Results: There was 1 dose-limiting toxicity (DLT) (transient G4 thrombocytopenia) at the 20 mg/m^2 dose. Other G3/G4 toxicities include G3 transient thrombocytopenia, G3/G4 neutropenia (G3 – 5 pts, G4 – 5 pts), G3 anemia (5 pts), G3 hypophosphatemia (1 pt), G3 hypokalemia (1 pt), G3 nausea (1 pt), and G3 pruritus (1 pt). Of 2042 ECGs analyzed, 1 pt had an increase in QTcF from baseline of >60 ms and 1 pt had QTcF >500 ms at 20 mg/m^2. LBH589 plasma concentration peaked at the end of the 0.5 h infusion, then declined with a mean terminal half-life of 16 h. Median C_{max} with 20 mg/m^2 was 1000 ng/mL. The AUC_{0-inf} of LBH589 increased linearly with IV doses of 10−20 mg/m^2. No significant accumulation of LBH589 was seen. There was a dose-dependent ⩾2-fold increase in HA 7 days after one dose in 43%, 50%, and 60% of patients, respectively, at 10 mg/m^2, 15 mg/m^2, and 20 mg/m^2. One week after the second dose at 20 mg/m^2, 80% of patients had increased HA. One CTCL pt had a complete response; 1 PTCL pt had a partial response that has persisted for more than 7 months; 1 prostate cancer pt had a confirmed partial response in nodal disease and a >50% drop in PSA.
Conclusions: The maximum tolerated dose of LBH589 given IV weekly on a 3 of 4 week schedule is 20 mg/m^2. Preliminary evidence of antitumor activity was seen.

703 POSTER

A phase I and pharmacokinetic (PK) study of BIBW 2992, an oral irreversible dual EGFR/HER2 inhibitor

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Background: BIBW 2992 is a novel oral, potent and irreversible inhibitor of EGFR and HER2. A phase I pharmacokinetic study is reported including the effect of food on the pharmacokinetics of BIBW 2992.
Materials: Patients eligible for this trial had advanced solid malignancies. Oral daily BIBW 2992 dose was doubled in successive cohorts until toxicity > grade 2 occurred, when escalation of no more than 50% was allowed. Sequencing of tumour DNA for EGFR was performed in objective responders. An expanded cohort of patients at the 40 mg dose group (N = 16) was assessed for the effect of food on BIBW 2992 PK parameters. PK sampling was performed in all patients on days 1−2 and at steady state of the initial treatment course. Trough PK samples were taken during the initial and repeated treatment courses. For patients taking part on the food effect arm two single dose PK profiles were taken with a wash out time of two weeks in between.
Results: 47 evaluable patients have been treated (24 male); median age was 56 years (range 31−78). The BIBW 2992 dose was escalated from 10 to 50 mg. Three dose-limiting toxicities (DLT) were seen in cycle 1; one patient developed dyspnoea with interstitial changes at 30mg and fully recovered on discontinuation of BIBW 2992; two developed grade 3 acneiform rash at doses of 40 mg and 50 mg, which resolved on discontinuation and dose reduction. Other adverse events were mild (grade 1 or 2): nausea, diarrhoea, hand-foot syndrome and fatigue.
Three patients with NSCLC had confirmed durable Partial Response to treatment (duration of 26, 20 and 8+ months respectively). Two of them were found to have activating deletion mutations in the EGFR domain (exon 19). A further 8 patients with a variety of advanced malignancies remained on treatment with BIBW 2992 for more than 6 months. Updated clinical data will be presented at the meeting.
Generally, maximum plasma concentrations and exposure of BIBW 2992 increased with dose either after single dose or at steady state. There was no deviation from dose-proportional PK. BIBW 2992 exhibited a high apparent volume of distribution indicating a high tissue distribution of the drug. Data from the food effect arm will be presented as well.
Conclusion: The recommended phase II BIBW 2992 dose of 50mg daily is well tolerated. Partial Response or durable Stable Disease (>6 months) were seen in 23% of the patients. PK studies indicate that BIBW 2992 exposure increased with dose on day 1 and at steady state. Further clinical studies of BIBW 2992 in phase II is warranted.

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A phase I dose escalation and pharmacokinetic study of BIBF 1120, a novel tyrosine kinase inhibitor against VEGFR, PDGFR and FGFR, in combination with docetaxel in advanced chemonaive hormone refractory prostate cancer patients (HRPC)

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Background: BIBF 1120 is an oral potent kinase inhibitor targeting multiple tyrosine receptors such as VEGFR, PDGFR, FGFR involved in tumor angiogenesis. Objectives were to determine the maximum tolerated dose (MTD), to evaluate safety, and to characterize the pharmacokinetic (PK) profile of BIBF 1120 in combination with docetaxel and prednisone to chemonaive patients with advanced HRPC.
Methods: Twice daily escalating doses of BIBF 1120 were given (2×100 mg, n = 3; 2×150 mg, n = 3; 2×200 mg, n = 3; and 2×250 mg, n = 12) on the days without chemotherapy. Docetaxel (75 mg/m^2) was given every three weeks along with prednisone (2×5 mg per day). A 3 + 3 dose escalation design was followed. Hematological toxicity of ⩾CTCAE grade 3 was not considered as dose limiting toxicity (DLT) during the first cycle. Twelve patients were treated on the MTD level.
Results: A total of 21 patients (median age 68 years, range 58−79) received up to 6 courses of BIBF 1120 in combination with docetaxel. The MTD of BIBF 1120 was established at 2×250 mg BIBF 1120. BIBF 1120 related toxicity observed so far in 15 patients was of mild to moderate intensity (CTCAE grade 1, 2) with non-hematological toxicity consisting of diarrhoea (53%), asthenia (53%), nausea (33%), abdominal pain (20%), and vomiting (13%). With respect to DLT, a reversible CTCAE grade 3 drug-related ALT increase has been observed in one patient at 2×250 mg during the first cycle. During subsequent cycles, further DLTs of CTCAE grade 3 have been observed in another patient at 2×250 mg of BIBF 1120 (combined AST- and ALT elevation) and in three patients at 2×200 mg (diarrhoea, AST- and ALT elevations). In preliminary analyses, there was no increase of docetaxel related hematological toxicity associated with the addition of BIBF 1120. At 2×250 mg BIBF 1120, eight of twelve patients showed a confirmed decline of PSA ⩾ 50%, which may indicate antitumour activity. Thus far, PK of docetaxel and BIBF 1120 was analyzed from 6 patients (n = 3, 2×100 mg, n = 3, 2×150 mg BIBF 1120). The interim PK analysis suggests no significant change in the docetaxel plasma concentrations before and after 3 weeks of continuous daily treatment with BIBF 1120.
Conclusions: BIBF 1120 can be given safely front line at a dose of 250 mg twice daily together with docetaxel in patients with advanced HRPC. First signs of efficacy have been observed.

705 POSTER

Evaluation of thyroid function in an open-label Phase I study of AZD2171 with gefitinib

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Introduction: AZD2171 is an oral, highly potent and selective tyrosine kinase inhibitor of VEGFR-1, -2 and -3. Given that several modulating effects of VEGF on the thyroid gland have been described, thyroid function changes were evaluated in patients receiving AZD2171 with gefitinib as part of an ongoing Phase I study.
Methods: Patients received once-daily, oral AZD2171 (20–45 mg) and gefitinib (250 or 500 mg) (van Cruijsen et al. Proc Am Soc Clin Oncol 2006:abst 3017). The normal range of thyroid-stimulating hormone (TSH) used in this study was 0.3−5 mU/L; an increase from normal baseline to >5 mU/L was considered abnormal. Depending upon the centre, thyroxine (T4) was measured as either total (normal range 50–150 mmol/L) or free (normal range 8–22 pmol/L). Assessments were weekly for the first month of treatment and then fortnightly until withdrawal.

Results: Among 83 patients with baseline TSH measurements, 73 had normal baseline levels and at least two post-dose readings (Table). TSH levels increased in 27/73 (37%) patients with a median (min, max) time to first increase of 29 days (7–245); all increases occurred at AZD2171 ⩾30 mg. In the 27 patients with increased TSH levels, 6 had reductions in free/total T4 to below the normal range; of which 2 received subsequent levothyroxine therapy. Patients have responded to replacement therapy without the need for AZD2171 dose reduction or interruption.
Conclusion: AZD2171 with gefitinib increased TSH levels in 37% of patients. Notably, few patients developed reductions in free/total T4 or symptoms that required replacement therapy and no patients required adjustment of AZD2171 dose. Monitoring of thyroid function is recommended in patients receiving AZD2171 and replacement therapy should be considered for patients with reductions in free/total T4 or who have clinical symptoms suggestive of incipient hypothyroidism. The association between thyroid function changes and VEGF tyrosine kinase inhibitors warrants further investigation.

Gefitinib dose (mg)	250			500				
AZD2171 dose (mg) n[a]	20 n = 2	30 n = 15	45 n = 7	20 n = 6	25 n = 5	30 n = 21	37.5 n = 11	45 n = 6
TSH increases to >5 mU/L, n (%)	0	5 (33%)	4 (57%)	0	0	10 (48%)	6 (55%)	2 (33%)
Free T4 reduced below LLN[b]	2/7			3/14				
Total T4 reduced below LLN[b]	1/2			0/4				

LLN, lower limits of normal T4 based on reference range of centres (LLN for free T4 = 11 pmol/L [n = 10] or 8 pmol/L [n = 11]); [a]Patients with normal baseline and at least 2 post-dose readings; [b]Calculated for patients with TSH increased above 5 mU/L

706 POSTER

A phase I dose escalation pharmacokinetic (PK) and pharmacodynamic (PD) study of weekly and twice weekly erlotinib in advanced stage solid malignancies

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Background: Erlotinib (Tarceva®) is a potent oral tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR). At the current recommended daily dose of 150 mg/day there is activity in advanced stage NSCLC, but with frequent grade 1/2 rash and diarrhea. We performed a phase I dose escalation study of erlotinib with a once and twice weekly schedule to assess the PKs, PDs, and to determine if toxicities would be less on an intermittent but high dose schedule.
Material and Methods: A standard dose escalation schedule starting at 1400 mg once/week and 600 mg twice/week with increments of 200 mg to 4 dose cohorts/schedule was utilized with three patients per cohort. A cycle consisted of 3 weeks of therapy. PKs were performed on cycle 1 and 2. PDs on normal skin punch biopsies were performed at baseline and following cycle 1. Tumour evaluation was done following every 2nd cycle. Subjects were treated until progression or unacceptable toxicity. Known EGFR status was not required for enrollment.
Results: 32 patients were enrolled from Oct 2004-April 2006. Median age 58 years (28−74 years); median PS 1 (0−2); and median prior palliative systemic regimens 2 (0−6). In the once weekly schedule the maximum tolerated dose (MTD) was not reached with the top dose of 2000 mg/week. A median of 2 cycles were delivered (1−14), with 3/13 patients achieving stable disease ⩾3 months. 4/13 patients experienced G1 rash and 6/13 patients G1 diarrhea during the first 2 cycles. In the twice weekly schedule the MTD was reached at 1200 mg twice/week with 2/6 subjects experiencing G3 rash. The recommended dose level is 1000 mg twice/week. A median of 4 cycles were delivered (1−28) with 2 partial responses, 1 minor response and 6 stable disease ⩾ 3 months out of 19 patients in total. G1/2 rash or diarrhea occurred in 13 and 9 patients respectively. The PK data demonstrated a variable but linear pattern. At 1000 mg twice/week the median Cmax, Tmax and AUC0−24 hr was 6.28 μg/ml, 2 hours and 135 μg·h/ml respectively. PD analysis is ongoing.
Conclusions: A once weekly and twice weekly high dose schedule of erlotinib is feasible, with MTD not reached in the once weekly schedule. A recommended dose of 1000 mg twice/week has clinical activity, is generally well tolerated, and results in significantly higher systemic exposure than the 150 mg once daily dose.

707 POSTER

Cell death and autophagy induced by INNO-406, a novel Bcr-Abl inhibitor, in Philadelphia-positive leukaemias

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Background: Imatinib mesylate (IM) induces cell death via apoptosis in Bcr-Abl$^+$ leukemias, however, we recently identified that IM induces also non-apoptotic cell death, suggesting the tuning of cellular fate by Bcr-Abl might be more complicated (Okada M, Blood 2004). Here we assessed the regulation of cellular survival and death of Bcr-Abl$^+$ leukemias more precisely, using a novel Bcr-Abl tyrosine kinase inhibitor, INNO-406 which is 25−55-fold more potent than IM (Kimura S, Blood 2005).
Methods: K562, KT-1 and BV173 cell lines derived from CML patients were examined. Cell death and mitochondrial outer membrane potential (MOMP) were assessed by propidium iodide (PI) and $DiOC_6$ staining. Apoptosis was assessed by DNA fragmentation, caspase activation, and morphological analysis. Expression patterns of Light-chain-3 (LC3) were examined by immunofluorescence staining and western blotting. For in vivo study, NOD/SCID mice were xenografted with primary leukemic cells from CML patients, and were treated by INNO-406.
Results: INNO-406 induced apoptosis in all cell lines examined (i.e. loss of MOMP, increase of subG1 fraction, DNA fragmentation and caspase-3 activation). Co-treatment with zVAD, a pan-caspase inhibitor, prevented apoptotic cell death, however, cells still underwent non-apoptotic cell death lacking apoptotic features. When apoptosis was blocked, we also found the increase of cells having hallmarks of autophagy (i.e. the autophagosome formation, punctate formations of LC3 and the accumulation of LC3-II isoform) in INNO-406-treated CML cell lines, suggesting the participation of autophagy in response to Bcr-Abl blockade. Blocking autophagy pathway by chloroquine (CQ) treatment resulted in the remarkable increase of cell death under INNO-406 treatment with or without zVAD. While, in vivo CML model, INNO-406 treatment increased typical apoptotic cells as well as cells having "necklace-like" nuclei uncommon for apoptosis, which were negative for activate caspase-3, further implicating the involvement of caspase-independent cell death regulatory pathway in vivo in primary Bcr-Abl$^+$ leukemic cells.
Conclusion: INNO-406 appears to cause both caspase-dependent/-independent cell death in Bcr-Abl$^+$ cells, and also causes autophagy as a result of resistance to INNO-406-mediated cell death under caspase inhibition. Further studies for the precise mechanisms for determining cellular fate may help the development of novel therapeutic strategies against Bcr-Abl$^+$ leukemias.

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AMG 386, a first-in-class, selective angiopoietin 1/2-neutralizing peptibody, in combination with chemotherapy in adult patients with advanced solid tumors

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Background: AMG 386 is a selective angiopoietin 1/2-neutralizing peptibody that inhibits angiogenesis by preventing interaction between angiopoietins and Tie2 receptors. This open-label study evaluated the safety, pharmacokinetics (PK), and antitumor activity of AMG 386 in combination with FOLFOX-4 (F), carboplatin + paclitaxel (CP), or docetaxel (D) in adult patients (pts) with advanced solid tumors.
Methods: Three cohorts of 6−9 pts received 1 full cycle of chemotherapy (cycles equal 2 weeks for F and 3 weeks for D 75 mg/m^2 or CP). Administration of AMG 386 10 mg/kg IV weekly was started on day 1 of cycle 2 for patients who did not experience a dose-limiting toxicity (DLT) to chemotherapy during cycle 1, and continued until disease progression or intolerance. Safety and tolerability, tumor response (by RECIST), PK profiles of AMG 386 and chemotherapy agents, and formation of antibodies to AMG 386 were assessed.
Results: As of March, 2007, 26 pts have been enrolled in the study. Twenty-one pts received AMG 386 plus chemotherapy: 6 pts in the F cohort, 7 in