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

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**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.

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**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**

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**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.

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

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**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.