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

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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.

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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