treatment in patients with common *EGFR* mutations will define whether a third-generation EGFR TKI could become standard first-line treatment in these patients. Preliminary results from the phase I AURA trial with osimertinib at 80 mg/d in a cohort of treatment-naive metastatic *EGFR*-mutant NSCLC patients have shown a RR of 67% and 18-month PFS of 57%.[17] This activity compares favorably with the 9-month PFS of 55% with gefitinib treatment in *EGFR*-mutant lung cancer patients from the IPASS trial,[18] or 68% with afatinib in the LUX-Lung 3 trial,[19] suggesting that osimertinib might have the efficacy to become the standard of care as first-line treatment in *EGFR*-mutant NSCLC patients independently of basal T790M status.

Lack of available tissue for molecular assessment is a common feature in daily practice, because it happens for patients with bone metastases (because of the requirement for sample decalcification impairing DNA quality) and is reported in up to 50% of *EGFR*-mutant NSCLCs.[20] Other challenging situations include poor location or size of the tumor at the time of disease progression that is not eligible for a biopsy, or risks of complications that contraindicate rebiopsy.[21] Moreover, because of the spatial heterogeneity of metastases, single-site biopsies might not be representative of the overall predominant resistance mechanisms for a specific patient.[22] As a result, up to 23% of tumor specimens available at the time of acquired resistance have been reported as providing limited, low-quality material for tumor genotyping,[6,21,23] and might not be representative of the entire genomic landscape of the tumor.[22,24]

Liquid biopsies on the basis of ctDNA analysis have many potential applications such as: (1) surrogate samples for tumor molecular analysis[25]; (2) potential dynamic marker for monitoring of the efficacy of targeted therapies[26,27]; (3) early detection of resistance mutations[28]; and (4) real-time sampling of multifocal clonal evolution.[29] ctDNA T790M analysis is a biomarker for prediction of outcome with osimertinib. In a recent retrospective analysis from phase I and II AURA trials, T790M status was analyzed according to central blood test genotyping using the BEAMing method (allelic fraction for positive results for *T790M* $\geq$ 0.06%). The analysis reported equal efficacy of osimertinib independently of whether the T790M research was performed in plasma or in the tissue in *EGFR*-mutant patients with disease progression according to RECIST during first-generation EGFR TKI treatment, with improved outcome among *T790M*-positive NSCLC patients. Among patients whose T790M status in the tumor was unknown, median PFS with osimertinib was approximately 16 months and 4 months for those with ctDNA *T790M*-positive and *T790M*-negative status, respectively.[11] The efficacy of osimertinib in ctDNA T790M-negative tumors appeared similar to the efficacy of standard second-line chemotherapy reported in the IMPRESS trial with a better toxicity profile.[30]

The prospective efficacy of osimertinib according to ctDNA T790M results has been recently evaluated in a cohort of previously treated *EGFR*-mutant NSCLC patients. Among evaluable patients, osimertinib gave a partial response rate of 62.5% with a 6- and 12-month PFS of 66.7% and 52%, respectively.[31] These results are comparable with the efficacy reported with osimertinib in patients with *T790M* mutation detected in a tumor biopsy,[10,14] supporting the use of liquid biopsies for personalized treatment among these patients.

A new challenge in the treatment of *EGFR*-mutant NSCLC patients is to better understand whether plasmatic progression (*T790M*-positive in ctDNA, a liquid biopsy) occurs earlier than disease progression according to RECIST and whether switching to osimertinib treatment only on the basis of plasmatic progression could improve the overall outcome of patients compared with

standard procedure (treatment switching on the basis of RECIST criteria[32]) or compared with upfront osimertinib. Continuing EGFR TKI treatment beyond disease progression according to RECIST is feasible and might delay salvage therapy, highlighting the challenge in identifying whether radiologic disease progression is the optimal time to switch treatment.[33-36] Moreover, it remains unknown whether switching to third-generation EGFR TKIs in this setting might increase the delay time to subsequent therapies, introducing a new concept of therapeutic algorithm. Of note, efficacy of osimertinib among patients whose T790M status in the tumor is unknown appears at least similar to second-line platinum-based chemotherapy[11,30] with a better toxicity profile.[14]

On the basis of these new challenges we initiated the phase II AZD9291 (Osimertinib) Treatment on Positive PLasma T790M in EGFR-mutant NSCLC Patients (APPLE) trial among *EGFR*-mutant and EGFR-TKI naive NSCLC patients with 2 main study aims: (1) to understand if a sequenced strategy (gefitinib followed by osimertinib) is of value compared with upfront osimertinib regarding the clinical efficacy and the occurrence of brain metastases; and (2) to explore whether liquid biopsies could become the new standard procedure for defining disease progression versus disease progression according to RECIST. Finally, the trial will also explore the mechanisms of acquired resistance to osimertinib, on the basis of the results of an optional biopsy at the time of disease progression.

Materials and Methods

Study Design

The APPLE trial is a randomized, open-label, multicenter, 3-arms, phase II study in advanced, *EGFR*-mutant and EGFR TKI naive NSCLC patients, to evaluate the best strategy of sequencing gefitinib and osimertinib treatment.

Baseline blood samples for ctDNA *EGFR* T790M central testing (cobas EGFR Mutation Test v2, Roche Molecular Diagnostics, Pleasanton, CA) and adequate tissue sample in quantity and quality for translational research will be collected and stored at the Medical University of Gdansk (Poland). Baseline T790M status will be unknown.

Upon report of adequate sample for ctDNA *EGFR* T790M test by the central laboratory, patients will be randomized to (Figure 1):

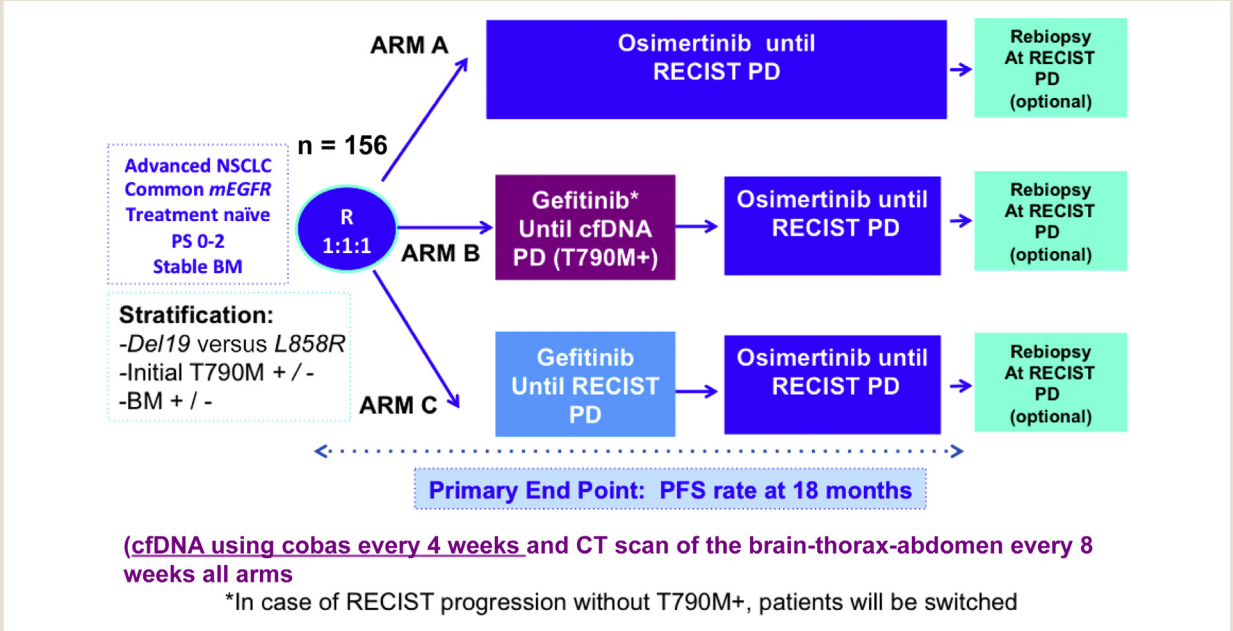
- Arm A: first-line treatment with osimertinib 80 mg daily until disease progression according to RECIST;
- Arm B: first-line gefitinib 250 mg daily until emergence of ctDNA *T790M*-positive status and then switch to osimertinib 80 mg daily until second disease progression according to RECIST; or
- Arm C: first-line gefitinib 250 mg daily until disease progression according to RECIST and then switch to osimertinib 80 mg daily until second disease progression according to RECIST.

A monthly plasmatic ctDNA T790M test will be performed as exploratory analyses in all arms, and will be used as a predictive marker for treatment decision-making only in arm B.

Basal ctDNA T790M status will be blinded in arms A and C, and will only be reported in arm B during the first part of treatment (gefitinib period until disease progression). During osimertinib treatment, T790M status will be blinded in all 3 arms.

Moreover, an optional rebiopsy at disease progression according to RECIST during osimertinib treatment will be strongly

Figure 1 Trial Design: Randomized, Open-label, Multicenter, Phase II Trial



Abbreviations: BM = brain metastases; cfDNA = cell-free tumor DNA; COBAS = cobas EGFR Mutation Test from Roche Molecular Diagnostics (Pleasanton, CA); CT = computed tomography; NSCLC = non–small-cell lung cancer; PFS = progression-free survival; PS = performance status; RECIST = Response Evaluation Criteria In Solid Tumors.

Table 1 Main Inclusion and Exclusion Criteria

Key Inclusion Criteria
Stage IV NSCLC with a pathological diagnosis of adenocarcinoma carrying common *EGFR*-activating mutations associated with EGFR TKI sensitivity (*Del19* or *L858R*); performed locally; no other *EGFR* mutations will be allowed
EGFR TKI treatment-naive eligible to receive first-line treatment with EGFR TKI
Blood sample available for ctDNA *EGFR* T790M central testing and adequate tissue sample in quantity and quality for translational research
WHO performance status of 0 to 2, with no clinically significant deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks
Patients with brain metastases are allowed provided they are stable and have not received steroids for at least 7 days before treatment start
At least 1 lesion, not previously irradiated that can be accurately measured at baseline according to RECIST 1.1 criteria
Adequate bone marrow, renal, hepatic, and liver function within 21 days from randomization
Written informed consent must be given according to GCP, and national/local regulations
Key Exclusion Criteria
Treatment with any of the following:
• Previous treatment with any systemic anticancer therapy for locally advanced/metastatic NSCLC including chemotherapy, biologic therapy, immunotherapy, or any investigational drug
• Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study drug
• Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug
Patients currently receiving (or unable to stop use at least 1 week before receiving the first dose of study drug) medications or herbal supplements known to be potent inhibitors or inducers of cytochrome P450 (CYP) 3A4; antacids could be taken in a time-separate manner, at least 8 hours from gefitinib
Leptomeningeal carcinomatosis; spinal cord compression
Any unresolved toxicities (CTCAE Grade >2) from previous anticancer therapies
Patients will not be eligible if they have evidence of active malignancy (other than nonmelanoma skin cancer or localized cervical cancer or localized and presumed cured prostatic cancer) within 2 years of first dose of study drug and are not receiving specific treatment for these malignancies at baseline assessment
Evidence of severe or uncontrolled systemic diseases, active bleeding diatheses, or active infection including hepatitis B, hepatitis C, and HIV
Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant gastrointestinal resection that would preclude adequate absorption of osimertinib or gefitinib
Past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = circulating tumor DNA; EGFR = epidermal growth factor receptor; GCP = good clinical practices; ILD = interstitial lung disease; NSCLC = non–small-cell lung cancer; RECIST = Response Evaluation Criteria In Solid Tumors; TKI = tyrosine kinase inhibitor; WHO = World Health Organization.

encouraged to investigate the mechanisms of acquired resistance to osimertinib.

The local investigator may choose to continue treatment with osimertinib beyond disease progression according to RECIST, if, in their opinion, the patient continues to obtain clinical benefit. Information on postprogression treatment will be captured.

The APPLE trial is an academic study sponsored by the European Organization for Research and Treatment of Cancer (EORTC) and financially supported by AstraZeneca. It has been designed by the EORTC Lung Cancer Group and follows its Standard of Conduct, in particular a cocoordination by a senior (R.D.) and a junior (J.R.) investigator.

An Independent Ethics Committee and Institutional Review EORTC board has approved the protocol and approximately 40 sites will enroll patients.

Eligibility Criteria

Main patient inclusion and exclusion criteria are detailed in Table 1.

Primary Study End Point

The primary objective is to evaluate the best strategy for sequencing gefitinib and osimertinib treatment in *EGFR*-mutant advanced NSCLC patients. The objective is assessed according to PFS rate at 18 months (PFSR-18). This study is designed with an understanding of the difficulty of having a primary end point that solidly covers all arms because one study drug is given in arm A and 2 study drugs are used in arms B and C.

Therefore, the primary end point, PFSR-18, will be assessed in all arms, yet this end point will be used to formally compare arm B with arm C. With this restriction, the Table 2 criteria for success of the arm (applicable to arms B and C only) should be carefully reviewed. Further information from secondary end points as well as the costs of treatment should be considered if the arm is judged as a winner to be further explored.

Secondary and Exploratory End Points

Secondary and exploratory end points are summarized in Table 2.

Regarding translational research, any patient who consents to enter the trial will have to consent for the translational research.

The main objectives of translational research study are, but not limited to, the following:

- To describe the presence of T790M mutations and original activating *EGFR* mutations in plasma of patients treated with gefitinib and osimertinib longitudinally within the arms and to compare the presence of these mutations across the arms A, B, and C.
- To describe the associations between the presence of these mutations and response evaluations according to RECIST, longitudinally within the arms.

Table 2 End Points

Primary	Secondary	Exploratory
PFS Rate at 18 Months	• PFS measured from switching to osimertinib according to RECIST 1.1 criteria • Proportion of patients receiving osimertinib on the basis of the determination of ctDNA T790M mutation-positive • Time to progression during osimertinib treatment • PFS-2 (defined as the sum of the PFS with gefitinib and the PFS with osimertinib treatment) • ORR with osimertinib treatment • Treatment duration • OS • Time to radiological brain progression • Safety	• Prospective for cfDNA T790M mutation testing during treatment with gefitinib • Prospective for cfDNA T790M mutation testing during treatment with osimertinib • PFS and OS taking into account treatments administered after osimertinib treatment • Resistance mechanisms to osimertinib • RECIST 1.1 progression during osimertinib treatment with blinded T790M status • Activating *EGFR* mutation levels in ctDNA

Abbreviations: cfDNA = cell-free tumor DNA; ctDNA = circulating tumor DNA; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors.

- To describe the associations between the presence of these mutations and response and PFS to osimertinib in arm A, B, and C.
- To assess mechanisms of resistance to osimertinib and compare the presence of molecular resistance alterations in tissue samples and plasma samples collected at the time of disease progression.

Statistical Considerations

The study design is a 1-stage A'hern design—single proportion, with a 1-sided $\alpha = 0.08$ and 92% power ($\beta = 8\%$).

In arms B and C of this trial, if the result is compatible with a PFSR-18 of 60% in the studied population, the strategy should be further explored. However, if we are unable to show that the PFSR-18 in the studied population is at least 40%, the strategy should be rejected from further exploration.

Forty-nine eligible patients who start treatment are needed in each arm. To declare the arm worthwhile for further exploration, at least 25 of 49 patients should be free of disease progression at 18 months.

An additional 5% of patients will be accrued to take into account patients who might be ineligible or not start treatment. Thus, using a 1:1:1 ratio for randomization, a total of 156 patients will be accrued in this study (52 patients in each arm).

In this study a minimum of 18 months of follow-up is needed after the last patient entry.

Study Assessments

For objective tumor assessment, contrast-enhanced computed tomography of the chest, abdomen, and brain will be performed every 8 weeks and retrospectively reviewed by 2 independent radiologists for blinded independent central review using RECIST and adjudicated, if required. Plasma samples will be collected during the screening visit and every 4 weeks while patients are within active treatment with gefitinib or osimertinib and at the time of disease progression.

Conclusion

The APPLE trial gives the unique opportunity to test a sequenced strategy (gefitinib followed by osimertinib) versus upfront osimertinib and prospectively validate liquid biopsies as a new tool to detect early tumor progression compared with conventional disease progression according to RECIST in TKI-naive *EGFR*-mutant advanced NSCLC patients. Moreover, we will assess the dynamic predictive value of liquid biopsies for response to treatment and explore the mechanisms of acquired resistance to osimertinib.

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Disclosure

The authors have stated that they have no conflicts of interest.

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