squamous disease are excluded. DLTs are defined as grade 3−4 clinical AEs or prolonged grade 3−4 lab results for cycle 1 only.
Results: 14 pts (7 male; 7 female) have been treated from Dec 2007 to Mar 2009 for a median of 6 cycles (range 1−20). 14 pts are evaluable for safety and 13 for efficacy. Median ECOG PS is 1. Grade 3 anorexia, dehydration and acneiform rash (face) have been identified as DLT in 1 patient at 0.16 mg/kg/week. Enrollment continues in cohort 4 at 0.48 mg/kg/w. Most common adverse events have been diarrhea (79%), fatigue (64%), injection site reaction (57%), rash (57%), anorexia (50%) and nausea (50%) with 1 treatment-related SAE (the above-cited DLT). Of 9 pts withdrawn, 2 had disease progression, 5 toxicity or treatment delay, 1 patient decision, 1 death unrelated to treatment. 3 of 13 pts (23%) have confirmed partial response. 5 patients are currently on treatment for a median of 9 cycles (range 5−21 cycles).
Conclusions: IMO-2055 appears to be well tolerated at dosages up to 0.32 mg/kg in combination with E and B. Pending completion of cohort 4, enrollment of additional pts will continue at a recommended Phase 2 dose level. Anti-tumor activity has been seen in pts with advanced, pretreated NSCLC. Controlled trials should be feasible to evaluate the promising combination of IMO-2055 plus E and B.

9149 POSTER

Phase II study of bevacizumab in combination with cisplatin and docetaxel as first line treatment of patients (p) with metastatic non squamous non-small-cell lung cancer (NSCLC)

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Background: Bevacizumab (B), in addition to platinum-based chemotherapy, is indicated for 1st line treatment of p with advanced NSCLC other than predominantly squamous cell histology. B has been shown to improve progression free survival (PFS) and overall survival (OS) when combined with cisplatin/gemcitabine and carboplatin/paclitaxel, respectively. However, there are limited data on the safety and efficacy of B in combination with other widely used chemotherapy doublets for NSCLC. This is a single-arm, open-labeled, single-stage phase II trial of cisplatin (C), docetaxel (D) and B for NSCLC.
Methods: Eligibility criteria: chemo-naïve, stage IIIB wet or IV, non-squamous NSCLC, PS 0−1, no brain metastases and no history of gross hemoptysis. P received D (75 mg/m^2), C (75 mg/m^2), and B (15 mg/kg iv) on day 1 every 3 weeks for up to 6 cycles, followed by B 15 mg/kg alone every 3 weeks until disease progression or toxicity. Primary endpoint: PFS.
Results: 50 p were enrolled (enrollment completed): 24% female, median age 60 (36−74), PS 1: 64%, adenocarcinoma: 72%; stage IV: 92%. Two p did not start treatment. Median follow-up is 5.3 months (range 0−13.6). Median number of cycles of B was 7 (range 0−18). 56% completed 6 cycles of treatment; 24% received $\geqslant$ 12 cycles of B. Most frequent grade $\geqslant$ 3 toxicities: diarrhea (14.6%), fatigue (14.6%), dyspnea (9.8%), anorexia (4.9%), alopecia (4.9%), esophagitis (4.9%), constipation (4.9%), mucositis (12.2%), proteinuria (4.9%); hematological toxicities: neutropenia (22%), febrile neutropenia (9.8%), leucopenia (14.6%), lymphopenia (4.9%). Of interest, 41.5% developed grade <3 epistaxis and 17% hypertension (1 p grade 3). One p died due to hemoptysis. 46 p were evaluable for response: 29 PRs (ORR: 63%). 18 of 48 p have experienced progression or death with a median SLP of 7.8 months (95% CI: 6.6-NR). Median OS is 13.5 months (95% CI: 12.7−13.6; 81.2% p censored); 1-year survival is 83.9% (95% CI: 67.4%-92.5%).
Conclusions: Treatment with C, D and B, followed by maintenance B in 1st line of advanced nonsquamous NSCLC shows an acceptable toxicity profile and promising efficacy. Final results will be presented.

9150 POSTER

Phase I trial of vorinostat in combination with erlotinib for advanced non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations after erlotinib progression (NCT00503971): The TARZO trial

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Background: We treated 217 pts with EGFR mutations with first- or second-line erlotinib, attaining a response of 70% and progression-free survival of 14 months. EGFR mutations are associated with Hsp90 for stability, and inhibition of Hsp90 may represent a novel strategy for the treatment of EGFR-mutant NSCLCs that become resistant to EGFR tyrosine kinase inhibitors. Vorinostat inhibits histone deacetylase (HDAC), inducing acetylation of Hsp90 and increases levels of E-cadherin. These findings prompted us to initiate a phase I study in erlotinib-treated pts with EGFR mutations progressing to erlotinib. At the time of progression, instead of stopping erlotinib, we added vorinostat, with the aim of defining the maximum tolerated dose (MTD) and attaining disease stabilization.
Methods: A 3+3 rule dose escalation was used to determine the maximum tolerated dose (MTD) of oral erlotinib 150 mg QD in combination with oral vorinostat (dose level 1 [DL1], 300 mg QD on days 1−7 every 21 days; DL2, 400 mg QD on days 1−7 every 21 days, and; DL3, 400 mg QD on days 1−7 and 15−21 in a 28-day cycle). Cycles were repeated for a maximum of 6 until progressive disease or intolerable toxicity. Pts with advanced NSCLC with EGFR mutations (exon 19 del and L858R) after erlotinib progression and ECOG $\leqslant$2 were eligible.
Results: The combination was administered to 12 pts (median age, 59 years; range 41−77) at 3 dose levels. One pt remains on treatment. The MTD of the combination was reached at erlotinib 150 mg QD plus vorinostat 400 mg QD on days 1−7 and 15−21 in a 28-day cycle. There was a single DLT in the third cohort (Grade 3 diarrhea). The most common drug-related toxicities of any grade in the first cycle of treatment were anemia (77.8%), skin alterations (66.7%), diarrhea (66.7%), xerostomy (55.6%), asymptomatic changes in liver function tests (55.6%), and asthenia (55.6%). There were no Grade $\geqslant$3 drug-related adverse events during the first cycle of treatment and the overall analysis of cycles showed asthenia (11.1%), somnolence (11.1%) and hyporexia (11.1%). No accumulated toxicity was observed. Of 10 pts evaluable for efficacy, seven had stable disease as best response (median duration of treatment 6.0 cycles, range 3−12).
Conclusion: The combination of vorinostat and erlotinib appears to be well tolerated in this group of advanced NSCLC pts with EGFR mutations after erlotinib progression; the combination demonstrated prolonged disease stabilization. A phase II trial will be initiated.

9151 POSTER

Treatment of patients with advanced non-small-cell lung cancer (NSCLC) with erlotinib: results from clinical practice

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Background: The EGFR-TKI erlotinib has shown benefit in pretreated NSCLC. Post-hoc subgroup analyses of randomized studies suggest that nonsmokers, women, and patients with adenocarcinoma histology may have a superior response to treatment. We performed a retrospective analysis to answer the question, whether these 3 response criteria can be used in routine clinical practice for selection of patients.
Methods: We analyzed all consecutive patients with NSCLC starting treatment with erlotinib between May 2005 and January 2009. Response was assessed radiologically using RECIST criteria.
Results: 121 caucasian patients were analysed. 9 patients who were unfit to receive conventional chemotherapy including one patient on chronic haemodialysis were treated with erlotinib 1st line.
Response: 16.5% of patients demonstrated a partial remission, 33.9% experienced stable disease. Partial remissions were seen more frequently in never-smokers, in females, and in patients with adenocarcinoma histology. The disease control rate (PR + SD) was higher in non-smokers than in ex-smokers or smokers, and in male than in female patients.

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

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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

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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

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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