391 POSTER

A Phase I randomized trial to assess the effects of Src inhibitor AZD0530 on renal function in healthy volunteers

R. Chetty[1], N. Dalton[1], M. Rimmer[1], N. Cockburn[1], I. Smith[1], A. Swaisland[1], J. Hargreaves[1], M. Stuart[1]. [1]*AstraZeneca, Alderley Park, Macclesfield, United Kingdom*

Background: AZD0530 is a Src inhibitor under investigation for the treatment of cancer. Previous studies have shown an increase in plasma creatinine (Cr) after dosing with AZD0530. The aim of this study was to determine the cause of this increase and to assess the effects of AZD0530 on renal function in healthy volunteers.
Methods: A total of 56 healthy male volunteers were assigned to either single-dose (n = 28; randomized to placebo or AZD0530 500 mg po) or multiple-dose treatment (n = 28; randomized to placebo or AZD0530 125 mg od po for 14 days). Renal function variables assessed before and after AZD0530 treatment included inulin clearance (CL), CrCL, and plasma cystatin C levels. ANCOVA was used for statistical analysis.
Results: The results (Table) ruled out the following causes of increased plasma Cr: (1) analytical interference, as tandem mass spectrometry (MSMS) analysis confirmed the increase in plasma Cr; (2) decreased glomerular filtration rate (GFR), as inulin CL was not affected; and (3) increased Cr production, as Cr excretion rate was not affected. However, mean fractional excretion of Cr decreased in the active treatment group in both cohorts suggesting that renal tubular secretion of Cr is reduced after dosing with AZD0530. This finding was supported by *in vitro* evidence that AZD0530 competes with Cr for renal clearance via the organic cation transporter hOCT2. AZD0530 had no effect on renal hemodynamics, solute handling, osmotic regulation or water balance.

	Multiple dose		Single dose	
Mean	AZD0530 125 mg (n = 21)	Placebo (n = 7)	AZD0530 500 mg (n = 21)	Placebo (n = 7)
Age (range), years	37 (18–51)	35 (22–44)	39 (24–55)	39 (30–53)
Inulin CL, ml/min				
Baseline	116	121	116	133
Change* (80% CI)	5 (2, 8)	−9 (−16, −3)	0 (−3, 2)	7 (1, 13)
MSMS plasma Cr, μmol/l				
Baseline	72.3	75.8	77.8	70.8
Change* (80% CI)	15.4 (13.6, 17.2)	5.9 (2.7, 9.1)	16.7 (15.2, 18.2)	−2.2 (−4.9, 0.5)
MSMS Cr excretion rate, μmol/min				
Baseline	11.8	14.2	12.3	11.6
Change* (80% CI)	0.3 (−0.2, 0.8)	−0.5 (−1.5, 0.6)	1.3 (0, 2.6)	0.5 (−2, 3)
Fractional excretion of Cr				
Baseline	1.42	1.50	1.38	1.21
Change* (80% CI)	−0.26 (−0.28, −0.23)	−0.05 (−0.10, 0)	−0.16 (−0.26, −0.05)	0.12 (−0.10, 0.34)

*Adjusted using an ANCOVA model fitted to change from baseline with treatment as a fixed effect and age and baseline value as covariates.

Conclusions: The increase in plasma Cr seen with AZD0530 dosing is due to a reduction in renal tubular secretion of Cr. AZD0530 has no effect on GFR, renal hemodynamics, solute handling, osmotic regulation or water balance.

392 POSTER

A phase I/II multicenter trial of BMS-690514, an ErbB-VEGFR inhibitor, in patients with advanced NSCLC who are erlotinib naive or previously treated with erlotinib

J.C. Soria[1], E. Felip[2], R. Herbst[3], N. Hannah[4], S. laurie[5], J.P. Armand[6], F. Shepherd[7], D. Berman[8]. [1]*Institut Gustave Roussy, Medecine, Villejuif, France;* [2]*Institut Català d'Oncologia, Medecine, Barcelona, Spain;* [3]*The University of Texas MD Anderson Cancer Center, Medecine, Houston, USA;* [4]*Indiana Cancer University, Medecine, Indianapolis, USA;* [5]*TThe Ottawa Hospital Cancer Centre and the University of Ottawa, Division of Medical Oncology, Ottawa, Canada;* [6]*Institut Claudius regaud, Medecine, Toulouse, France;* [7]*Princess Margaret Hospital, Department of Medical Oncology, Toronto, Canada;* [8]*BMS, Department of Medical Oncology, Princeton, USA*

Background: BMS-690514 is an oral, potent inhibitor of EGFR, HER2, ErbB4, and VEGFR1−3 with activity in a wide range of tumor cell lines. The Phase 1 portion defined an MTD of 200 mg/day.
Methods: In the phase 2 portion, 2 cohorts of advanced NSCLC patients (erlotinib naive and prior erlotinib) were treated at the MTD. The objectives were to assess clinical activity, safety profile and to explore biomarkers of BMS-690514. Eligible patients (pts) $\geqslant$ 18 years with advanced or metastatic (stable brain metastases allowed), and measurable NSCLC of any histology, ECOG $\leqslant$ 1, adequate cardiovascular, renal (serum creatinine $\leqslant$1.5 ULN allowed) and other organ functions. Tumor assessments were performed every 8 weeks using modified WHO criteria. Biomarkers of ErbB and VEGFR signalling included tumor tissue (ErbB pathway gene amplification and mutations), skin biopsies, arterial blood pressure and plasma samples (soluble VEGFR).
Results: As of February 2008, in the Phase 2 portion, 42 pts (27 M/15 F) with a median age 63 years in erlotinib naive (n = 17) and 59 years in prior erlotinib (n = 25) have been treated. 59% pts and 88% pts, respectively, had received at least 2 prior lines of treatment. 18% pts and 8% pts, respectively, had received prior VEGF inhibitors. The majority of drug-related AEs have been mild-moderate and reversible following drug interruption and include diarrhea (77% G $\leqslant$ 2; 2% G3), rash (67% G $\leqslant$ 2; 2% G3), proteinuria (24% G $\leqslant$ 2; 12% G2); asthenia (24% G $\leqslant$ 2; 2% G3), arterial hypertension (15% G $\leqslant$ 2; 7% G3−4) and acute renal insufficiency (14% G $\leqslant$ 2). 14% of pts had dose reductions and 5% were discontinued for drug-related AEs.
As of the cut-off date, evidence of tumor shrinkage has been observed in both cohorts. One erlotinib naive pt with a deletion in EGFR exon 19 experienced a PR (34.3+ wks on study) and 3 pts experienced tumor shrinkage of 21−41% (7.4+ to15.4+wks on study) including 1 with EGFR mutation and 1 with wild type EGFR. In the prior erlotinib cohort, 1 PR (11.4+wks) was observed in a pt with a best response of PD on erlotinib and 4 pts (including 2 with the T790M mutation) have had 7−24% tumor shrinkage (4.7+ to 15.3+ wks on study). PD biomarkers for VEGFR inhibition demonstrate an increase in mean systolic BP and a decrease in sVEGFR2. Immunohistochemical biomarkers of EGFR signaling in skin biopsies demonstrate an increase in p27 and decrease in pMAPK.
Conclusions: BMS-690514 200 mg/day was generally well tolerated, with mild-moderate, reversible, and predominantly mechanism-based AEs. Based on PD biomarkers, BMS-690514 inhibits both EGFR and VEGFR signalling. Encouraging evidence of anti-tumor activity was seen in previously treated patients with NSCLC, including those with prior erlotinib exposure and with T790M mutation.

393 POSTER

First-in-man Phase I trial of BYK408740, an oral histone deacetylase inhibitor, in patients with advanced malignancies

J.E. Ang[1], B. Hauns[2], A. Mais[2], A. Parker[1], R. Lal[1], D. Olmos[1], M. Mollenhauer[2], A. Walz[2], J.S. de Bono[1]. [1]*Royal Marsden Hospital, Drug Development Unit, Sutton, United Kingdom; 2. Nycomed GmbH, Exploratory Clinical Development, Konstanz, Germany*

Background: BYK408740 has been shown to be a specific and potent histone deacetylase (HDAC) inhibitor with broad anti-neoplastic activity *in vitro* and *in vivo*. This is the first-in-human Phase I trial of BYK408740.
Methods: Patients (pts) with advanced solid tumours refractory to standard therapy or for which no standard therapy exist, are eligible for this ongoing trial. Primary objectives are to evaluate safety, tolerability and pharmacokinetics (PK), and to determine the maximum tolerated dose and dose-limiting toxicities (DLT). Secondary objectives are to assess pharmacodynamics (PD) and to explore anti-tumour efficacy of BYK408740. Pts are dosed once daily (QD) d1−5 in a 14-day cycle in sequential cohorts of 3−6 pts with 100% or 50% dose increments. Serial ECGs are done in all pts to evaluate effects on QTc interval. Pts are restaged radiologically after 4 treatment cycles and graded according to RECIST criteria. Blood samples for PK and PD are taken on days 1, 5 and 47 of treatment. PD assessments incorporate the measurements of histone acetylation and HDAC enzyme activity.
Results: 12 pts, median age 59.5 years (range 41−66), have been treated thus far: 3 pts each at 100 mg, 200 mg, 400 mg, and 600 mg QD. All pts dosed in the first 3 dose-levels have received at least 2 treatment cycles while 3 pts have received 4 cycles. 3 pts in the 600 mg dose level cohort are currently on study. While no DLT has been encountered to date, the most frequent adverse events include fatigue, nausea, diarrhoea and weight loss. Cardiac toxicity has notably not been a concern in clinical assessments so far. 2 pts had non-progressive disease after 8 weeks of treatment. PK profiles for the 100 mg, 200 mg and 400 mg cohorts have been analysed. Generally, high exposure of BYK408740 was obtained, indicating good bioavailability. The apparent $t_{1/2}$ of oral BYK408740 ranged from 2.7 to 4.4 hours. In all dose levels analysed, a low variability in PK was seen. The degree of HDAC enzyme inhibition was drug dose-dependent and ranged from 50% to 100%. On the other hand, although histone H4 acetylation level increased after dosing, this did not differ significantly between different dose levels.

Conclusion: Oral BYK408740 at 600 mg QD continuously d1−5 in a 14 day cycle is well-tolerated. BYK408740 shows a favourable PK profile, with high bioavailability and low inter-pt variability. The modulation of plasma biomarkers further indicates drug activity. Dose escalation on this schedule continues.

394 POSTER

Final results of a Phase I study of cediranib, a VEGFR signaling inhibitor, in Japanese patients with advanced solid tumors

H. Murakami[1], N. Yamamoto[1], N. Boku[2], K. Yamazaki[2], N. Yamamoto[3], Y. Yamada[4], K. Yamada[3], T. Puchalski[5], E. Shin[6], T. Tamura[3]. *[1]Shizuoka Cancer Center, Division of Thoracic Oncology, Shizuoka, Japan; [2]Shizuoka Cancer Center, Division of Gastrointestinal Oncology and Endoscopy, Shizuoka, Japan; [3]National Cancer Center, Division of Internal Medicine, Tokyo, Japan; [4]National Cancer Center, Division of Gastrointestinal Oncology, Tokyo, Japan; [5]AstraZeneca, Research and Development, Wilmington, DE, USA; [6]AstraZeneca, Research and Development, Osaka, Japan*

Background: Cediranib (AZD2171) is a highly potent and selective inhibitor of vascular endothelial growth factor (VEGF) signaling. The purpose of this Phase I study was to evaluate the safety and tolerability of increasing doses of cediranib in Japanese patients (pts), with additional assessments of pharmacokinetics (PK) and efficacy.
Methods: In the dose-ascending phase (part A), pts with advanced solid tumors refractory to standard therapies received once-daily oral cediranib (10−45 mg). Doses were escalated in successive cohorts until the maximum tolerated dose (MTD) was identified. In the expanded-cohort phase (part B), 24 pts with non-small-cell lung cancer (NSCLC) and colorectal cancer (CRC) received cediranib at the MTD.
Results: Between Oct 2005 and March 2007 a total of 40 pts (mean age: 55 [26−73], male/female: 24/16, PS 0/1: 13/27) were recruited. In part A, 16 pts with NSCLC (5), CRC (4) or other tumor types (7) received cediranib 10 (3), 20 (3), 30 (3) or 45 (7) mg/day. Since 3/6 evaluable pts receiving 45 mg/day experienced DLTs (proteinuria, proteinuria + diarrhea, and thrombocytopenia), cediranib 30 mg/day was defined as the MTD for further investigation in part B. Following a single dose of cediranib 10−45 mg, the maximum plasma concentration was achieved 2−4 hours post dosing and the mean terminal half-life ranged from 19−28 hours. At 20 mg/day, the unbound minimum plasma concentration was 3.85 times the human umbilical vein endothelial cell proliferation IC50. Overall common adverse events (AEs) and laboratory abnormalities of CTCAE grade 1−4//3−4 were diarrhea (85/10%), hypertension (80/0%), hand–foot syndrome (68/2.5%), blood erythropoietin increased (73/0%), blood TSH increased (70/0%), and proteinuria (68/10%). Upward tendency in VEGF and reductions in soluble VEGFR-2 were observed in part B. The PK parameters and overall AE profile were similar to those seen in a Western population. Of 32 pts who were eligible for RECIST assessments there were 2 confirmed partial responses (alveolar soft tissue sarcoma and CRC) and 24 pts with stable disease $\geqslant$8 weeks; the disease control rate was 81% (26/32). Six pts in part A have continued with cediranib for more than 1 year.
Conclusions: Once-daily oral cediranib at doses of 30 mg or less was generally well tolerated in this population of Japanese pts with a manageable adverse event profile and was associated with encouraging antitumor activity.

395 POSTER

Phase I study of XL844, a novel Chk1 and Chk2 kinase inhibitor, in combination with gemcitabine in patients with advanced malignancies

A. Tse[1], S. Yazji[2], A. Naing[3], D. Matthews[4], G. Schwartz[1], K. Lawhorn[3], R. Kurzrock[3]. *[1]Memorial Sloan-Kettering Cancer Center, Medicine, New York, USA; [2]Exelixis, Clinical Development, South San Francisco, CA, USA; [3]MD Anderson Cancer Center, Investigational Cancer Therapeutics, Houston, TX, USA; [4]Exelixis, Oncology Discovery, South San Francisco, CA, USA*

Background: XL844 is a potent inhibitor of the cell cycle checkpoint kinases Chk1 and Chk2, which are implicated in tumor cell resistance to cytotoxic chemotherapy. In vitro clonogenic assays and in vivo mouse xenograft studies have shown that XL844 potentiates the activity of chemotherapeutic agents such as gemcitabine.
Methods: Patients (Pts) with advanced malignancies were enrolled in successive cohorts of a Phase 1 study with an initial 6-week (wk) treatment cycle followed by 4-wk cycles. During the first 5 weeks of the initial cycle, pts received oral XL844 on the first 2 days of each week and received a gemcitabine infusion (800 mg/m^2) 8 hours prior to the first XL844 dose in wks 3−5. Thereafter, pts received the combination in wks 1−3 of subsequent cycles. Tumor response was assessed approximately every 2 cycles. Serial blood samples were collected for plasma pharmacokinetic (PK) assessment.
Results: In this ongoing study, 20 pts have been treated in 4 cohorts at XL844 doses of 0.8, 1.1, 1.6 and 2.35 mg/kg/day. Tumor types included colorectal carcinoma (CRC, 8 pts), ocular melanoma and gastric carcinoma (2 pts each), clear cell carcinoma, rhabdomyosarcoma, mesothelioma, gastroesophageal junction, pancreatic, periampullary, endometrial and small intestinal adenocarcinoma (1 pt each). Five pts achieved stable disease (SD) for $\geqslant$4 months (mo) including 1 pt each with periampullary cancer (9+mo), ocular melanoma (6.5 mo), CRC (5 mo), rhabdomyosarcoma (4.5 mo), and gastric carcinoma (4 mo). Treatment-related adverse events (AEs) included nausea and vomiting (1 pt each). Two DLTs occurred to date: 1 grade 4 thrombocytopenia (Cohort 1), and 1 grade 3 lipase elevation (Cohort 4). The maximum tolerated dose has not yet been reached and dose escalation is ongoing. A preliminary PK analysis for XL844 indicates that mean exposure (C_{max} and AUC) increased proportionally to dose between 0.8 and 1.6 mg/kg. Mean $t_{1/2}$ ranged from 2−4.6 hrs on Day 1 and 4.2–27.9 hrs on Day 2. Minimal accumulation was observed after multiple doses of XL844. No apparent PK interaction between XL844 and gemcitabine was observed.
Conclusions: XL844 was generally well tolerated. Stable disease ($\geqslant$4 mo) was observed in patients with various tumor types. The MTD has not yet been defined and dose escalation continues.

396 POSTER

Effect of oral (PO) casopitant, a novel NK-1 receptor antagonist, on the pharmacokinetics (PK) and safety profile of intravenous (IV) docetaxel

L. Adams[1], B. Johnson[2], J. Bauman[3], P. Lebowitz[4], K. Zhang[5], T. Webb[6], E. Gartner[7], R. Hohl[8], U. Dandamudi[9], L. Lewis[9]. *[1]GlaxoSmithKline, Discovery Medicine, Research Triangle Park, NC, USA; [2]GlaxoSmithKline, CPK/M&S, Research Triangle Park, NC, USA; [3]GlaxoSmithKline, Clinical Operations, Research Triangle Park, NC, USA; [4]GlaxoSmithKline, Discovery Medicine, Collegeville, PA, USA; [5]GlaxoSmithKline, Discovery Biometrics, Research Triangle Park, NC, USA; [6]Genesis Cancer Center, Clinical Research, Hot Springs, AR, USA; [7]Karmanos Cancer Institute, Hudson-Webber Cancer Research Center, Detroit, MI, USA; [8]University of Iowa, Holden Comprehensive Cancer Center, Iowa City, IA, USA; [9]Dartmouth-Hitchcock Medical Center, Clinical Pharmacology, Lebanon, NH, USA*

Background: Casopitant, in combination with a standard pre-medication regimen of a 5HT3 antagonist and dexamethasone (5HT3/Dex), is currently in development for the prevention of chemotherapy-induced nausea and vomiting. Because casopitant is a weak-to-moderate inhibitor of CYP3A4, this study evaluated whether oral casopitant would modify the PK and safety profile of the CYP3A4 substrate, docetaxel, in cancer patients (pts).
Methods: Pts scheduled to receive at least two doses of weekly IV docetaxel (20−40 mg/m^2) were enrolled in a randomized two-period crossover study. They received docetaxel (0 h) and a 5HT3/Dex regimen (8 mg PO ondansetron, −0.5 h and 8 mg PO Dex −12 h, −1 h and +12 h) alone, and the same regimen of docetaxel and 5HT3/Dex in combination with oral casopitant (150 mg PO, −1.0 h). The PK and safety profile of docetaxel was studied.
Results: Twelve pts have been enrolled in the study. Descriptive safety data for 10 pts and a planned interim evaluation of PK data for five evaluable pts who have completed study follow-up are presented herein; data for the remaining pts are currently being analyzed for presentation of final study data for all 12 pts at the meeting. The geometric mean (CV%) AUC for docetaxel treatment without casopitant was 968 (40%) ng.h/mL and for docetaxel co-administered with casopitant was 1080 (31%) ng.h/mL, whereas the Cmax was 819 (43%) ng/mL for docetaxel without casopitant and 866 (26%) ng/mL for docetaxel after co-administration with casopitant. AE profiles were similar in both regimens and only one AE, diarrhea, was considered related to study medication. Two SAEs, severe pseudomonal pneumonia and orbital cellulitis, were not considered related to study medication. There were no differences in absolute neutrophil count or in other hematological values between the two regimens.
Conclusions: Based on interim data, the addition of a single-dose 150 mg oral casopitant to a regimen of single-dose IV docetaxel and 5HT3/Dex does not appear to result in a clinically relevant change in the pharmacokinetic disposition or the safety profile of docetaxel.