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Phase 1 dose-escalation study of S-222611, an oral reversible dual tyrosine kinase inhibitor of EGFR and HER2, in patients with solid tumours

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Abstract ***Background:*** S-222611 is a reversible inhibitor of EGFR, HER2 and HER4 with preclinical activity in models expressing these proteins. We have performed a Phase 1 study to determine safety, maximum tolerated dose (MTD), pharmacokinetic profile (PK) and efficacy in patients with solid tumours expressing EGFR or HER2.

Patients and methods: Subjects had advanced tumours not suitable for standard treatment, expressing EGFR or HER2, and/or with amplified *HER2*. Daily oral doses of S-222611 were escalated from 100 mg to 1600 mg. Full plasma concentration profiles for drug and metabolites were obtained.

Results: 33 patients received S-222611. It was well tolerated, and the most common toxicities, almost all mild (grade 1 or 2), were diarrhoea, fatigue, rash and nausea. Only two dose-limiting toxicities occurred (diarrhoea and rash), which resolved on interruption. MTD was not reached. Plasma exposure increased with dose up to 800 mg, exceeding levels eliciting pre-clinical responses. The plasma terminal half-life was more than 24 h, supporting once daily dosing. Responses were seen over a wide range of doses in oesophageal, breast and renal tumours, including a complete clinical response in a patient with HER2-positive breast

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carcinoma previously treated with lapatinib and trastuzumab. Four patients have remained on treatment for more than 12 months. Downregulation of pHER3 was seen in paired tumour biopsies from a responding patient.

Conclusions: Continuous daily oral S-222611 is well tolerated, modulates oncogenic signalling, and has significant antitumour activity. The recommended Phase 2 dose, based on PK and efficacy, is 800 mg/day.

1. Introduction

Dysregulation of signalling via the ERBB receptor tyrosine kinase family is one of the most common oncogenic drivers in epithelial tumours [1]. The complexity of signalling mediated by the various ERBB receptors predicts that specific inhibition of a single family member may be insufficient to gain sustained control of neoplastic proliferation [1]. The early generation of ERBB inhibitors are associated with significant on-target toxicities [2], and new, more potent, broader spectrum, less toxic ERBB inhibitors are required.

S-222611, an oral agent, is a novel, reversible, selective and potent inhibitor of EGFR, HER2 and HER4 kinases. S-222611 inhibits the ERBB kinases with IC_{50} values for EGFR, HER2 and HER4 of 1.5, 7.2 and 2.5 nM, respectively. In pre-clinical studies S-222611 has activity against EGFR- and HER2-expressing human cell lines and xenografts [3]. In healthy male volunteers, single doses up to 400 mg (the maximum tested) were well tolerated with an adverse event profile indistinguishable from placebo. Systemic exposure (C_{max} and AUC_{0-inf}) was proportional to dose and mean $t_{1/2\lambda z}$ ranged from 20.8 to 25.6 h, independent of dose, supporting once daily administration, without an important food effect.

We have conducted a Phase 1 dose-escalation study of S-222611 in patients with advanced solid tumours expressing EGFR and/or HER2. The primary objectives were to evaluate safety and define the maximum tolerated dose (MTD) of S-222611. Secondary objectives were pharmacokinetic (PK) evaluation of S-222611 and assessment of tumour response. We also studied pharmacodynamic markers in paired tumour biopsies.

2. Patients and methods

2.1. Study population and drug administration

This was a dose-escalation study of continuous once-daily oral treatment with S-222611. Eligible patients had histologically confirmed solid tumours not amenable to established treatments, expressing EGFR (1+ to 3+ by immunohistochemistry) and/or overexpressing HER2 (3+ or 2+ using immunohistochemistry, or amplification by FISH). Breast and gastric cancer patients had HER2-positive tumours (3+ using immunohistochemistry, or 2+ and amplified *HER2* by FISH). Colorectal cancer patients with *KRAS* mutation were excluded. Other eligibility criteria included written informed consent; Eastern Cooperative Oncology Group (ECOG) performance status 0–1; recovery from all previous therapy-related toxicities to Common Terminology Criteria for Adverse Events v4.0 (CTCAE) Grade $\leqslant$1; and adequate bone marrow, renal, hepatic and left ventricular function. The study was approved after review by the relevant regulatory and independent ethics committees (EudraCT Number: 2009-017817-31), and conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice.

S-222611 (Shionogi & Co. Ltd, Osaka, Japan) was administered as a single dose on Day 1 with continuous daily dosing from Day 8. All doses were administered as tablets containing 100 mg S-222611, within 30 min of eating breakfast. Based on the concentrations demonstrating efficacy in preclinical tumour models and toxicity studies, and the tolerability and pharmacokinetics obtained with single doses in healthy volunteers, a continuous daily dose of 100 mg was selected as the starting dose. Subsequent dose levels planned were 200, 400, 800, 1200 and 1600 mg daily. Dose reduction was allowed following dose interruption for toxicity. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Dose escalation followed a 3 + 3 design with cohort expansion to six patients if one dose limiting toxicity (DLT) was reported during the first 28-day cycle. The MTD was defined as the highest dose at which DLT occurred in no more than one of six patients during the first cycle. After the dose had been escalated to 1600 mg, the cohorts at 400 mg and 800 mg were expanded to six patients to obtain additional PK data. DLT definitions included any Grade 3 or 4 non-haematological toxicity, and Grade 2 nausea, vomiting or diarrhoea for $\geqslant$7 days despite supportive therapy.

2.2. Study procedures

Screening tests at baseline included physical examination, computerised tomography, full blood count, clotting, tests of renal and liver function, electrocardiogram (ECG), measurement of left ventricular ejection fraction (LVEF), and ophthalmic examination because