SUMMARY ATTACHMENT

Study Title:	Efficacy study of gefitinib in treatment-naïve patients with *EGFR* mutant NSCLC according to *TP53* mutational status **TEMPLE - *T*P53** in ***E*GFR** **M**utant NSCLC **P**atients: a **L**ook towards the **E**fficacy of gefitinib
Protocol number:	ESR-16-12101
Study Phase:	IV
Name of Study Interventions:	Gefitinib
Name of Sponsor:	Azienda Ospedaliera Universitaria Integrata Verona
Number of Study Site(s) and Countries:	16 centers in Italy
Study Rationale	The results of previous analysis, albeit exploratory and underpowered for conclusive interpretations, suggested that the decoding of tumor heterogeneity might improve the understanding of the oncogenic mechanism and help to identify clinically relevant subgroups of patients, leading to a better management of the therapeutic resistance to targeted agents. To this end, a prospective biomarker-driven clinical trial with gefitinib in treatment-naïve patients with EGFR mutant NSCLC was designed, to evaluate the efficacy of gefitinib according to the TP53 mutational status. Concurrently, a translational research study sub-proposal was planned to evaluate (and quantify) sensitizing EGFR mutations, T790M and concomitant genetic alterations with NGS, in the tissue, in the blood and in the urine of the enrolled patients.
Objectives	*Primary objective* To determine the efficacy in term of PFS rate at 12 months of gefitinib in the treatment of patients with advanced EGFR mutant NSCLC, according to the TP53 mutational status. [Time Frame: At baseline and every 8 weeks from time of first dose, participants will be followed by PET-CT, CT or MRI scans for RECIST 1.1 until date of progression]. *Secondary objectives* • To assess the efficacy of gefitinib according to TP53 mutational status regarding OS [Time Frame: From first dose to end of study or date of death from any cause, whichever comes first, assessed every 8 weeks]. • To assess the efficacy of gefitinib according to TP53 mutational status regarding ORR according to RECIST 1.1 [Time Frame: At baseline and every 8 weeks from time of first dose, participants will be followed by PET-CT, CT or MRI scans for RECIST 1.1 until date of progression]. • To assess the efficacy of gefitinib according to TP53 mutational status regarding Time to treatment failure (TTF) [Time Frame: From first dose to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death, assessed every 8 weeks]. • To assess the efficacy of gefitinib according to TP53 mutational status regarding Disease Control Rate (DCR) according to RECIST 1.1 [Time Frame: At baseline and every 8 weeks from time of first dose, participants will be followed by PET-CT, CT or MRI scans for RECIST 1.1 until date of progression].

	• To assess the efficacy of gefitinib according to TP53 mutational status regarding Duration of response (DoR) according to RECIST 1.1 [Time Frame: At baseline and every 8 weeks from time of first dose, participants will be followed by PET-CT, CT or MRI scans for RECIST 1.1 until date of progression]. • To assess the safety and tolerability profile of gefitinib according to TP53 mutational status, as assessed by number and severity of AEs as recorded on the case report form (CRF, Annex1), clinical chemistry, haematology, urinalysis, vital signs, physical examination, weight, ECG and WHO Performance status (PS). [Time Frame: AEs will be collected from baseline until 28 days after the last dose]. • To evaluate the efficacy data according to the proportion of mutated alleles for EGFR and the presence of coexisting genetic alterations. • To monitor and quantify EGFR mutations (including T790M) in plasma and urine during treatment. • To determine the feasibility of re-biopsies at the time of progression for biomarkers analysis related to mechanisms of resistance and decision-making for second-line treatment. • To assess the feasibility and the applicability of innovative technologies (NGS) in the diagnosis and monitoring of lung cancer patients. • To compare the results obtained in tissue, in blood and urine with NGS.
Endpoint	*Primary endpoint* Progression-free survival (PFS) rate at 12 months *Secondary endpoints* • Overall survival (OS) • Objective response rate (ORR) • Time to treatment failure (TTF) • Disease control rate (DCR) • Duration of response (DoR) • Adverse events (AEs) graded according to CTCAE V4.0 • Translational research studies
Methodology:	This was a prospective biomarker-driven study of gefitinib in treatment-naïve patients with EGFR mutant NSCLC, to evaluate the efficacy of gefitinib according to the TP53 mutational status. The study consisted of a Screening phase to establish study eligibility (including the availability of tumour tissue for analysis) and document baseline measurements. In an Open-label treatment phase, to ascertain efficacy and safety of gefitinib according to the TP53 mutational status until protocol-defined disease progression. In the Follow-up phase, to monitor survival status and subsequent NCSLC cancer therapy.
Inclusion criteria	• EGFR mutation status (EGFR exon 19 deletions or exon 21 p.L858R • substitution mutations) • Male or female, minimum age 18 years. • ECOG performance status of 0 to 2. • Adequate haematological function: haemoglobin > 9 g/dL, neutrophils count >1.5 × 109/L, platelet count > 100 × 109/L. • Adequate coagulation: INR ≤ 1.5. • Adequate liver function: total bilirubin < 1.5 × ULN, ALT and/or AST < 2.5 × ULN, alkaline phosphatase < 5 ULN, except in the presence of exclusive bone metastases and in the absence of any liver disorder. • Adequate renal function: calculated creatinine clearance ≧ 50 mL/min (Cockroft-

	Gault) and proteinuria < 2+ (dipstick). • Oral swallowing capability, patient capable of proper therapeutic compliance, and accessible for correct follow-up. • Life expectancy of at least 3 months. • Women of childbearing age, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine pregnancy test within 7 days before beginning treatment. Not eligible: women who are pregnant or in the period of lactation. • All sexually active men and women of childbearing age must use an effective contraceptive method during the study treatment and for a period of at least 12 months following the last administration of trial drugs. Not eligible: sexually active men and women of childbearing age who are not willing to use an effective contraceptive method during the study. • Written Informed Consent (IC) must be signed and dated by the patient and the investigator prior to any trial-related intervention
Exclusion criteria	• Active second malignancy; i.e., patient known to have potentially fatal cancer present for which he/she may be (but not necessarily) currently receiving treatment. • Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enrol in the trial provided all chemotherapy was completed > 6 months prior and/or bone marrow transplant > 2 years prior to first day of study treatment. • Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD. • Patients with moderate to severe hepatic impairment (Child Pug B or C) due to cirrhosis. • Patients with active keratitis and severe ocular diseases. • Spinal cord compression, symptomatic and unstable brain metastases, requiring steroids over the last 4 weeks prior to enrollment in this study. • Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of gefitinib. • Non-study related surgical procedures less than or equal to 7 days prior to administration of study drug. In all cases, the patient must be sufficiently recovered and stable before treatment administration. • Females who are pregnant or breastfeeding. • Refusal to use adequate contraception for fertile patients (females and males) for 24 weeks after the last dose of gefitinib. • Patients with other serious diseases or clinical conditions, including but not limited to uncontrolled active infection and any other serious underlying medical processes that could affect the patient's capacity to participate in the study. • Any other reason the investigator considers the patient should not participate in the study.
Study intervention, dose, mode of administration	Gefitinib 250 mg per os (p.o.), daily. Gefitinib is started at a fixed dose of 250 mg per day. Treatment with gefitinib is continuous. Tablets should be taken at a fixed time each day and at least 1-hour before or 2 hours after the ingestion of food. Each 28-day period of treatment will represent one cycle, with dosing initiated on Cycle 1 Day 1.
Study Period:	The study closed on 30/04/2018 before the start.
The reason for	In consideration of emerging evidence in literature, Principal Investigator decided to

the premature termination of the trial	redesign the study with elements of greater scientific and clinical relevance.
Summary of results	No results available