Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

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Title of trial:	A phase II single-arm trial of BIBW 2992 in EGFR FISH positive non-small cell lung cancer patients
Coordinating Investigators:	[redacted]
Trial sites:	Multicentre study (i.e. 13 enrolling centres, including 10 centres entering patients) conducted in Italy
Publication (reference):	Data of this study have not been published.
Clinical phase:	II
Objectives:	The primary objective was to explore the efficacy of afatinib once daily in patients with EGFR FISH-positive advanced non-small cell lung cancer (NSCLC) stage IIIB or IV (including first and second line patients).
Methodology:	Open-label, single-arm clinical trial with a treatment period of variable duration and repeated treatment courses of 28 days until tumour progression.

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No. of patients:	
planned:	enrolled: 280 (screened) entered: 70
actual:	enrolled: 223 patients (enrolled / screened) entered: 69 Afatinib 50mg once daily: entered: 69; treated: 69; analysed (for primary endpoint): 69 A total of 225 patients were enrolled in the study, and 70 patients were entered and started study treatment. However, source data were found to be missing for 2 patients, one of them a screening failure. This was identified as a possible serious non-compliance issue. It was decided to remove the 2 patients from the database. Hence, they are not included in any of the analyses presented in this report, bringing the number of enrolled and entered patients to 223 and 69, respectively. The 223 enrolled patients comprised 118 patients and 5 of these patients who were re-screened.
Diagnosis and main criteria for inclusion:	Patients with a pathologically-confirmed diagnosis of NSCLC stage IIIB or IV with EGFR FISH positive adenocarcinoma, bronchoalveolar carcinoma, or squamous cell carcinoma were eligible to participate. The inclusion of patients with squamous cell carcinoma was only allowed following the implementation of Protocol Amendment 1 (dated 15 Mar 2010).
Test product:	Afatinib (BIBW 2992) film-coated tablets
dose:	50 mg once daily, with dose reductions to 40 mg once daily and, in a second step, to 30 mg once daily, following the protocol-defined dose reduction scheme
mode of admin.:	Oral
batch no.:	See Appendix 16.1.6
Reference therapy:	Not applicable
Duration of treatment:	Each patient could continue treatment as long as they tolerated treatment, until disease progression (according to the Response Evaluation Criteria in Solid Tumors [RECIST] version 1.0), and neither the patient nor the investigator requested treatment discontinuation.

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Criteria for evaluation:

Efficacy / clinical pharmacology:	Tumour response was assessed according to RECIST version 1.0. The primary endpoint was objective response rate defined as confirmed complete response (CR) or partial response (PR). Secondary efficacy endpoints were time to objective response, duration of objective response, disease control (CR, PR, stable disease [SD]), duration of disease control, progression-free survival (PFS), and overall survival (OS). Pharmacokinetic characteristics of afatinib were also assessed.
Safety:	Safety was assessed in terms of adverse events (AEs), laboratory safety parameters, vital signs including left ventricular ejection fraction (LVEF), and Eastern Cooperative Oncology Group (ECOG) performance status.
Statistical methods:	All data were summarised using descriptive statistics. Response rates with exact 95% Clopper-Pearson confidence intervals (95% CI) and Kaplan-Meier estimates with 95% CI were calculated. No formal statistical inferences were planned or performed.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Disposition, demographic and baseline characteristics

A total of 223 patients were screened. This number included 5 patients who were rescreened and were assigned 2 patient numbers. Thus, the total of patients enrolled in the study was 218. Of the screened patients, 69 patients entered the study and were treated with afatinib. The 69 patients (first-line: 40 patients, second-line, after prior chemotherapy: 29 patients) formed the treated set and as such, the basis for the main analyses in this trial. All entered and treated patients had discontinued study treatment and completed the trial. The most frequent reason for treatment discontinuation was progressive disease (PD) (81.2% of all treated patients) followed by AEs other than PD (15.9%). The mean overall compliance was 92.8% (standard deviation [SD] 12.86).

All patients were White; 50.7% of all patients were male. The mean age was 63.8 years (SD: 11.3). Most patients were either ex-smokers (59.4%) or current smokers (10.1%); 30.4% of patients had never smoked.

The predominant tumour histology was adenocarcinoma (88.4%); bronchoalveolar carcinoma and squamous cell carcinoma were reported for 4.3% and 7.2% of patients, respectively. The clinical stage at diagnosis was IV in

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Efficacy / clinical pharmacology results (cont.):

60.9% of patients, IIIB in 11.6% of patients, and <IIIB in 27.5% of patients.

Only EGFR FISH positive patients were eligible for inclusion in the study; patients with high polysomy or gene amplification were considered as FISH positive. The analysis of the EGFR mutation and K-ras status was to be performed only in EGFR FISH positive patients; however, neither was part of the eligibility criteria. All 69 patients were EGFR FISH positive. Twelve of 55 patients with known EGFR mutation status (12/55, 21.8%) were EGFR mutation positive. Of the 12 EGFR mutation positive patients, 5 had an Exon 19 mutation; none had an Exon 21 mutation. Ten out of 48 patients with known K-ras status were K-ras mutation positive (10/48, 20.8%).

Efficacy

The percentage of patients with confirmed objective tumour response was 13.0%. Regardless of confirmation, the response rate was 18.8%. Disease control was achieved in 50.7% of patients.

Median PFS was 8.43 weeks (95% CI 7.43, 15.71). The probability to be alive and progression-free was 27.2% at Week 24 and 9.1% at Week 56.

Fifty-nine patients (85.5%) had an OS event. Median OS was 50.43 weeks (95% CI 33.43, 64.00). The probability to be alive was 44.2% at Week 56 and 25.0% at Week 104.

Compared with the overall trial population, increased objective response rates, disease control rates, and longer median PFS times were consistently seen for patients with EGFR gene amplification, EGFR mutation positive patients, female patients, and never-smokers (based on the analysis of predefined patient subgroups). Prolonged OS was seen in patients with EGFR gene amplification, patients with EGFR high polysomy / gene amplification, EGFR mutation positive patients, never-smokers, and patients with an ECOG score of 0. In patients with squamous tumour histology (n=5), the best confirmed tumour response was SD in 4 patients and PD in 1 patient; PFS ranged between 8.0 weeks and 71.3 weeks, and OS between 20.0 weeks and 145.6 weeks.

Pharmacokinetics

Pharmacokinetic data were analysed by dose level, i.e. for the starting dose of afatinib 50 mg and for patients with PK samples collected after dose reductions to 40 mg or 30 mg. In the 50 mg dose group, individual pre-dose plasma concentrations of afatinib appeared to remain stable over the treatment periods. For patients in the 30 mg and 40 mg dose groups, PK data availability was

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Efficacy / clinical pharmacology results (cont.):	limited, thus limiting the calculation of pharmacokinetic parameters. No differences in pre-dose plasma concentrations of afatinib between first- and second-line patients were observed.
Safety results:	The analysis of safety was based on the treated set; i.e. all 69 patients who were entered and had received at least 1 dose of study medication. The median treatment duration with afatinib was 8.14 weeks. A total of 31 patients (44.9%) had 1 dose reduction; 15 out of 31 patients had a second dose reduction. *Adverse events* All patients experienced at least one treatment-emergent AE. The 3 most common AEs were rash/acne+ (all grades: 84.1%) and diarrhoea (all grades: 82.6%), followed by stomatitis+ (all grades: 39.1%). The most frequent AE of grade 3 was rash/acne+ (27.5%), followed by diarrhoea (10.1%). All other AEs of grade 3 occurred in <10% of patients. AEs of grade 4 were reported in 5.8% of patients. The incidence of drug-related AEs was 92.8%. The most common related AEs were rash/acne+ (82.6%), followed by diarrhoea (78.3%), stomatitis (37.7%), and fatigue (20.3%). All other drug-related AEs occurred in <20% of patients. The profiles of AEs leading to dose reduction or to treatment discontinuation were consistent with the overall AE profile of afatinib. Adverse events that led to a dose reduction of afatinib were reported in 44.9% of patients; the most frequent terms were diarrhoea and rash/acne+, reported for 20.3% and 18.8% of patients, respectively. Overall, 34.8% of patients reported an AE that led to the discontinuation of study treatment. The most common AEs leading to discontinuation were diarrhoea (7.2%) and rash/acne+ (7.2%). In 9 patients (13.0%), AEs leading to treatment discontinuation were judged as drug-related. The most frequent preferred / grouped terms of related AEs leading to discontinuation were diarrhoea and rash/acne+, reported in 5 patients (7.2%) and 4 patients (5.8%), respectively. SAEs occurred in 50.7% of patients. The most frequent preferred terms were malignant neoplasm progression and diarrhoea, which were reported for 5 patients (7.2%) and 4 patients (5.8%), respectively. Overall, 14 patients (20.3%) experienced treatment-emergent AEs that led to the patient's death. None of the AEs leading to death was considered as drug-related. In 7 patients (10.1%), the AE leading to death was from the SOC of benign, malignant, and unspecified neoplasms. Four patients (5.8%) had fatal AEs from the SOC of respiratory,

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Safety results (cont.):

thoracic and mediastinal disorders; the preferred terms were respiratory distress in 1 patient and respiratory failure in 3 patients. In 3 patients (4.3%), the fatal AEs were general disorders and administration site conditions (death: 2 patients, general physical health deterioration: 1 patient).

AEs of special interest

In-depth analyses were performed for diarrhoea, rash/acne+, and stomatitis+. Diarrhoea occurred in 82.6% of patients; drug-related diarrhoea was reported for 78.3% of patients. 7.2% of patients discontinued study treatment due to diarrhoea. The overall incidence of rash/acne+ was 84.1%, the incidence of drug-related rash/acne+ was 82.6%. Rash/acne+ led to treatment discontinuation in 7.2% of patients.

The incidence of stomatitis+ was 39.1% (drug-related stomatitis+: 37.7%). No patient discontinued study treatment due to stomatitis+.

Although not pre-specified, the trial database was searched for patients with possible ILD-like events using the broad SMQ of ILD, and 1 patient (1/69, 1.4%) was identified (pneumonitis grade 3). The event was considered as not drug-related. The patient recovered from the event.

Clinical laboratory evaluations, vital signs, and LVEF data

Few patients had worst on-treatment values for laboratory safety parameters of grade 3 or higher. For most of these patients, the values had returned to lower grades until the end of treatment. No patient fulfilled the laboratory criteria defined to identify potential Hy's law cases (defined as AST or ALT >3 ULN together with ALKP<2 ULN in combination with total bilirubin ≥2 ULN).

There were no clinically meaningful changes in mean values for vital signs during the study. Significant LVEF decreases (i.e. decreases of ≥20% from the baseline LVEF value, and a decrease below the lower limit of normal of the respective centre [or below 50% if the lower limit of normal was missing]) were not reported.

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Conclusions:

Based on the primary endpoint (i.e. objective response rate; 13.0% in all patients) and secondary efficacy endpoints (such as the disease control rate: 50.7%), this study showed modest efficacy of afatinib 50 mg monotherapy in first- or second-line patients with NSCLC that was EGFR FISH positive. Improved efficacy outcomes were observed in a smaller subset of EGFR FISH positive patients whose tumours harboured EGFR mutations (objective response rate: 25.0%; disease control rate: 66.7%). Afatinib showed limited activity in EGFR FISH positive but EGFR mutation negative patients (objective response rate: 9.3%; disease control rate: 46.5%) that was, however, encouraging when compared with other afatinib trials in EGFR mutation negative patients. Efficacy of afatinib was observed across different tumour histologies, including patients with squamous histology.

The safety data and adverse event profile of afatinib in the present study were consistent with results of previous studies investigating a dose of afatinib 50 mg.