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

R. Krauss[1], F. Wagner[2], R. Doblhofer[1], B. Dietrich[1], J. Ehlert[3], M.H.G. Kubbutat[3], A. Lingnau[3], F. Totzke[3], C. Schächtele[3], B. Hentsch[1]. *[1]4SC AG, Development, Planegg, [2]Charité Research Organisation GmbH, Berlin, [3]ProQinase GmbH, Freiburg, Germany*

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

Y. Onozawa[1], Y. Fujisaka[2], H. Yasui[1], T. Kurata[3], K. Yamazaki[1], I. Goto[2], N. Machida[1], J. Watanabe[4], X. Shi[5], N. Boku[1]. *[1]Shizuoka Cancer Center, Division of Gastrointestinal Oncology, Shizuoka, [2]Osaka Medical College, First Department of Internal Medicine, Osaka, [3]Osaka Medical College, Chemotherapy Center, Osaka, [4]Shizuoka Cancer Center, Division of Female Medicine, Shizuoka, [5]AstraZeneca, Research and Development, Osaka, Japan*

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

M. Fotin-Mleczek[1], C. Lorenz[1], K. Duchardt[1], K.J. Kallen[1], S. Huber[2]. *[1]CureVac GmbH, Research and Development, Tübingen, [2]Universitätsklinikum Tübingen, Department of Radio-Oncology, Tübingen, Germany*

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

showed pronounced tumour regression, causing complete and sustained eradication of the tumour in 3/7 mice. Median survival in the combination group was 45 days after start of treatment, compared to 9 days for untreated mice, 11 days for mice receiving immunotherapy and 17.5 days for mice in the radiation group.
Conclusions: These findings highlight that integration of immunotherapies with standard cancer therapies such as radiation creates highly synergistic anti-tumour effects, that may have the potential to enable long-term survival in cancer patients and ultimately to open a therapeutic avenue to cancer cure.

1254 POSTER

DNA Vaccine Expressing Alpha-fetoprotein With the Degradation Signal From Ornithine Decarboxylase Provides Notable Protective Immunity Against Hepatocellular Carcinoma in Mice

A. Morozov[1], V. Morozov[2], T. Astakhova[3], A. Timofeev[1], V. Karpov[4]. *[1]Engelhardt Institute of Molecular Biology RAS, CSF, Moscow, Russian Federation; [2]Robert-Koch Institute, p13, Berlin, Germany; [3]N.K. Koltsov Institute of Developmental Biology RAS, Biochemistry, Moscow, [4]Engelhard Institute of Molecular Biology RAS, CSF, Moscow, Russian Federation*

Background: Alpha-fetopotein (AFP) is a marker of hepatocellular carcinoma (HCC). DNA vaccines against AFP were shown to generate strong immune response. Previously we demonstrated that DNA vaccine bearing HIV-1 reverse transcriptase (RT) gene and mouse ornithine decarboxylase (ODC) degradation signal at the 3′-end induced a strong Th1 immune response against RT HIV-1 in mice. We proposed that the DNA vaccine bearing AFP which is directed for degradation in proteasome would induce strong CD8+CTL response against tumour cells expressing AFP and might be efficient in preventing HCC.
Materials and Methods: Vectors expressing the following proteins were designed: murine AFP (mAFP), mAFP lacking exportation signal (pΔAFP), mAFP+ODC degradation signal (pAFPODCsignal), mAFP+ODC degradation signal but without exportation signal (pΔAFPODCsignal). After transfection of 293T cells the protein expression was examined by SDS-and Native PAGE and Western blot. The efficacy of proteasomal degradation was evaluated by cycloheximide chase, proteasome inhibition assay and immunofluorescence. Proteins in transfected cells were also examined by confocal microscopy using anti-AFP and anti-calnexin antibodies. Tumours in C57BL mice were induced by subcutaneous admittance of 2×10^5 hepatoma cells from Hepa 1−6 cells line. Vaccine trials were performed on mice. In therapeutic trial [48 animals: 6 groups (8 mice in each)] 14 days after tumour cell challenge mice were vaccinated intramuscularly with 100 μg of plasmid. In “prevention” trial (18 mice: 3 groups) mice were vaccinated four times (50 μg, 2 week intervals) and 2 weeks after the last vaccination were challenged with tumour cells.
Results: All plasmids were well expressed in transfected cells, but only the ΔAFPODCsignal protein degraded fast in the proteasome (half life 1.5−2h). pΔAFPODCsignal was further used in animal trail. No significant protection was demonstrated in the therapeutic experiment. However, preventive vaccination trial yielded 300% reduction in mean tumour volume compared to the control group and 500% reduction compared to the non-immunized group on day 65 after tumour cell challenge.
Conclusions: The ΔAFPODCsignal is fast degrading protein that provokes immune response resulting in retardation of tumour growth in vaccinated animals. We considered pΔAFPODCsignal a promising candidate vaccine against HCC.

1255 POSTER

Outcomes in Patients 70 Years and Older Enrolled in Phase I Studies at Vall D'Hebron University Hospital

R. Morales Barrera[1], O. Castillo-Fernández[2], I. Braña[1], R. Dienstmann[1], J. Cortes[1], E. Felip[1], J.M. Del Campo[1], J. Carles[1], J. Rodon[1], J. Tabernero[1]. *[1]Vall d' Hebron University Hospital, Medical Oncology, Barcelona, Spain; [2]National Oncology Institute, Medical Oncology, Panama, Panama*

Background: Patients aged ⩾70 years are generally underrepresented in cancer clinical trials and little is known about outcomes in this population in phase I trials.
Methods: Data were collected from 246 eligible patients treated in Phase I trials with multiple agents between 2005 and 2007. We compared results between two subgroups: pts <70 years (n = 97) and pts ⩾70 years (n = 49) using Fisher, Mann-Whitney U, Kaplan Meier and log rank tests.
Results: Median age was 61.7 years. 20% patients were ⩾70 years. There were no differences in baseline and treatments characteristics between both groups (gender, ECOG PS, previous treatment lines, metastatic sites, Royal Mardsen Hospital Prognostic Score Index, time to diagnosis of advanced disease and phase I trial enrolment, treatment duration, type of trial − single agent or combination). Toxicity was the main reason for discontinuation of treatment in 6% of patients ⩾70 years versus 8.6% the younger patients (p = 0.40). Partial response/stable disease as best response was 47% in <70 years and 51% en ⩾70 years (p = 0.39). Median survival in elderly patients was 34.9 weeks (CI 14.3–53.4) and in younger patients was 40.4 weeks (CI 31.0–49.7) log rank test=0.13. Analysis of the elderly patient cohort found that those that had received more than three previous lines of therapy (HR 2.0, 95% CI 1.11–3.74), had lung metastasis (HR 1.89 95% CI 1.03–3.48), and high white blood cell count (⩾10,500/mm$^{3)}$ (HR 3.7 95% CI 1.36–10.15) were associated with worse outcome.
Conclusion: Elderly patients suitable for Phase I studies have similar outcomes as compared to younger patients. Age by itself should not be an absolute contraindication to enrol patients in Phase I trials.

1256 POSTER

Evaluation of Enrollment in Oncology Phase I Clinical Trials

A.J. van der Biessen[1], M.A. Cranendonk[1], B. van der Holt[2], J. Verweij[1], M.J.A. de Jonge[1], R.H.J. Mathijssen[1]. *[1]Erasmus MC University Hospital, Medical Oncology, Rotterdam, [2]Erasmus MC University Hospital, Trials and Statistics, Rotterdam, The Netherlands*

Background: Trial participation of cancer patients (pts) lacking standard treatment options is crucial for the development of new anti-cancer drugs. The main reasons to participate are hope for remission or even cure. The aim of this study was to increase insights into motives and other variables influencing pts to participate in phase I oncology trials.
Methods: Over 2 years, all pts with advanced solid tumours, referred to our outpatient clinic to be informed about phase I trials, were included. Pts were seen by a staff-physician or nurse practitioner during a 40-min intake and if applicable, they received written information about a phase I study. During (a) successive visit(s), patient and physician decided if he/she was or was not willing and able to participate. In our evaluation, we included the following variables: ways of referral, distance from residence to hospital, tumour type, time since primary diagnosis, number of prior treatments (both regular and experimental), WHO performance status at visits, age, gender, and marital status. In addition, specific reasons for refusing informed consent were scored. Data were first compared between patients who did, or did not, give informed consent to participate in a trial. Next, the same analyses were performed, restricted to patients who gave informed consent, and data were compared between patients who actually did or did not start phase I treatment.
Results: Between Oct 2008 and Dec 2010, a total of 366 pts (189 men, 177 women) were evaluated, with a median age of 59 years (range, 18−78), and median WHO performance of 1. Most tumours originated from the GI tract (45%). Of all pts 71% was treated before, with a median of 2 treatment lines (range, 1−7). Informed consent was not signed by 146 pts (40%) of which 54% refused mostly because of disappointing expectations of the treatment, and fear for side effects/condition. Patients already treated with multiple lines gave informed consent more often than others (P < 0.001). After signing informed consent another 10% was not eligible according to protocol criteria and 7% due to clinical deterioration. Finally 43% participated in a phase I trial.
Conclusion: Despite specific referral to our hospital, more than half of all pts that were informed about a phase I trial finally did not participate. Reasons for both participating and not participating were quite diverse. Possibly, enrollment can be increased by referral to a dedicated and experienced trial-team.

1257 POSTER

Phase I Safety and Tolerability Study of Olaparib (AZD2281) in Combination With Liposomal Doxorubicin (PLD) in Patients With Advanced Metastatic Solid Tumours

C. Sessa[1], R. von Moos[2], T. Digena[1], G. Del Conte[3], L. Viganò[3], E. Gallerani[1], R. Cathomas[2], A. Fasolo[3], D. Schneider[4], L. Gianni[3]. *[1]Oncology Institute of Southern Switzerland, Bellinzona, [2]Kantonsspital Graubünden, Chur, Switzerland; [3]San Raffaele Institute, Department of Medical Oncology, Milan, Italy; [4]AstraZeneca AG, Zug, Switzerland*

Background: Olaparib (O) is an orally active PARP inhibitor shown to be an active and well-tolerated monotherapy in patients with *BRCA*-mutated ovarian and breast cancer.
Methods: Phase I, open-label, ascending (3+3 design) dose cohort study evaluating the safety and tolerability of O combined with PLD (ClinicalTrials.gov NCT00819221). Patients (Pts) with advanced metastatic solid tumours received oral O bid in combination with PLD (40 mg/m^2 IV every 28 days). O 50 mg (for 7 days) was assessed followed by parallel