in table below indicated the accumulation of P. In combined administration of P600 and L1250, no PK interaction was observed. Long term disease control of partial response and stable disease over three months was observed in 3 of 13 pts in part A and 11 of 17 pts in part B.
Conclusions: P was well tolerated and safe in Japanese pts. A monotherapy dose of 800 mg/day was recommended for Japanese pts. Any combined dose levels of P and L were recommendable.

	Dose (mg)	N	AUC0−24 (μg·hr/mL), GeoMean [95% CI]			
			day 1	day 15	day 22	day 37
Part A (P)						
level 1	400 → 800	3	402.3 (N = 3) [260.2, 621.9]	–	739.5 (N = 8) [514.5, 1062.8]	–
level 2	800 → 800	7	324.6 (N = 7) [173.0, 608.9]	–	739.5 (N = 8) [514.5, 1062.8]	
level 3	1000 → 1000	3	305.0 (N = 3) [26.2, 3548.6]	–	759.5 (N = 3) [177.7, 3246.1]	–
Part B (P/L)						
level 1	400/1000	3	–	–	–	–
level 2	400/1500	3	–	–	–	–
level 3	800/1000	4	–	–	–	–
level 4	600/1250	7				
		P	–	1331.4 (N = 3) [946.0, 1873.9]	–	1188.8 (N = 6) [815.3, 1733.3]
		L		28.4 (N = 3) [9.7, 83.1]	–	29.5 (N = 6) [19.4, 44.9]

1251 POSTER

Preclinical and Clinical Development of 4SC-203 − a Novel Multi-target Kinase Inhibitor

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4SC-203 is a novel small molecule selective-spectrum kinase inhibitor of the benzothiazole chemical class displaying a unique selectivity profile against FLT3, FLT3 mutants, AXL, ALK, FAK, VEGF-R2, and TRK receptors in both *in vitro* studies with an inhibitory activity on cell line growth in the low nanomolar range. Furthermore, in preclinical studies 4SC-203 has shown a pronounced anti-tumour activity in acute myeloid leukaemia (AML)-related *in vivo* models. In a first in man study in healthy volunteers 4SC-203 proved to be well tolerated over the whole concentration range investigated and to have a favourable pharmacokinetic profile.
FLT3 represents an attractive therapeutic target in AML, as this kinase is frequently over-expressed or mutated in patients with this disease, which causes uncontrolled cell growth. Activating FLT3 mutations can be identified in approximately one third of these patients, a subgroup associated with a dismal prognosis due to a high relapse rate, with currently no satisfactory treatment option available. Beyond FLT3, 4SC-203 has been shown to inhibit kinases involved in angiogenesis (EPHA, EPHB and VEGF receptors which are responsible for stimulating the cellular responses required for blood vessel formation) and metastasis (e.g. AXL and FAK). 4SC-203 was co-developed with ProQinase GmbH, Freiburg, Germany (www.proqinase.com).
In a randomised, double-blind, placebo-controlled, Phase I dose escalation study (ClinicalTrials.gov Identifier: NCT01054937) the safety, tolerability, and pharmacokinetics of 4SC-203 was assessed in 60 healthy, male volunteers aged 20 to 46 years. Cohorts of eight subjects each, radomised in a 6:2 ratio (active:placebo), received ascending single intravenous doses of the compound. The dose range comprised 0.041 to 2.5 mg/kg body weight.
Treatment in all cohorts was well tolerated with headache and reactions on the injection site being the most common side effects. There was no indication on target organ toxicity. No relevant changes in laboratory parameters, vital signs and ECG were apparent during the course of the study. 4SC-203 shows a favourable PK-profile with dose proportionality for both AUC and C_{max}. Geometric mean terminal half-lives up to about 30 h were observed in the high dose groups.
Preclinical and final Phase I clinical data of 4SC-203 will be presented.

1252 POSTER

First Report of the Safety, Tolerability, and Pharmacokinetics of Saracatinib (AZD0530) in Japanese Patients With Advanced Solid Tumours

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Background: Saracatinib is a selective, oral Src inhibitor that has demonstrated antitumour activity in patients with advanced solid tumours. This open-label, multicentre, dose-escalation, Phase I study evaluated the safety and tolerability of saracatinib in Japanese patients. Study sponsored by AstraZeneca; clinicaltrials.gov NCT00704366.
Methods: Eligible patients received saracatinib continuous once-daily oral dosing 7 days after a single dose in ascending dose cohorts until dose-limiting toxicity (DLT) or disease progression. DLT was defined as grade 4 haematological toxicity, grade 3/4 febrile neutropenia or any other grade 3/4 toxicity which, in the opinion of the investigator, was related to saracatinib in the period from the single dose up to 21 days of continuous dosing. Pharmacokinetics and preliminary efficacy were also evaluated. Adverse events (AEs) were evaluated according to CTCAE v3.0.
Results: Twelve patients (median age 57 years [range 38−78]; male: n = 7; PS 0/1: n = 5/7) received saracatinib doses of 50 mg (n = 3), 125 mg (n = 6), or 175 mg (n = 3). Tumour types included colorectal (n = 4), lung (n = 4), breast, oesophagus, stomach, and ovary (n = 1 each). Median number of prior chemotherapy regimens was 3 (range 1−10). The median duration of exposure was 65, 44, and 16 days in the 50, 125, and 175 mg groups, respectively. The most common AEs were diarrhoea (67%), nausea (67%), decreased appetite (58%), lymphopenia (50%) and pyrexia (50%). The most common AEs of grade ⩾3 were leukopenia, lymphopenia, neutropenia, and haemoglobin decreased (all 17%). DLTs occurred in two patients, both in the 175 mg group: grade 3 AST increased associated with grade 2 ALT increase, grade 3 GGT increased (n = 1); and grade 3 hypoxia (n = 1). Following a single dose, saracatinib median t_{max} across the doses was 2−4 hours, and thereafter plasma concentrations declined in a biphasic manner, with mean terminal $t_{1/2}$ of approximately 45 hours. Steady-state exposure was generally achieved 10−14 days after initiation of continuous dosing. Saracatinib exposures at the doses tested were 0.8−2.1 fold of those in Western patients. Of 11 patients with evaluable target lesions, three had stable disease (50 mg n = 2; 125 mg n = 1). One patient with lung cancer was treated for 570 days (ongoing at data cut-off).
Conclusion: Saracatinib exhibited an acceptable tolerability profile in Japanese patients with advanced solid tumours. The MTD was considered to be 125 mg.

1253 POSTER

Two-component Messenger RNA-based Vaccines Provide Strong Anti-tumoral Effect Especially in Combination With Radiation Therapy

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Background: Complexation of mRNA with the cationic protein protamine generates two-component tumour vaccines with two principle activities: antigen expression and immune stimulation.
Compared to their single components, two-component mRNA vaccines induce superior innate as well as balanced adaptive immune responses: these comprise humoral as well as T cell mediated immunity and include induction of memory T cells. Immunization of mice bearing ovalbumin (Ova) positive E.G7 tumours with a two-component anti-Ova mRNA vaccine mediates a strong anti-tumour response also under therapeutic conditions. Anti-tumour efficacy depends on the size of established tumours at the beginning of treatment.
Material and Methods: To test whether a combination of our vaccine with radiotherapy could achieve a therapeutic effect against large, clinical size tumours, mice were inoculated with E.G7 tumour cells and left untreated until the tumours reached a volume of around 200–250 mm^3. Mice were treated either with immunotherapy alone, radiation alone or combined radioimmunotherapy.
Results: Immunotherapy alone was only marginally effective against these large tumours, whereas radiation of the tumours induced transient growth stagnation for about 7 days. However, combined radioimmunotherapy dramatically improved anti-tumour efficacy. All mice treated this way