Name of Sponsor: AIO-Studien-gGmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: GIOTRIF®		
Name of Active Ingredient: Afatinib		

Title of Study:

Maintaining ERBB blockade in *EGFR*-mutated lung cancer (MARBLE) - 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

Study Sites:

Universitätsklinikum Essen, Lungenklinik Ballenstedt/Harz gGmbH, LMU München, Pius Hospital Oldenburg

Publication (reference):

None at the time of this report

Study Dates:	Phase of Development:
First site open for recruitment: 05-Nov-2015 First Patient Treated: 02-Jun-2016 Last Patient Completed: 28-Nov-2017 Early Termination (FU-1 of last patient): 16-Jan-2018	Phase II

Objectives:

Primary objectives

To compare the efficacy of afatinib maintenance with pemetrexed maintenance following induction therapy with platinum/pemetrexed in patients with metastatic *EGFR* mutated non-small-cell lung cancer progressing after treatment with afatinib as first tyrosine kinase inhibitor with respect to progression-free survival.

Secondary objectives

To compare afatinib maintenance with pemetrexed maintenance after induction therapy with platinum/pemetrexed with respect to

- Overall survival (OS)
- Objective response rate, Clinical benefit rate (RECIST1.1)
- Safety / toxicity
- Quality of Life (QoL)

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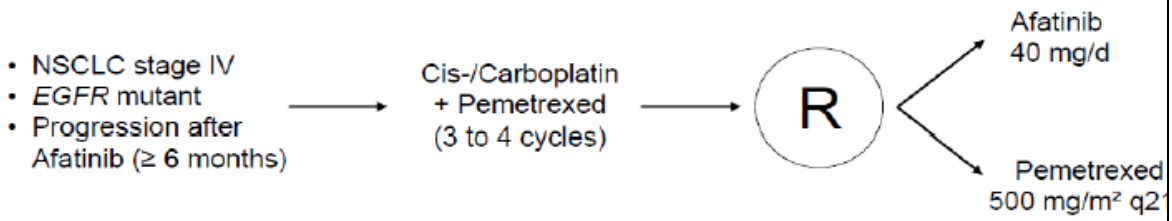
Methodology:



Arm A: Afatinib

40 mg/d (30, or 20 mg/d in case of dose reduction during 1st line treatment)

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

Number of Patients:

Planned: 210 patients

Screened: 5 patients

Analyzed: 4 patients

Diagnosis and Main Criteria for Inclusion:

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 were enrolled. Patients with mixed histology were eligible if NSCLC was the predominant histology

Test Product, Dose and Mode of Administration, Batch Number:

Afatinib, 40mg/d per os, E135167-0003L001, E135167-0005L002

Duration of Treatment:

until progression

Reference Therapy, Dose, and Mode of Administration, Batch Number:

Pemetrexed, 500 mg/m² i.v. on d1 of each 21-day cycle, C283554C, C556499C

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Name of Finished Product: GIOTRIF®		
Name of Active Ingredient: Afatinib		

Criteria for Evaluation:

Primary Endpoint

The primary endpoint of this study is progression-free survival (RECIST 1.1).

Secondary Endpoints

- Overall survival (OS)
- Objective response rate, clinical benefit rate (RECIST 1.1)
- Lung cancer symptom scale / Health-Related Quality of Life (HRQoL) (EORTC QLQ-C30, QLQ-LC13)
- Safety, toxicity (intensity and incidence of adverse events, graded according to US NCI CTCAE Version 4.03)

Statistical Methods:

No statistical analysis was performed. The planned analyses are described in the study protocol.

Summary of Results:

Five patients were screened in this study. Four of these patients were randomized and received study medication. All four patients were female and between 55 and 67 years old. Two patients received Pemetrexed; treatment duration was three and 15 cycles, respectively. Two patients received Afatinib, for a duration of two and five cycles. Reasons for End of treatment were global deterioration of health and adverse event, disease progression, withdrawal of the informed consent and death.

Safety Results:

In total, 38 adverse events were observed. 18 of these 38 adverse events were considered related to study medication. Two were considered related to Afatinib and 16 were considered related to Pemetrexed.

With Afatinib, the following ≥ grade 3 events were observed: fatigue (considered related to study drug), tumor cachexia, tumor pain and peritonitis perforative (fatal event). The following adverse events ≥ grade 3 were observed with Pemetrexed: leucopenia (considered related to study drug), pain in extremity (considered serious) and hyperglycemia.

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Name of Finished Product: GIOTRIF®		
Name of Active Ingredient: Afatinib		

Efficacy Results:

Efficacy results were not summarized.

Two patients died due to underlying disease, one patient had progression and one patient was still alive and without progression at termination of the study.

Median PFS was expected as 3.8 (standard care) and 5.5 months (experimental), respectively. One standard care patient was censored after 9.7 months and one patient had an event after 2.7 months. The two patients in the experimental arm had PFS of 3.2 and 1.3 months, respectively.

No conclusion can be drawn due to small sample size.

Conclusions:

Due to the small number of subjects enrolled in the study, significance of the data obtained is very limited, and overall conclusions cannot be drawn.

Date of Report:

23-Nov-2018

The study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.