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.

708 POSTER

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

CP, and 8 in D; 9 pts were men, mean age was 59.3 years, and 20 pts had stage-IV disease. No AMG 386-related DLTs or AMG 386-related serious adverse events (SAEs) were reported. AEs reported after administration of AMG 386 plus chemotherapy included diarrhea (n = 7), nausea (n = 7), neutropenia (n = 6), and thrombocytopenia (n = 6). Six pts experienced SAEs. Of these, 1 pt had a grade-3 thrombosis not considered related to AMG 386 or chemotherapy. No neutralizing antibodies to AMG 386 were observed. F, CP, and D co-administered with AMG 386 did not appear to affect the PK profile of AMG 386. AMG 386 had no apparent effect on the PK profile of F, CP, or D. Tumor response data are available for 15 pts. One pt receiving AMG 386 plus CP for bladder cancer refractory to gemcitabine/cisplatin had a complete response (CR) at week 8 (confirmed at week 16). One pt receiving AMG 386 plus F for pancreatic cancer had a confirmed partial response (PR) at week 12 and continues to do well at week 30. Stable disease in 12 pts and progressive disease in 1 pt were also observed.
Conclusions: Weekly AMG 386 in combination with F, CP, or D appeared to be well tolerated. An early CR in bladder cancer and PR in pancreatic cancer suggested promising antitumor activity of AMG 386 in combination with chemotherapy. Further clinical studies of AMG 386 in combination with chemotherapy and other targeted agents are warranted.

709 POSTER

Characterization of electrocardiographic QTc interval in patients (pts) with advanced solid tumors: pharmacokinetic–pharmacodynamic evaluation of sunitinib

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Background: Prolongation of the QTc interval occurs with various drugs and is associated with increased risk of arrhythmia, including torsades de pointes. This study examined the effect of therapeutic and supratherapeutic exposures of sunitinib (SU) on QTc interval changes in pts with advanced solid tumors. SU is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET, and FLT3, approved for the treatment of advanced RCC and imatinib-resistant or -intolerant GIST.
Materials and Methods: In this single-blind study, pts with advanced solid tumors were evaluated by serial EKG assessments on day −1 (D −1), then received a single dose of moxifloxacin (internal positive control) on D1, a single dose of placebo on D2, followed by a 1-wk course of SU (loading dose on D3 and D9, maintenance dose of 50 mg/d on D4–8). Granisetron (G) was given prior to dosing on D3 and D9, to minimize risk of nausea/vomiting, and prior to placebo on D2, to assess its effect on QTc interval. Serial triplicate ECGs time-matched to those on D −1 were performed before and after drug/placebo administration on D1, 2, 3, 9. Fridericia's correction for heart rate (QTcF) was used for the primary analyses. Loading doses on D3 and D9 were administered to increase plasma levels ⩾2x those normally achieved with an oral dose of 50 mg/d.
Results: 24 pts were evaluable. Moxifloxacin produced a placebo-adjusted QTc prolongation in the expected range, validating the study design. G did not affect ECG profile and was generally successful in preventing confounding by nausea/vomiting. SU produced QTc interval changes that correlated with drug exposure. At the 24 h postdose timepoint on D3 (therapeutic levels), maximum QTcF (placebo-adjusted time-matched correction) was 9.6 ms (90% CI: 4.1–15.1). On D9 (supra-therapeutic levels), the maximum QTcF was 15.4 ms (90% CI: 8.4–22.4). No pts developed 'severe' QTc prolongation (⩾ CTCAE grade 3) or had QTc values >500 ms at any time during the study.
Conclusions: SU treatment was associated with dose-dependent QTc interval prolongation, but the clinical significance is unclear. No pt developed QTc prolongations considered severe or values >500 ms (⩾CTC grade 3) with either therapeutic or supratherapeutic exposures in this study.

710 POSTER

Assessment of renal function in patients with cancer

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Aim: To assess the validity of measured creatinine clearance and estimated glomerular filtration rates (GFR) against radio-isotope GFR in cancer patients undergoing chemotherapy or radiotherapy.
Method: Radio-isotope Tc^{99m} DTPA GFR results were reviewed from April 2005 to January 2007. Cases with 24 hour urinary collection for creatinine clearance (CrCl) measured within 4 weeks of the isotope GFR were identified from this group. The urinary CrCl and estimated GFRs from the Cockroft-Gault, Modification of Diet in Renal Disease (MDRD) 175 ID-MS version and the Wright formulae were compared with the isotope GFR. Pearson correlation coefficients and mean absolute percentage errors were calculated. The cases with an isotope GFR of <50 millilitres per minute (ml/min) were analysed and the sensitivity and specificity of each formula were calculated. The sensitivity was set at 95% in order to minimise the numbers of cases inaccurately being reported as >50ml/min. The specificity was reported with the sensitivity set at 95%.
Results: 367 cases were identified. The mean age was 55 years (range 20−85), 66 were male and 301 were female. 237 (65%) cases had a gynaecological malignancy. The mean normalised isotope GFR was 81 ml/min (range 22–171). The correlation coefficients of the isotope GFR to the urinary CrCl, Cockroft-Gault, MDRD and Wright formulae were 0.57, 0.62, 0.68 and 0.7 respectively. The mean absolute percentage error was 28 for the urinary CrCl, 24 for the Cockfroft-Gault, 24 for the MDRD and 19 for the Wright formulae. 39 cases were identified with a GFR of <50 ml/min. The specificity was 33%, 46%, 39% and 66% for the CrCl, Cockroft-Gault, MDRD and Wright formulae respectively.
Conclusion: The urinary CrCl measurement is the most unreliable method of renal assessment tested here. The Wright formula gives the closest estimate of the isotope GFR in comparison to the Cockroft-Gault and the MDRD formulae. We would recommend the use of the Wright formula in follow up assessment of renal function during radiotherapy and chemotherapy after initial assessment with an isotope GFR.

711 POSTER

Sunitinib (SU) plus docetaxel (D) in patients (pts) with advanced solid tumors: a phase I dose-escalation and pharmacokinetic (PK) study

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Background: SU is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET, and FLT3, approved multinationally for the treatment of advanced RCC and imatinib-resistant or -intolerant GIST. In a mouse xenograft model of breast cancer, SU enhanced the antitumor activity of D. This study was designed to assess the maximum tolerated doses (MTDs), PK profile and overall safety of SU administered in combination with D in pts with advanced solid tumors. Preliminary efficacy data were also collected.
Materials and Methods: This is an ongoing multicenter, open-label, phase I, dose-finding study of SU+D in pts with advanced solid tumors. Successive cohorts of pts were to receive oral SU at 25, 37.5, or 50 mg daily on a 6 wk cycle (4 wks on followed by 2 wks off treatment; 4/2 schedule) or 3 wk cycle (2 wks on followed by 1 wk off treatment; 2/1 schedule) in combination with IV D at 60 or 75 mg/m^2 every 21 days (q21d). The MTD was defined as the highest dose at which 0 of 3 or 1 of 6 pts encountered dose-limiting toxicities (DLTs) during cycle 1. Safety/tolerability were assessed by AEs and clinical laboratory analyses. Antitumor activity was assessed by CT or MRI scans and objective response determined by RECIST.
Results: 44 pts were enrolled as of Feb 2007, including 11 with mRCC and 15 with NSCLC. 10 pts received SU on the 4/2 schedule and 34 on the 2/1 schedule. On the 4/2 schedule, 2 DLTs were observed at D 60 mg/m^2/37.5 mg SU: G3 bilateral weakness and febrile neutropenia. On the 2/1 schedule, neutropenia (with or without fever; maximum G4) was the most commonly observed DLT (n = 5) occurring at the following dose levels: D 60 mg/m^2/25 mg SU (n = 2/9), D 75 mg/m^2/50 mg SU (n = 2/2) and D 75 mg/m^2/37.5 mg SU (n = 1/17), and was manageable/reversible. Other DLTs included: G3 GI hemorrhage (n = 1). The MTDs were SU 25 mg and D 60 mg/m^2 with the 4/2 schedule and SU 37.5 mg and D 75 mg/m^2 with the 2/1 schedule. Most frequently observed G3/4 adverse events on the 2/1 schedule included: fatigue (18/0%), neutropenia (12/47%), diarrhea (6/0%), stomatitis/oral discomfort (6/0%), and nausea (3/0%). The PK analysis is ongoing for pts receiving D 75 mg/m^2 and SU 37.5 mg on the 2/1 schedule.
Conclusions: The combination of oral SU 37.5 mg/day on the 2/1 schedule with D 75 mg/m^2 IV q21d has a manageable safety profile and was selected for further study in pts with advanced solid tumors. PK and preliminary efficacy analyses are ongoing to support these dosing combinations.