

NSCLC mit EGFR-Mutation

AIO-TRK-0114: A randomized, open-label, phase II study of maintaining pan-ERBB blockade following platinum-based induction chemotherapy in patients with EGFR mutated, metastatic non-small-cell lung cancer progressing after treatment with afatinib as first EGFR-targeting agent (Short Title: MARBLE: Maintaining ERBB blockade in EGFR-mutated lung cancer)

AIO-Studie

Studiennummer/-Code: AIO-TRK-0114 - MARBLE
Status: Studie wurde vorzeitig abgebrochen, wegen mangelnder Rekrutierung
Letzte Aktualisierung: Jan. 2018

EudraCT-No.	2014-001983-36
Coordinating Investigator	Prof. Dr. Martin Schuler Universitätsklinikum Essen, Westdeutsches Tumorzentrum Innere Klinik (Tumorforschung) Hufelandstraße 55, 45147 Essen, Germany Phone: +49 – 201 – 723 2000, Fax: +49 – 201 – 723 5924 E-Mail: martin.schuler@uk-essen.de
Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8, 14057 Berlin, Germany Phone: +49-30 – 814534431, Fax: +49-30 – 322932926
Study design	<p>Patients who have progressed after treatment with afatinib as first tyrosine kinase inhibitor (TKI) will be screened while they are receiving second-line (induction) treatment consisting of cisplatin / carboplatin plus pemetrexed given in 21-day cycles. Patients who do not progress (i.e. complete or partial response, or stable disease – CR, PR or SD) after completion of at least three and not more than four chemotherapy cycles will be randomized (1:1 ratio) to receive maintenance therapy with either afatinib (40 mg/d or last tolerated dose during treatment with afatinib as first TKI) or pemetrexed (500 mg/m² or 375 mg/m² if dose reduction was required every 21 days) until disease progression or treatment discontinuation because of patient decision or toxicity.</p> <p>• NSCLC stage IV • EGFR mutant • Progression after Afatinib (≥ 6 months)</p> <pre>graph LR; A["• NSCLC stage IV • EGFR mutant • Progression after Afatinib (≥ 6 months)"] --> B["Cis-/Carboplatin + Pemetrexed (3 to 4 cycles)"]; B --> C((R)); C --> D["Afatinib 40 mg/d"]; C --> E["Pemetrexed 500 mg/m² q21d"];</pre>
Anticipated start date	01/2015 (FPI)
Duration of study	40 months
Indication	Non-small-cell lung cancer with somatic <i>EGFR</i> mutations
Countries Total number of sites	Planned: Germany and other European countries In total: up to 30 experienced thoracic oncology sites
Primary objective	To compare the efficacy of afatinib maintenance with pemetrexed maintenance following induction therapy with platinum/ pemetrexed in patients with metastatic <i>EGFR</i> mutated non-small-cell lung cancer progressing after treatment with afatinib as first tyrosine kinase inhibitor with respect to progression-free survival

Secondary objectives	<p>To compare afatinib maintenance with pemetrexed maintenance after induction therapy with platinum/pemetrexed with respect to</p> <ul style="list-style-type: none"> • Overall survival • Objective response rate, Clinical benefit rate (RECIST1.1) • Safety / toxicity • Quality of Life
Planned sample size	In total, up to 210 patients will be randomized
Inclusion Criteria	<ol style="list-style-type: none"> 1. Histologically or cytologically confirmed diagnosis of non-small-cell lung cancer (NSCLC) with no curative therapeutic option. Patients with Stage IV (UICC 7th edition) disease or Stage IIIB disease not amenable to curative intent surgery or radiotherapy are enrolled. Patients with mixed histology are eligible if NSCLC is the predominant histology 2. Documented somatic <i>EGFR</i> mutation as determined by medically accepted assay technology 3. Patients with documented progression after response (CR/PR) or stable disease (SD) for at least 6 months of treatment with afatinib as first tyrosine kinase inhibitor (either given as first-line therapy or being switched to afatinib after up to 4 courses of platinum-based chemotherapy) 4. Patients who have completed 3 or 4 cycles of cisplatin or carboplatin plus pemetrexed induction chemotherapy prior to randomization leading to documented response (CR/PR) or SD according to RECIST 1.1 5. At least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 6. Male or female patient with age ≥ 18 years 7. ECOG performance status ≤ 2 8. Adequate organ and bone marrow function, defined as all of the following: Before the last cycle of induction chemotherapy or after hematopoietic recovery from the last cycle of induction chemotherapy: <ul style="list-style-type: none"> • Absolute neutrophil count (ANC) $\geq 1,500 / \text{mm}^3$ • Platelet count $\geq 100,000 / \text{mm}^3$ • Creatinine clearance $\geq 45 \text{ ml} / \text{min}$ (calculated according to Cockcroft and Gault, or Tc99m-DPTA clearance or similar methodology). Patients with creatinine clearance of 45 to 79 ml/min should refrain from using NSAID at least 2 days before and 2 days after infusion of pemetrexed. Long-acting NSAID should be terminated 5 days before pemetrexed infusion. • Total serum bilirubin ≤ 1.5 times upper limit of institutional normal (ULN) • Serum aspartate amino transferase (AST) and serum alanine amino transferase (ALT) ≤ 3 times the upper limit of institutional normal (ULN) (≤ 5 times ULN if liver function abnormalities are due to underlying malignancy) 9. Recovered from any previous therapy related toxicity to \leq Grade 1 at study entry (except for stable sensory neuropathy \leq Grade 2 and alopecia) 10. Written informed consent 11. Ability to comply with the protocol for the duration of the study, including hospital/office visits for treatment and scheduled follow-up visits and examinations
Exclusion Criteria	<ol style="list-style-type: none"> 1. Systemic therapy for metastatic disease or relapse other than (a) first-line therapy with afatinib or (b) afatinib given as first EGFR-targeting agent following up to 4 courses of platinum-based chemotherapy with no disease progression between first-line chemotherapy and initiation of afatinib (prior adjuvant chemotherapy is allowed) and 3 to 4 cycles of induction chemotherapy with cisplatin or carboplatin and pemetrexed following afatinib failure

2. Prior treatment with erlotinib, gefitinib or other investigational or approved EGFR-targeting small molecules or antibodies
3. Known EGFR T790M mutation (analysis not mandatory)
4. Major surgery within 4 weeks before starting study treatment or scheduled for surgery during the projected course of the study
5. Extended radiotherapy within 4 weeks prior to randomization, except as follows:
 - a. Palliative, limited local radiation to non-target lesions (e.g. isolated bone metastases) may be allowed up to 2 weeks prior to randomization, and
 - b. single dose palliative treatment for symptomatic metastasis outside above allowance to be discussed with sponsor prior to enrolling
6. Active brain metastases except for the followings:
 - Asymptomatic brain metastases incidentally found during screening process which do not require local treatment in the opinion of the investigator.
 - Asymptomatic brain metastases for which local treatment has been given: stable for at least 4 weeks of lower dose corticosteroids (e.g., dexamethasone up to 4 mg/d) and/or non-enzyme-inducing anti-convulsants treatment before study randomization.
 - Brain metastases controlled after surgery and/or radiotherapy
7. Meningeal carcinomatosis
8. Previous or concomitant malignancies at other sites, except effectively treated non-melanoma skin cancers, carcinoma in situ of the cervix, non-invasive bladder cancer, ductal carcinoma in situ of the breast, or effectively treated malignancy that has been in remission for more than 3 years and is considered to be cured. Definitively treated localized low/intermediate risk prostate cancer (Gleason score ≤ 7) is allowed when a rise in serum PSA level by ≥ 2 ng/mL above the nadir is excluded
9. Known pre-existing interstitial lung disease
10. Any history or presence of poorly controlled gastrointestinal disorders that could affect the absorption of the study drug in the opinion of the investigator (e.g. Crohn's disease, ulcerative colitis, chronic diarrhea, and malabsorption)
11. Clinically relevant cardiovascular abnormalities as judged by the investigator such as uncontrolled hypertension, congestive heart failure \geq NYHA grade III, unstable angina or myocardial infarction within the past 6 months, or poorly controlled cardiac arrhythmia in the opinion of investigator
12. Any history of or concomitant condition that, in the opinion of the investigator, would compromise the patient's ability to comply with the study or interfere with the evaluation of the efficacy and safety of the test drug, or renders the patient at high risk of treatment complications
13. Women of child-bearing potential and men who are able to father a child, unwilling to be abstinent or use adequate contraception prior to study entry, for the duration of study participation and for at least 2 weeks after treatment has ended
14. Female patient pregnant or breast-feeding
15. Known active infection with HBV, HCV or HIV
16. Any contraindications for therapy with pemetrexed
17. Known hypersensitivity to afatinib or the excipients of any of the trial drugs
18. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 60 days prior to treatment start
19. Pleurocentesis or paracentesis should be considered in patients with clinically significant pleural effusions or ascites if clinically indicated.

	However, per SmPC of pemetrexed the presence of effusion is not an exclusion criteria
Investigational Medicinal Product	Afatinib, Pemetrexed
Treatment schedule after randomization	<p>Arm A: Afatinib 40 mg/d (30, or 20 mg/d in case of dose reduction during 1st line treatment)</p> <p>Arm B: Pemetrexed 500 mg/m² (375 mg/m² in case of dose reduction during induction therapy) i.v. on d1 of each 21-day cycle</p>
Primary endpoint	<ul style="list-style-type: none"> • Progression-free survival (RECIST 1.1)
Secondary endpoints	<ul style="list-style-type: none"> • Overall survival • Objective response rate, clinical benefit rate (RECIST 1.1) • Health-related quality of life (HRQOL) • Severity and frequency of adverse events according to NCI Common Terminology Criteria for Adverse Events (CTCAE Version 4.03)
Randomization procedure	<p>Block randomization will be applied by an IRT to guarantee balanced group numbers. To increase homogeneity between the treatment groups, the 1:1 randomization will be stratified by</p> <ul style="list-style-type: none"> • (1) <i>EGFR</i> mutation (L858R vs. del 19 vs. other), and • (2) Best overall response during induction phase (CR/PR vs. SD)
Scientific rationale	<p>Metastatic non-small-cell lung cancers (NSCLC) harboring somatic <i>EGFR</i> mutations (in particular exon 21 mutations leading to L858R amino acid exchange, and exon 19 mutations leading to in-frame deletions, also called "common mutations") exhibit "oncogenic dependency" on mutant receptor signaling. This provides an opportunity for small molecule inhibitors of the <i>EGFR</i> tyrosine kinase (<i>EGFR</i>-TKI). Compounds such as erlotinib and gefitinib are highly effective in patients with <i>EGFR</i>-mutated NSCLC, but disease control is only transient. Re-biopsies taken at clinical progression have revealed that the majority of cases with acquired resistance to <i>EGFR</i>-TKI are selected for additional <i>EGFR</i> mutants. Prime example is the <i>EGFR</i> T790M "gatekeeper mutation", which is thought to affect the drug-target interaction of reversible inhibitors. This "generic" resistance mutation reduces the potency of any reversible <i>EGFR</i>-TKI and therefore maintains <i>EGFR</i> signaling in the presence of reversible <i>EGFR</i>-TKI. Clinically, patients frequently show oligotopic disease progression while remaining tumor lesions are still controlled. Currently, these findings rarely are therapeutically exploited. Patients progressing on first-line treatment with an <i>EGFR</i>-TKI are regularly switched to platinum-based combination chemotherapy.</p> <p>Recently, the irreversible pan-ERBB blocker afatinib was shown to be highly effective in treatment-naïve as well as in medically pretreated patients with <i>EGFR</i> mutated NSCLC. Objective responses or prolonged disease control have been observed in patients with NSCLC harboring "common <i>EGFR</i> mutations", but also in patients with "rare mutations". The pivotal LUX-Lung 3 and 6 trials conducted in treatment-naïve patients with metastatic, <i>EGFR</i> mutated NSCLC have demonstrated superior clinical efficacy of afatinib over cisplatin/pemetrexed or cisplatin/gemcitabine chemotherapy. The median progression-free survival time of afatinib-treated patients with "common" <i>EGFR</i> mutations in LUX-Lung 3 and 6 exceeded those observed in most prospectively randomized trials of first-generation, reversible <i>EGFR</i>-TKI. Moreover, a significant overall survival benefit of first-line afatinib (HR=0.81, p=0.037) has been demonstrated in a combined analysis of patients from the LUX-Lung 3 and 6 studies with cancers harboring "common" <i>EGFR</i> mutations,</p>

	<p>which was carried by the group with <i>EGFR</i> exon 19 deletion mutations. These results provide the rationale for first-line treatment with afatinib of patients with metastatic NSCLC harboring somatic <i>EGFR</i> mutations. Nevertheless, disease control with afatinib is also transient. At present clinical mechanisms of acquired resistance to afatinib are mostly unclear. However, in analogy to the EGFR-TKI experience it can be expected that a large proportion of <i>EGFR</i> mutated NSCLC progressing after initial response to afatinib will maintain their "oncogenic dependency" on ERBB family signaling. This hypothesis is backed by scientific evidence obtained in another cancer with "oncogenic dependency" on ERBB family signaling: It is clinically effective and thus common practice in metastatic <i>HER2</i>-amplified breast cancer to maintain <i>HER2</i> targeting by trastuzumab upon progression on first line treatment with trastuzumab-based combination therapy. Accordingly, the concept of maintained blockade of the major oncogenic signal in <i>EGFR</i> mutated NSCLC over more than one treatment line has been explored in the randomized phase III trial LUX-Lung 5. This multicenter study enrolled patients with heavily pretreated NSCLC that have demonstrated clinical benefit from prior EGFR-TKI treatment. In the first part of LUX-Lung 5, all patients received afatinib. In the second part, patients progressing after having derived benefit from afatinib monotherapy were then randomized between single agent chemotherapy alone (paclitaxel) or paclitaxel combined with afatinib. Patients maintained on afatinib in combination with paclitaxel showed a significant and clinically meaningful benefit in terms of median progression-free survival time (HR=0.6, p=0.003). This study thus provided the first prospectively generated proof-of-principle for maintaining ERBB blockade over multiple treatment lines in patients with <i>EGFR</i>-mutated NSCLC.</p> <p>While LUX-Lung 5 has studied an extensively pretreated patient population (\geq third line), this randomized phase II study, MARBLE, will explore the clinical benefit of maintaining pan-ERBB blockade in patients with <i>EGFR</i> mutated, metastatic NSCLC progressing after first-line treatment with afatinib and induction chemotherapy with pemetrexed and platinum.</p>
Sample Size Calculation	<p>To detect an improvement of median PFS from 3.8 months to 5.5 months, corresponding to a hazard ratio of 0.69, 181 PFS failures are necessary to provide 80% power for the log-rank test (alpha = 0.05, one-sided). A total of 210 patients will have to be randomized. It is expected that this number of patients can be recruited within 24 months by a network of 30 experienced thoracic oncology centers. This results in total study duration of 40 months.</p>
Interim analyses	No interim analysis is planned for this study.
Statistical analysis	<p>An observed cases approach will be applied, and missing data will not be imputed. A significance level of 10% two-sided (corresponding to 5% one-sided) will be applied. Efficacy analysis will primarily be evaluated within the per-protocol analysis group.</p> <p>PFS and OS will be analyzed descriptively using the Kaplan-Meier method and compared between groups with a Cox-regression with the factors study site, stratification factors (<i>EGFR</i> mutation and best overall response during induction phase) and treatment group. Response endpoints will be compared between groups using a Cochran-Mantel-Haenszel chi-square test stratified by the same factors. Health-Related Quality of Life (HRQoL) will be evaluated descriptively.</p> <p>Adverse Events and Serious Adverse Events will be summarized overall and by severity; 90% confidence intervals for event rates will be calculated.</p>
Study plan	<p>FPI: 01/2015 LPI: 12/2016 LPO: 06/2018 LPLV: 06/2018 Planned data base lock for primary endpoint analysis: 06/2017</p>

	Planned study report of primary analysis: 09/2017
Risk benefit assessment	<p>The safety, feasibility and validity of the original hypothesis of the proposed trial is supported by clinical findings from LUX-Lung 5 such as</p> <ul style="list-style-type: none"> • Median survival of patients with known <i>EGFR</i> mutated NSCLC treated in both parts A and B of LUX-Lung 5 was more than 12 months. • Median PFS for part A of the LUX-Lung 5 study was 3.15 months for the entire population, 4.14 months for patients clinically enriched by prior benefit from EGFR-TKI, and 3.98 months for patients with centrally confirmed <i>EGFR</i> mutations. • Median PFS for patients treated in part B of the LUX-Lung 5 study with afatinib plus paclitaxel was 5.6 months as compared to 2.8 months in patients randomized to chemotherapy (HR=0.6, p=0.0031). <p>As the MARBLE study will address a novel treatment scenario a statistical model can only be built around assumptions. Hence, the study hypothesis is based on reported findings in similar populations or is extrapolated from comparable clinical settings:</p> <ul style="list-style-type: none"> • The biology of <i>EGFR</i> mutated NSCLC is more favorable than of an unselected stage IV NSCLC population such as in PARAMOUNT. I.e. Patients with <i>EGFR</i> mutated NSCLC have higher response rates and prolonged disease control than patients with <i>EGFR</i> wild type NSCLC. The theoretical advantage of <i>EGFR</i> mutated NSCLC over unselected populations can be estimated from the control arms of prospective clinical trials incorporating chemotherapy in <i>EGFR</i>-stratified populations and in unselected populations. • However, cisplatin/pemetrexed may be less active when used as second-line treatment after an EGFR-TKI or afatinib, as <i>EGFR</i> mutated subclones have been shown to be more sensitive to chemotherapy than <i>EGFR</i> wild type subclones. This may result in weak but significant selection against NSCLC subclones with "common" <i>EGFR</i> mutations. However, this assumption cannot be substantiated or quantified from currently available clinical trial reports. • Median PFS (investigators' assessment) of first-line cisplatin/pemetrexed in <i>EGFR</i> mutated NSCLC (LUX-Lung 3) was 6.7 months. In an unselected contemporary population with "non-squamous NSCLC" (PARAMOUNT), median PFS of first-line cisplatin/pemetrexed was 5.6 months. Hence, the median PFS of patients with <i>EGFR</i>-mutated NSCLC is at least 1.2 times longer. • Median PFS of second-line carboplatin/pemetrexed is reported in the range of 3.5 to 4.2 months. Applying the "factor 1.2" this translates into a theoretical median PFS of 5.04 months in <i>EGFR</i> mutated NSCLC. However, the time of induction therapy (2.8 months for 4 cycles) has to be subtracted, resulting in a theoretical median "treatment-free" PFS of 2.24 months. • Pemetrexed maintenance following 4 courses of cisplatin/pemetrexed (PARAMOUNT) increased the median PFS by 1.3 months. Applying the "factor 1.2" this translates in a prolongation of median PFS by pemetrexed maintenance in <i>EGFR</i> mutated NSCLC by at least 1.56 months. <p>Following induction therapy with 3-4 x cisplatin/pemetrexed in patients progressing after treatment with afatinib as first TKI pemetrexed maintenance is expected to result in a median PFS of at least 3.8 months. This estimation is based on a numerical PFS of at least 2.24 + 1.56 months (= 3.8 months).</p> <p>Maintenance treatment with afatinib should at least result in the same median PFS. To be considered clinically superior the median PFS achieved with afatinib maintenance should at least be 5.5 months.</p>