Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report:	05 Mar 2008
Study title:	Phase II open-label study to investigate the efficacy and safety of PTK787/ZK 222584 orally administered once daily or twice daily at 1250 mg as second-line monotherapy in patients with Stage IIIB or Stage IV non-small-cell lung cancer (NSCLC)
Sponsor's study number:	91411 (308801)
NCT number:	NCT00160043
EudraCT number:	2004-002290-22
Sponsor:	Bayer HealthCare
Clinical phase:	Phase II
Study objectives:	**Primary objective:** To investigate the clinical efficacy of PTK787/ZK222584 as second-line monotherapy in patients with Stage IIIB/IV NSCLC **Secondary objective:** To investigate the safety, tolerability and the pharmacodynamic activity of the above treatment
Test drug:	VEGF-Tyrosine Kinase Inhibitor (BAY86-5127, Vatalanib, PTK787/ZK 222584)
Name of active ingredient(s):	Vatalanib/ VEGF-Tyrosine Kinase Inhibitor
Dose:	1250 mg q.d.(once daily) or b.i.d.(twice daily) (500 mg a.m. + 750 mg p.m.)
Route of administration:	Oral
Duration of treatment:	Patients were treated until disease progression or unacceptable toxicity
Reference drug:	Not Applicable
Indication:	Non-small-cell lung cancer
Diagnosis and main criteria for inclusion:	Patients with histologically or cytologically proven stage IIIB or IV NSCLC who had disease relapsed or refractory after 1 prior platinum-based chemotherapy or combined chemo-radio therapy regimen; life expectancy 3 months; World Health Organization (WHO) performance status of 0 to 1; and adequate bone marrow, kidney, and liver function.

Study design:	Prospective, multicenter, proof-of-concept study. Initiated as a single-cohort study with patients receiving study drug once daily (q.d.) and amended to include another cohort with patients receiving study drug twice daily (b.i.d.). Each cohort was managed and analyzed separately.
Methodology:	This is a prospective, single-arm, multi-center, proof-of-concept Phase-II study to investigate the efficacy and safety of PTK787/ ZK 222584 in pretreated patients with Stage IIIB/IV NSCLC. A total of 55 evaluable patients will be required for this clinical study. All patients are scheduled to receive a fixed dose (i.e., independent of body weight or surface) of 1250 mg per day for up to 12 months of treatment (in case of sustained clinical benefit, continuation of treatment may be decided). Evaluations of clinical response will be based on Response Evaluation Criteria in Solid Tumors (RECIST). The primary endpoint will be the response rate after 12 weeks of treatment. Secondary endpoints will include the patients' "best overall response" to the study treatment and the time to progression. As additional pharmacodynamic evaluations, DCE-MRI assessment of tumor permeability and vascularity will be performed at selected centers. Moreover, serum samples will be collected and stored for evaluation of protein biomarkers, depending on the clinical response of the patients to the study treatment.
Study center(s):	France (3), Germany (3)
Publication(s) based on the study (references):	T. C. Gauler, B. Besse, A. Mauguen, J. B. Meric, V. Gounant, B. Fischer, T. R. Overbeck, H. Krissel, D. Laurent, M. Tiainen, F. Commo, J. C. Soria, and W. E. E. Eberhardt. Phase II trial of PTK787/ZK 222584 (vatalanib) administered orally once-daily or in two divided daily doses as second-line monotherapy in relapsed or progressing patients with stage IIIB/IV non-small-cell lung cancer (NSCLC). Ann Oncol (2012) 23 (3): 678-687 first published online May 26, 2011
Study period:	Study Start Date: **01 Mar 2005** Study Completion Date: **19 Nov 2008**
Early termination:	Not applicable
Number of subjects:	Planned: 110 patients: 55 per cohort Analyzed: 112 patients: 54 patients in the q.d. cohort and 58 patients in the b.i.d. cohort

Criteria for evaluation

Efficacy:

Primary efficacy variable

- Response rate (p) at 12 weeks in per protocol set (PPS). Responders included patients with confirmed complete response(CR), partial response (PR) or stable disease.

Secondary efficacy variables

- Best overall response (BOR) was described using frequency tables;
- Time to tumor progression (TTP), progression free survival (PFS), and overall survival (OS) were described using Kaplan-Meier plots;

Safety: Adverse event (AE), clinical laboratory evaluations, physical examinations, vital signs, WHO performance status and electrocardiogram (ECG).

Pharmacodynamics: DCE-MRI variables:

Primary:

- AUCe(180) uncorrected and AUCe(180) corrected for arterial input function

Secondary:

- Mean Ktrans and mean reduction [%] of individual baseline Ktrans values were displayed by time point and cohort using descriptive statistics;
- Number of patients with reduction of Ktrans to ≤60% from baseline value was described by time point and cohort using frequency tables;
- AUCe(60) uncorrected and AUCe(60) corrected for arterial input function

Statistical methods:	**Primary efficacy variable:** Null hypothesis: $p \leq 0.10$, alpha = 0.05 (one-sided). A two-sided 90% confidence interval for p was computed according to Clopper-Pearson. **Secondary efficacy variables:** Descriptive statistics **Safety variables:** Descriptive statistics Pharmacodynamic variables: Descriptive statistics
Substantial protocol changes:	• Protocol amendment 1 from 29 Jun 2005 introduced the following changes: ▪ Voluntary additional DCE-MRI on Day 3, Day 29, and at end of study • Protocol amendment 2 from 10 Oct 2005 introduced the following changes: ▪ Addition of a second treatment cohort, to permit the treatment of patients with a regimen of twice daily dosing, with a total daily dose of 1250 mg PTK787/ZK 222584, 500 mg in the morning and 750 mg in the evening, 12 hours apart ▪ Potential risk of bleeding/hemorrhage ▪ Interruption of PTK787/ZK222584 before, during, and after radiotherapy ▪ Special attention to neurological toxicity and hypertension • Protocol amendment 3 from 11 Oct 2006 introduced the following changes: ▪ Continuation of treatment after 12 months ▪ Add as secondary objectives (progression free survival and overall survival)

Subject disposition and baseline

From March to December 2005, 56 patients were screened for the q.d. cohort and, from November 2005 to July 2006, 62 patients were screened for the b.i.d. cohort. Of these, 2 patients in the q.d. cohort and 3 in the b.i.d. cohort did not meet the eligibility criteria. One patient in the b.i.d. cohort withdrew consent before starting the study. A total of 54 patients in the q.d. cohort and 58 patients in the b.i.d. cohort started treatment with PTK/ZK.

PTK/ZK treatment was discontinued prematurely by 11 (20.4%) patients in the q.d. cohort and 16 (28.6%) patients in the b.i.d. cohort. The main reasons for discontinuation were AEs occurring for 7 (13.0%) patients in the q.d. cohort and for 11 (19.6%) patients in the b.i.d. cohort. Death was the reason

for premature discontinuation for 2 patients in both treatment cohorts, and withdrawal of consent for 2 patients in the q.d. cohort and 1 patient in the b.i.d. cohort. Two patients in the b.i.d. cohort discontinued the treatment due to 'other reasons' (specified as 'planned heart catheter' and 'patient wanted surgical tumor resection').

The full analysis set (FAS) comprised 54 patients from the q.d. cohort and 56 patients from the b.i.d. cohort. Two patients from the b.i.d. cohort were excluded from the FAS due to reasons specified as 'wrong indication' and 'no target lesions'. The per protocol set (PPS) comprised patients who had assessment of the primary efficacy variable available, no major protocol deviations and who were not replaced. These included 43 patients in the q.d. cohort and 45 patients in the b.i.d. cohort. The safety analysis set (SAF) comprised all patients who had at least one study drug administration, i.e. 54 patients from the q.d. cohort and 58 patients from the b.i.d. cohort.

The majority of patients were treated until disease progression. Median treatment duration was 64 days in the q.d. cohort (range 8 - 604 days) and 84 days (range 4 - 475 days) in the b.i.d. cohort. At the time of data base closure, the treatment was ongoing for 1 patient in the q.d. cohort and for 2 patients in the b.i.d. cohort. The data regarding these patients will not be added to the data base and no re-analyses will be done. The CRFs of these patients will be evaluated for potential safety concerns and will be filed to the trial master file. In case the development of PTK/ZK will be resumed, these additional data will be implemented into the integrated safety database.

In general, the cohorts were similar for their baseline demographic and tumor characteristics. Most patients were Caucasian (q.d.: 94.4%; b.i.d.: 91.1%), male (q.d.: 70.4%; b.i.d.: 66.1%), and had a smoking history (q.d.: 88.9%; b.i.d.: 91.1%). The mean age was 57.2 ± 8.8 years. Most tumors were of stage IV (q.d.: 74.1%; b.i.d.: 71.4%), and the major histologic subtypes were adenocarcinoma (q.d.: 57.4%; b.i.d.: 62.5%) and squamous cell carcinoma (q.d.: 31.5%; b.i.d.: 17.8%). All patients had received prior chemotherapy, most commonly cisplatin: 44 (81.5%) patients in the q.d. cohort and 44 (75.9%) patients in the b.i.d. cohort.

Efficacy

The primary efficacy analysis was response rate at 12 weeks in PPS. Responders included subjects with confirmed CR or PR at any time point, or SD for at least 12 weeks from the start of treatment. Confirmation after at least 4 weeks was required for CR and PR. The response rate at 12 weeks was similar in both cohorts (PPS): q.d.: 44.2% and b.i.d. 44.4% (see the table below). In the q.d. cohort, the responders included 19 (44.2%) patients with SD for ≥ 12 weeks, and in the b.i.d. cohort, 2 (4.4%) patients with confirmed PR and 18 (40.0%) patients with SD for ≥ 12 weeks. Following these results, the null hypotheses of $p \leq 0.10$ was rejected for both cohorts.

Response rate at 12 weeks (PPS and FAS)

			Responders		90% CI
Cohort		**N**	**n**	**%**	**%**
PPS	q.d.	43	19	44.2	(31.2, 57.8)
	b.i.d.	45	20	44.4	(31.7, 57.7)
FAS	q.d.	54	19	35.2	(24.4, 47.2)
	b.i.d.	56	21	37.5	(26.7, 49.4)

The best overall response in FAS is presented in a table below. In the q.d. cohort, 1 (1.9%) patient had confirmed PR and 27 (50.0%) had SD for 4 to at least 12 weeks, and 23 (42.6%) patients had PD. In the b.i.d. cohort, 3 (5.4%) patients had confirmed PR, 37 (66.1%) patients SD for 4 to at least 12 weeks, and 12 (21.4%) had PD.

Best overall response (FAS)

	q.d. (N = 54)		b.i.d. (N= 56)		Total (N = 110)	
	No	%	No	%	No	%
PR	1	1.9	3	5.4	4	3.6
SD at least 12 weeks	18	33.3	18	32.1	36	32.7
SD 4 weeks + *	6	11.1	10	17.9	16	14.5
SD 4 weeks	3	5.6	9	16.1	12	10.9
PD	23	42.6	12	21.4	35	31.8
Missing[#]	3	5.6	4	7.1	7	6.4

*SD for 4 weeks and no information at week 12
[#]Patients who discontinued and who had no RECIST evaluation (q.d.: AEs n=2, withdrawal of consent n=1; b.i.d.: AEs n=2, withdrawal of consent n=1, death n=1)

The secondary efficacy variables TTP, PFS and OS were slightly longer in the b.i.d. cohort compared to the q.d. cohort: TTP 2.9 vs. 2.0 months, PFS 2.8 vs. 2.2 months, and OS 9.0 vs. 7.0 months in the b.i.d. vs. q.d. cohorts (FAS). See the table below for further details.

Time to event data: TTP, PFS, and OS (FAS)

		N	Events	Censored	Median (months)	95% CI
TTP	q.d.	54	52	2	2.0	1.0 to 3.7
	b.i.d.	56	51	5	2.9	2.8 to 4.0
PFS	q.d.	54	54	0	2.2	1.0 to 2.9
	b.i.d.	56	53	3	2.8	2.2 to 3.7
OS	q.d.	54	47	7	7.0	4.3 to 12.9
	b.i.d.	56	37	19	9.0	7.0 to 11.5

Safety evaluation

Altogether 1342 AEs were reported for 111 patients: 573 AEs in 54 patients in the q.d. cohort and 769 AEs in 57 patients in the b.i.d. cohort. Patients reported AEs most frequently in the following system organ classes (SOCs): gastrointestinal disorders (q.d. cohort: 42 patients, 77.8%; b.i.d. cohort: 50 patients, 86.2%); general disorders and administration site conditions (q.d. cohort: 37 patients, 68.5%; b.i.d. cohort: 35 patients, 60.3%); nervous system disorders (q.d. cohort: 33 patients, 61.1%; b.i.d. cohort: 36 patients, 62.1%); and respiratory, thoracic and mediastinal disorders (q.d. cohort: 28 patients, 51.9%; b.i.d. cohort: 36 patients, 62.1%).

In total, the most frequent AEs by PT were nausea (52.7%), vomiting (45.5%), and dizziness (33.9%). Nausea was less common in the q.d. cohort 44.4% patients vs. 60.3% patients in the b.i.d. cohort.

Vomiting was reported by 44.4% patients from the q.d. cohort and 46.6% patients from the b.i.d. cohort. Dizziness was more frequent in the q.d. cohort with 38.9% patients vs. 29.3% patients in the b.i.d. cohort.

Overall, the majority of the reported AEs (81.2%) were of NCI CTC grade 1 or 2. The proportion of grade 3 AEs was 20.9% in the q.d. cohort and 14.2% in the b.i.d. cohort, and of grade 4 AEs 1.9% in the q.d. cohort and 1.6% in the b.i.d. cohort. Most patients experienced grade 3 AEs: 59.3% patients in the q.d. cohort and 56.9% in the b.i.d. cohort. Grade 4 AEs occurred less frequently: 18.5% patients in the q.d. cohort and 20.7% patients in the b.i.d. cohort. Overall, the most frequent grade 3/4 AEs were increased gamma-glutamyl transferase, γ-GT, dyspnea, hypertension, and nausea. Of these, grade 3 dyspnea was more frequent in the q.d. cohort (q.d. 14.8%; b.i.d. 10.3%), while grade 3/4 increased γ-GT (q.d. 9.3%; b.i.d. 17.2%), grade 3 hypertension (q.d. 9.3%; b.i.d. 13.8%); and grade 3 nausea (q.d. 7.4%; b.i.d. 12.1%) were more frequent in the b.i.d. cohort.

A total of 761 (56.7%) AEs were assessed as treatment-related by the investigators: 313 (54.6%) AEs in the q.d. cohort and 448 (58.2%) in the b.i.d. cohort. These were experienced by 107 patients: 51 (94.4%) in the q.d. cohort and 56 (96.6%) in the b.i.d. cohort. Overall, the most frequent treatment-related AEs were nausea (50.9% patients), vomiting (40.2% patients), dizziness (33.0% patients), and increased γ-GT (21.4% patients). Treatment-related nausea, asthenia, anorexia, and increased gamma-glutamyltransferase were less frequent in the q.d. cohort, while treatment-related dizziness was slightly more common in the q.d. cohort. The incidence of treatment-related grade 3/4 AEs was similar in both cohorts (grade 3: 50.0% patients in the q.d. cohort and 55.2% in the b.i.d. cohort; grade 4: 14.8% in the q.d. cohort and 12.1% in the b.i.d. cohort).

Two patients in the q.d. cohort and 3 patients in the b.i.d. cohort died before the end of study. The causes of deaths were: acute severe lung bleeding (assessed as possibly treatment-related); pulmonary hemorrhage/ edematous pancreatitis; sudden death (possible pulmonary embolism); and progression of study disease. For 1 patient in the q.d. cohort the cause of death remained unclear.

A total of 53 SAEs were reported for 23 (42.6%) patients in the q.d. cohort and 36 SAEs for 21 (36.2%) patients in the b.i.d. cohort. The most frequent SAEs by SOC were gastrointestinal disorders (q.d.: 11 SAEs in 4 patients; b.i.d.: 10 SAEs in 8 patients), and respiratory, thoracic and mediastinal disorders (q.d.: 9 SAEs in 8 patients; b.i.d.: 8 SAEs in 8 patients). The most frequent SAEs by PT were pulmonary embolism (q.d.: 2 patients; b.i.d.: 4 patients) and dyspnea (q.d.:3 patients; b.i.d.: 1 patient).

The study drug was withdrawn from 11 patients due to SAEs: 5 patients in the q.d. cohort and 6 patients in the b.i.d. cohort. In addition, the study drug was withdrawn due to AEs from 3 patients in the q.d. cohort and 7 patients in the b.i.d. cohort.

Laboratory analyses consisted of hematology, serum chemistry and urinalysis. Clinically relevant changes in laboratory values were reported at each time point. The proportions of patients with clinically relevant changes in laboratory values were 11.1% in the q.d. cohort and 29.3% in the b.i.d. cohort at baseline; 25.5% in the q.d. cohort and 30.2% in the b.i.d. cohort on Day 28; and 22.5% in the q.d. cohort and 34.9% in the b.i.d. cohort at the end of study. For most patients with new or worsened laboratory abnormalities, the events were of NCI CTC grade 2 or 3.

The WHO performance status was 1 for most patients during the whole study. No notable changes were observed in vital signs during the treatment. A slight weight loss was observed in both treatment groups at the end of study: the median weight loss was -2.5 kg in the q.d. cohort, and -3.5 kg in the b.i.d cohort.

Clinically relevant abnormal changes in ECG were reported for 8 patients in the q.d. cohort and 7 patients in the b.i.d. cohort. The investigators' comments on the changes included tachycardia for 4 patients in the q.d. cohort and QT prolongation for 4 patients with in the b.i.d. cohort. No accumulation of specific ECG changes was observed during the study.

Pharmacodynamic results

DCE-MRI was performed for 39 patients from the q.d. cohort and for 35 patients from the b.i.d. cohort on Day 2 and for 34 patients from the q.d. cohort and 27 patients from the b.i.d. cohort on Day 28. The mean values of Ktrans (bi-directional transfer constant) were reduced in both cohorts on Day 2 compared to baseline (FAS): q.d. -35.2% (35 patients) and b.i.d. -37.3% (23 patients). On Day 28, the reduction was greater in the b.i.d. cohort: -45.2% (10 patients) compared to q.d. -37.2% (29 patients). No clear differences were observed in the reduction values between responders and non-responders. However, there was a consistently greater mean reduction of Ktrans for the bid cohort at all time points.

Overall conclusions

Single-agent treatment with PTK/ZK was active as a second line treatment of patients with stage IIIB/IV NSCLC after failure of first-line chemotherapy. A trend towards higher efficacy was observed in patients with b.i.d. treatment versus those with q.d. treatment. The toxicity profile of PTK/ZK treatment was mild in both groups.