There was no difference between patients with adenocarcinoma and non-adenocarcinoma histology. In 12%, the response lasted for at least a year. 79% of these patients were never-smokers with adenocarcinoma. None of the longterm responders was a current smoker, and 93% had adenocarcinoma histology.
Survival: Never-smokers had a median progression free survival (PFS) and overall survival (OS) of 7.5 and 13 months, respectively. Ex-smokers had a PFS and OS of 3.5 and 7.5 months, and current smokers had a PFS and OS of 2 and 5.5 months, respectively. Gender or histology had no significant effect on PFS or OS. Treatment line did not influence PFS or OS, in particular patients treated with erlotinib 1st line experienced a similar PFS and OS compared with chemotherapeutically pretreated patients. The patient on haemodialysis tolerated erlotinib well and had SD for 11 months.
Conclusions: The above clinical criteria may be valid for prediction of partial responses and of longterm response to erlotinib. However, except for smoking, the clinical selection criteria do not predict PFS and OS. This may be due to the significant survival advantage we found for patients with SD compared with patients progressing radiologically. Furthermore, our data indicate that erlotinib may be effective as a first-line monochemotherapy in selected patients. Our retrospective data need to be confirmed with larger patient numbers (e. g. from registries) in order to define the clinically and economically appropriate method of patient selection.

9152 POSTER

A population pharmacokinetic analysis for BIBF 1120, an angiokinase inhibitor, in patients with advanced non-small cell lung cancer

P. Stopfer[1], M. Freiwald[1], K.H. Liesenfeld[1], R. Bruno[2], L. Hodge[2], C. Eschbach[3], M. Reck[4], J. von Pawel[5], R. Kaiser[6], A. Staab[1]. *[1]Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Drug Metabolism and Pharmacokinetics, Biberach, Germany; [2]Pharsight Corporation, Drug development, Mountain View, USA; [3]Asklepios Krankenhaus, Hamburg-Harburg, Hamburg, Germany (4) Hospital Grosshansdorf, Department of Thoracic Oncology, Grosshansdorf, Germany (5)Asklepios Kliniken, München-Gauting, Gauting, Germany (6)Boehringer Ingelheim Pharma GmbH & Co KG, Clinical Research/Oncology, Biberach, Germany*

Background: BIBF 1120 (VargatefTM*) is a potent angiokinase inhibitor, targeting vascular endothelial, platelet-derived and fibroblast growth factor receptor tyrosine kinases. The objective of the population pharmacokinetic (PK) analysis was to describe the PK of BIBF 1120 in patients with advanced/metastatic non-small cell lung cancer (NSCLC) and to explore the impact of patient factors on the PK parameters of BIBF 1120 using data from a double-blind, randomized Phase II study.
Methods: In this double-blind multicenter trial, 73 patients with an Eastern Cooperative Oncology Group (ECOG) score of 0−2 with locally advanced or metastatic (stage IIIB/IV) relapsed NSCLC after failure of first- or second-line chemotherapy were randomly assigned to continuous twice-daily treatment with 150 mg or 250 mg of BIBF 1120 until disease progression or limiting toxicity. Trough samples for PK analysis were taken at various visits. Sparse absorption profiles were determined at two visits. PK data from 71 patients (736 plasma samples) were available. Demographics, laboratory values and cancer-specific covariates including baseline ECOG score were tested for their effect on PK parameters. The analysis was performed using NONMEM (Non-linear Mixed Effects Modeling).
Results: A one-compartment model with first-order absorption (ka) and elimination rate described the PK data adequately. The slightly delayed absorption was accounted for by a lag time of 20 minutes. Clearance (CL/F), volume of distribution (V/F) and ka were 697 L/h, 8170 L and 1.31h^{-1}, respectively. Interindividual and interoccasion variability estimates for CL/F and V/F were moderate to high. None of the covariates tested showed a clinically relevant effect on the PK parameters of BIBF 1120 and thus none were included in the model. A trend towards lower CL/F values with increased liver enzymes was observed but its effect was small.
Conclusion: BIBF 1120 plasma concentrations in NSCLC patients were described by a one-compartment model. No clinically relevant covariates influencing the PK of BIBF 1120 were detected. An international Phase III trial program investigating BIBF 1120 in NSCLC, LUME-Lung, is now recruiting patients.
*Trade name not FDA approved

9153 POSTER

Safety and efficacy of sunitinib in patients with non-small cell lung cancer and irradiated brain metastases

S. Novello[1], C. Camps[2], F. Grossi[3], J. Mazieres[4], L. Abrey[5], J. Fain[6], S. Patyna[7], P. Selaru[7], R. Chao[7], G. Scagliotti[1]. *[1]University of Turin, Thoracic Oncology Unit, Turin, Italy; [2]University General Hospital of Valencia, Medical Oncology, Valencia, Spain; [3]National Institute for Cancer Research, Medical Oncology, Genoa, Italy; [4]Hôpital Larrey, Unite de Cancerologie Cervico-Thoracique, Toulouse, France; [5]Memorial Sloan-Kettering Cancer Center, Department of Neurology, New York, USA; [6]Texas Oncology, Hematology/Oncology, Austin, USA; [7]Pfizer Oncology, Development, La Jolla, USA*

Background: The prognosis of patients (pts) with NSCLC and brain metastases (BrMs) is poor. Preclinical data suggest that VEGF signaling is essential for the growth of BrMs, thus antiangiogenic agents may have activity in this population. Sunitinib (SU) is an oral, multitargeted inhibitor of VEGFRs, PDGFRs, KIT, FLT3, CSF-1R, and RET that has single-agent antitumor activity in refractory NSCLC. This phase II study [NCT00372775: Pfizer] assessed the safety and efficacy of SU in NSCLC pts with previously irradiated BrMs.
Materials and Methods: NSCLC pts $\geqslant$18 years of age who had received whole brain radiation therapy (WBRT) for BrMs and $\leqslant$2 prior systemic therapies were eligible to receive SU at a starting dose of 37.5 mg with continuous daily dosing (CDD) in 4-week (wk) cycles. Antitumor efficacy was based on overall (RECIST) and intracranial bidimensional (WHO criteria) tumor assessments. Intracranial disease was assessed by MRI. Safety was assessed by monitoring AEs and focused on neurologic status. Health-related quality of life was assessed using FACT/NCCN Lung Symptom Index (FLSI) and Brain Symptom Index (FBrSI). Study termination was to occur if 3 cases of intracranial hemorrhage (ICH) associated with neurologic deficit were identified.
Results: Fifty-nine pts received SU for a median of 2 cycles (range: 1, 10). The median age of pts was 60 yrs (range: 35, 77), most were male (n = 36, 61%) and had good performance status (ECOG 0/1, n = 56; ECOG 2, n = 1). Most pts had adenocarcinoma (n = 37, 62.7%) or squamous cell carcinoma (n = 11, 18.6%). The most frequent AEs of any grade (G) were fatigue (n = 17, 29%), anorexia (n = 14, 24%), and nausea (n = 13, 22%). Neurologic AEs occurred in 5 pts (9%) and included increased intracranial pressure, visual hallucination, and gait disturbance (each n = 1 and G2). One pt had convulsion and peripheral motor neuropathy (both G3) and one pt had G4 mental impairment. ICH was not reported. Stable disease was reported in 12 (23%) of 53 pts via RECIST and in 10 (26%) of 39 pts with measurable BrMs via WHO. Median PFS was 9.9 wks (95% CI: 7.0, 13.4). Median OS was 19.4 wks (95% CI: 11.4, 38.6). Mean change from baseline in FLSI and FBrSI scores did not differ significantly at any time point.
Conclusions: Oral SU 37.5 mg on a CDD schedule had a manageable safety profile, and no cases of ICH were reported. Although not the focus of this study, preliminary data suggest SU may have antitumor activity in pts with NSCLC; further studies are warranted.

9154 POSTER

Clinical outcomes in patients with EGFR mutations: pooled analysis of NSCLC patients treated with either an EGFR TKI or chemotherapy

L. Paz-Ares[1], D. Soulières[2], B. Klughammer[3], I. Melezínek[4], J. Moecks[5], L. Keil[6], T. Mok[7]. *[1]Hospital 12 de Octubre, Medical Oncology, Madrid, Spain; [2]Centre Hospitalier de l'Université, de Montréal, Montréal, Canada; [3]F. Hoffmann-La Roche Ltd, Pharmaceutical Division, Basel, Switzerland; [4]Roche Products Ltd, Pharmaceutical Division, Welwyn Garden City, United Kingdom; [5]BIOMCON GmbH, Pharmaceutical Division, Mannheim, Germany; [6]Roche Diagnostics GmbH, Pharmaceutical Research, Penzberg, Germany; [7]The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China*

Background: NSCLC with EGFR tyrosine-kinase (TK) mutations appears to be highly sensitive to EGFR TK inhibitors (TKIs). As mutations occur in only 10−30% of patients (pts) with advanced NSCLC (which is variable according to ethnicity), it is difficult to conduct large-scale investigations in this subgroup to identify any associations between *EGFR* mutations and therapeutic outcomes. We therefore aimed to summarise published data through a pooled analysis of high-level study results.
Materials and Methods: Data were collated from published phase II/III studies and relevant internal, but not yet published, sources that reported PFS outcomes among pts with *EGFR* mutations, treated with either chemotherapy or EGFR TKI monotherapy (erlotinib or gefitinib). Most papers reported median PFS (time), or % PFS at a fixed time, so these data were used as the basis for our analysis. To facilitate a weighted, pooled

analysis, we used the assumption that PFS times were exponentially distributed, as described by the survival function $S_{exp}(t) = \exp(-\lambda t)$, where λ is the constant hazard rate. This is the simplest parametric assumption for a survival analysis. For an observed median PFS, the estimated value of λ for each study was obtained from the equation $\lambda = \ln(2)/\text{median PFS}$. For a reported % PFS at a fixed time $S_{exp}(T) = \gamma$, then λ was estimated by $-\ln(\gamma)/T$. The results of individual studies were pooled by calculating the overall mean of $\ln(2)/\lambda$ weighted by group size for each treatment group to obtain an estimate of the pooled median PFS.

Results: Data from 27 studies were included in our summary (6 chemotherapy, 13 gefitinib, 8 erlotinib). The number of patients included with *EGFR* mutations (total/1st-/2nd-line) were chemotherapy 192/170/22; gefitinib 413/311/102; erlotinib 341/185/156. Pooled median PFS values are presented in the table.

Conclusions: The results shown here provide a concise summary of the many reports on clinical outcomes in NSCLC pts with *EGFR* mutations. The summary of published data suggests that pts with *EGFR* mutations obtained a greater benefit from EGFR TKI therapy than from conventional chemotherapy. The use of EGFR TKIs as first-line therapy vs platinum-doublet chemotherapy in advanced *EGFR* mutation positive NSCLC pts is currently being investigated in ongoing prospective studies.

	Pooled median PFS months	
	First-line	Second-line
Chemotherapy	6.4	4.1
Gefitinib	9.7	8.8
Erlotinib	13.6	13.3

9155 POSTER

Sunitinib combined with pemetrexed and cisplatin in patients with advanced solid malignancies: phase I dose escalation study

N. Blais[1], D.R. Camidge[2], D.J. Jonker[3], D. Soulières[1], R.C. Doebele[2], A. Ruiz-Garcia[4], A. Thall[4], R. Chao[4], S.G. Eckhardt[2], L.Q. Chow[3]. [1]*Hôpital Notre-Dame du CHUM, Medical Oncology, Montreal, Canada;* [2]*University of Colorado Cancer Center, Division of Medical Oncology, Aurora, USA;* [3]*The Ottawa Hospital Cancer Center, Department of Medicine, Ottawa, Canada;* [4]*Pfizer Oncology, Development, La Jolla, USA*

Background: Sunitinib malate (SU) is an oral multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, FLT3, CSF-1R and RET, approved multinationally to treat advanced RCC and imatinib-resistant/intolerant GIST. Preclinical studies in NSCLC xenograft models suggest that antitumor activity is enhanced by the addition of SU to pemetrexed (Pem). The maximum tolerated dose (MTD) of SU/Pem has previously been established. The MTD, safety and efficacy of SU/Pem/Cisplatin (Cis) are reported for the first time [NCT00528619: Pfizer].

Materials and Methods: Patients (Pts) in successive dose-escalation cohorts received oral SU (37.5−50 mg) either once daily on the continuous daily dose (CDD) schedule or Schedule 2/1 (2 wks of a 3 wk cycle), with Pem 400−500 mg/m^2 IV q21d and Cis 75 mg/m^2 q21d. MTD was defined as the highest dose at which $\leqslant$1/6 pts had dose-limiting toxicity (DLT) with $\leqslant$2/3 or 2/6 pts having DLTs at the next highest dose. Safety, pharmacokinetic (PK) profiles, and efficacy were also evaluated.

Results: As of March 2009, 16 pts with advanced solid tumors received SU/Pem/Cis. Five pts were treated on the CDD schedule (SU 37.5 mg/Pem 400 mg/m^2/Cis 75 mg/m^2) and 1 pt had a DLT (G4 neutropenia); MTD (CDD schedule) was not determined. On Schedule 2/1, 11 pts were treated (SU 37.5 mg/Pem 400 mg/m^2/Cis 75 mg/m^2 [n = 7]; SU 37.5 mg/Pem 500 mg/m^2/Cis 75 mg/m^2 [n = 3]; SU 50 mg/Pem 500 mg/m^2/Cis 75 mg/m^2 [n = 1]); one DLT occurred (G3 subclavian vein thrombosis; SU 37.5 mg/Pem 400 mg/m^2/Cis 75 mg/m^2). Determination of the Schedule 2/1MTD is ongoing. Most frequent non-hematologic AEs for pts on all SU/Pem/Cis schedules were constipation, nausea, diarrhea and fatigue. G3/4 hematological AEs in all cohorts were neutropenia (7/14 pts), anemia (4/16 pts) and thrombocytopenia (3/16 pts). G3 febrile neutropenia occurred in 2 pts. No significant PK interactions were identified on the SU/Pem arm; PK data for the SU/Pem/Cis arm are being investigated and will be presented. Of 4 evaluable pts on the CDD schedule, 1 pt had a partial response (PR; SCLC) and 1 pt had stable disease (SD; $\leqslant$6 mos; lung neuroendocrine carcinoma). Of 10 evaluable pts on Schedule 2/1, 1 PR (penile carcinoma) was observed and 5 pts had SD (>3mos [n = 3]; <3 mos [n = 2]).

Conclusions: The combination of SU/Pem/Cis was better tolerated on Schedule 2/1 compared with the CDD schedule. Determination of the MTD (Schedule 2/1) is ongoing. Antitumor responses were observed on both schedules.

9156 POSTER

Safe and long-lasting tumour control with erlotinib in advanced non-small cell lung cancer

S. Quadrini[1], R. De Sanctis[1], B. Gori[1], E. Del Signore[1], L. Stumbo[1], R. Sollami[1], V. Frantellizzi[1], P. Grassi[1], M. Di Seri[1], F. Longo[1]. [1]*Policlinico Umberto I, Oncologia Medica A, Roma, Italy*

Background: Erlotinib, an EGFR tyrosine kinase inhibitor, demonstrated significantly prolonged survival, with low toxicity profile, in patients (pts) with advanced non small cell lung cancer (NSCLC), who had progressed after standard chemotherapy. The aim of our study was to estimate the efficacy and tolerability of erlotinib in pts with locally advanced/metastatic NSCLC, who had failed prior taxane and/or platinum-based chemotherapy.

Patients and Methods: Since EMEA approval through February 2009, thirty-one NSCLC pts received erlotinib (150 mg orally once daily) until disease progression or unacceptable toxicity. Safety profile was assessed according to NCI-CTCAE, version 3.0. Antitumour activity was evaluated by CT-scan every 3 months and response graded according to RECIST criteria. Kaplan-Meier method was used to estimate PFS and OS.

Results: The men-to-women ratio was 2/1. Median age was 66 years (range 39−77). ECOG PS was 0−1 in 18 pts (58%) and 2 in 13 pts (42%). 27 pts had data available for response evaluation. Erlotinib was administered as II-line treatment in 20 pts (65%) and III or superior line in 11 pts (35%). Median treatment duration was 9.9 months (range 1−37). Five pts (16%) had partial response (PR), lasting a median of 22 months (range 12−29), and 17 pts (55%) had stable disease (SD), lasting a median of 9 months (range 5−29), giving a disease control rate (DCR, complete response CR or PR or SD) of 71%. Nine pts (29%) had progressive disease after a median of 3 months (range 1−5). At the time of analysis, 11 pts are still on treatment (1 PR and 10 SD). Median overall survival (OS) was 8 months (95% CI, 4−18), with a 1-year survival rate of 42%. Median progression-free survival (PFS) was 5 months (95% CI, 3−15). Erlotinib was generally well tolerated. The most common adverse events (AEs) were rash (54%; maximum grade: G3, 12%) and diarrhea (22%; G3, 3%). For G2 AEs affecting quality of life we considered dose interruptions (3−5 days) or, if necessary, a dose reduction to 100 mg/day (29%); for G3 toxicity we reduced erlotinib dose at 100 mg/day (22%).

CONCLUSION: The safety profile appears favorable and manageable. Although modest response rate to erlotinib was observed, DCR was not restricted to any subgroup of pts who may achieve a long-term survival.

9157 POSTER

Retrospective review of efficiency of erlotinib or pemetrexed or docetaxel compared to docetaxel as subsequent line therapy in advanced non-small cell lung cancer (NSCLC) following failure of platinum-based chemotherapy

M.T. Almodovar[1], A. Luis[2], M.P. Ferreira[1], J. Duro da Costa[1]. [1]*Instituto Português de Oncologia, Pneumologia, Lisboa, Portugal;* [2]*Instituto Português de Oncologia, Oncologia, Lisboa, Portugal*

Randomised trials of advanced non-small cell lung cancer (NSCLC) have demonstrated the activity of pemetrexed and docetaxel in second-line and erlotinib in second and third-line setting after failure of platinum-based chemotherapy. Here we explore the outcomes of these agents' uses in clinical practice.

A retrospective review of the NSCLC database at Portuguese Institute of Cancer in Lisbon, Portugal was undertaken. Patients who have received chemotherapy after failure of platinum-based chemotherapy were identified and a chart review was undertaken to access their clinical benefits. The use of pemetrexed and erlotinib in clinical setting was allowed in 2005 in Portugal. Patients were divided in two groups: those who had pemetrexed, erlotinib or docetaxel according to their doctors choice based on clinical data as 2nd line chemotherapy (Group A) and those who had docetaxel as 2nd line chemotherapy (Goup B). Primary outcome was overall survival (OS) after 2nd line chemotherapy and secondary outcomes were response rate (RR) and time to progression (TTP).

Results: We studied 102 patients who had 2nd line chemotherapy, 63 in group A and 39 in group B. OS was 42 weeks in group A and 31 weeks in group B (p = 0.2). Response rate was 22% in group A and 15% in group B. Median TTP was 17 weeks in group A and 14 weeks in group B (p = 0.5). In both groups there was 3rd line chemotherapy (44% in group A and 41% in group B).

Conclusion: For patients with advanced NSCLC who progressed following first-line platinum-based chemotherapy, although not significantly different, survival, RR and TTP were better in the group of patients in whom their clinicians chose their treatment according to their clinical characteristics. Maybe this was due the use of to 3rd line chemotherapy in a large number of patients in both groups.