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EORTC protocol 1613-LCG

APPLE trial: Feasibility and activity of AZD9291 (osimertinib) treatment on Positive PLasma T790M in EGFR mutant NSCLC patients

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Protocol summary

Title of the Study	APPLE trial: Feasibility and activity of AZD9291 (osimertinib) treatment on Positive PLasma T790M in EGFR mutant NSCLC patients
Objective(s)	**Primary objective** To evaluate the best strategy for delivering osimertinib (AZD9291) in NSCLC patients with EGFR mutation. The objective is assessed by Progression Free Survival rate at 18 months (PFSR-OSI-18). **Secondary objectives** • To evaluate PFS on osimertinib measured from randomization by RECIST criteria 1.1. • To evaluate PFS measured from switching to osimertinib by RECIST criteria 1.1. • To determine the proportion of patients receiving osimertinib based on the determination of cfDNA T790M mutation positive. • To evaluate PFS-2. • To evaluate Overall Response Rate (ORR) to osimertinib. • To evaluate the Treatment duration. • To evaluate Time to progression (TTP) on osimertinib (measured from switching to osimertinib). • To evaluate Overall Survival (OS). • To evaluate brain progression free survival (BPFS). • Safety. **Exploratory objectives** • To assess the feasibility of prospective cfDNA T790M mutation testing during treatment with gefitinib as a predictor of treatment progression and its correlation with RECIST 1.1 progression. • To assess the feasibility of prospective cfDNA T790M mutation testing during treatment with osimertinib as a predictor of efficacy. • To assess the change in tumor size upon switching to osimertinib. • To describe the treatments and outcomes of the treatments administered after osimertinib. • To evaluate the resistance mechanisms to osimertinib (by optional biopsy at disease progression on osimertinib). • To evaluate osimertinib efficacy in patients with acquired resistance to gefitinib based on RECIST progression with blinded T790M status. • To monitor the activating EGFR mutation levels in cfDNA.

Methodology	This is a randomized, open-label, multicenter, three-arms, phase II study in advanced, EGFR mutant and EGFR TKI naïve NSCLC patients, to evaluate the best strategy for delivering osimertinib. Advanced EGFR mutant NSCLC and EGFR-TKI naïve patients, will be randomized to: • arm A: first-line treatment with osimertinib until RECIST progression • arm B: gefitinib until emergence of cfDNA T790M positive status ("cfDNA T790M positive progression") and then switch to osimertinib until second RECIST progression. as of protocol version 4.0, patients in Arm B on gefitinib will switch to osimertinib on RECIST 1.1 progression only • arm C: gefitinib until RECIST progression and then switch to osimertinib until second RECIST progression In all arms, plasmatic cfDNA T790M test will be performed as exploratory analysis. However, only in arm B it will be used as a predictive marker for making treatment decision. Moreover, as an optional test, a re-biopsy at RECIST progression to osimertinib will be strongly encouraged to investigate the mechanisms of AR to osimertinib. The estimated duration of the study is 6 years, given that all patients have ended their treatment according to End of Study definition.
Number of patients Number planned (Statistical design) Number analyzed	This study is designed with an understanding of the difficulty of having a primary endpoint which solidly covers all arms. The primary endpoint PFSR-OSI-18, will be assessed in all arms, yet this endpoint will be used to evaluate arm B and arm C. With this restriction, the below criteria for a success of the arm (applicable B and C) should be viewed as exploratory and further information from secondary endpoints as well as the costs should be considered if the arm is judged as feasible to be further explored. The study design is a 1-Stage Ahern Design - Single Proportion, with Progression Free Survival rate at 18 months (PFSR-OSI-18) as primary endpoint. It was designed with a 1-sided alpha = 0.08 and 92% power (beta = 8%). In arm B and C of this trial, if the result is compatible with a progression free survival rate at 18 months (PFSR-OSI-18) of 60% in the studied population, the strategy should be further explored. However, if we are unable to demonstrate that the PFSR-OSI-18 in the studied population is at least 40%, the strategy should be rejected from further exploration. 49 eligible patients who started treatment are needed in each arm. To declare the arm worthwhile for further exploration, at least 25 out of 49 patients should be a success at 18 months. Additional 5% patients will be accrued to take into account patients who might be ineligible or not starting treatment. Hence, using a 1:1:1 ratio for randomization, a total of 156 patients will be accrued in this study (52 pts in each arm) within 26 months and an additional 24 months of follow up after the last patient entry is needed to allow the assessment of the primary endpoint.

	In this study a minimum of 18 months of follow up is needed after the last patient entry.
Diagnosis and main criteria for inclusion	**Inclusion criteria** *Registration* • Pathological diagnosis of adenocarcinoma of the lung carrying common EGFR activating mutations associated with EGFR-TKI sensitivity (Del19 or L858R); performed locally; no other EGFR mutations will be allowed. In case of other (than EGFR) concomitant mutations, discussion with EORTC Headquarters is mandatory; • Stage IV NSCLC; • Blood sample available for cfDNA EGFR T790M central testing; • Adequate tissue sample in quantity and quality for translational research; • Age ≥18 years; • EGFR TKI treatment-naïve eligible to receive first-line treatment with EGFR TKI; • Prior adjuvant and neo-adjuvant therapy is permitted (chemotherapy, radiotherapy, investigational agents) if performed more than 12 months before registration; • Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations. Maximum time elapsed between registration and treatment start should be four weeks, although every effort should be made to start treatment as quickly as possible. *Randomization* • Report of adequacy sample for cfDNA EGFR T790M test by central laboratory; • Prior palliative radiotherapy or surgical procedures are allowed if completed at least 4 weeks before the randomization; • Patients with brain metastases are allowed provided they are stable (i.e., without evidence of progression by imaging for at least two weeks prior to the first dose of trial treatment and without deterioration of any neurologic symptoms), and have not received steroids for at least 7 days before randomization; • Baseline tumor assessment scans are done within 21 days before randomization; • Evaluable disease as defined below; • At least one lesion, not previously irradiated and not chosen for biopsy during the study screening period, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis of ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI), and which is suitable for accurate repeated measurements. • WHO Performance Status 0-2, with no clinically significant deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks;

	• Adequate bone marrow, renal, hepatic and liver function within 21 days form randomization and defined as follows:
	  • Absolute neutrophil count ≥1.5 x 10^9/L;
	  • Platelet count ≥100 x 10^9/L;
	  • Hemoglobin ≥9 g/dL;
	  • Alanine aminotransferase (ALT) ≤2.5x the upper limit of normal (ULN) if no demonstrable liver metastases or ≤5xULN in the presence of liver metastases;
	  • Aspartate aminotransferase (AST) ≤2.5xULN if no demonstrable liver metastases or ≤5xULN in the presence of liver metastases;
	  • Total bilirubin ≤1.5xULN if no liver metastases or ≤3xULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or liver metastases;
	  • Serum creatinine ≤1.5xULN concurrent with creatinine clearance ≥50 mL/min (measured or calculated by Cockcroft and Gault equation).
	• No significant comorbidity that according to the investigator would hamper the participation on the trial;
	• Female patients should be using adequate contraceptive measures, as defined by the investigator, during the treatment until 6 weeks after last dose of osimertinib. They should not be breastfeeding, and must have a negative pregnancy test (serum or urine) prior to first dose of study drug (within 72 hours); or female patients must have an evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:
	  • Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments.
	  • Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the post-menopausal range for the institution.
	  • Documentation of irreversible surgical sterilization by hysterectomy, bilateraloophorectomy, or bilateral salpingectomy but not tubal ligation.
	• Male patients should be willing to use barrier contraception, i.e., condoms as defined by the investigator, during the treatment until 4 months after last dose of osimertinib;
	  • Male patients will be advised to arrange for the freezing of sperm samples prior to the start of the study should they wish to father children, and not to donate sperm until 6 months after discontinuation of study treatment. (as per Investigator Brochure, IB)
	• Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and

	follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
	
	Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory. Patients with a buffer range from the normal values of +/- 5 % for hematology and +/- 10% for biochemistry are acceptable. A +/- 3 days deviation is also allowed except for the pregnancy test.
	
	Exclusion criteria at randomization
	
	• Treatment with any of the following:
	  • Prior treatment with any systemic anti-cancer therapy for locally advanced/metastatic NSCLC including chemotherapy, biologic therapy, immunotherapy, or any investigational drug;
	  • Prior treatment with an EGFR-TKI;
	  • Major surgery (excluding placement of vascular access) within 4 weeks before randomization;
	  • Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks before randomization.
	  • Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of study drug) medications or herbal supplements known to be potent inhibitors or inducers of cytochrome P450 (CYP) 3A4; antiacids could be taken in a time-separate manner, at least 8 hours from gefitinib;
	  • Other anti-cancer therapies and alternative medications such as homeopathy, etc;
	  • Treatment with an investigational drug within five half-lives of the compound or any of its related material, if known;
	
	• Leptomeningeal carcinomatosis; spinal cord compression;
	• Any unresolved toxicities from prior systemic therapy (e.g., adjuvant chemotherapy) greater than CTCAE grade 2 at the time of randomization;
	• Patients will not be eligible if they have evidence of active malignancy (other than non-melanoma skin cancer or localized cervical cancer or localized and presumed cured prostatic cancer) within 2 years before randomization and are not receiving specific treatment for these malignancies at baseline assessment;
	• Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol;
	• Active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Active infection will include any patients receiving intravenous treatment for infection; active hepatitis B infection will, at a minimum, include all patients who are Hepatitis B surface antigen positive (HbsAg positive) based on serology assessment. Screening for chronic conditions is not required;

	• 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;
	• Any of the following cardiac criteria:
	  • Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 ECGs using local clinic ECG machine-derived QTcF value
	  • Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG, e.g., complete left bundle branch block, third-degree heart block, second-degree heart block, PR interval >250 msec or history of episodes of bradycardia (<50 BPM);
	  • Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval.
	  • Abnormal cardiac function: LVEF <50% (assessed by MUGA or ECHO)
	• Past medical history of ILD (Interstitial Lung Disease), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.

Treatment Test product, dose and mode of administration Duration of treatment	Arm A (intervention): osimertinib 80 mg QD until RECIST progression. Arm B (intervention): gefitinib 250mg QD until cfDNA T790M positive test (criteria for defining progression disease), irrespective of RECIST 1.1 criteria, then patients will receive osimertinib 80 mg QD until RECIST progression. If patients have RECIST progression without cfDNA T790M positive test, they will be switched to osimertinib. Note: as of protocol version 4.0, patients in Arm B on gefitinib will switch to osimertinib on RECIST 1.1 progression only
Reference therapy, dose and mode of administration	Arm C (active control arm): gefitinib 250mg QD until RECIST progression, irrespective of cfDNA T790M test, then patients will receive osimertinib 80 mg QD until second RECIST progression.
Criteria for evaluation Efficacy	**Progression Free Survival Rate at 18 months (PFSR-OSI-18)** The endpoint is evaluated primarily in arm B and arm C. The primary endpoint, Progression Free Survival Rate at 18 months (PFSR-OSI-18) is defined as the proportion of patients at 18 months who are alive and non-progressing after switching to osimertinib. Patients who are still on gefitinib, alive and without progression at 18 months will be counted as a success with respect to the primary endpoint. Practically, the time point of disease evaluation corresponding to the primary endpoint is 18 months after randomization. Therefore, disease evaluation at 18 months (+/- 14 days) is required for all patients who are still alive and without progression on osimertinib at the 18th month. The above disease evaluation is

	also required if patients are without progression and are still on gefitinib at 18 months. Patients without adequate disease assessment at 18 months will be considered as failures. The adequacy of the disease assessments will be subject to the medical review plan which will be completed prior to the interim/final analysis of the study. The baseline to determine disease progression at 18 months is the baseline at randomization. For patients switching to osimertibnib, the nadir of the measurements to determine progression is defined as the nadir after switching to osimertinib. Progression of the disease will be defined based on one or several of the following criteria: Documented radiological progression as defined by RECIST 1.1, using baseline at randomization; Development of new lesions after switching to osimertinib; Unequivocal (according to physician's assessment) deterioration of non-measurable lesions after switching to osimertinib.
Safety	**Adverse events** All adverse events will be recorded; the investigator will assess whether those events are related to osimertinib (reasonable possibility, no reasonable possibility) or gefitinib (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events. The collection period will start from randomization and all adverse events must be followed until resolution or stabilization. **General evaluation of adverse events** This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, for adverse event reporting. A copy of the CTCAE can be accessed from the EORTC home page https://www.eortc.be/services/doc/ctc/. Hematological toxicity will be assessed on the basis of regular blood tests. The nadir count will be computed at each study medication administration and graded according to the CTCAE version 4.0. Non hematological acute side effects will be assessed and reported separately for each study medication administration, and graded according to the CTCAE version 4.0. Planned safety analysis and tabulations are described in the statistics section. **Serious adverse events** Serious adverse events are defined by the Good Clinical Practice Guideline. Serious adverse events should be immediately reported according to the procedure detailed in this protocol.

	Toxic deaths Toxic death is defined as death due to toxicity (defined as adverse events that are not confirmed as unrelated). The cause of death must be reported as "toxicity". The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to therapy). **Evaluability for safety** All patients who have started the treatment (either gefitinib or osimertinib) will be included in overall safety analyses. For hematological events, the medical review team may decide that blood counts have not been performed and/or reported according to the protocol and are therefore inadequate for the evaluation of one/several hematological parameters in some patients. Parameters that will be identified and monitored will be the following: • Any grade 3-4 non hematological or grade 4 hematological toxicity at least possibly related to the treatment; • % of treatment interruptions, schedule modifications and dose modifications; • Compliance to the requirement of minimum dose intensity of 70% (treatment tolerability rule); • Unexpected grade 2 toxicity at least possibly related to the treatment; • Worsening of toxicity if data will be available at the time of DSM. Patients who have discontinued treatment because of toxicity will always be included in the safety analyses.
Statistical methods	**Analysis populations** • Intention-to-treat population: All randomized patients will be analyzed in the arm they were allocated by randomization. • Per protocol population: All patients who are eligible and have started their allocated treatment (at least one dose of the study drug(s) in chemotherapy trials) • Safety population: All patients who have started their allocated treatment (at least one dose of the study drug(s) in chemotherapy trials) A patient will be considered to be eligible if he/she did not have any deviation from the patient entry criteria listed in the protocol. Potential eligibility problems will be assessed by the Clinical Research Physician at time of medical review. **Statistical methods** **Analysis of the primary endpoint** The primary analysis will be performed to per-protocol population.

	Patients with success is defined by the primary endpoint. The PFSR-OSI-18 in each arm and their 84% confidence intervals will be provided. In case the number of patients analyzed in each arm exceeds or less than what is foreseen above, the 84% confidence interval will be used for the decision. **Time to event endpoints** The analyses of the primary and secondary endpoints will be performed on per-protocol population. **Estimates and confidence intervals** Estimates of the median PFS-OSI, TTP-OSI, PFS2-OSI and OS are obtained by the Kaplan Meier technique. The 84% and 95% confidence intervals (CI) for the median will be calculated using the reflected CI method. Estimates of the event-free rate at fixed time point (18 months) will be obtained using the Kaplan Meier technique and 84% 2-sided CI will be calculated by Greenwood's estimation of the standard deviation. Estimates of hazard ratios and their 84% 2-sided CI will be obtained by Cox regression. In addition 95% 2-sided CI will be provided for both the estimates of event rates and hazard ratios. Kaplan Meier Curves will be drawn for both the experimental and control arms on the same plot. **Inference: Test statistics for comparisons** Cox regression (Score Test) will be used to compare the experimental versus the control arms adjusted by the stratification factors in randomization (except for centers) at 1-sided 10% significant level. **Toxicity** Analysis for toxicity is based on the safety population. The worst grade of toxicity/adverse events observed over the whole treatment period (excluding re-challenge period for Arm A) according to CTCAE version 4 will be displayed. No formal statistical analysis will be performed to compare toxicity in both arms. **Response Rate** Patients with response categories progression, early death and unknown will be considered as failing to respond to treatment. The response rates in each arm and their 95% confidence intervals will be provided. In addition, response rates in the 2 arms will be compared using a two-sample test at 5% 2-sided level.
Translational research	The translational research is mandatory for this protocol. Any patient who consent to enter the trial will have to consent for the translational research. **Objectives** The main objectives of translational research study are, but not limited to, the following: • to describe quantitatively the presence of T790M EGFR 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 by RECIST 1.1 longitudinally within the arms. • 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 in formalin-fixed paraffin-embedded (FFPE) samples obtained from patients at baseline and at the time of progress on osimertinib by next generation sequencing and compare the presence of molecular resistance alterations in tissue samples and plasma samples taken on progression. **Human Biological material** • plasma sample taken during screening visit and each treatment visit (every 4 weeks) while patients are within active treatment with gefitinib or osimertinib. Note: if gefitinib or osimertinib is temporarily discontinued due to toxicity, plasma sample should still be obtained. The last plasma sample should be taken from patients who progress on osimertinib by RECIST 1.1 evaluation (all three arms). • FFPE processed biopsy samples at baseline (residual tumor from diagnostic sample) and from progressing tumor lesions obtained from patients receiving osimertinib.

1 Background and introduction

1.1 Incidence

Lung cancer is the third most frequent cancer worldwide with 1.8 million new cases diagnosed in 2012, and the leading cause of cancer-related death worldwide (1.59 million deaths in 2012) [Ref. 1, Ref. 2]. The SEER database currently shows that 60% of non-small-cell lung cancers (NSCLC) are diagnosed in advanced stage [Ref. 3]. Platinum-based doublet chemotherapy is the standard first-line treatment for non-selected patients with advanced NSCLC who have a good performance status [Ref. 4], with a median survival that rarely exceeds 10 months without maintenance treatment [Ref. 5].

Recent progress has been achieved in the management of patients with advanced NSCLC with the identification of tumor-specific molecular alterations, especially in adenocarcinoma histologic subtype, and the development of drugs that target the respective deregulated signaling pathways [Ref. 6, Ref. 7], establishing tumor genotyping as an essential routine diagnostic tool in clinical practice [Ref. 8]. Approximately 50% of advanced NSCLC tumors have a genetic alteration but only 20%-25% of them are actionable oncogenic driver mutations [9]. Moreover, it has been reported that NSCLC patients whose tumor harbors a known oncogenic drivers and receive a matched targeted agent live significantly longer than those who have a driver mutation but do not receive personalized treatment (hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.53–0.9; p = 0.006) [Ref. 10], supporting the clinical benefit of this policy [9]. The most frequent genetic alterations in advanced NSCLC are *KRAS* mutation ~29% of tumors, *EGFR* mutation ~11%, *ALK* rearrangement ~5%, *BRAF* and *PIK3CA* mutations in ~2%, respectively; and *HER2* mutation in 1% of tumors [Ref. 9]. Also, *MET* mutation (exon 14) [Ref. 11] and *ROS1* rearrangements [Ref. 12] have been reported in 4% and 1% of patients with NSCLC, respectively. These oncogenic drivers are almost always mutually exclusive in patients with NSCLC [Ref. 10].

1.2 EGFR mutant advanced NSCLC patients: First-line treatment

There are several classes of activating somatic *EGFR* mutations being the in-frame deletions in exon 19 (*Del19*) and single point mutations in exon 21 (*L858R*) the most common EGFR mutation subtypes. *EGFR* mutations are more frequent in Asian than Caucasian population (~50% vs. 10%) [Ref. 13]. EGFR mutations predict sensitivity to first-generation reversible EGFR tyrosine kinase inhibitors (TKI) erlotinib and gefitinib, and the second-generation irreversible EGFR-TKI such as afatinib. These drugs demonstrated to improve the response rate (RR), progression-free survival (PFS) and quality of life over standard first-line platinum-doublet chemotherapy in several randomized phase III trials in EGFR mutant advanced NSCLC patients. To date, no differences in overall survival (OS) versus standard platinum-doublet chemotherapy have been reported in these trials, possibly due to the high crossover rate to the TKI arm following disease progression in chemotherapy-treated patients [Ref. 14]. However, despite initial dramatic responses and substantial PFS to EGFR TKI observed in phase III clinical trials, most of EGFR mutant NSCLC patients develop acquired resistance (AR) after a median of approximately 12 months from treatment initiation [Ref. 14]. The substitution of threonine to methionine at amino acid position 790 (T790M) in exon 20 of the EGFR gene is the most common type of AR mutation observed, which accounts for 49-70% of AR to EGFR-TKIs using different detecting methods [Ref. 15, Ref. 16, Ref. 17]. Originally T790M mutation was thought to represent an acquired mutation, however, sequencing technologies have revealed the presence of this mutation in EGFR TKI-naïve lung cancer patients, with a variable frequency, from <1% to 79.9% by different tests [Ref. 18, Ref. 19, Ref. 20].

For those EGFR mutant lung cancer patients who progress on EGFR TKI, discontinuation of EGFR TKI and the addition of alternative systemic treatment are common in daily clinical practice, and chemotherapy is the standard of care. In a recent phase III trial (IMPRESS) in EGFR mutant lung cancer patients, mainly

Asian population, with RECIST progression on EGFR TKI, the pemetrexed and platinum-based second-line chemotherapy conferred a 34% of RR with a median PFS of 5.4 months, but with a grade ≥ 3 adverse events in 42% of patients [Ref. 21]. Biomarker analysis from the IMPRESS trial, reported only benefit of continuing EGFRTKI beyond progression in combination with chemotherapy among T790M negative patients, with a trend toward improvement in PFS of 6.7 months vs. 5.4 months [Ref. 22].

1.3 Osimertinib. Efficacy and Safety

Osimertinib (AZD9291, Tagriso ®) is an oral, irreversible, mutant-selective EGFR TKI designed to have activity against tumors bearing sensitizing EGFR mutations and T790M resistance mutations that spares the wild type form of the receptor [Ref. 23].

The phase I AURA trial with osimertinib [Ref. 24] enrolled 253 advanced EGFR mutant NSCLC patients with acquired resistance to erlotinib or gefitinib into dose escalation and expansion cohorts. Prospective T790M status by central laboratory testing was required in expansion cohorts and T790M status was optional for dose escalation cohorts. Patients were included in doses of osimertinib of 20 mg up to 240 mg daily. The ORR was 51% with no differences according to each dose levels of osimertinib. The dose of 80 mg daily was considered as optimal to maximize efficacy and minimize skin and gastrointestinal adverse events observed at the higher doses. According to T790M status, the ORR and PFS were 71% and 9.7 months for T790M positive tumors versus 24.6% and 3 months for T790M negative tumors, respectively [Ref. 10]. In the updated result of the trial with 283 patients (31 patients dose escalation and 252 in expansion cohorts, and 163 T790M positive by central testing) confirmed an ORR of 59% and 23% in the T790M positive and negative patient groups, respectively. At 80 mg the T790M positive cohort achieved an ORR of 54% and a median PFS 13.5 months by centrally reviewed data monitoring [Ref. 25].

In an expansion cohort form the phase I AURA trial (NCT01802632), osimertinib at doses of 80 mg/day or 160 mg/day (sequential cohorts) was administered to 60 treatment-naïve patients with EGFR mutant advanced NSCLC patients (30 patients per arm). The central mutation test reported T790M in 8% of patients. The ORR was 75% (95% CI 66 - 82). The median PFS has not been reached. Overall, the 12-month PFS rate was 71.7%. Grade ≥ 3 AEs were reported by 33% of patients, mainly skin rash and diarrhea, especially with the higher doses [Ref. 26], supporting the efficacy of osimertinib in first-line setting at dose of 80 mg/day. The ongoing FL-AURA (NCT02296125) phase III trial will compare the efficacy measured by PFS and safety of osimertinib (80 mg/d) as first-line treatment to standard of care EGFR TKI (gefitinib 250 mg/d or erlotinib 150 mg/d) in advanced NSCLC patients with common EGFR mutations. In the control arm, crossover to osimertinib will be allowed in case of progression.

In the AURA 2 phase II study, osimertinib 80 mg/day in 199 pre-treated T790M positive advanced NSCLC patients reported a 71% of RR with an immature PFS of 8.6 months and the frequency of treatment-related Grade ≥3 AEs was low (11%) [Ref. 27].

Osimertinib 80 mg once daily has an acceptable safety profile for the intended advanced NSCLC population. In the Phase II studies:

The majority of all causality adverse events (AEs) reported with osimertinib were mild to moderate. Common Terminology Criteria for Adverse Events (CTCAE) ≥Grade 3 events were reported in 29.4% of patients, with 11.7% of CTCAE ≥Grade 3 considered related to osimertinib by the investigator.

Serious adverse events (SAEs) were reported in 20.2% of patients; 5.1% of SAEs were considered causally related to osimertinib by the investigator.

Thirteen patients (3.2%) experienced an AE with the outcome of death; 4 of these deaths (3 patients had AEs of interstitial lung disease [ILD], and 1 patient had an AE of pneumonitis) were considered possibly

related to treatment with osimertinib. In 8 patients, the investigator considered the death to be due to both NSCLC (disease under investigation) and a fatal AE.

The most commonly reported adverse events were low-grade gastrointestinal disturbances primarily: diarrhea (42.3% all grades; 1.0% ≥Grade 3); rash and acne (grouped term: 41.4% all grades; 4.4% Grade ≥3); dry skin (grouped term: 30.9% all grades; none ≥Grade 3), and paronychia 17.5% all grades; none ≥Grade 3).

Nowadays, osimertinib prescription as second-line treatment is restricted to patients with AR to EGFR TKI based on RECIST progression criteria and T790M positivity in a re-biopsy. However, patients whose tumors have progressed on EGFR TKI may be unable or unwilling to provide an additional biopsy for testing of T790M status. Genotyping of cell free circulating plasma DNA (cfDNA) may provide an early and non-invasive option to identify patients who progress to EGFR TKI unable to provide tissue biopsies. Moreover, plasma T790M genotyping results might mirror tumor heterogeneity [Ref. 28].

1.4 Rationale and relevance for patients and the scientific community

Other than radiological techniques are awaited to indicate disease progression and switch treatment in lung cancer patients, particularly where new treatment prescription at AR requires a new tissue biopsy that may lead to potential complications. Moreover, in clinical trials, tumor tissue for treatment eligibility is a significant barrier to trial enrollment and delays treatment initiation [Ref. 7].

A new challenge in the treatment of EGFR mutant NSCLC patients with AR to EGFR TKI is to know whether plasmatic progression (T790M positive in cfDNA, a liquid biopsy) occurs earlier than RECIST progression and whether switching to osimertinib based only on plasmatic progression could improve the overall outcome of patients compared with standard procedure (treatment switching based on RECIST progression in a Computed Tomography (CT) scan). Recent results reported equal efficacy of third-generation EGFR TKI independently whether the T790M research was performed in plasma or in the tissue in EGFR mutant patients with RECIST progression on first-generation EGFR TKI [Ref. 29], suggesting that liquid biopsies could become new standard tests in the near future. Liquid biopsies could also serve as dynamic predictive marker of efficacy on third generation EGFR TKI and also a tool to anticipate radiological progression. Indeed, switch to osimertinib as second-line treatment in EGFR mutant NSCLC patients based only on RECIST progression is justified by the fact that in T790M negative patients the efficacy of osimertinib as second-line treatment appears similar to standard second-line chemotherapy with a better toxicity profile.

At the moment there is no data from randomized phase III trials supporting osimertinib as first-line treatment in EGFR mutant NSCLC patients. However, the efficacy of osimertinib to cover the pre-existing T790M mutation in EGFRTKI-naïve patients (as contrary to gefitinib or afatinib, chronic treatment with osimertinib did not cause acquired resistance in PC-9 –Del19- cells in vitro through gain of T790M [Ref. 30]), the efficacy of osimertinib in sensitizing EGFR mutations, and the promising 9 month PFS of 81% with osimertinib in first-line, even when only 8% of tumors were de novo T790M positive, compared with other EGFR TKI in first-line (9 months PFS of 55% with gefitinib in EGFR mutant lung cancer patients in the IPASS trial [Ref. 31], or 68% with afatinib in EGFR mutant NSCLC patients with common mutations in LUX-Lung 3 trial [Ref. 32]), suggest the choice of osimertinib as investigational first-line treatment in EGFR mutant NSCLC patients. No trial so far has proposed plasma levels as a predictive dynamic marker for making treatment decisions in EGFR mutant NSCLC patients to EGFR TKI compared with classical RECIST criteria. Also it is unknown whether switch strategy is better than upfront third-generation irreversible EGFR TKI.

Based on of these new challenges we hereby propose a phase II study in EGFR mutant and EGFR-TKI naïve NSCLC patients. Patients will be randomized to first-line treatment with osimertinib until RECIST progression (arm A) or gefitinib until cfDNA T790M positive progression (arm B) or RECIST progression (arm C) and then switch to osimertinib until second RECIST progression.

The proposed trial will answer several questions: are liquid biopsies the new standard treatment for defining disease progression in this population? What is the association between biological progression and radiological progression? What is the best treatment approach with third generation EGFR TKI as first-line treatment: upfront or sequential?.

In conclusion, the phase II APPLE trial gives the opportunity to prospectively validate liquid biopsies as a new standard for testing tumor progression compared with conventional radiological procedure in EGFR mutant advanced NSCLC patients. Moreover based on the sequential T790M test during treatment we will assess the predictive value of liquid biopsies. APPLE trial will examine the best strategy for delivering osimertinib (upfront versus sequential treatment after 1st generation EGFR TKI) in EGFR mutant NSCLC patients. Finally, the trial will also explore the mechanisms of acquired resistance to osimertinib based on the results of an optional biopsy upon progression.

2 Objectives of the trial

2.1 Primary objective

To evaluate the best strategy for delivering osimertinib (AZD9291) in NSCLC patients with EGFR mutation. The objective is assessed by Progression Free Survival rate at 18 months (PFS-18) in arm B and arm C (see further details in Chapter 8). No direct comparison with respect to the primary endpoint is planned between any arms.

2.2 Secondary objectives

- To evaluate PFS on osimertinib measured from randomization by RECIST criteria 1.1 [Ref. 33].
- To evaluate PFS measured from switching to osimertinib by RECIST criteria 1.1 [Ref. 33].
- To determine the proportion of patients receiving osimertinib based on the determination of cfDNA T790M mutation positive.
- To evaluate PFS-2.
- To evaluate Overall Response Rate (ORR) to osimertinib.
- To evaluate the Treatment duration.
- To evaluate Time to progression (TTP) on osimertinib (measured from switching to osimertinib).
- To evaluate Overall Survival (OS).
- To evaluate brain progression free survival (BPFS).
- Safety.

2.3 Exploratory objectives

- To assess the feasibility of prospective cfDNA T790M mutation testing during treatment with gefitinib as a predictor of treatment progression and its correlation with RECIST 1.1 progression.
- To assess the feasibility of prospective cfDNA T790M mutation testing during treatment with osimertinib as a predictor of efficacy.
- To assess the change in tumor size upon switching to osimertinib.
- To describe the treatments and outcomes of the treatments administered after osimertinib.
- To evaluate the resistance mechanisms to osimertinib (by optional biopsy at disease progression on osimertinib).

- To evaluate osimertinib efficacy in patients with acquired resistance to gefitinib based on RECIST progression with blinded T790M status.
- To monitor the activating EGFR mutation levels in cfDNA.

2.4 Endpoints

2.4.1 Primary endpoint

PFS Rate at 18 months. Details and definition of the primary endpoint can be found in Section 7.2.1

2.4.2 Secondary endpoints

- PFS measured from switching to osimertinib by RECIST criteria 1.1 [Ref. 33].
- Proportion of patients receiving osimertinib based on the determination of cfDNA T790M mutation positive.
- Time to progression on osimertinib.
- PFS-2.
- Overall Response Rate (ORR) to osimertinib.
- Treatment duration.
- Overall Survival (OS).
- Brain progression free survival (BPFS).
- Safety.

2.4.3 Exploratory endpoints

- Prospective for cfDNA T790M mutation testing on treatment with gefitinib;
- Prospective for cfDNA T790M mutation testing on treatment with osimertinib;
- PFS and OS taking into account treatments administered after osimertinib;
- Resistance mechanisms to osimertinib;
- RECIST 1.1 progression to osimertinib with blinded T790M status [Ref. 33].
- Activating EGFR mutation levels in cfDNA.

3 Patient selection criteria

3.1 Inclusion criteria

3.1.1 Registration

- Pathological diagnosis of adenocarcinoma of the lung carrying common *EGFR* activating mutations associated with EGFR-TKI sensitivity (Del19 or L858R); performed locally; no other EGFR mutations will be allowed. In case of other (than EGFR) concomitant mutations, discussion with EORTC Headquarters is mandatory;
- Stage IV NSCLC;
- Blood sample available for cfDNA EGFR *T790M* central testing;
- Adequate tissue sample in quantity and quality for translational research;
- Age ≥18 years;
- EGFR TKI treatment-naïve eligible to receive first-line treatment with EGFR TKI;
- Prior adjuvant and neo-adjuvant therapy is permitted (chemotherapy, radiotherapy, investigational agents) if performed more than 12 months before registration;
- Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations.

Maximum time elapsed between registration and treatment start should be four weeks, although every effort should be made to start treatment as quickly as possible.

3.1.2 Randomization

- Report of adequacy sample for cfDNA EGFR T790M test by central laboratory;
- Prior palliative radiotherapy or surgical procedures are allowed if completed at least 4 weeks before randomization;
- Patients with brain metastases are allowed provided they are stable (i.e. without evidence of progression by imaging for at least two weeks prior to the first dose of trial treatment and without deterioration of any neurologic symptoms), and have not received steroids for at least 7 days before randomization;
- Baseline tumor assessment scans are done within 21 days before randomization;
- Evaluable disease as defined below;
    - At least one lesion, not previously irradiated and not chosen for biopsy during the study screening period, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis of ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI), and which is suitable for accurate repeated measurements.
- WHO Performance Status 0-2, with no clinically significant deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks;
- Adequate bone marrow, renal, hepatic and liver function within 21 days from randomization and defined as follows:
    - Absolute neutrophil count ≥1.5 x 10^9/L;
    - Platelet count ≥100 x 10^9/L;
    - Hemoglobin ≥9 g/dL;
    - Alanine aminotransferase (ALT) ≤2.5x the upper limit of normal (ULN) if no demonstrable liver metastases or ≤5xULN in the presence of liver metastases;
    - Aspartate aminotransferase (AST) ≤2.5xULN if no demonstrable liver metastases or ≤5xULN in the presence of liver metastases;
    - Total bilirubin ≤1.5xULN if no liver metastases or ≤3xULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or liver metastases;
    - Serum Creatinine ≤1.5xULN concurrent with creatinine clearance ≥50 mL/min (measured or calculated by Cockcroft and Gault equation);
- No significant comorbidity that according to the investigator would hamper the participation on the trial;
- Female patients should be using adequate contraceptive measures as defined by the investigator, during the treatment until 6 weeks after last dose of osimertinib. They should not be breastfeeding, until 12 months after the last dose, and must have a negative pregnancy test (serum or urine) prior to first dose of study drug (within 72 hours); or female patients must have an evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:
    - Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments.
    - Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the post-menopausal range for the institution.

  - Documentation of irreversible surgical sterilization by hysterectomy, bilateraloophorectomy, or bilateral salpingectomy but not tubal ligation.

- Male patients should be willing to use barrier contraception, i.e., condoms as defined by the investigator, during the treatment until 4 months after last dose of osimertinib.
  - Male patients will be advised to arrange for the freezing of sperm samples prior to the start of the study should they wish to father children, and not to donate sperm until 6 months after discontinuation of study treatment. (as per Investigator Brochure, IB)
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory. Patients with a buffer range from the normal values of +/- 5 % for hematology and +/- 10% for biochemistry are acceptable. A +/- 3 days deviation is also allowed except for the pregnancy test.

3.2 Exclusion criteria at randomization

- Treatment with any of the following:
  - Prior treatment with any systemic anti-cancer therapy for locally advanced/metastatic NSCLC including chemotherapy, biologic therapy, immunotherapy, or any investigational drug;
  - Prior treatment with an EGFR-TKI;
  - Major surgery (excluding placement of vascular access) within 4 weeks before randomization;
  - Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks before randomization.
- Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of study drug) medications or herbal supplements known to be potent inhibitors or inducers of cytochrome P450 (CYP) 3A4 (see Appendix E); antiacids could be taken in a time-separate manner, at least 8 hours from gefitinib.
- Other anti-cancer therapies and alternative medications such as homeopathy, etc;
- Treatment with an investigational drug within five half-lives of the compound or any of its related material, if known;
- Leptomeningeal carcinomatosis; spinal cord compression;
- Any unresolved toxicities from prior systemic therapy (e.g., adjuvant chemotherapy) greater than CTCAE grade 2 at the time of randomization;
- Patients will not be eligible if they have evidence of active malignancy (other than non-melanoma skin cancer or localized cervical cancer or localized and presumed cured prostatic cancer) within 2 years before randomization and are not receiving specific treatment for these malignancies at baseline assessment;
- Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol;
- Active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Active infection will include any patients receiving intravenous treatment for infection; active hepatitis B infection will, at a minimum, include all patients who are Hepatitis B surface antigen positive (HbsAg positive) based on serology assessment. Screening for chronic conditions is not required;

- 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;
- Any of the following cardiac criteria:
    - Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 ECGs using local clinic ECG machine-derived QTcF value
    - Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG, e.g., complete left bundle branch block, third-degree heart block, second-degree heart block, PR interval >250 msec or history of episodes of bradycardia (<50 BPM);
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT síndrome family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval.
    - Abnormal cardiac function: LVEF <50% (assessed by MUGA or ECHO)
- Past medical history of ILD (Interstitial Lung Disease), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.

4 Trial Design

This is an open-label, randomized, three-armed, multicentric, phase II study in *EGFR* mutant advanced NSCLC patients.

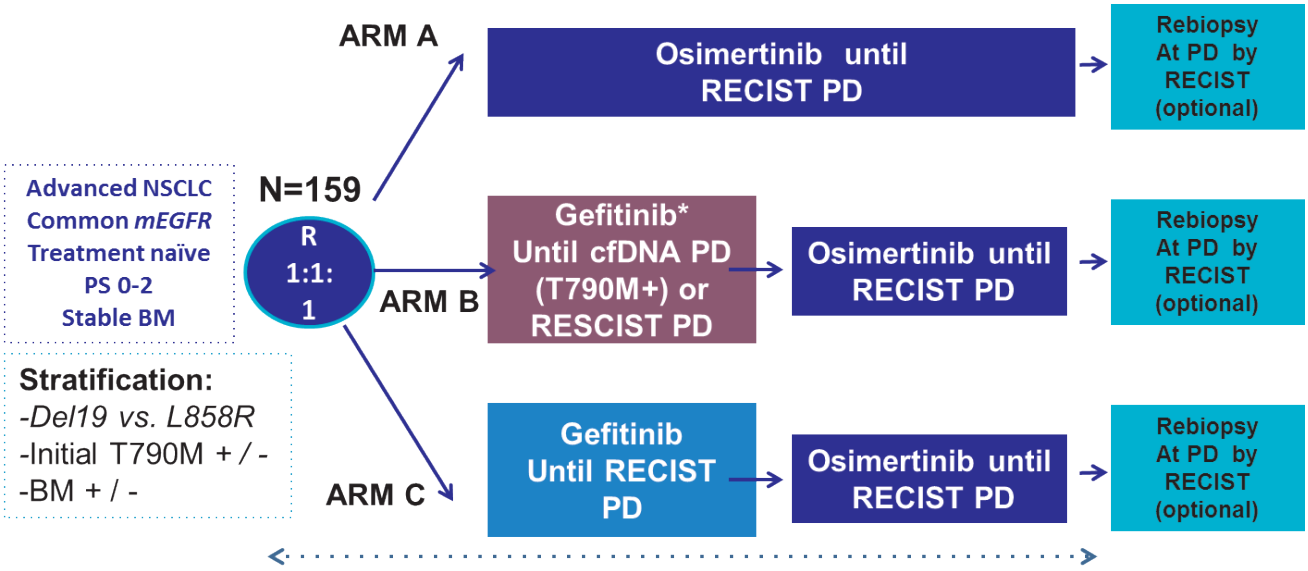
Patients will first be registered into the EORTC ORTA system (registration = step 1) after signing the informed consent form and completion of all screening tests and confirmation of eligibility criteria for registration. The site will immediately send the blood samples for circulating free DNA EGFR T790M (cfDNA T790M) testing to the central lab (within 24 hours at maximum) at the Medical University of Gdansk (Poland). Once the sample is assessed and acknowledged for adequacy by the central lab, the result is entered in ORTA by EORTC (step 2), the site will be notified whether they can further proceed to patient randomization in the EORTC ORTA system. Should the sample not be deemed adequate by the central lab the site will be requested to send another blood sample for testing. Patients will be randomized (step 3) after verification of all eligibility criteria to receive one of the following:

- Osimertinib (arm A) until PD according to RECIST 1.1;
- Gefitinib until emergence of positive T790M status ("cfDNA T790M positive progression") (arm B) followed by osimertinib until second PD according to RECIST 1.1;
- Gefitinib until PD according to RECIST 1.1 followed by osimertinib until PD according to RECIST 1.1 (arm C).

In arm B, if patients have RECIST 1.1 progression without cfDNA T790M positive test, they will be switched to osimertinib.

As of protocol v. 4.0, the T790M tests no longer need to be performed in arms A, B or C, including in Arm B for patients still on gefitinib. These patients should continue on gefitinib until progression by RECIST 1.1 as in Arm C.

Maximum time elapsed between registration and treatment start should be four weeks, although every effort should be made to start treatment as quickly as possible. Basal cfDNA T790M status was blinded in arms A and C, and only reported in arm B during the first part of treatment (gefitinib period until disease progression). During osimertinib treatment, T790M status was blinded in the three arms of the study - progression of disease on osimertinib is defined according RECIST 1.1 criteria.



4.1 Treatment beyond progression

The local investigator may choose to continue treatment with osimertinib beyond RECIST 1.1 PD, if, in their opinion, the patient continues to receive clinical benefit. However, this should be discussed with the EORTC HQ. Information on post-PD treatment needs to be provided to EORTC HQ and follow-up must follow chapter 6 according to the treatment arm.

In case of oligo-progressive disease (please refer to chapter 0) in a known metastatic lesion local therapy (radiotherapy / surgery / cryotherapy) will be allowed after mandatory discussion with EORTC headquarters. This procedure will be reported in the CRF. Information on post-PD treatment needs to be provided to EORTC HQ and follow-up must follow chapter 6 according to the treatment arm.

5 Therapeutic regimens, expected toxicity, dose modifications

Osimertinib (AZD9291) and gefitinib are considered as Investigational Medicinal Products.

5.1 Osimertinib

5.1.1 General information

DrugBank number: DM09330

Other names: AZD9291

Trade name: Tagrisso

Molecular weight: 499.62

Description: orally taken, beige, filmcoated tablet containing 40 mg or 80 mg of osimertinib expressed as free base (equivalent of 47.7 mg or 95.4 mg of osimertinib mesalate).

Osimertinib (TAGRISSO ™1, laboratory code AZD9291) is an oral, irreversible inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor activating mutation (EGFRm) and the resistance mutation (T790M) specifically.

For more general information related to osimertinib please refer to the latest version of the Investigator Brochure.

5.1.2 Drug supply

Drug supplies and re-supplies will be provided free of charge by [redacted] (for procedures: see study drug guidelines that will be provided at the time of activation).

The osimertinib drug product is provided in the high-density polyethylene bottles, 35 tablets per bottle.

All instructions pertaining to drug management and drug supply can be found in the study drug guidelines (provided as a separate document).

5.1.3 Packaging, dispensing and storage

Drug labels will comply with good manufacturing practice (GMP) and will be printed in the national language. The storage conditions for study drug will be described on the medication label.

Osimertinib must be stored at room temperature (between 15-30°C or 59-86°F).

Osimertinib tablets should not be used beyond the expiration date provided by the manufacturer.

Study drug will be prepared and dispensed by the pharmacist at the investigator's institution. The pharmacy must maintain an individual record for the patient.

The clinical trial centers will keep a trial specific authorization list which determines the persons responsible for handling of the investigational drugs. The responsible person will follow the standard practice and directive (Annex 13).

For more information regarding the packaging, storage and dispensing of osimertinib please refer to the latest version of the Investigator Brochure and the drug guidelines.

5.1.4 Drug reconciliation procedures

Accountability of the investigational study drug(s) is under the responsibility of the investigator and can be delegated to an appropriately qualified person.

Study drug accountability should be maintained by each site.

In addition to internal accountability documentation on site, EORTC study-specific accountability and drug destruction forms will be supplied for this purpose, if site-specific forms are deemed not sufficiently detailed or do not provide enough information, according to EORTC Quality Assurance criteria.

The drug accountability and destruction forms will be verified during monitoring visits.

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification by EORTC in order to allow drug destruction or return procedure.

Both the unused and expired study medication must be destroyed, upon authorization of the sponsor, according to local regulations and procedures, and a copy of the destruction form must be returned to the EORTC HQ.

The medication provided for this trial is to be used only as indicated in this protocol and only for the patients entered in this study.

5.2 Gefitinib

5.2.1 General information

DrugBank number: DM00317

Other names: ZD1839

Trade name: IRESSA 250

Molecular weight: 446.90

Description: orally taken, brown, round, biconvex tablets containing 250 mg of gefitinib

Gefitinib (IRESSA™, laboratory code) is an oral, reversible inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor activating mutation (EGFRm).

For more general information related to gefitinib please refer to the latest version of the Summary of Product Characteristics (SmPC).

5.2.2 Drug supply

Drug supplies and re-supplies will be provided free of charge by [redacted] (for procedures: see study drug guidelines that will be provided at the time of activation).

Gefitinib is provided in in the high-density polyethylene bottles, 30 tablets per bottle.

All instructions pertaining to drug management can be found in the study drug guidelines (provided as a separate document).

For more information regarding the supply of gefitinib please refer to the latest version of the SmPC.

5.2.3 Packaging, dispensing and storage

Drug labels will comply with the good manufacturing practice (GMP) and will be printed in the national language. The storage conditions for study drug will be described on the medication label.

Gefitinib must be stored at room temperature (between 15-30°C or 59-86°F).

Gefitinib tablets should not be used beyond the expiration date provided by the manufacturer.

Study drug will be prepared and dispensed by the pharmacist at the investigator's institution. The pharmacy must maintain an individual record for the patient.

The clinical trial centers will keep a trial specific authorization list which determines the persons responsible for handling of the investigational drugs. The responsible person will follow the standard practice and directive (Annex 13).

For more information regarding the packaging, storage and dispensing of gefitinib please refer to the latest version of the SmPC.

5.2.4 Drug reconciliation procedures

Accountability of the investigational study drug(s) is under the responsibility of the investigator and can be delegated to an appropriately qualified person.

Study drug accountability should be maintained by each site.

In addition to internal accountability documentation on site, EORTC study-specific accountability and drug destruction forms will be supplied for this purpose, if site-specific forms are deemed not sufficiently detailed or do not provide enough information, according to EORTC Quality Assurance criteria.

The drug accountability and destruction forms will be verified during monitoring visits.

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification by EORTC in order to allow drug destruction or return procedure.

Both the unused and expired study medication must be destroyed, upon authorization of the sponsor, according to local regulations and procedures, and a copy of the destruction form must be returned to the EORTC HQ.

The medication provided for this trial is to be used only as indicated in this protocol and only for the patients entered in this study.

5.3 Initial dose and schedule

Advanced *EGFR* mutant NSCLC and EGFR-TKI naïve patients, will be randomized to:

- Arm A: osimertinib 80 mg QD until RECIST 1.1 progression.
- Arm B: gefitinib 250mg QD until cfDNA T790M positive test (criteria for defining progression disease), irrespective of RECIST 1.1 criteria, then patients will receive osimertinib 80 mg QD until RECIST 1.1 progression. If patients have RECIST 1.1 progression without cfDNA T790M positive test, they will be switched to osimertinib.
- Arm C: gefitinib 250mg QD until RECIST 1.1 progression, irrespective of cfDNA T790M test, then patients will receive osimertinib 80 mg QD until RECIST 1.1 progression.

Continuation of osimertinib post-PD is allowed on individual basis provided that in the opinion of treating physician, patient may benefit from this therapy (please refer also to section 4.1).

Osimertinib or gefitinib must be swallowed with a glass of water and must not be mashed or chewed. The tablets can be taken preferably in the morning with or without meals

The initial dose of osimertinib 80 mg once daily can be reduced to 40 mg once daily. The initial dose for gefitinib (250 mg once daily) cannot be reduced to a lower dose.

5.4 Treatment duration

- In ARM A (osimertinib): Treatment should be administered until documented disease progression by RECIST 1.1 criteria, unacceptable toxicity, or patient refusal. Continuation of osimertinib post-PD is allowed on individual basis provided that in the opinion of treating physician, patient may benefit from this therapy.
- In ARM B (gefitinib): Treatment should be administered until RECIST 1.1 progression at which point osimertinib will be started. In case of unacceptable toxicity to any of both drugs or patient refusal, treatment can be discontinued. Continuation of osimertinib post-PD is allowed on individual basis provided that in the opinion of treating physician, patient may benefit from this therapy.
- In ARM C (gefitinib): Treatment should be administered until documented disease progression by RECIST 1.1 criteria, unacceptable toxicity, or patient refusal. Then patients will receive osimertinib until RECIST 1.1 progression. In case of unacceptable toxicity to any of both drugs or patient refusal, treatment can be discontinued. Continuation of osimertinib post-PD is allowed on individual basis provided that in the opinion of treating physician, patient may benefit from this therapy.

5.5 Withdrawal criteria

Whatever the disease status, the treatment will always be discontinued in case of

- AE or intercurrent illness that, in the opinion of the investigator, warrants the patient's withdrawal from study treatment;
- Patient refusal or lost to follow-up;
- Excessive toxicity precluding further therapy, according to the responsible physician;
- Any adverse events specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AE in section 5.6 and subsections

- Significant non-compliance/non-adherence with the protocol schedule in the opinion of the investigator or the sponsor;
- PD according to RECIST 1.1 to osimertinib; continuation of osimertinib post-PD is allowed on individual basis provided that in the opinion of treating physician, patient may benefit from this therapy;
- Pregnancy;
- Start of a new anticancer treatment.

Patients discontinuing therapy not according to the protocol should not receive any other cancer treatment before their disease progresses, unless this is clearly not in the interest of the patient according to the local investigator.

After progression to osimertinib, the treatment will be left to the discretion of the treating physician. Any anti-cancer therapy other than the study drug given as single agent will not be considered as part of the protocol treatment.

5.6 Dose and schedule modifications

Dose modifications are required only for toxicities that are not considered to the disease or disease-related processes under investigation. Dose modifications are not required for events that are not considered clinically significant such as isolated laboratory abnormalities, alopecia.

Note: Persistent grade 1 AE, lasting longer than 10 days under appropriate treatment, should be considered and treated as a grade 2 event.

5.6.1 Osimertinib

All patients start treatment with osimertinib at 80 mg daily irrespective if the patient received osimertinib as first-line treatment or as sequential treatment after gefitinib. Only 1 dose reduction with osimertinib (to 40 mg) will be allowed during the study.

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade) not attributable to the disease or disease-related processes under investigation, where the Investigator considers the AE of concern to be specifically associated with the study drug dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

If the toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset, study drug may be restarted at the same dose (starting dose) or a lower dose (40 mg) using the rules below for dose modification (Table "Recommended dose modifications with osimertinib). There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption. If restarting at the same dose level, patients should be closely monitored for 3 days following the restart of treatment. If within 3 days there is recurrence of same toxicity, a dose reduction should be considered at the Investigator's discretion.

If the toxicity does not resolve to ≤CTCAE grade 2 after 3 weeks of withholding osimertinib, then the patient should be withdrawn from the study treatment and observed until resolution of the toxicity. There will be no individual modifications to treatment schedule in response to toxicity, only potential dose reduction or dose interruption.

If an AE subsequently requires dose interruption, study drug may restart at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the investigator as described above.

Recommended dose modifications with osimertinib

Target Organ	Adverse reaction	Modification
Pulmonary	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue osimertinib
Cardiac	QTc† interval greater than 500 msec on at least 2 separate ECGsb	Withhold osimertinib until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec within 3 weeks of withholding osimertinib, then resume at 40 mg dose or at 80 mg (at the discretion of the investigator, to allow for situations where causality in relation to osimertinib may be difficult to determine)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
	Asymptomatic, absolute decrease in LVEFc of 10% from baseline and below 50%	Withhold osimertinib for up to 2 weeks. • If improved to baseline LVEF, resume. • If not improved to baseline, permanently discontinue.
	Symptomatic congestive heart failure	Permanently discontinue osimertinib
Other	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks
	If improvement to Grade 1 within 3 weeks	Resume at 80 mg or 40 mg daily
	If no improvement to Grade1 within 3 weeks	Permanently discontinue osimertinib

5.6.1.1 Interstitial Lung Disease (ILD)/pneumonitis like toxicity

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease/pneumonitis is observed, an interruption in study treatment dosing is recommended, and the Sponsor study team should be informed.

It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema or pulmonary hemorrhage. The results of full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters) will be captured by eCRF.

In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued.

5.6.1.2 QTc prolongation

In light of the potential for QT changes associated with osimertinib, electrolyte abnormalities (hypokalemia, hypomagnesaemia, hypocalcemia) must be corrected to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment.

Patients with QTcF prolongation to >500 msec should have study treatment interrupted and regular ECGs performed until resolution to <481 msec or recovery to baseline if baseline QTcF is >481 msec and then restarted at a reduced dose of 40 mg, or 80mg at the discretion of the investigator. If the toxicity does not resolve to ≤ grade 1 within 21 days of withholding osimertinib the patient will be permanently withdrawn from study treatment.

5.6.1.3 Erythema multiforme and Stevens-Johnson syndrome

Case reports of Erythema multiforme (EM) and Stevens-Johnson syndrome (SJS) have been uncommonly and rarely reported, respectively, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM and SJS. If signs and symptoms suggestive of EM develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted or discontinued immediately.

5.6.1.4 Aplastic anaemia

Rare reports of aplastic anaemia have been reported in association with osimertinib treatment. Some cases had a fatal outcome. Before initiating treatment, patients should be advised of signs and symptoms of aplastic anaemia including but not limited to persistent fever, bruising, bleeding, and/or pallor. If signs and symptoms suggestive of aplastic anaemia develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. Osimertinib should be discontinued in patients with confirmed aplastic anaemia.

5.6.1.5 Changes in cardiac contractility

Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

5.6.1.6 Keratitis

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

5.6.2 Gefitinib

The initial dose for gefitinib (250 mg once daily) cannot be reduced to a lower dose. The dose of gefitinib may be withheld or discontinued if clinically indicated at the discretion of the Investigator

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade) not attributable to the disease or disease-related processes under investigation, where the Investigator

considers the AE of concern to be specifically associated with the study drug dosing will be interrupted and optimal supportive therapy administered as required in accordance with local practice/guidelines.

If the toxicity resolves or reverts to CTCAE grade to baseline within 2 weeks of onset, study drug may be restarted at the same dose. If restarting at the same dose level, patients should be closely monitored for 3 days following the restart of treatment. If within 3 days there is recurrence of same toxicity patient should be withdrawn from the study treatment and observed until resolution of the toxicity.

For Grade 2 dermatological events, dosing may be continued at investigator discretion with optimal and appropriate supportive therapy administered as required in accordance with local practice / guidelines.

5.7 Concomitant treatments

5.7.1 Osimertinib

The use of any natural/herbal products or other “folk remedies” should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF. In vitro data have shown that the principal CYP enzyme responsible for the Phase I metabolism of osimertinib is CYP3A4.Once enrolled all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known to be potent inducers of CYP3A4 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of adverse events. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of osimertinib.

All concomitant medications should be captured on the eCRF. Guidance on medicines to avoid, medications that require close monitoring and on washout periods is provided (see Appendix E).

If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see above), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon BCRP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Appendix E).

Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.

Please refer to Appendix E for any further information on guidance for concomitant medications.

5.7.2 Gefitinib

Gefitinib is metabolized by the CYP3A4 and the CYP2D6.

Drugs which inhibit CYP3A4 activity (ketoconazole, posaconazole, voriconazole, proteasome inhibitors, claritromicin, telitromicine) might increase plasmatic concentrations of gefitinib. There are no data about the concomitant treatment with drugs that inhibit CYP2D6.

Plasmatic dose of gefitinib can be reduced when is administered concomitantly with drugs which increase CYP3A4 activity such as: phenytoin, rifampicin, barbiturates or St John’s Wort.

Antiacids such as omeprazole can increase the gastric pH and it reduces plasmatic concentrations of gefitinib. Omeprazol and other proton pump inhibitors cannot be used in combination with gefitinib.

Those patients under treatment with warfarin should be monitored as per standard practice because there is an increased risk of hemorrhagic events or INR alteration.

5.7.3 Supportive care in case of toxicity

Please refer to Appendix F.

5.7.4 Other concomitant therapies

In case of RECIST 1.1 progression on a known lesion during osimertinib treatment, surgery, radiotherapy and cryotherapy will be allowed.

No other systemic anticancer therapies will be allowed.

Administration of Covid vaccine will be a treating physician decision after evaluation of benefit-risk ratio and depending of local vaccine availability and compliance with local regulatory guidelines. In cancer patients, the use of inactivated virus vaccines are usually permitted and live vaccines are generally prohibited in those receiving immunosuppressive treatments. Information on the mRNA based COVID-19 vaccines when used in cancer patients is currently not available. See Appendix F for EMA recommendations.

6 Clinical evaluation, laboratory tests and follow-up

As described in chapter 4, a cycle of treatment is defined as 28 days of once daily treatment with osimertinib or gefitinib.

In arm A, after 24 weeks, the duration between study visits will change from every 28 days (4 weeks) to every 56 days (8 weeks).

In arm B and C, study visits will be every 28 days (4 weeks) until the switch to osimertinib. After that, one visit will be performed 28 days after osimertinib initiation, the second one at 8 weeks with radiological evaluation and then every 56 days (8 weeks) if no progression on the first CT scan after osimertinib initiation.

6.1 Arm A

6.1.1 Before randomization

Baseline assessments need to be performed within 21 days prior to randomization:

- Signature of the informed consent;
- Assessment of eligibility criteria;
- Assessment of the baseline signs and symptoms and adverse events based on CTCAE version 4.0, performance status and medical history;
- Collection of concomitant medication;
- Demographics, physical examination, including vital signs, height, weight and blood pressure;
- Laboratory examination including:
    - hematology: white blood cell (WBC) with differential count, platelets (PLTs), hemoglobin (Hb);
    - biochemistry: blood urea nitrogen (BUN), serum creatinine and calculated creatinine clearance (by Cockcroft), uric acid, albumin, total bilirubin, Alkaline Phosphatase (AP), Aspartate AminoTransferase (AST/ASAT), Alanine AminoTransferase (ALT/ALAT), Gamma-Glutamyl Transferase (GGT), sodium, potassium, Lactic Dehydrogenase (LDH), total calcium, phosphorus, magnesium, glucose;

Note: * Electrolyte abnormalities (hypokalemia, hypomagnesaemia, hypocalcemia) must be corrected to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment.

- Beta HCG (serum) for women of childbearing potential. This test must be negative within 72h before first dose of treatment;
- Stick urinalysis;

- Digital ECG with QTc interval; no alteration in QTc interval should be reported before osimertinib initiation;
- LVEF assessed by MUGA or ECHO
- Collection of plasma sample for central T790M status;
- Collection of tumor sample for translational research (please refer to section 10.2);
- Thoracic and upper abdomen contrasted-enhanced CT scan (including adrenal glands) and brain CT scan; if a patient is allergic to contrast adequate premedication as per local practice should be provided. Should there be any further constraint, the EORTC Headquarters should be contacted as soon as possible.
- Ophthalmological examination;
- Geriatric G8 assessment for 70 years old patients or older.

6.1.2 During treatment

In women of childbearing potential, pregnancy test (serum or urine beta HCG) is to be performed every 4 weeks (+/- 2 days) or more frequently if required by national regulations/institution guidelines.

6.1.2.1 Every 4 weeks (+/- 2 days) for the first 24 weeks

- Adverse events and Performance Status assessment;
- Collection of concomitant medication;
- Physical examination, including vital signs, height, weight and blood pressure;
- Laboratory examination including:
  - hematology: please see section 6.1.1;
  - biochemistry: please see section 6.1.1;
- Collection of plasma sample for central T790M status to be performed every 28 days during all treatment duration independently of medical visits. The results of this test will be blinded for the investigator;
- Digital ECG with QT interval;
- Ophthalmological examination if clinically indicated.

6.1.2.2 At week 12 (+/- 2 days)

- LVEF assessed by MUGA or ECHO

6.1.2.3 Every 8 weeks (+/-3 days) after week 24

After week 24, the duration between study visits will change from every 28 days (4 weeks) to every 56 days (8 weeks) until discontinuation of osimertinib, please refer to criteria sections 5.4 and 5.5. Radiological evaluation will follow section 6.1.2.4.

- Adverse events and Performance Status assessment;
- Collection of concomitant medication;
- Physical examination, including vital signs, height, weight and blood pressure;
- Laboratory examination including:

- hematology: please see section 6.1.1;
- biochemistry: please see section 6.1.1.

- Digital ECG with QT interval;
- LVEF assessed by MUGA or ECHO if clinically indicated
- Ophthalmological examination if clinically indicated.

6.1.2.4 Radiological evaluation every 8 weeks (+/- 7 days), first scan at 8 weeks after baseline scan

Tumor assessments by thoracic and upper abdomen contrasted-enhanced CT scan (including adrenal glands) and brain CT scan every 8 weeks independently of delayed or interrupted doses. If a patient is allergic to contrast adequate premedication as per local practice should be provided. Should there be any further constraint, the EORTC Headquarters should be contacted as soon as possible.

The same schedule for radiologic assessment needs to be performed until both criteria are met:

- **end of osimertinib treatment;**
- **the second documented, RECIST 1.1 radiological progression.**

6.1.3 At the end of treatment

Treatment is continued until objective PD to osimertinib according to RECIST 1.1, or other discontinuation criteria are met (such as toxicity, patient refusal, etc) please refer to sections 5.4 and 5.5.

When the treatment is decided to be permanently stopped, an end of treatment visit needs to be performed at 30 days after last protocol treatment (+/- 7 days) and the following assessments are required:

- Adverse event collection;
- Performance Status and clinical examination including vital signs, height, weight and blood pressure;
- Collection of concomitant medication;
- In case objective progression as per RECIST 1.1 and an optional tissue biopsy can be performed, results will be collected in the study.

A 28-day follow-up LVEF assessment by MUGA or ECHO will be required if an on-treatment assessment was abnormal at the time of discontinuation of study treatment, to confirm reversibility of the abnormality.

Patients who discontinue study drug for reasons other than objective disease progression will additionally continue assessments for objective PD; please refer to section 6.1.2.4.

6.1.4 During Follow-up

After end of treatment, patients will be followed up every 8 weeks for:

- Any anti-cancer therapy administered after osimertinib. Response to new anti-cancer therapy will be collected if available;
- Survival status;
- Complementary examination will be performed according local physician standards.
- Contrast-enhanced CT scan of the thorax and upper abdomen and brain CT scan should be performed every 8 weeks until a second progression as per RECIST 1.1. If a patient is allergic to contrast adequate premedication as per local practice should be provided. Should there be any further constraint, the EORTC Headquarters should be contacted as soon as possible.

6.2 Arm B

6.2.1 Before randomization

Baseline assessments need to be performed within 21 days prior to randomization:

- Signature of the informed consent;
- Assessment of eligibility criteria;
- Assessment of the baseline signs and symptoms and adverse events based on CTCAE version 4.0, performance status and medical history;
- Collection of concomitant medication;
- Demographics, physical examination, including vital signs, height, weight and blood pressure;
- Laboratory examination including:
    - hematology: please refer to section 6.1.1;
    - biochemistry: please refer to section 6.1.1;
    - Beta HCG (serum) for women of childbearing potential. This test must be negative within 72h before first dose of treatment;
    - Stick urinalysis.
- Digital ECG with QT interval; no alteration in QT interval should be reported before osimertinib initiation;
- LVEF assessed by MUGA or ECHO
- Collection of plasma sample for central T790M status;
- Collection of tumor sample for translational research (please refer to section 10.2);
- Thoracic and upper abdomen contrasted-enhanced CT scan (including adrenal glands) and brain CT scan; if a patient is allergic to contrast adequate premedication as per local practice should be provided. Should there be any further constraint, the EORTC Headquarters should be contacted as soon as possible.
- Geriatric G8 assessment for 70 years old patients or older.

6.2.2 During treatment on gefitinib

6.2.2.1 Every 8 weeks (+/- 2 days)

- Adverse events and Performance Status assessment;
- Collection of concomitant medication;
- Physical examination, including vital signs, height, weight and blood pressure;
- Laboratory examination including:
    - hematology: please see section 6.1.1;
    - biochemistry: please see section 6.1.1;
    - Pregnancy test: serum (or urine) beta HCG in women of childbearing potential or more frequently if required by national regulations/institution guidelines.

6.2.2.2 Radiological evaluation every 8 weeks (+/- 7 days), first scan at 8 weeks after baseline scan

Tumor assessments by thoracic and upper abdomen contrasted-enhanced CT scan (including adrenal glands) and brain CT scan every 8 weeks independently of delayed or interrupted doses. If a patient is allergic to contrast adequate premedication as per local practice should be provided. Should there be any further constraint, the EORTC Headquarters should be contacted as soon as possible.

In case of disease progression according to RECIST 1.1 criteria, patients will be switched to osimertinib at the next per protocol planned medical visit (4 weeks since previous medical visit as per section 6.2.2.1).

IMPORTANT: this every 8 week schedule remains in place, as per calendar, also after the switch to osimertinib.

6.2.3 During treatment on osimertinib

Patients must stop gefitinib 48 hours before osimertinib initiation.

In women of childbearing potential, pregnancy test (serum or urine beta HCG) is to be performed every 4 weeks (+/- 2 days) or more frequently if required by national regulations/institution guidelines.

6.2.3.1 Day 1 cycle 1 (within 3 days prior to actual osimertinib dosing)

- Adverse events and Performance Status assessment;
- Physical examination, including vital signs, height, weight and blood pressure;
- Collection of concomitant medication;
- Laboratory examination including:
  - hematology: please see section 6.1.1;
  - biochemistry: please see section 6.1.1.
- Digital ECG with QT interval;
- LVEF assessed by MUGA or ECHO
- Ophthalmological examination.

6.2.3.2 Every 4 weeks (+/-2 days) from week 1 until week 24

- Adverse events and Performance Status assessment;
- Collection of concomitant medication;
- Physical examination, including vital signs, height, weight and blood pressure;
- Laboratory examination including:
  - hematology: please see section 6.1.1;
  - biochemistry: please see section 6.1.1.
- Digital ECG with QT interval;
- Ophthalmological examination if clinically indicated.

6.2.3.3 At week 12 (+/- 2 days)

- LVEF assessed by MUGA or ECHO

6.2.3.4 Every 8 weeks (+/- 3 days) from week 24

After week 24, the duration between study visits will change from every 28 days (4 weeks) to every 56 days (8 weeks) until discontinuation of osimertinib, please refer to criteria sections 5.4 and 5.5. Radiological evaluation will follow section 6.2.3.5.

- Adverse events and Performance Status assessment;
- Collection of concomitant medication;
- Physical examination, including vital signs, height, weight and blood pressure;
- Laboratory examination including:
  - hematology: please see section 6.1.1;
  - biochemistry: please see section 6.1.1.

- Digital ECG with QT interval;
- LVEF assessed by MUGA or ECHO if clinically indicated
- Ophthalmological examination if clinically indicated.

6.2.3.5 Radiological evaluation every 8 weeks (+/- 7 days), first scan at 8 weeks after baseline scan

Tumor assessments by thoracic and upper abdomen contrasted-enhanced CT scan (including adrenal glands) and brain CT scan every 8 weeks independently of delayed or interrupted doses. If a patient is allergic to contrast adequate premedication as per local practice should be provided. Should there be any further constraint, the EORTC Headquarters should be contacted as soon as possible.

6.2.4 At the end of treatment

Treatment is continued until objective PD to osimertinib according to RECIST 1.1, or other discontinuation criteria are met (such as toxicity, patient refusal, etc) please refer to sections 5.4 and 5.5.

When the treatment is decided to be permanently stopped, an end of treatment visit needs to be performed at 30 days after last protocol treatment (+/- 7 days) and the following assessments are required:

- Adverse event collection;
- Performance Status and clinical examination;
- Collection of concomitant medication;
- In case of objective progression on osimertinib by RECIST 1.1 an optional tissue biopsy can be performed, results will be collected in the study.

A 28-day follow-up LVEF assessment by MUGA or ECHO will be required if an on-treatment assessment was abnormal at the time of discontinuation of study treatment, to confirm reversibility of the abnormality.

Patients who discontinue study drug for reasons other than objective disease progression will additionally continue assessments for objective PD; please refer to section 6.2.5.

6.2.5 During Follow-up

After end of treatment, patients will be followed up every 8 weeks for:

- Any anti-cancer therapy administered after osimertinib. Response to new anti-cancer therapy will be collected if available;
- Survival status;
- Complementary examination will be performed according local physician standards.

If treatment was interrupted without any objective PD per RECIST 1.1 being identified, follow-up will also include, until objective disease progression per RECIST 1.1:

- Contrast-enhanced CT scan of the brain, thorax and upper abdomen performed every 8 weeks. If a patient is allergic to contrast adequate premedication as per local practice should be provided. Should there be any further constraint, the EORTC Headquarters should be contacted as soon as possible.

6.3 Arm C

6.3.1 Before randomization

Baseline assessments need to be performed within 21 days prior to randomization:

- Signature of the informed consent;
- Assessment of eligibility criteria;
- Assessment of the baseline signs and symptoms and adverse events based on CTCAE version 4.0, performance status and medical history;
- Collection of concomitant medication;
- Demographics, physical examination, including vital signs, height, weight and blood pressure;
- Laboratory examination including:
    - hematology: please refer to section 6.1.1;
    - biochemistry: please refer to section 6.1.1;
    - Beta HCG (serum) for women of childbearing potential. This test must be negative within 72h before first dose of treatment;
    - Stick urinalysis.
- Digital ECG with QT interval; no alteration in QT interval should be reported before osimertinib initiation;
- LVEF assessed by MUGA or ECHO
- Collection of plasma sample for central T790M status;
- Collection of tumor sample for translational research (please refer to section 10.2);
- Thoracic and upper abdomen contrasted-enhanced CT scan (including adrenal glands) and brain CT scan; if a patient is allergic to contrast adequate premedication as per local practice should be provided. Should there be any further constraint, the EORTC Headquarters should be contacted as soon as possible.
- Geriatric G8 assessment for 70 years old patients or older.

6.3.2 During treatment on gefitinib

6.3.2.1 Every 8 weeks (+/- 2 days)

- Adverse events and Performance Status assessment;
- Collection of concomitant medication;
- Physical examination, including vital signs, height, weight and blood pressure;
- Laboratory examination including:
    - hematology: please see section 6.1.1;
    - biochemistry: please see section 6.1.1;
    - Pregnancy test: serum (or urine) beta HCG in women of childbearing potential or more frequently if required by national regulations/institution guidelines.

6.3.2.2 Radiological evaluation every 8 weeks (+/- 7 days)

Tumor assessments by brain, thoracic and upper abdomen contrasted-enhanced CT scan (including adrenal glands) every 8 weeks independently of delayed or interrupted doses. If a patient is allergic to contrast adequate premedication as per local practice should be provided. Should there be any further constraint, the EORTC Headquarters should be contacted as soon as possible.

In case of progression on gefitinib according RECIST 1.1 criteria, independently of T790M status, patients will be switched to osimertinib at the next per protocol planned medical visit (4 weeks since previous medical visit as per section 6.3.2.1).

IMPORTANT: this every 8 week schedule remains in place, as per calendar, also after the switch to osimertinib.

6.3.3 During treatment on osimertinib

In case of progression on gefitinib according RECIST 1.1 criteria, independently of plasmatic T790M status, patients must be switched to osimertinib at the next per protocol planned medical visit (4 weeks since previous medical visit as per section 6.3.2.1).

Patients must stop gefitinib 48 hours before osimertinib initiation.

In women of childbearing potential, pregnancy test (serum or urine beta HCG) is to be performed every 4 weeks (+/- 2 days) or more frequently if required by national regulations/institution guidelines.

6.3.3.1 Day 1 cycle 1 (within 3 days prior to actual osimertinib dosing)

- Adverse events and Performance Status assessment;
- Physical examination, including vital signs, height, weight and blood pressure;
- Collection of concomitant medication
- Laboratory examination including:
  - hematology: please see section 6.1.1;
  - biochemistry: please see section 6.1.1.
- Digital ECG with QT interval;
- LVEF assessed by MUGA or ECHO
- Ophthalmological examination.

6.3.3.2 Every 4 weeks (+/-2 days) from week 1 until week 24

- Adverse events and Performance Status assessment;
- Collection of concomitant medication;
- Physical examination, including vital signs, height, weight and blood pressure;
- Laboratory examination including:
  - hematology: please see section 6.1.1;
  - biochemistry: please see section 6.1.1.
- Digital ECG with QT interval;
- Ophthalmological examination if clinically indicated.

6.3.3.3 At week 12 (+/- 2 days)

- LVEF assessed by MUGA or ECHO

6.3.3.4 Every 8 weeks (+/- 3 days) from week 24

After week 24, the duration between study visits will change from every 28 days (4 weeks) to every 56 days (8 weeks) until discontinuation of osimertinib, please refer to criteria sections 5.4 and 5.5. Radiological examination will follow section 6.3.3.5.

- Adverse events and Performance Status assessment;
- Collection of concomitant medication;
- Physical examination, including vital signs, height, weight and blood pressure;

- Laboratory examination including:
  - hematology: please see section 6.1.1;
  - biochemistry: please see section 6.1.1.
- Digital ECG with QT interval;
- LVEF assessed by MUGA or ECHO if clinically indicated
- Ophthalmological examination if clinically indicated.

6.3.3.5 Radiological evaluation every 8 weeks (+/- 7 days), first scan at 8 weeks after baseline scan

Tumor assessments by thoracic and upper abdomen contrasted-enhanced CT scan (including adrenal glands) and brain CT scan every 8 weeks independently of delayed or interrupted doses. If a patient is allergic to contrast adequate premedication as per local practice should be provided. Should there be any further constraint, the EORTC Headquarters should be contacted as soon as possible.

6.3.4 At the end of treatment

Treatment is continued until objective PD to osimertinib according to RECIST 1.1, or other discontinuation criteria are met (such as toxicity, patient refusal, etc) please refer to sections 5.4 and 5.5.

When the treatment is decided to be permanently stopped, an end of treatment visit needs to be performed at 30 days after last protocol treatment (+/- 7 days) and the following assessments are required:

- Adverse event collection;
- Performance Status and clinical examination;
- Collection of concomitant medication;
- In case objective progression as per RECIST 1.1 and an optional tissue biopsy can be performed, results will be collected in the study.

A 28-day follow-up LVEF assessment by MUGA or ECHO will be required if an on-treatment assessment was abnormal at the time of discontinuation of study treatment, to confirm reversibility of the abnormality.

Patients who discontinue study drug for reasons other than objective disease progression will additionally continue assessments for objective PD; please refer to section 6.3.5.

6.3.5 During Follow-up

After end of treatment, subjects will be followed up every 8 weeks for:

- Any anti-cancer therapy administered after osimertinib. Response to new anti-cancer therapy will be collected if available;
- Survival status.
- Complementary examination will be performed according local physician standards.

If treatment was interrupted without any objective PD per RECIST 1.1 being identified, follow-up will also include, until objective disease progression per RECIST 1.1:

- Contrast-enhanced CT scan of the thorax and upper abdomen and brain CT scan performed every 8 weeks; if a patient is allergic to contrast adequate premedication as per local practice should be provided. Should there be any further constraint, the EORTC Headquarters should be contacted as soon as possible.

6.4 Summary tables

6.4.1 Arm A

	Before randomization	During treatment			At the end of treatment	Follow-up
		From week 1 to week 24		After week 24		
		Every 4 weeks (+/- 2 days)	Every 8 weeks (+/- 7 days)	Every 8 weeks (+/- 7 days)		
Signature of Informed Consent	x					
Eligibility criteria	x					
Medical history	x					
Baseline symptom assessment	x					
Concomitant medication	x	x		x	x	
AE and PS assessment	x	x		x	x	
Physical examination, including vital signs, height, weight and blood pressure	x	x		x	x	
Lab exam[1]	x	x		x	x	
Collection of plasma sample for central T790M status	x	x				
Collection of tissue sample	x					
Pregnancy test[2]	x[2]	every 4 weeks (+/- 2 days) or more frequently if required by national regulations/institution guidelines.				
Stick urinanalysis	x					
ECG	x	x		x		
LVEF assessed by MUGA or ECHO	x	x[4]		x[5]		
Imaging evaluation[3]	x[3]		x[3]	x[3]	x[3]	x[3]

	Before randomization	During treatment			At the end of treatment	Follow-up
		From week 1 to week 24		After week 24		
		Every 4 weeks (+/- 2 days)	Every 8 weeks (+/- 7 days)	Every 8 weeks (+/- 7 days)		
Ophthalmological examination	x	x[5]		x[5]	x[5]	
G8 assessment[6]	x[6]					
Survival status						x
Optional tissue biopsy					x[7]	

[1] hematology: white blood cell (WBC) with differential count, platelets (PLTs), hemoglobin (Hb); biochemistry: blood urea nitrogen (BUN), serum creatinine and calculated creatinine clearance (by Cockcroft), uric acid, albumin, total bilirubin, Alkaline Phosphatase (AP), Aspartate AminoTransferase (AST/ASAT), Alanine AminoTransferase (ALT/ALAT), Gamma-Glutamyl Transferase (GGT), sodium, potassium, Lactic Dehydrogenase (LDH), total calcium, phosphorus, magnesium, glucose

[2] the test must be negative within 72 hours before treatment start

[3] Contrasted enhanced CT scan of the thorax and upper abdomen (including adrenal glands) and brain CT scan. The same schedule for radiologic assessment needs to be performed until both criteria are met: (a) end of osimertinib treatment; (b) the second documented, RECIST 1.1 radiological progression.

[4] at week 12 on osimertinib and if clinically indicated

[5] if clinically indicated

[6] for 70 years old patients or older

[7] In case of RECISTS 1.1 progression

6.4.2 Arm B

	Before randomization	During treatment with gefitinib	During treatment with osimertinib*				At the end of treatment	Follow-up
			From week 1 to week 24			After week 24		
		Every 8 weeks (+/- 7 days)	Day 1 cycle 1**	Every 4 weeks (+/- 2 days)	Every 8 weeks (+/- 7 days)	Every 8 weeks (+/- 7 days)		
Signature of Informed Consent	x							
Eligibility criteria	x							
Medical history	x							
Baseline symptom assessment	x							
Concomitant medication	x	x	x	x		x	x	
AE and PS assessment	x	x	x	x		x	x	
Physical examination, including vital signs, height, weight and blood pressure	x	x	x	x		x	x	
Lab exam[1]	x	x	x	x		x	x	
Collection of plasma sample for central T790M status	x							
Collection of tissue sample	x							
Pregnancy test[2]	x[2]		every 4 weeks (+/- 2 days) or more frequently if required by national regulations/institution guidelines.					
Stick urinanalysis	x							
ECG	x		x	x		x		

	Before randomization	During treatment with gefitinib	During treatment with osimertinib*				At the end of treatment	Follow-up
			From week 1 to week 24			After week 24		
		Every 8 weeks (+/- 7 days)	Day 1 cycle 1**	Every 4 weeks (+/- 2 days)	Every 8 weeks (+/- 7 days)	Every 8 weeks (+/- 7 days)		
LVEF assessed by MUGA or ECHO	x		x	x[4]		x[5]		
Imaging evaluation[3]	x[3]	x[3]			x[3]	x[3]	x[3]	x[3]
Ophthalmological examination			x	x[5]		x[5]	x[5]	
G8 assessment[6]	x[6]							
Survival status								x
Optional tissue biopsy							x[7]	

[1] hematology: white blood cell (WBC) with differential count, platelets (PLTs), hemoglobin (Hb); biochemistry: blood urea nitrogen (BUN), serum creatinine and calculated creatinine clearance (by Cockcroft), uric acid, albumin, total bilirubin, Alkaline Phosphatase (AP), Aspartate AminoTransferase (AST/ASAT), Alanine AminoTransferase (ALT/ALAT), Gamma-Glutamyl Transferase (GGT), sodium, potassium, Lactic Dehydrogenase (LDH), total calcium, phosphorus, magnesium, glucose

[2] the test must be negative within 72 hours before treatment start

[3] Contrasted enhanced CT scan of the thorax and upper abdomen (including adrenal glands) and brain CT scan. **IMPORTANT: this every 8 week schedule remains in place, as per calendar, also after the switch to osimertinib.** If treatment was interrupted without any objective PD per RECIST 1.1 being identified, imaging needs to be continued until objective disease progression per RECIST 1.1.

[4] at week 12 on osimertinib and if clinically indicated

[5] if clinically indicated

[6] for 70 years old patients or older

[7] In case of RECISTS 1.1 progression

*Patients must stop gefitinib 48 hours before osimertinib initiation.

** within 3 days prior to actual osimertinib dosing

6.4.3 Arm C

	Before randomization	During treatment with gefitinib		During treatment with osimertinib*				At the end of treatment	Follow-up
				From week 1 to week 24			After week 24		
			Every 8 weeks (+/- 7 days)	Day 1 cycle 1**	Every 4 weeks (+/- 2 days)	Every 8 weeks (+/- 7 days)	Every 8 weeks (+/- 7 days)		
Signature of Informed Consent	x								
Eligibility criteria	x								
Medical history	x								
Baseline symptom assessment	x								
Concomitant medication	x		X	x	x		x	x	
AE and PS assessment	x		X	x	x		x	x	
Physical examination, including vital signs, height, weight and blood pressure	x		X	x	x		x	x	
Lab exam[1]	x		x	x	x		x	x	
Collection of plasma sample for central T790M status	x								
Collection of tissue sample	x								
Pregnancy test[2]	x[2]	x		every 4 weeks (+/- 2 days) or more frequently if required by national regulations/institution guidelines.					
Stick urinanalysis	x								
ECG	x			x	x		x		

	Before randomization	During treatment with gefitinib		During treatment with osimertinib*				At the end of treatment	Follow-up
				From week 1 to week 24			After week 24		
			Every 8 weeks (+/- 7 days)	Day 1 cycle 1**	Every 4 weeks (+/- 2 days)	Every 8 weeks (+/- 7 days)	Every 8 weeks (+/- 7 days)		
LVEF assessed by MUGA or ECHO	x			x	x[4]		x[5]		
Imaging evaluation[3]	x[3]		x[3]			x[3]	x[3]	x[3]	x[3]
Ophthalmological examination				x[5]	x[5]		x[5]	x[5]	
G8 assessment[6]	x[6]								
Survival status									x
Optional tissue biopsy								x[7]	

[1] hematology: white blood cell (WBC) with differential count, platelets (PLTs), hemoglobin (Hb); biochemistry: blood urea nitrogen (BUN), serum creatinine and calculated creatinine clearance (by Cockcroft), uric acid, albumin, total bilirubin, Alkaline Phosphatase (AP), Aspartate AminoTransferase (AST/ASAT), Alanine AminoTransferase (ALT/ALAT), Gamma-Glutamyl Transferase (GGT), sodium, potassium, Lactic Dehydrogenase (LDH), total calcium, phosphorus, magnesium, glucose

[2] the test must be negative within 72 hours before treatment start

[3] Contrasted enhanced CT scan of the thorax and upper abdomen (including adrenal glands) and brain CT scan. **IMPORTANT: this every 8 week schedule remains in place, as per calendar, also after the switch to osimertinib.** If treatment was interrupted without any objective PD per RECIST 1.1 being identified, imaging needs to be continued until objective disease progression per RECIST 1.1.

[4] at week 12 on osimertinib and if clinically indicated

[5] if clinically indicated

[6] for 70 years old patients or older

[7] In case of RECISTS 1.1 progression

*Patients must stop gefitinib 48 hours before osimertinib initiation.

** within 3 days prior to actual osimertinib dosing

7 Criteria of evaluation

7.1 Evaluation of efficacy

Objective tumor response and time to progression will be measured according to the RECIST criteria (version 1.1, Ref. 33).

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.

Imaging datasets will be collected on an ongoing basis and reviewed retrospectively (details in section 15.4).

The following paragraphs are a quick reference to the RECIST criteria (version 1.1). The complete criteria are included in the published RECIST document [Ref. 33] also available at http://www.eortc.be/RECIST.

7.1.1 Measurability of tumor lesions at baseline

7.1.1.1 Definitions

- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - *tumor lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥ 10 mm with CT scan or clinical examination [using calipers]. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component > 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- **Non-measurable lesions** - All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.
- **Target Lesions**. When more than one measurable tumor lesion or malignant lymph node is present at baseline all lesions up to *a maximum of 3 lesions total* (and a maximum of 2 *lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a *short* axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 3) is to be calculated and recorded.
- **Non-target Lesions**. All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm), plus any measurable lesions over and above those

listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

7.1.1.2 Methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

- **Clinical Lesions**. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.
- **Chest X-ray**. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions > 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **CT, MRI**. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for bone scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).
- **Cytology, Histology**. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

7.1.2 Tumor response evaluation

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumor markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

Table 1: Integration of Target, non-Target and New lesions into response assessment

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this category also requires**
Patients with Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 8 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression [or evidence of unequivocal disease progression] at that time should be reported as "*symptomatic deterioration*". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.				

7.1.2.1 Frequency of tumor re-evaluation

Tumor evaluation is done through CT scan of the brain, thorax and upper abdomen (including adrenal glands) every 8 weeks.

The baseline imaging is done within 14 days from randomization and thereafter every 8 weeks.

For the patients in arm B that will switch their treatment based on the biological PD, the baseline imaging will be the most recent one (regularly done as per schedule) to the treatment start to osimertinib.

7.1.2.2 Date of progression

This is defined as the first day when the RECIST (version 1.1) criteria for PD are met. Refer to Ref. 33 as well as below (section 7.2.1) for further information on what constitutes early progression, assessment of progression of non-target disease, new lesions and usage of FDG-PET to diagnose progression.

7.1.3 Oligoprogression

This is defined as the first day when the RECIST (version 1.1) criteria for PD are met however the number of new lesions is up to 3 and amenable to local therapies (stereotactic radiotherapy or surgery).

7.1.4 Reporting of tumor response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable.

Early death is defined as any death occurring before the first per protocol time point of tumor re-evaluation.

Patients' response will be classified as "not evaluable" if insufficient data were collected to allow evaluation per these criteria.

7.2 Endpoints Definition

7.2.1 Progression Free Survival Rate at 18 months (PFSR-OSI-18)

The primary endpoint in this study is Progression Free Survival rate according to RECIST 1.1 "while receiving osimertinib" at 18 months (PFSR-OSI-18). This endpoint is evaluated in arm B and C. In arm A, the endpoint is assessed to simply provide a point estimate for PFSR-OSI-18 and the corresponding confidence interval.

The primary endpoint is defined as the proportion of patients at 18 months who are alive and did not experience an event for PFS-OSI according to the definition in section 7.2.2.

Practically, the time point of disease evaluation corresponding to the primary endpoint is 18 months after randomization. Therefore, disease evaluation at 18 months (+/- 14 days) is required for all patients who are still alive and without an event for PFS-OSI at the 18th month. Disease evaluation done within a window of +/- 2 weeks will be taken into account for the 18-month assessment.

Progression Free Survival rate according to RECIST 1.1 "while receiving osimertinib" at 18 months (PFSR-OSI-18) will be estimated using the Kaplan Meier technique in order to take into account possible failures of follow-up not due or related to the event of interest (progression or death).

7.2.2 PFS by RECIST 1.1 while receiving osimertinib (PFS-OSI)

This endpoint is evaluated in arm B and C. In arm A, the endpoint is assessed to simply provide a point estimate for median PFS-OSI and the corresponding confidence interval.

ARM A:

For patients in arm A, progression Free Survival "while receiving osimertinib" (PFS-OSI) is defined as the time interval between the date of randomization and the date of disease progression according to the RECIST criteria (version 1.1) or death whichever comes first (i.e. calculated as the difference between the two dates). This corresponds to the classical definition of PFS according to RECIST v1.1.

For each patient, the value for PFS-OSI will be used in the analysis regardless of whether or not intercurrent events occur such as protocol treatment discontinuation or further use of other anticancer therapies or use of concomitant medication etc... **As a consequence, tumor re-evaluation should continue until the event of interest despite the occurrence of any intercurrent event.**

Patients alive and free of progression prior to the analysis cut-off date are censored at the date of the last disease assessment before the cut-off date.

ARM B and C:

- **For patients in arm B and C switching to osimertinib**, progression Free Survival "while receiving osimertinib" (PFS-OSI) is defined as the time interval between the date of randomization and the date of disease progression or death "after switching to osimertinib" whichever comes first (i.e. calculated as the difference between the two dates), thus taking into account the influence of the switching strategy under investigation on the following treatment line.

  The baseline to determine disease progression is the baseline at randomization. For patients in arm B and C switching to osimertinib, the nadir of the measurements to determine progression is defined as the nadir after switching to osimertinib. Disease progression is defined in section 7.1.2 and date of progression is defined in section 7.1.2.2.

- **For patients in arm B and C who do not start osimertinib for any reason**, PFS-OSI is defined as the time interval between the date of randomization and the date of disease progression according to the RECIST criteria (version 1.1) or death whichever comes first (i.e. calculated as the difference between the two dates). This corresponds to the classical definition of PFS according to RECIST v1.1.

  For each patient, the value for PFS-OSI will be used in the analysis regardless of whether or not intercurrent events occur such as protocol treatment discontinuation or further use of other anticancer therapies or use of concomitant medication etc... **As a consequence, tumor re-evaluation should continue until the event of interest despite the occurrence of any intercurrent event**.

If neither event has been observed prior to the analysis cut-off date, then the patient is censored at the date of the last disease assessment before the cut-off date.

7.2.3 Proportion of patients receiving osimertinib based on the determination of cfDNA T790M mutation positive

The proportion of patients receiving osimertinib based on the determination of cfDNA T790M is the number of patients receiving at least 1 dose of osimertinib based on the determination of cfDNA T790M (positive mutation). This endpoint is only defined and applicable for Arm B.

7.2.4 Time to progression on osimertinib (TTP-OSI)

Time to progression on osimertinib is defined as the time interval between the date receiving osimertinib and the date of disease progression. Death is not counted as an event.

The baseline to determine disease progression is the baseline at randomization. For patients in arm B and C switching to osimertinib, the nadir of the measurements to determine progression is defined as the nadir after switching to osimertinib.

Disease progression is defined in section 7.1.2 and date of progression is defined in section 7.1.2.2. If the event has not been observed or if the patient dies before the analysis cut-off date, then the patient is censored at the date of the last disease assessment or the date of death prior the cut-off date. Patients not receiving osimertinib are excluded for this endpoint. The nature of this endpoint is different in Arm A (first line progression) from Arm B and C (second line progression).

7.2.5 PFS-2

In Arm A, PFS-2 is calculated as the time between randomization and the second PD by RECIST 1.1 or death, irrespective of treatment(s) received.

In Arm B and C, PFS-2 is calculated as the time between randomization and the second PD by RECIST 1.1 or death after switching to osimertinib, the first PD being PD by RECIST 1.1 or by positive cfDNA T790M status. For patients unable to start osimertinib, PFS-2 is calculated as the time between randomization and the second PD by RECIST 1.1 on any subsequent off protocol anticancer treatment line.

If no PFS-2 event has been observed prior to the analysis cut-off date, then the patient is censored at the date of the last disease assessment before the cut-off date.

7.2.6 Overall Response Rate (ORR) to osimertinib

Overall Response Rate (ORR) to osimertinib is an overall rate including patients with documented complete response (CR) or partial response (PR) while patients are receiving osimertinib, where CR and PR are defined according to the principles mentioned in section 7.1.2. Patients not receiving osimertinib will not be included in the ORR to osimertinib analysis.

The nature of this endpoint is different in Arm A (first line ORR) from Arm B and C (second line ORR).

7.2.7 Treatment duration

Treatment duration will be measured from the time of randomization until the protocol treatment stops. In Arms B and C, if patients receive osimertinib , the duration is calculated till osimertinib stops.

7.2.8 Overall Survival (OS)

Overall survival (OS) is defined as the time interval between the date of randomization and the date of death from any cause. Patients still alive at the analysis cut-off date are censored at the last date known to be alive (before the cut-off date).

7.2.9 Brain progression free survival (BPFS)

Brain progression free survival is defined as the time interval between the randomization and the date of brain progression (progression within target lesions in the brain, unequivocal progression in non-target lesions in the brain, or appearance of new lesions in the brain) or death whichever comes first.

Disease progression is defined in section 7.1.2 and date of progression is defined in section 7.1.2.2. CT scan will be used to evaluate new or recurrence progression in the brain. If the event has not been observed or if the patient dies or has PD that hampered further assessment/evaluation of brain progression, then the patient is censored at the date of the last follow up examination or day of death.

7.2.10 Exploratory endpoint: change in tumor size

Change in tumor size is defined as the difference in each tumor evaluation from the baseline measurement at the time of starting or switching to osimertinib. More information about this endpoint can be found in [Ref. 35].

7.3 Evaluation of safety

7.3.1 Adverse events

All adverse events will be recorded; the investigator will assess whether those events are related to osimertinib (reasonable possibility, no reasonable possibility) or gefitinib (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events.

The collection period will start from randomization and all adverse events must be followed until resolution or stabilization.

7.3.2 General evaluation of adverse events

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, for adverse event reporting. A copy of the CTCAE can be accessed from the EORTC home page https://www.eortc.be/services/doc/ctc/.

Hematological toxicity will be assessed on the basis of regular blood tests. The nadir count will be computed at each study medication administration and graded according to the CTCAE version 4.0.

Non hematological acute side effects will be assessed and reported separately for each study medication administration, and graded according to the CTCAE version 4.0.

Planned safety analysis and tabulations are described in the statistics section.

7.3.3 Serious adverse events

Serious adverse events are defined by the Good Clinical Practice Guideline.

Serious adverse events should be immediately reported according to the procedure detailed in this protocol (see chapter on Reporting Serious Adverse Events).

7.3.4 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events that are not confirmed as unrelated). The cause of death must be reported as "toxicity".

The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to therapy).

7.3.5 Evaluability for safety

All patients who have started the treatment (either gefitinib or orsimertinib) will be included in overall safety analyses.

For hematological events, the medical review team may decide that blood counts have not been performed and/or reported according to the protocol and are therefore inadequate for the evaluation of one/several hematological parameters in some patients.

Parameters that will be identified and monitored will be the following:

- Any grade 3-4 non hematological or grade 4 hematological toxicity at least possibly related to the treatment;
- % of treatment interruptions, schedule modifications and dose modifications;
- Compliance to the requirement of minimum dose intensity of 70% (treatment tolerability rule);
- Unexpected grade 2 toxicity at least possibly related to the treatment;
- Worsening of toxicity if data will be available at the time of DSM.

Patients who have discontinued treatment because of toxicity will always be included in the safety analyses.

7.4 Evaluation of frailty using the G8 geriatric screening tool

7.4.1 Background

Older cancer patients have a much more heterogeneous general health status compared to young cancer patients. Some older patients are in perfect general health, while others are vulnerable or frail. Frailty is a well-known concept in geriatric medicine [Ref. 36]. It is defined as a multi-factorial syndrome, resulting in a reduction of the physiological reserve and of the capability to resist stressful events (homeostatic capacity). Frailty is associated with an increased risk of unfavorable clinical events: disability, hospitalization, institutionalization, death. In oncology, the construct of frailty is as well used to describe patients with increased risk of treatment-associated morbidity and mortality. Presence of frailty can be detected by a so-called (Comprehensive) Geriatric Assessment (GA). Performance of GA is advised in older cancer patients by the International Society of Geriatric Oncology, SIOG [Ref. 37]. GA is time consuming (takes about 30 minutes). Therefore, short geriatric screening tools such as the G8 have been developed as a short and easy to use measurement of general health status. The G8 score has been specifically developed in oncology, includes 8 items, takes a few minutes to complete, and can be completed by any health care worker [Ref. 38]. The score ranges from 1 to 17. A score greater than 14 indicates that there is little risk that further GA reveals significant problems in the further assessed GA domains. The G8 was shown to strongly predict functional decline and overall survival [Ref. 39]. G8 is by far the best studied geriatric screening tool in oncological patients, and also has better performance for detection of geriatric problems than other geriatric screening tools such as VES-13 [Ref. 40].

7.4.2 Assessments

G8 will be measured in all patients aged 70 years and above at baseline. G8 has to be completed by the clinician, the nurse or the trained coder. This screening tool includes 7 items of the Mini Nutritional Assessment and the age of the patient. The English version of G8 is included as a protocol appendix (Appendix D).

7.4.3 Objective

The inclusion of the G8 screening tool in EORTC trials will allow a uniform, easy and established approach of frailty at baseline. The G8 tool itself has been developed as a screening tool, and not a tool for follow-up.

The treating physician may decide which actions are needed based on the G8 result (e.g. further geriatric assessment in case of a G8 score of less or equal to 14; geriatric interventions if specific problems are detected within specific geriatric domains).

The assessment of frailty as defined by G8 in all patients aged 70 years and above entered in EORTC trials will allow interpretation of whether new treatment strategies have been tested in both fit and less fit patients which has importance for the generalizability of the study results.

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

This study is designed with an understanding of the difficulty of having a primary endpoint which solidly covers all arms. The primary endpoint PFSR-OSI-18 as defined in Chapter 0, will be assessed in all arms, yet this endpoint will be used to evaluate arm B and arm C. With this restriction , the below criteria for a success of the arm (applicable B and C) should be viewed as exploratory and further information from secondary endpoints as well as the costs should be considered if the arm is judged as feasible to be further explored.

The study design is a 1-Stage Ahern Design - Single Proportion, with Progression Free Survival rate at 18 months (PFSR-OSI-18) as primary endpoint. It was designed with a 1-sided alpha = 0.08 and 92% power (beta = 8%).

In arm B and C of this trial, if the result is compatible with a progression free survival rate at 18 months (PFSR-OSI-18) of 60% in the studied population, the strategy should be further explored. However, if we are unable to demonstrate that the PFSR-OSI-18 in the studied population is at least 40%, the strategy should be rejected from further exploration.

49 eligible patients who started treatment are needed in each arm. To declare the arm worthwhile for further exploration, at least 25 out of 49 patients should be a success (see definition of the primary endpoint in section 7.2.1) at 18 months.

Additional 5% patients will be accrued to take into account patients who might be ineligible or not starting treatment. Hence, using a 1:1:1 ratio for randomization, a total of 156 patients will be accrued in this study (52 pts in each arm) within 26 months and an additional 24 months of follow up after the last patient entry is needed to allow the assessment of the primary endpoint. The estimated duration of the study is 6 years, given that all patients have ended their treatment according to End of Study definition (section 8.4).

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

8.1.2 Power to detect a difference in brain progression free survival (BPFS)

In this study, a special emphasis is given to the secondary endpoint BPFS. Formal comparison between arm A versus B and A versus C with respect to BPFS will be made. The power of such comparison is given below.

With a 1-sided alpha = 5% (so that a 1-sided family wise error: 10%, taking into account 2 comparisons), and looking for an improvement in BPFS at 18 months from 75% to 87.5% (equivalent to 54% reduction in risk of progression, i.e. HR = 0.46), 36 BPFS events will give an approximately 70% power to detect the above difference.

8.1.3 Randomization and stratifications

Patients will be centrally randomized (for practical details, see chapter on registration / randomization procedure). A minimization technique will be used for random treatment allocation stratifying by institution, Type of mutation (Del19 vs. L858R), Initial T790M (Yes vs. No) and Brain Metastasis (Yes vs. No).

8.2 Statistical analysis plan

Analyses described below will be done separately for each arm, except for the secondary endpoint BPFS where comparisons between the arms (i.e. A vs. B, B vs. C and A vs. C) will be conducted.

8.2.1 Analysis populations

- Intention-to-treat population: All randomized patients will be analyzed in the arm they were allocated by randomization.
- Per protocol population: All patients who are eligible and have started their allocated treatment (at least one dose of the study drug(s) in chemotherapy trials)
- Safety population: All patients who have started their allocated treatment (at least one dose of the study drug(s) in chemotherapy trials)

A patient will be considered to be eligible if he/she did not have any deviation from the patient entry criteria listed in chapter 3 of the protocol. Potential eligibility problems will be assessed by the Clinical Research Physician at time of medical review.

8.2.2 Statistical methods

Analysis of the primary endpoint

The primary analysis will be performed to per-protocol population.

Patients with success is defined by the primary endpoint in Section 7.2.1. The PFSR-OSI-18 in each arm and their 84% confidence intervals will be provided. In case the number of patients analyzed in each arm exceeds or less than what is foreseen above (Section 8.1.1), the 84% confidence interval will be used for the decision.

Time to event endpoints

The analyses of the primary and secondary endpoints will be performed on per-protocol population. Comparison between arms are foreseen for BPFS endpoint only.

Estimates and confidence intervals

Estimates of the median PFS-OSI, TTP-OSI, PFS2-OSI and OS are obtained by the Kaplan Meier technique. The 84% and 95% confidence intervals (CI) for the median will be calculated using the reflected CI method.

Estimates of the event-free rate at fixed time point (18 months) will be obtained using the Kaplan Meier technique and 84% 2-sided CI will be calculated by Greenwood's estimation of the standard deviation. Estimates of hazard ratios and their 84% 2-sided CI will be obtained by Cox regression. In addition 95% 2-sided CI will be provided for both the estimates of event rates and hazard ratios. Kaplan Meier Curves will be drawn for both the experimental and control arms on the same plot.

Inference: Test statistics for comparisons (for BPFS)

Cox regression (Score Test) will be used to compare the experimental versus the control arms adjusted by the stratification factors in randomization (except for centers) at 1-sided 10% significant level.

Toxicity

Analysis for toxicity is based on the safety population. The worst grade of toxicity/adverse events observed over the whole treatment period (excluding re-challenge period for Arm A) according to CTCAE version 4 will be displayed. No formal statistical analysis will be performed to compare toxicity in both arms.

Response Rate

Patients with response categories progression, early death and unknown will be considered as failing to respond to treatment. The response rates in each arm and their 95% confidence intervals will be provided. In addition, response rates in the 2 arms will be compared using a two-sample test at 5% 2-sided level.

8.2.3 Pre-planned sensitivity or exploratory analyses

A sensitivity analysis of efficacy based on intent to treat (ITT) population will be conducted in addition to the primary analysis based on per protocol population.

Sensitivity analyses will be conducted on PFS-OSI rate at 18 months according to RECIST 1.1 (primary endpoint) to verify the robustness of the results vis-à-vis the missing data. Once the main analysis is completed, PFSR-OSI-18 will be analyzed as binary endpoint. The following sensitivity analyses will be conducted:

- Patients lost-to-follow up before 18 months, i.e. with missing assessments at 18 months (using the window of ± 2 weeks) and at all times thereafter will be considered as having an event at 18 months (worst case scenario). Only patients with the confirmation they are alive and progression free at 18 months (status for PFS not missing at 18 months or after and status at 18 months is no progression) will be considered event free at 18 months.
  In details,
  - Patients alive and without any progression by RECIST 1.1 at 18 months will be counted as a success irrespective of treatment(s) received (still under protocol treatment or switched to investigator's choice standard treatment including no further systemic anticancer therapy documented).
  - Patients who progress on gefitinib by RECIST 1.1 or by positive cfDNA T790M status testing prior to 18 months and are switched to osimertinib (T790M positive) and progression free at 18 months after switching to osimertinib will be counted as a success.
  - Patients who progress on gefitinib by RECIST 1.1 or by positive cfDNA T790M status prior to 18 months and are switched to osimertinib (T790M positive) and progress by RECIST 1.1 after switching to osimertinib prior to 18 months will be counted as a failure.
  - Patients with a progression by RECIST 1.1 prior to 18 months and not able to start osimertinib prior to 18 months for any reason will be counted as a failure.
- Complete case analysis: the analysis will be restricted to patients with available PFS data at 18 months (complete case analysis).

In addition, sensitivity analyses will be conducted in which patients who will have started any other cancer treatment before their disease progresses will be considered as having an event at the date of start of the other cancer treatment.

Exploratory analysis of BPFS and OS according to the presence of T790M mutation status and the presence of original activating EGFR mutation in the plasma will be performed. In addition, exploratory endpoint on change in tumor size (see chapter 7) will be performed.

8.2.4 Prognostic factor analyses

No prognostic factor (PF) analyses will be conducted.

8.2.5 Data recoding and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomization – date of past event + 1) and presented using the median and range. For example, on the randomization checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of randomization – last administration/diagnosis +1).

Other delays (e.g. re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose …) are presented using the median and range (minimum, maximum).

$$\text{DI observed} = \left[\frac{mg}{m^2 \times \ weeks}\right] = \frac{total \ \ dose \ \left[\frac{mg}{m^2}\right]}{total \ \ duration \ \left[weeks\right]}$$

The relative dose intensity is calculated as the ratio of the dose intensity as calculated above to the dose intensity indicated in the protocol. The dose intensity indicated in the protocol is obtained as the dose specified per cycle (in mg/m²).

The dose intensity and the relative dose intensity are presented using median and ranges. The relative dose intensity can also be presented in categories (≤70%, >70-90%, >90-110%, >110-120%.

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

8.3 Interim analyses

No interim analysis (IA) is foreseen in this protocol.

8.4 End of study

End of study occurs when all of the following criteria have been satisfied:

1. Thirty days after all patients have stopped protocol treatment

2. The trial is mature for the analysis of the primary endpoint as defined in the protocol

3. The database has been fully cleaned and frozen for this analysis

9 Trial Governance and Data Monitoring

9.1 Study committees

9.1.1 Study Management Group (SMG)

The Study Management Group is set up for this study. It consists of the EORTC Headquarters team in charge of running the study (clinical research physician, statistician, clinical scientist, project manager and data managers) and the principal study coordinator.

The EORTC Headquarter team is responsible for the day -to-day conduct of the trial. The Study Coordinator will assist the team in case of problems with patient evaluation (eligibility, treatment compliance, safety).

The Study Management Group also performs the medical review as indicated below.

9.1.2 Study Steering Committee (SSC)

The Study Steering Committee for this study is composed of the study coordinators, the representatives of Academic Groups collaborating to the study, at least one representative of the EORTC Headquarters (Study Clinical Research Physician or Clinical Scientist) and one representative of the EORTC.

This committee provides the general oversight of the study and has the executive power. The SSC monitors study progress and conduct and advises on its scientific credibility. The SSC will consider and act, as appropriate, upon the recommendations of the independent data monitoring committee.

9.1.3 Independent Data Monitoring Committee (IDMC)

The independent data monitoring committee for EORTC studies (IDMC) is in charge of the independent oversight of this study. The composition of the IDMC is described in EORTC Policy "Independent Data Monitoring Committees for EORTC studies" (ref. EORTC POL004) and its functioning is ruled by the charter annexed to the Policy.

The study-specific experts on the IDMC performing this review will be selected for their relevant expertise with the disease and/or treatments assessed in the study.

The IDMC reports its recommendations in writing to the Study Management Group through the project manager to the Study Steering Committee and other relevant parties (supporting bodies, collaborative groups…).

9.2 Data Monitoring

9.2.1 Monitoring during medical review meetings

The medical review will be performed on a regular basis by the medical representative assisted as needed by the study management group. The main study coordinator will, in particular, support the Study Medical Representative during the medical review process and will assist the team in case of problems with patient evaluation (safety, eligibility, treatment compliance). The main study coordinator is also responsible for the review and approval of the medical review plan and medical review reports.

If at any time during the course of the study, the medical review identifies safety signals or other elements that could affect the potential risks and benefits to the study participants. These will be reported to the Study Steering Committee and may trigger a review by the EORTC Independent Data Monitoring Committee (IDMC).

9.2.2 Monitoring by the IDMC

The IDMC will be asked to give advice on whether the accumulating data from the trial justifies continuing recruitment of further patients or further follow-up.

The IDMC will review the trial whenever safety problems or other elements are identified during the medical review or by the SMG and/or SSC that could affect the potential risks and benefits for study participants.

The IDMC will also review the intermediate reports of accumulating data according to the study interim monitoring plan described in the statistical section of this protocol. If a decision is made to continue without change, the IDMC may advise on the frequency of future reviews of the data on the basis of accrual and event rates.

While the trial is ongoing the accumulating data will generally remain confidential, unless the SSC and IDMC agree that the data should be made public.

10 Translational research

The translational research is not optional for this protocol. Any patient who consent to enter the trial will have to consent for the translational research.

10.1 Main objectives

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

- to describe quantitatively the presence of T790M EGFR 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 by RECIST 1.1 longitudinally within the arms.
- 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 in formalin-fixed paraffin-embedded (FFPE) samples obtained from patients at baseline and at the time of progression on osimertinib by next generation sequencing and compare the presence of molecular resistance alterations in tissue samples and plasma samples taken on progression.
- To assess pharmaco-kinetics and/or pharmaco-dynamics of the different drugs, as potential resistance mechanisms in blood samples taken at baseline and during the course of treatment.

Detailed statistical analysis plan will be presented in a separate document prior to TR analysis.

10.2 Human Biological material

- Blood sample that would have been taken during screening visit and treatment each visit (every 4 weeks) while patients are within active treatment with gefitinib or osimertinib. Note: if gefitinib or osimertinib is temporarily discontinued due to toxicity, plasma sample should still be obtained. The last plasma sample should be taken from patients who progress on osimertinib by RECIST 1.1 evaluation (all three arms). Please refer to chapter 6.
- FFPE processed biopsy samples at baseline (residual tumor from diagnostic sample) and from progressing tumor lesions obtained from patients receiving osimertinib.

10.3 Data storage, transfer and development of technical appendices

The translational projects will be the result of the work of collaborating institutions and EORTC HQ. Statistical analysis plan will be jointly developed for each project. These documents will be developed and approved before starting any analysis. They will specify the analytical and methodological details. Clinical and patient-reported outcome data will be stored in the EORTC clinical database and biological investigational data will be stored in respective collaborating institutions. Transfer of data will be performed according to applicable policies in each organization (e.g. EORTC POL008) or according to jointly approved data transfer charters.

10.4 General principles for human biological material (HBM) collection

Human biological material (HBM) collection involves the collection and storage of biological material, residual biological material or derivatives in compliance with ethical and technical requirements.

Biobanking refers to the chain of procedures that encompass the life cycle of the biological material, e.g. from collection, shipping to long term storage and use, and may also be subject to local regulation and/or national/international legislation.

In this study, biological material will be centralized and stored at Medical University of Gdansk. From here, the biological material will be used or distributed to the other research laboratories involved in the translational research (TR) projects specified in this protocol or defined in the future.

The following principles apply to storage of HBM:

- The biobank will have a designated manager responsible for collection and will act as a communication point with the EORTC.
- The collected HBM should be documented, i.e. the amount remaining and its location.
- The Study Steering Committee (SSC)/Group committee will be responsible for TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol. In the absence of a SSC, responsibilities of the SSC are transferred to the Group and/ or EORTC HQ as applicable.
- Final decisions on the use of HBM will be determined by a majority vote of the SSC/Group committee. Additional expertise may be sought through advisory non-SSC/Group committee members.

Access to HBM (see EORTC Biobanking Policy POL020): HBM may be used for another purpose for which it was originally collected, subject to meeting ethical principles/and is covered by informed consent/ethics approval. In the case of secondary use of HBM, (i.e. for new TR projects that are not specified in the clinical study protocol and that were not foreseen at the time of protocol writing) interested parties may apply for the use of HBM and will follow the next steps:

- A short description of the new TR projects will be written and submitted to EORTC HQ for coordination with the appropriate SSC/Group committee.
- The SSC/Group committee will prioritize the TR projects. Access procedures defined by the SSC/Group committee will build on the following key points:
    - Project prioritization
        - should be strongly based on scientific merit,
        - should consider the contribution of the different investigators to the trial and TR project,
        - will take into consideration if the applicant is an EORTC member or not (whilst maintaining the principle of access to the wider scientific community and commitments owed to study participants and ethical committees).

  - Protection of confidentiality must be respected.

- An EORTC HQ feasibility check, including recommendations for regulatory and ethical matters and other restrictions on the use of the HBM, will take place. If in the event the HBM collections are still retained at individual clinical sites, the TR project leader and the involved EORTC Group are responsible for collecting and providing information on availability of HBM for the feasibility assessment.
- Prioritized TR projects will then be reviewed by the Translational Research Advisory Committee (TRAC).
- Once SSC/Group committee prioritization, the EORTC HQ feasibility assessment, and TRAC review are complete and when all applicable competent Ethics Committees approvals are in place and ethical principles are met, the TR project can be activated and HBM release and analysis can commence.
- The EORTC Board will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the SSC/Group committee and the TR project leader(s), as needed.

11 Investigator authorization procedure

Investigators will be authorized to register and/or randomize patients in this trial only once they have returned the following documents to the EORTC Headquarters:

- The updated signed and dated curriculum vitae of the Principal Investigator in English (not older than 2 years) with a GCP training proof.
- The (updated) list of normal ranges for the investigator's institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator's institution.
- The Confirmation of interest by Principal Investigator Form (CIF), stating that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.
- The Study Agreement between EORTC and investigator's institution.
- A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent Sheet (PISIC). Version numbers and dates must be clearly stated on each page. The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations. In case patients receive treatment at a satellite institution, i.e. outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be transmitted to the EORTC Headquarters. Please keep in mind that all communication is done ONLY between the primary institution and the EORTC HQ.
- The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

The center specific list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law.

The new investigator will be added to the "authorization list", and will be allowed to register/randomize patients in the trial as soon as

- All the above-mentioned documents are available at the EORTC HQ.
- All applicable national legal and regulatory requirements are fulfilled.

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

12 Patient randomization procedure

Patient randomization will only be accepted from authorized investigators (see chapter on “investigator authorization procedure").

A patient can only be randomized after verification of eligibility. Both the eligibility check and randomization must be done before the start of the protocol treatment.

Subjects should be registered shortly after signing the informed consent the **EORTC online randomization system** (ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet. To access the interactive randomization program, the investigator needs a username and a password (which can be requested at http://orta.eortc.be/).

In case of problems EORTC participants can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday to randomize patients via the EORTC call center. Randomization via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (http://orta.eortc.be/) and it is updated annually.

Through Internet:	http://orta.eortc.be/
In case of problems randomization by phone:	+32 2 774 16 00

12.1 Registration (step 1)

A list of questions to be answered during the registration procedure is included in the registration checklist, which is part of the case report forms.

STANDARD INFORMATION REQUESTED:

- EORTC institution number
- EORTC protocol number (1613)
- Step number: (1 - New patient)
- Name of the responsible investigator
- Patient's code *(maximum 4 alphanumerics, a unique code to help identify the patient within your institution - not the patient initials)*

Patient's birth date (day/month/year) or year of birth (as allowed per applicable legislation)

PROTOCOL SPECIFIC QUESTIONS:

- All registration criteria will be checked one by one
- Date of written informed consent (*day/month/year*)

Once registration criteria have been verified, a **sequential patient identification number (“seqID”)** will be allocated. This number will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

All SAMPLE SHIPMENTS and REPORTS must be identified with the EORTC Id (seqID) attributed at registration

12.2 Central lab review procedure of baseline sample (step 2)

After registration and shipment of the sample, the central laboratory will assess the blood sample for circulating free DNA EGFR T790M (cfDNA T790M). The cfDNA T790M results of the central lab will be entered in the ORTA system (step 2) by EORTC HQ.

If the analysis failed for any technical reason, the site will be allowed to send second blood sample for evaluation.

A patient who has not been registered before the cfDNA T790M central testing will not be accepted for the study at a later date and cannot be entered for the second step of the study. All eligibility criteria must be met before proceeding to step 3 (below).

At the end of step 2, once the cfDNA T790M results have been verified, the site will be informed by a notification email if, following the cfDNA T790M results the patient is eligible to start the randomization procedure (step 3).

12.3 Randomization procedure (step 3)

A patient who has not been registered and had the cfDNA T790M tested by the central lab will not be accepted for the study at a later date and cannot be checked for eligibility by the third step of the study.

An exhaustive list of questions to be answered during the randomization procedure is included in the eligibility checklist, which is part of the case report forms.

STANDARD INFORMATION REQUESTED:

- Institution number
- Protocol number (1613)
- Step number: (3 – Existing patient)
- Name of the responsible investigator

The patient will have to be selected in the list of patients that have already been registered in the first step. Once the patient has been identified in the list, select the corresponding patient's code. The patient's code and date of birth will automatically be inserted in the identification screen.

PROTOCOL SPECIFIC QUESTIONS:

- All eligibility criteria will be checked one by one
- Actual values of the eligibility parameters will be requested when applicable
- Stratification factors

Once eligibility and stratification factors have been checked, the treatment will be randomly allocated to the patient (minimization technique) and the site will be informed of it by an automatic notification email if the patient is eligible.

13 Forms and procedures for collecting data

13.1 Case report forms and schedule for completion

Data will be reported on the forms specifically designed by the EORTC Headquarters for this study. Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, with the exception of the SAE form and the Pregnancy notification form which are paper CRFs.

SERIOUS ADVERSE EVENTS AND PREGNANCY NOTIFICATION FORMS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter on Reporting Serious Adverse Events).

A. Before the treatment starts:

The patient must be registered/randomized in the trial by INTERNET or in case of problems by phone.

The electronic CRFs to be completed for a patient are available on the VISTA/RDC website one hour after the registration/randomization on http://rdc.eortc.be/ or on http://www.eortc.org in the section ”Research Tools”.

The paper SAE and Pregnancy Notification forms will be made available to the institution at the time the institution is authorized.

B. During/after treatment

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

ALL Forms must be electronically approved and sent by the responsible investigator or one of his/her authorized staff members with the exception of the paper SAE and Pregnancy Notification forms which need to be signed and dated individually by the responsible investigator or one of his/her authorized staff members

13.2 Data flow

The forms must be completed electronically, with the exception of the paper forms (SAE form and Pregnancy Notification), according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorized to enter data (with a sample of their signature) must be identified on the signature log and sent to the EORTC Headquarters by the responsible investigator before the start of the study. To enter the RDC system, the investigator or authorized staff member needs to use the same username and password that are used to access the interactive randomization program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

The EORTC Headquarters will perform extensive consistency checks on the received data. Corrections of obvious data errors will be done by the EORTC Data Manager, as outlined on the convention list, which can be downloaded from the EORTC trial specific webpage: http://www.eortc.be/protoc/. Queries will be issued in order to resolve other inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

The EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other study related issues.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

13.3 HBM* sample registration and tracking

Once the patient is registered, this procedure might take up to one hour, the investigator or his/her authorized staff must log on "Samples" website at https://samples.eortc.be/ or by clicking on the link "Samples Website" at the bottom of the page http://rdc.eortc.be.

"Samples" is a web-based tracking tool designed to register, manage and track Human Biological Materials collected in the frame of EORTC clinical trials.

Details about access the "Samples" Website, register samples and tracking shipments are described on the guidelines of HBM* management.

(*) Human Biological Material

14 Reporting of Serious Adverse Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

14.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An **Adverse Event** is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is defined as “any noxious and unintended response to a medicinal product related to any dose administered”.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a medically important event or reaction.
  Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

SAR: A **Serious Adverse Reaction** is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

Inpatient hospitalization: a hospital stay equal to, or greater than, 24 hours.

Second primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

14.2 Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
- A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

By EORTC convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

14.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 https://www.eortc.be/services/doc/ctc/.

14.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in this table:

Relationship to the protocol treatment	Description
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event
No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE form and if necessary the reason for the decision will also be recorded.

14.5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following reference documents:

- For osimertinib: Investigator's Brochure (The RSI is the IB section entitled "Reference safety information".)
- For gefitinib: *Summary of Product Characteristics (SmPC) (The RSI is section 4.8 in the SmPC.)*

14.6 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from the time a subject is randomized until 30 days after last protocol treatment administration and to any SAE that occurs outside of the SAE detection period (after the 30-days period), if it is considered to have a reasonable possibility to be related to the protocol treatment or study participation.

In addition, SAEs occurring after the subject signed the study-specific informed consent and prior to the initial dose of study drug will be collected **only if** they are considered by the Investigator to be causally related to required study procedures.

Signed Patient Informed Consent till randomization:	Only SAE* as result of a protocol-required intervention
Randomization till 30 days after last protocol treatment administration:	All SAEs

From day 31 after last protocol treatment administration:	Only related SAEs

Any secondary malignancy should also be reported in expedited way on a SAE form with the appropriate seriousness criteria!

All reporting must be done by the principal investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

All SAE-related information must be faxed or e-mailed to:

EORTC Pharmacovigilance Unit:

Fax No. +32 2 772 8027 or pharmacovigilance@eortc.org

To enable the Sponsor to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principal investigator or any authorized staff member (i.e. on the signature list).

14.7 Reporting responsibilities for EORTC

The EORTC Pharmacovigilance Unit will forward all SAE reports to the appropriate persons within the EORTC Headquarters and to the pharmacovigilance contact at the pharmaceutical company as per pharmacovigilance agreement.

The EORTC Pharmacovigilance Unit will provide a six-monthly summary which will be added in the Trial Status Report and which will be accessible to all participating investigators.

The EORTC Pharmacovigilance Unit will take in charge the reporting of SUSARs to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM) and all participating investigators whenever applicable.

14.8 Pregnancy reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any adverse outcome to the mother or the child should be reported. This also applies to pregnancies in female partners of a male patient participating in this trial.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 4 months after last protocol treatment administration must be reported to the EORTC Pharmacovigilance Unit
- This must be reported within 24 hours of first becoming aware of the event by fax, to the Pharmacovigilance Unit on a Pregnancy Notification Form
- If an SAE occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE reporting chapter

15 Quality assurance

15.1 Control of data consistency

Data forms will be entered in the EORTC Headquarters database by using the VISTA/RDC (Remote Data Capture) system. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

15.2 On-site monitoring

The EORTC Headquarters will perform on-site monitoring visits according to the approved study-monitoring plan.

The first visit in a participating site will be performed within 3 to 6 months after the first patient's registration / randomization at this site. Frequency and number of subsequent visits will depend on site's accrual and quality observed during the first visit.

The aim of these site visits will be:

- to verify that the site facilities remain adequate for performing the trial
- to verify that the principal investigator and site staff involved in the trial are working in compliance with GCP and protocol requirements
- to assess the consistency of data reported on the case report forms with the source data
- to check that Serious Adverse Events have been properly reported and that follow-up information or queries are correctly fulfilled
- to assist the site in resolving any outstanding queries
- to control the drug accountability process

15.3 Audits

The EORTC is responsible for the performance of the EORTC investigators.

The investigator, by accepting to participate in this protocol, agrees that EORTC, any third party (e.g. a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives …). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

If applicable, the company(ies) supplying the study drug(s) may have access to anonymized data but will not have access to source documents.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters Compliance and Audits immediately (contact at: Complianceandaudits@eortc.org).

In this way EORTC can provide support in preparing and/or facilitating the inspection. EORTC representatives/delegates may also attend the inspection.

15.4 Quality assurance and quality control in imaging

15.4.1 Control of data completeness

The EORTC HQ will track all scans of all patients received from the sites and will request/query missing/incomplete scans. Furthermore, if the scans arrive in unacceptable quality or in a non-acceptable format, the site will be informed to provide substitute scans.

Scans will be uploaded by the participating centers via the EORTC imaging platform.

Please refer to the imaging guidelines for more details.

15.4.2 Imaging guidelines "read and understood" acknowledgment page signature

This is the first page of the imaging guidelines. Every site participating in an EORTC study with imaging, must comply with the minimum requirements established as specified in the imaging guidelines. The first page of the imaging guidelines must be signed and returned to the EORTC HQ for every new version of the imaging guidelines. The page must be signed by the head of radiology department. This is mandatory from all institutions in this study before activation to participate in it.

15.4.3 Scan quality control

- QC will be performed on an on-going basis.
- The EORTC Imaging manager will be reviewing all scans for all patients to check for artifacts and to ensure compliance with the imaging guidelines and study protocol.
- Every subsequent scan on the same patient must be done with the same scanner across all visits. In case of scanner breakdown or change of scanners in the department, you need to notify the EORTC HQ.

15.4.4 Central review

Retrospective central review of the images will be organized. For more information, see the independent central review charter.

16 Ethical considerations

16.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at

https://www.ema.europa.eu/documents/scientific-guideline/ich-e6-r1-guideline-good-clinical-practice_en.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

16.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and date of birth or year of birth (as allowed per applicable legislation) will also be reported on the case report forms.

16.3 Informed consent

All patients will be informed about

- the aims of the study
- the possible adverse events
- the procedures and possible hazards to which the patient will be exposed
- the mechanism of treatment allocation
- strict confidentiality of any patient data
- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient's informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements

17 Administrative responsibilities

17.1 The study coordinator

The Study Coordinator works closely with the study team to develop the outline and full protocol and discusses the contents of the reports with the study team. The Study coordinator is responsible for publishing the study results. He/she will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and contributes to the medical review of the patients.

Study coordinator:

17.2 The EORTC Headquarters

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

EORTC HEADQUARTERS

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Fax: +32 2 7723545

17.3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at membership@eortc.org.

Lung Cancer Group EORTC group

Chairman:

Secretary:

18 Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC participants.

The contact details of the EORTC are:

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Phone: +32 2 7741611
Fax: +32 2 7723545
e-mail: eortc@eortc.org

The trial is supported with the educational grant by [redacted] that also provides osimertinib and gefitinib for free.

19 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

20 Results dissemination policy

20.1 Study disclosure

20.1.1 Trial Registration

This trial will be registered in a public database (https://www.clinicaltrialsregister.eu). As the clinical trial (CT) regulation 536/2014 of the European Union (EU) becomes applicable, more information about this trial will be uploaded in this public database in compliance with European requirements on transparency. Information posted, among others, will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

In accordance with applicable EU regulations, a summary of the trial results will be made publicly available within one year of the end of study declaration.

EORTC as Sponsor of this trial will submit the summary of the results based on the final analysis report in compliance with the regulations.

20.1.2 Final Analysis Report

A Final Analysis Report that reports summary statistics of all the data collected for the study and presents an interpretation of the study results will be issued by the EORTC Headquarters. It will form the basis for the manuscript intended for publication. The Final Analysis Report or a summary thereof will be distributed to all participating groups, the supporting companies and ethics committees and the results will be posted in relevant public databases (as in section 20.1.1).

20.2 Publication policy

All publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy” version 5.0 dated November 2020.

In accordance with the Policy 009, results of the present study will be made public once the study data are mature for the final analysis of the primary study endpoint (as described in the section “statistics” of the present protocol), irrespective of the findings (positive or negative). Deviations from the results disclosure rules specified in the Policy require authorization by the Independent Data Monitoring Committee (IDMC).

The primary trial publication will be written on the basis of the final analysis report and shall be published in a peer-reviewed scientific journal within 1 year of the date of the database lock. The principal study coordinator is responsible for drafting the manuscript.

All publications ((papers, abstracts, presentations…) must be reviewed and approved by at least one EORTC Headquarters staff prior to submission to journal or congress or presentation. Approval and review by third parties involved in the study comply with all contractual agreement in place.

The authorship rules conform to the recommendations of the International Committee of Medical Journal Editors defining the roles of authors and contributors (http://icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html) and will be attributed for each publication in line with the EORTC Policy referred above. All contributors who do not meet sufficient criteria for authorship will be acknowledged in the publication.

Investigators will not independently publish site-specific results about the study endpoints until results of the whole study are published (or after one year following database lock if there is no publication). Deviations from this rule are authorized by the study IDMC.

Sources of funding or support to the study will be disclosed and acknowledged in the publication.

The name “EORTC” must be visible in the publications title or authors list.

20.3 Data sharing

EORTC is committed to ensuring that the data generated from its studies be put to good use by the cancer research community and, whenever possible, are translated to deliver patient benefit.

It is therefore EORTC's policy to consider for sharing upon request from qualified scientific and medical researchers all data generated from its research whilst safeguarding intellectual property, the privacy of patients and confidentiality.

Considering that ongoing research contributing to the completion of datasets must not be compromised by premature or opportunistic sharing and analysis of data, the EORTC will not release the data of its study until the primary study results have been published; unless authorization for release has been granted according to the terms of EORTC Policy 009.

Requests for accessing the data of published trials should be filed through the data sharing tab on the EORTC website (www.eortc.org).

Appendix A: References

Ref. 1 L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent, A. Jemal, Global cancer statistics, 2012, CA Cancer J Clin. 65 (2015) 87–108. doi:10.3322/caac.21262.

Ref. 2 J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, et al., Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, Int. J. Cancer. 136 (2015) E359-386. doi:10.1002/ijc.29210.

Ref. 3 www.seer.cancer.gov, (n.d.).

Ref. 4 M. Reck, S. Popat, N. Reinmuth, D. De Ruysscher, K.M. Kerr, S. Peters, et al., Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 25 Suppl 3 (2014) iii27-39. doi:10.1093/annonc/mdu199.

Ref. 5 J.H. Schiller, D. Harrington, C.P. Belani, C. Langer, A. Sandler, J. Krook, et al., Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer, N. Engl. J. Med. 346 (2002) 92–98. doi:10.1056/NEJMoa011954.

Ref. 6 S. Devarakonda, D. Morgensztern, R. Govindan, Genomic alterations in lung adenocarcinoma, Lancet Oncol. 16 (2015) e342-351. doi:10.1016/S1470-2045(15)00077-7.

Ref. 7 M. Reck, D.F. Heigener, T. Mok, J.-C. Soria, K.F. Rabe, Management of non-small-cell lung cancer: recent developments, Lancet. 382 (2013) 709–719. doi:10.1016/S0140-6736(13)61502-0.

Ref. 8 N.I. Lindeman, P.T. Cagle, M.B. Beasley, D.A. Chitale, S. Dacic, G. Giaccone, et al., Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology, J Mol Diagn. 15 (2013) 415–453. doi:10.1016/j.jmoldx.2013.03.001.

Ref. 9 Barlesi F, Mazieres J, Merlio JP, Debieuvre D, Masser J, Lena H, Ouafik L, Besse B, Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Intergroup (IFCT), The Lancet 2016, Epub ahead of Print. (n.d.).

Ref. 10 M.G. Kris, B.E. Johnson, L.D. Berry, D.J. Kwiatkowski, A.J. Iafrate, I.I. Wistuba, et al., Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs, JAMA. 311 (2014) 1998–2006. doi:10.1001/jama.2014.3741.

Ref. 11 P.K. Paik, A. Drilon, P.-D. Fan, H. Yu, N. Rekhtman, M.S. Ginsberg, et al., Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping, Cancer Discov. 5 (2015) 842–849. doi:10.1158/2159-8290.CD-14-1467.

Ref. 12 A.T. Shaw, S.-H.I. Ou, Y.-J. Bang, D.R. Camidge, B.J. Solomon, R. Salgia, et al., Crizotinib in ROS1-rearranged non-small-cell lung cancer, N. Engl. J. Med. 371 (2014) 1963–1971. doi:10.1056/NEJMoa1406766.

Ref. 13 S. Gahr, R. Stoehr, E. Geissinger, J.H. Ficker, W.M. Brueckl, A. Gschwendtner, et al., EGFR mutational status in a large series of Caucasian European NSCLC patients: data from daily practice, Br. J. Cancer. 109 (2013) 1821–1828. doi:10.1038/bjc.2013.511.

Ref. 14 N. Reguart, J. Remon, Common EGFR-mutated subgroups (Del19/L858R) in advanced non-small-cell lung cancer: chasing better outcomes with tyrosine-kinase inhibitors, Future Oncol. (2015) 1–13. doi:10.2217/fon.15.15.

Ref. 15 L.V. Sequist, B.A. Waltman, D. Dias-Santagata, S. Digumarthy, A.B. Turke, P. Fidias, et al., Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors, Sci Transl Med. 3 (2011) 75ra26. doi:10.1126/scitranslmed.3002003.

Ref. 16 M.E. Arcila, G.R. Oxnard, K. Nafa, G.J. Riely, S.B. Solomon, M.F. Zakowski, et al., Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay, Clin. Cancer Res. 17 (2011) 1169–1180. doi:10.1158/1078-0432.CCR-10-2277.

Ref. 17 H.A. Yu, M.E. Arcila, N. Rekhtman, C.S. Sima, M.F. Zakowski, W. Pao, et al., Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers, Clin. Cancer Res. 19 (2013) 2240–2247. doi:10.1158/1078-0432.CCR-12-2246.

Ref. 18 R. Rosell, M.A. Molina, C. Costa, S. Simonetti, A. Gimenez-Capitan, J. Bertran-Alamillo, et al., Pretreatment EGFR T790M mutation and BRCA1 mRNA expression in erlotinib-treated advanced non-small-cell lung cancer patients with EGFR mutations, Clin. Cancer Res. 17 (2011) 1160–1168. doi:10.1158/1078-0432.CCR-10-2158.

Ref. 19 M. Watanabe, T. Kawaguchi, S.-I. Isa, M. Ando, A. Tamiya, A. Kubo, et al., Ultra-Sensitive Detection of the Pretreatment EGFR T790M Mutation in Non-Small Cell Lung Cancer Patients with an EGFR-Activating Mutation Using Droplet Digital PCR, Clin. Cancer Res. 21 (2015) 3552–3560. doi:10.1158/1078-0432.CCR-14-2151.

Ref. 20 H.A. Yu, M.E. Arcila, M.D. Hellmann, M.G. Kris, M. Ladanyi, G.J. Riely, Poor response to erlotinib in patients with tumors containing baseline EGFR T790M mutations found by routine clinical molecular testing, Ann. Oncol. 25 (2014) 423–428. doi:10.1093/annonc/mdt573.

Ref. 21 J.-C. Soria, Y.-L. Wu, K. Nakagawa, S.-W. Kim, J.-J. Yang, M.-J. Ahn, et al., Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial, Lancet Oncol. 16 (2015) 990–998. doi:10.1016/S1470-2045(15)00121-7.

Ref. 22 Mok T, Soria JC, Kim SW, Wu YL, Nakagawa K, Yang JJ et al., Gefitinib/Chemotherapy vs Chemotherapy in EGFR Mutation- Positive NSCLC Resistant to First-Line Gefitinib: IMPRESS T790M Subgroup Analysis, J Thorac Oncol 2015. 10 (n.d.) issue 9; suppl 2, S207 (ORAL17.08).

Ref. 23 M.R.V. Finlay, M. Anderton, S. Ashton, P. Ballard, P.A. Bethel, M.R. Box, et al., Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor, J. Med. Chem. 57 (2014) 8249–8267. doi:10.1021/jm500973a.

Ref. 24 P.A. Jänne, J.C.-H. Yang, D.-W. Kim, D. Planchard, Y. Ohe, S.S. Ramalingam, et al., AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer, N. Engl. J. Med. 372 (2015) 1689–1699. doi:10.1056/NEJMoa1411817.

Ref. 25 Jänne P, Ahn M, Kim D, Kim S, Planchard D, Ramalingam SS, Frewer P, Cantarini M, Ghiorghiu S, Yang JC, A phase I study of AZD9291 in patients with EGFR-TKI-resistant advanced NSCLC – updated progression free survival and duration of response data, Ann Oncol. (2015) 1–8.

Ref. 26 S.S. Ramalingam, J.C.-H. Yang, C.K. Lee, T. Kurata, D.-W. Kim, T. John, et al., AZD9291, a mutant-selective EGFR inhibitor, as first-line treatment for EGFR mutation-positive advanced non-small cell lung cancer (NSCLC): Results from a phase 1 expansion cohort., ASCO Meeting Abstracts. 33 (2015) 8000.

Ref. 27 Mitsudomi T, Tsai CM, Shepherd F, Bazhenova L, Lee SJ, Chang GC, Crinò L et al., AZD9291 in Pre-Treated T790M Positive Advanced NSCLC: AURA2 Phase II Study, J Thorac Oncol 2015. 10 (9), suppl 2. S320 (n.d.).

Ref. 28 K.S. Thress, R. Brant, T.H. Carr, S. Dearden, S. Jenkins, H. Brown, et al., EGFR mutation detection in ctDNA from NSCLC patient plasma: A cross-platform comparison of leading technologies to support the clinical development of AZD9291, Lung Cancer. 90 (2015) 509–515. doi:10.1016/j.lungcan.2015.10.004.

Ref. 29 L.V. Sequist, J.W. Goldman, H.A. Wakelee, D.R. Camidge, H.A. Yu, A. Varga, et al., Efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small cell lung cancer (NSCLC) patients (pts)., ASCO Meeting Abstracts. 33 (2015) 8001.

Ref. 30 C.A. Eberlein, D. Stetson, A.A. Markovets, K.J. Al-Kadhimi, Z. Lai, P.R. Fisher, et al., Acquired Resistance to the Mutant-Selective EGFR Inhibitor AZD9291 Is Associated with Increased Dependence on RAS Signaling in Preclinical Models, Cancer Res. 75 (2015) 2489–2500. doi:10.1158/0008-5472.CAN-14-3167.

Ref. 31 T.S. Mok, Y.-L. Wu, S. Thongprasert, C.-H. Yang, D.-T. Chu, N. Saijo, et al., Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma, N. Engl. J. Med. 361 (2009) 947–957. doi:10.1056/NEJMoa0810699.

Ref. 32 L.V. Sequist, J.C.-H. Yang, N. Yamamoto, K. O'Byrne, V. Hirsh, T. Mok, et al., Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations, J. Clin. Oncol. 31 (2013) 3327–3334. doi:10.1200/JCO.2012.44.2806.

Ref. 33 E. Eisenhauer, P. Therasse, J. Bogaerts et al. New Response Evaluation Criteria in Solid Tumors: Revised RECIST Guideline (Version1.1). Eur J Cancer. 2009 Jan;45(2):228-47

Ref. 34 Dancey JE, Dodd LE, Ford R, et al. Recommendations for the assessment of progression in randomised cancer treatment trials. Eur J Cancer 2009 Jan;45(2):281–9.

Ref. 35 Theodore G. Karrison , Michael L. Maitland , Walter M. Stadler , Mark J. Ratain . Design of Phase II Cancer Trials Using a Continuous Endpoint of Change in Tumor Size: Application to a Study of Sorafenib and Erlotinib in Non – Small-Cell Lung Cancer, J Natl Cancer Inst. 2007 Oct 3;99(19):1455-61.

Ref. 36 Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013; 381(9868): 752-62.

Ref. 37 Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology Consensus on Geriatric Assessment in Older Patients With Cancer. J Clin Oncol 2014.

Ref. 38 Bellera CA, Rainfray M, Mathoulin-Pelissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol 2012; 23(8): 2166-72.

Ref. 39 Kenis C, Decoster L, Van Puyvelde K, et al. Performance of two geriatric screening tools in older patients with cancer. J Clin Oncol 2014; 32(1): 19-26.

Ref. 40 Decoster L, Van Puyvelde K, Mohile S, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations. Ann Oncol 2014.

Appendix B: Abbreviations

AE(se)	adverse event(s)
ALT/ALAT	alanine aminotransferase
AP	alkaline phosphatase
AR	acquired resistance
AST/ASAT	aspartate aminotransferase
BUN	blood urea nitrogen
cfDNA	cell free circulating plasma DNA
CIF	confirmation of interest by principal investigator form
CR	complete response
CT	computed tomography
CTCAE	common terminology for adverse events
EGFR	epidermal growth factor receptor
EGFR	EGFR tyrosinase kinase inhibitors
EGFR T790M	substitution of threonine to methionine at amino acid position 790 (T790M) in exon 20 of the EGFR gene
GGT	gamma-glutamyl transferase
Hb	hemoglobin
HMB	human biological material
IB	investigator's brochure
ICH/GCP	international conference on harmonization/ good clinical practice
INR	International Normalized Ratio
ITT	intent to treat
LDH	lactic dehydrogenase
MRI	magnetic resonance imaging
NSCLC	non-small-cell lung carcinoma
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PF	prognostic factor
PFS	progression free survival
PFSR-OSI-18	progression free survival rate at 18 months

PISIC	patient information sheet and informed consent
PR	partial response
PS	Performance Status
QD	daily dose
RDC	remote data capture
RECIST	response evaluation criteria in solid tumors
RR	response rate
SAE(s)	serious adverse event(s)
SAR	serious adverse reaction
SD	stable disease
SmPC	summary of product characteristics
SSC	study steering committee
SMG	Study management group
SUSAR	suspected unexpected serious adverse reaction
TKI	tyrosinase kinase inhibitors
TTP	time to progression
TR	translational research
TRAC	translational research advisory committee
UAR	Unexpected adverse reaction
ULN	upper limit of normal
WBC	white blood cells

Appendix C: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

Appendix D: G8 geriatric screening tool (Version 1.0 - December 2010)

To be completed by: Clinician, nurse or trained coder.

Notes: This screening tool includes 7 items of the Mini Nutritional Assessment and the age of the patient.

Score: Total score by adding up coded answers.

G8 Screening tool			
	Items	**Possible answers**	**Score**
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	**0:** severe reduction in food intake **1:** moderate reduction in food intake **2:** normal food intake	……..
B	Weight loss during the last 3 months?	**0:** weight loss >3kg **1:** does not know **2:** weight loss between 1 and 3 kg **3:** no weight loss	……..
C	Mobility	**0:** bed or chair bound **1:** able to get out of bed/chair but does not go out **2:** goes out	……..
E	Neuropsychological problems	**0:** severe dementia or depression **1:** mild dementia or depression **2:** no psychological problems	……..
F	Body Mass Index (weight in kg/height in m^2)	**0:** BMI less than 19 **1:** BMI 19 to less than 21 **2:** BMI 21 to less than 23 **3:** BMI 23 or greater	……..
H	Takes more than 3 medications per day	**0:** yes **1:** no	……..
P	In comparison with other people of the same age, how does the patient consider his/her health status?	**0:** not as good **0,5:** does not know **1:** as good **2:** better	……..
	Age	**0:** >85 **1:** 80-85 **2:** <80	……..
	Total score (0-17)		……..

Appendix E: Guidance regarding Potential Interactions With Concomitant Medications

Guidance regarding potential interactions with concomitant medications

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

1. Drugs inducing CYP3A4 metabolism that [redacted] strongly recommend are not combined with osimertinib

Osimertinib is metabolised by CYP3A4 and CYP3A5 enzymes.

A drug-drug interaction study of osimertinib evaluated in patients showed that there is potential for osimertinib being a victim when co-administered with strong inducers of CYP3A4 (osimertinib concentrations are decreased when co-dosed with rifampicin).

The following potent inducers of CYP3A4 must not be used during this study for any patient receiving osimertinib.

Table 1 Drugs inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to osimertinib start
Carbamazepine, phenobarbital, phenytoin Rifampicin, rifabutin, rifapentin St John's Wort	**3 weeks**
Phenobarbitone	**5 weeks**

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Please contact [redacted] with any queries you have on this issue.

2. Medicines whose exposures may be affected by osimertinib that [redacted] considers may be allowed with caution

Osimertinib may increase the concentration of sensitive breast cancer resistance protein (BCRP) substrates and Pgp substrates (concentration of the sensitive BCRP substrate, rosuvastatin, and sensitive Pgp substrate, fexofenadine, are increased).

Table 2 Exposure, pharmacological action and toxicity may be increased or decreased by osimertinib

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine Doxorubicin Daunorubicin Topotecan Aliskiren Dabigatran etexilate Digoxin	**Drugs are permitted but caution should be exercised and subjects monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with osimertinib**

3. Drugs that may prolong QT interval

The drugs listed in this section are taken from information provided by The Arizona Centre for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: https://crediblemeds.org/ndfa-list/.

The website categorizes drugs based on the risk of inducing Torsades de Pointes (TdP).

During screening the drugs that patients are currently prescribed should be checked opposite the ArizonaCert website.

4.1 Drugs with a known risk of Torsades de Pointes

The following drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended. These drugs must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table 3 and should not be co-administered with study treatment (osimertinib) and for a period of two weeks after discontinuing study treatment, however if it is considered essential for patient management to co-administer these drugs with study treatment (osimertinib) close monitoring of ECGs and electrolytes is recommended. The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such investigators are recommended to search the website to provide the most up to date information.

Table 3 Drugs* with known risk of TdP

Contraindicated drug	Withdrawal period prior to osimertinib start[&]
Anagrelide, aclarubicin, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacine, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine terlipressin	**2 days**

Table 3 Drugs* with known risk of TdP

Contraindicated drug	Withdrawal period prior to osimertinib start[&]
Cilostazol, cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromicyn, sevoflurane, sotalol, sparfloxacin, thioridazine	**7 days**
Azithromycin, bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpride, mesoridazine	**14 days**
Donezepil, terodiline	**3 weeks**
Levomethadyl, methadone, pimozide	**4 weeks**
Arsenic trioxide, Ibogaine	**6 weeks[#]**
Pentamidine	**8 weeks**
Astemizole, probucol, vandetanib	**4 months**
Amiodarone, chloroquine	**1 year**

* This list should be checked against the full and most current list presented in the CredibleMeds® website (https://www.crediblemeds.org/).

[&] Values determined from comprehensive review (internal to [redacted]) of each compound's PK half-life and determination of the wash-out period.

[#] Estimated value as pharmacokinetics of arsenic trioxide has not been studied.

4.2 Other TdP risk categories

Patients receiving drugs that prolong QT interval or may increase the risk of TdP from other TdP risk categories can be enrolled, notwithstanding other exclusions and restrictions, if these drugs are considered essential for patient management and the patient has been stable on therapy. Close monitoring with ECGs and electrolytes is recommended.

Patients with congenital long QT syndrome (CLQTS) are excluded from this study.

4.3 Guidance regardless of TdP risk category

Following study treatment initiation if it is considered essential for patient management to give drugs known to prolong QTc interval, regardless of TdP risk category, close monitoring with ECGs and electrolytes is recommended.

Appendix F: Specific protocol instructions during the COVID-19 crisis

Note: all instructions listed in this Appendix will be solely applicable during the COVID-19 crisis.

Furthermore, please ensure that any protocol deviations resulting from COVID-19 are:

- **Adequately documented in the eCRF's, as well as in the patient's medical records or in a Note To File (NTF) to be stored in your Study binder (ISF).**
- **Always begin any deviation text with "COVID-19".**

1. Introduction

Current information suggests that cancer patients have a higher risk of infection and serious complications from infections including COVID-19, than other patients.

It is strongly recommended that investigators exercise medical/clinical judgement, and decisions regarding each patient should be individualized after considering the overall goals of treatment, the patient's current oncologic status and treatment tolerance as well as their general medical condition.

In addition, investigators should adhere to local and institutional guidelines for SARS-CoV-2 infection and suspected COVID-19 infection.

2. COVID-19 risk-benefit assessment

EORTC trial 1613-LCG APPLE is enrolling patients with metastatic non-small cell lung cancer and with common EGFR activating mutations (del19 or L858R). The trial aims to evaluate the best strategy for delivering osimertinib in this patient population.

Treatment with EGFR inhibitors, such as osimertinib and gefitinib, represents a standard of care in this patient population, although the best sequential treatment strategy, as well as the role of the liquid biopsy in guiding the treatment decision are under active investigation. EGFR inhibitors increased significantly the patient survival, and the identification of the best treatment strategy is crucial to achieve further improvements of survival. In addition, the definition of the role of liquid biopsy might decrease the patient exposure to invasive procedures (i.e. tissue biopsy) and be essential to guide the treatment in the era of the personalized medicine. We believe that the APPLE trial is innovative with this respect and very important for the future lung cancer care.

There are risks about these treatments, and especially during the COVID19 crisis, these risks are significantly increased:

- The fact that included patients need to come for regular visits to the hospital every 4 weeks, significantly increases their exposure risk to persons who are contagious for COVID-19. General rules like social distancing (1.5 m) and avoidance of persons with possible signs or confirmed diagnosis should be applied. But COVID-19 can also be contagious in persons who don't have symptoms, so every hospital visit increases the risk of getting infected with "SARS-CoV2". In addition, age and comorbidities, in particular cardiovascular and diabetes, are risk factors for severe course of the infection.
- Both osimertinib and gefitinib are known to induce pneumonitis and interstitial lung disease. In addition, early reductions in leukocytes, lymphocytes, and neutrophils values have been observed with osimertinib, which stabilized over time and then remained above the lower limit of normal. These may represent additional risks for the patients.

- Osimertinib is also known to induce QT interval prolongation, and therefore, concomitant administration of drugs known to prolong QT interval is not allowed. Hydroxychloroquine sulphate and azithromycin may be used to treat COVID-19 infection. However, these drugs are known to prolong QT interval and cannot be administered with osimertinib. The risk related to drugs interaction might limit the treatment choice for the patients and this represents an additional risk.

3. Proposed measures for patients already enrolled during the COVID-19 crisis

Based on the above risk-benefit assessment, the study coordinators, in collaboration with EORTC, propose the following guidelines as long as the current COVID-19 crisis is ongoing.

a) Study treatment

Study drugs (osimertinib and gefitinib) are dispensed according to protocol sections 5.1.3 and 5.2.3. However, temperature-controlled shipments of osimertinib and gefitinib from the hospital to the patient's homes with a courier can be organized by the EORTC in the case that patients cannot come to the hospital due to the COVID-19 crisis.

Please refer to the IMP guidelines addendum for more detailed and specific instructions on drug shipment and storage conditions.

The process for shipping directly to subjects from sites must be fully documented and traceable in a note to file (NTF, template provided by EORTC).

The site must inform the EORTC 1613 study team (1613@eortc.org) upfront if a shipment of gefitinib and/or osimertinib needs to be organized for a patient.

Before provision of gefitinib and/or osimertinib bottles to the patient, the investigator must provide his/her approval to the patient or the qualified person in charge of patient care.

In case of any delays, the site needs to report this in the comment fields of the applicable CRFs and in the Source Data as well.

The PI should inform the patients that drug suppliers will be receiving their name and address for delivery and that they will not store this information.

Complement of information to provide to patients in relation to the processing of their personal data:

- To insure the continuity of the treatment and therefore patient's vital interests, patient's name and address will be communicated by the investigator or the staff of the hospital to the organization responsible for the drug supply.
- EORTC and/or the hospital will ensure that patient's name and address are processed in the secure way and are not used for any other purpose than for delivering the drugs to the patient.
- EORTC and/or the hospital will ensure that this additional information is not anymore stored by the drug suppliers once these exceptional measures are over and the treatment and/or follow-up are back to the normal.

The safety monitoring evaluations (hematology and biochemistry, ECG, echocardiogram, ophthalmological examination) should be performed as much as possible in accordance with the protocol chapter 6. If this is not possible, taking into consideration that osimertinib and gefitinib are marketed drugs in use since several years, some of the above safety evaluations are not critical. During COVID-19 crisis, it is very important that patients continue to receive the study treatment with minimal risks of infection.

Therefore, the following measures should be considered:

- Perform the safety monitoring evaluation at the center. Once the treating physician has assessed the results of the evaluations, organize a visit via a phone call/video call to assess the adverse events and patient's performance, and organize the drug shipment to the patient's home.
- Provide standard assessments (e.g. hematology, biochemistry) of the subject either by qualified staff of contracted laboratories or contractually secured healthcare providers who employ appropriate safety measures and excludes patients who are quarantined or living with or have been quarantined with a confirmed coronavirus case.
- If none of the above is possible, and the safety monitoring evaluations are to be skipped, then the treating physician has to evaluate the risk-benefit of the patient before skipping any assessment.
- If the patient has to switch from the treatment with gefitinib to the treatment with osimertinib, all the required evaluations have to be performed before the switch. However, echocardiogram and ophthalmological examination might be obtained later, as soon as this becomes possible, provided that the treating physician has carefully performed a risk-benefit assessment.

Patients receiving gefitinib who experience disease progression according to RECIST 1.1 should be switched to osimertinib at the next per protocol planned medical visit (4 weeks since previous medical visit), as per sections 6.2.3 and 6.3.3. Switch delays should be avoided as much as possible. However, if the patient is asymptomatic and is experiencing a clinical benefit and provided that the treating physician has carefully reviewed the risk-benefit assessment, switch to osimertinib might be delayed (the patient has to switch at the latest at the next per protocol planned visit, 4 weeks since the theoretical date of switch).

b) Study imaging procedures

For the baseline study imaging procedures, the protocol requirements have to be fully met.

For on-study imaging procedures, it is preferred that the patient has imaging performed at the investigative site as directed in the protocol sections 6.1.2.4, 6.2.2.2, 6.2.3.5, 6.3.2.2 and 6.3.3.5.

If difficulties are encountered to perform the imaging as per the protocol, there are several possibilities, in order of preference:

- Have the imaging performed offsite, locally according to the protocol-specified timing. Guidance should be given by the site to the local imaging facility about conducting scans with requirements (modality etc, as per Imaging Guidelines).
- Have the imaging performed at the site but delayed to a significant extent (with a window of 10 days from theoretical planned date per protocol) due to travel restriction / safety of the participant.
- Have the imaging performed offsite but delayed (with a window of 10 days from theoretical planned date per protocol) due to travel restriction / safety of the participant.
- Skip the imaging only if impossible to perform due to travel restriction / safety.

Particular attention should be given to the imaging for disease evaluation at 18 months (+/- 14 days) which should be done on time as this represents the primary endpoint evaluation of the trial.

For all above situations, the Site needs to report this in the comment fields of the applicable CRFs and in the Source Data as well.

c) Study physical visits

Patient Physical Visits can be changed into phone visits or video call visits where needed.

The site must inform the EORTC 1613 study team (1613@eortc.org) upfront if a physical visit will be replaced by a phone/video call visit.

d) Collection of samples for translational research

Collecting blood samples for assessing T790M status according to the protocol is a priority in the study, especially in arm B as these results influence the treatment decision.

If this is not possible, the study coordinators propose the following:

- If the patient is randomized in arm B and receiving gefitinib, continue to collect the blood samples for central T790M status according to the protocol section 6.2.2.1. However, if this is not possible, then, it might be skipped after prior discussion with EORTC Headquarters.
- If the patient is randomized in arm A and C, or if the patient already switched to osimertinib, collection of blood samples for central T790M status might be skipped, according to local situation.

e) Covid-19 vaccination during study participation

As per the European Medicines Agency (EMA):

- If physicians decide to administer SARS-CoV-2 vaccines in patients enrolled in the study, decisions should be individualized based on the risk of SARS-CoV-2 complications and potential benefit from the vaccine, general condition of the patient and the severity of COVID-19 outbreak in a given area or region and in accordance with the vaccine label. Furthermore the Country guidelines and/or institutional guidelines, must be followed.
- Treatment schedule should not be altered because of the COVID-19 vaccination.
- The administration of a SARS-CoV-2 vaccine stating the name of the vaccine used (e.g. Moderna, Pfizer BioNTech, AstraZeneca Oxford…) shall be added in the concomitant medication form in the eCRF and noted in the patient's Medical file. Any possible vaccine related AE should be captured in the AE forms in the eCRFs, specifying the potential relationship to the vaccine.

f) Serious adverse events reporting

- Sites should follow the SAE reporting as described in the protocol, e.g. the sites should continue to report SAEs immediately and no later than 24 hours form the time the investigator or site staff became aware of the event, as described in the protocol. There is no specific adaptations to the protocol defined SAE reporting procedure due to COVID-19.
- Should sites have any SAE reporting related questions, please contact us at pharmacovigilance@eortc.org
- Should there be a suspected or confirmed serious case of COVID-19 infection, this must be reported as SAE:
    - Please remember to provide the mandatory SAE information as per protocol and as per the CRF completion guidelines.
    - Please indicate if the COVID-19 infection was confirmed by a test.
    - Please provide as much information as available.

4. Additional guidance specifically for osimertinib during COVID-19 pandemic

Risk of ILD associated with the use of osimertinib

Symptoms of the coronavirus include fever, cough, shortness of breath, difficulty breathing and sometimes an abnormal chest scan. Please note that these symptoms are also symptoms of osimertinib-induced ILD/pneumonitis.

Physicians should be familiar with the accurate diagnosis of a coronavirus infection versus any other bacterial or viral lung infection versus symptoms suggestive of ILD since the management is different for each. A thorough evaluation should be performed to accurately identify the underlying pathology should

a patient present with these symptoms or an abnormal chest radiograph. From available publications, the principle difference in imaging findings (Chest X-ray/CT) between drug-induced ILD and COVID-19 is the rate of progression and resolution of abnormalities. Notably, some patients presenting early in their course may have no significant radiological changes, and initial imaging findings are unlikely to be able to discriminate between drug-induced ILD and COVID-19. Data are too limited to provide clear recommendations; however, imaging assessment should be performed as per standard management guidelines for drug-induced ILD. Improper management or treatment of either etiology could lead to severe pulmonary events or death.

As per standard management guidelines for drug-induced ILD, before initiation of steroid treatment, infectious causes of ILD should be excluded. This includes COVID-19 infection because steroid treatment should be avoided in COVID-19 as per available recommendations (e.g., CDC, WHO). However, a case-by-case assessment of the benefit/risk balance is needed for more severe cases of disease, e.g., ARDS/septic shock in COVID-19 patients (with ILD or viral pneumonia).

Similarly, a case-by-case assessment of the benefit/risk balance for an individual patient should be done for decisions on discontinuing or pausing treatment.

For osimertinib induced-ILD monitoring and management, please refer to the protocol (section 5.6 and subsections).

Patients should be reminded that, if a potential exposure to COVID-19 is suspected, they should notify the medical personnel of their participation in this clinical trial and medication they are taking. If a patient exhibits symptoms consistent with those of either drug-induced ILD or COVID-19, it is recommended that she/he should be advised to contact both the recommended COVID-19 point of contact (as per local guidance), as well as her/his investigator/oncologist by phone.

Risk of drug-drug interactions between osimertinib and empirical therapies used to treat COVID-19

At present several different drugs are empirically investigated for the treatment of COVID-19. The safety profile of these drugs in this unapproved indication is currently not known. Therefore, careful consideration should be taken when assessing the tolerability profile for these drugs in combination with osimertinib.

Things to consider with osimertinib regarding drug interactions include potentiation of QT prolongation with medications known to prolong the QTc interval, avoiding medications that are strong CYP3A4 inducers (or dose adjusting if avoidance is not possible), and the potential for increased exposure of BCRP or P-gp substrates.

It is deferred to the medical judgement of the investigator on using osimertinib concomitantly with any medication which is anecdotally used for treating COVID 19. Reference to the protocol inclusion/exclusion criteria and restrictions (please refer to section 5.7 and subsections, and Appendix E, for further information on concomitant medications) should be always be considered to maintain the safe use of osimertinib in the clinical trial. Additionally, reference to the respective labels of the concomitant medications should be made for additional information.

Risk of QT prolongation

Antimalarial hydroxychloroquine sulphate and antibiotic azithromycin are both known to cause QT prolongation. When the potential benefit of hydroxychloroquine sulphate and/or azithromycin is being considered to treat patients with COVID-19, these are not compatible with osimertinib treatment. Therefore, per current protocol (please refer to section 5.7 and subsections, and Appendix E, for further information on concomitant medications) osimertinib should not be given concomitantly with these drugs.

Other drugs with a potential risk of QT prolongation include antiretrovirals such as lopinavir/ritonavir. Particular caution must be used when considering concomitant treatment of these drugs with osimertinib.

Treatment for COVID-19 should be assessed on an individual case by case basis by the treating physician as well as the decision for discontinuing or pausing treatment with osimertinib.