intravenous administration of 28 mg ^{14}C-labelled sagopilone (14 kBq) over a period of 30 min. Pts who appeared to tolerate treatment and to have a clinical benefit were offered further treatment courses with unlabelled sagopilone.
Results: The disposition of sagopilone appears to be multi-exponential, with very rapidly decreasing plasma concentrations after the end of infusion, a high clearcance (83.4 L/h), a high volume of distribution (Vss 4739 L) and a long terminal half-life (68.1 h). The systemic exposure to metabolites was high since parent compound represented only about 5% of the AUC of total radioactivity. Biotransformation of sagopilone was found to be the preferred elimination pathway. Total radioactivity (sagopilone and metabolites) was excreted predominantly in feces, and 11.2% was excreted renally. The bulk of the dose was recovered within a week; by 14 days after administration, 73.5% of the radioactivity had been excreted.
Four pts died during the study because of progression of disease. Ten serious adverse events (SAEs) were reported for three pts; (9 SAEs considered unrelated, 1 SAE (dysphagia) considered unlikely related to study treatment). Most frequent adverse event (AE) was paraesthesia (16 AEs in 5 pts). Responses were measured according to RECIST, one pt obtained a complete (bile duct carcinoma) and one a partial response (rectal cancer).
Conclusions: Sagopilone shows a fast biotransformation and an extensive extravascular distribution. Its long terminal half-life may be attributed to the slow redistribution from tissues. Total radioactivity was excreted predominantly in feces. Tolerability and efficacy are in line with results from clinical trials reported previously.

1242 POSTER

Cediranib in combination with mFOLFOX6: results from the cohort expansion phase of a two-part Phase I study

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Background: Cediranib (RECENTIN™) is a highly potent and selective oral VEGF signaling inhibitor. Recent trials have shown that combining a VEGF signaling inhibitor with chemotherapy provides clinical benefit in patients with advanced cancers. In part 1 of this two-part study (study codes NCT00502567; 2171IL/0008), cediranib was evaluated with various chemotherapy regimens, including mFOLFOX6 (Shields AF *et al. J Clin Oncol* 2007;25(18S):abst 3544). Here we report results of an expansion cohort of patients treated with cediranib and mFOLFOX6 from part 2 of the study.
Materials and Methods: Cediranib 30 mg was given once daily with mFOLFOX6 every 2 weeks, at four centers in the USA. The primary objective was to determine the safety and tolerability of cediranib in combination with mFOLFOX6. A preliminary evaluation of efficacy (RECIST) was a secondary objective.
Results: In total, 47 patients received treatment. The most common primary tumor types were colorectal cancer (CRC) and pancreas (both n = 11), and biliary tract (n = 7). The mean (range) number of prior therapies was 1.7 (0–7). No unexpected adverse events (AEs) were observed, and the tolerability of cediranib with mFOLFOX6 was consistent with the known safety profiles for the individual treatments. The most common AEs irrespective of causality were fatigue (n = 35), diarrhea (n = 33), nausea (n = 32) and peripheral neuropathy (n = 31). Hypertension (n = 11, grade 3)/fatigue (n = 5, all grade 3) and neutropenia (n = 7, grade 3; n = 5, grade 4)/fatigue (n = 6, all grade 3) were the most common CTC grade $\geqslant$3 cediranib- and mFOLFOX6-related AEs, respectively. All hypertension AEs were considered manageable and none has led to permanent discontinuation of study treatment. The majority (75%) of patients had a dose reduction/pause. Of the 44 patients evaluable for efficacy, five (11%) experienced a best response of partial response; stable disease was observed in a further 23 (52%) patients. The overall median progression-free survival was 6.9 months (95% confidence interval: 4.7, 8.8).
Conclusions: In this group of heavily pretreated patients, combination treatment with cediranib 30 mg and mFOLFOX6 demonstrated encouraging preliminary evidence of antitumor activity with manageable AEs. Cediranib 20 mg in combination with FOLFOX/XELOX is currently in Phase III development in first-line CRC.

1243 POSTER

Phase I dose-escalation study of continuous oral treatment with the angiokinase inhibitor BIBF 1120 in patients with advanced solid tumors

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Background: BIBF 1120 (Vargatef™*) is a potent, orally available tyrosine kinase inhibitor (vascular endothelial growth factor receptor 1/2/3, platelet-derived growth factor receptor α/β and fibroblast growth factor receptor 1/3) that suppress tumor growth by angiogenesis inhibition.
Method: This study was designed to determine the safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics (PK) and preliminary efficacy of BIBF 1120 in advanced solid tumors. BIBF 1120 (150–250 mg) was given orally twice-daily by continuous 4-week dosing in one cycle.
Results: Twenty-one patients (11 males, 10 females, median age 62 years, range 41–81, ECOG performance status of 0–1) were treated at doses of 150 mg bid (n = 3), 200 mg bid (n = 12) and 250 mg bid (n = 6). Dose-limiting toxicities (DLTs) of reversible Grade 3/4 elevated liver enzymes occurred in three out of 12 patients at 200 mg bid and three out of six patients at 250 mg bid; 200 mg bid was determined as the MTD. Most of the reported adverse events were of CTC Grade 1 or 2 gastrointestinal disorders (e.g. diarrhea, abdominal pain, nausea and vomiting) which were seen in 85.7% of patients. No treatment-related deaths were reported. Best overall response was stable disease, seen in 16 (76.2%) patients, and median progression-free survival was 113 days (95% CI: 77–119 days). At the MTD of BIBF 1120, maximum plasma concentrations (C_{max}) of BIBF 1120 were reached at approximately 3 hours after dosing (range 1.98–4.00 hours); gMean C_{max} and $C_{max,ss}$ = 52.0 and 67.6 ng/mL. The gMean exposure (AUC_{0-24} and $AUC_{0-24,ss}$) to BIBF 1120 was 312 and 595 ng·h/mL. The gMean exposure (AUC_{0-12} and $AUC_{0-12,ss}$) to BIBF 1120 was 233 and 423 ng·h/mL; $t_{1/2} \approx$ 10.2–19.9 hours. The gMean values of accumulation ratios were 1.2–1.7. Pharmacokinetic analysis indicated that BIBF 1120 steady state was reached after 8 days of bid dosing, and C_{max} and AUC increased with increased dose within the dose range tested.
Conclusion: BIBF 1120 at 200 mg bid continuous dosing was well tolerated and appeared to provide some clinical benefit, and is therefore considered the recommended dose for continuous daily treatment for patients with advanced solid tumors. An international, randomized, placebo-controlled Phase III trial program, LUME-Lung, of BIBF 1120 in combination with standard 2nd-line NSCLC therapies is now recruiting patients.
*Trade name not FDA approved.

1244 POSTER

The pharmacokinetic effect of the specific ETA receptor antagonist zibotentan (ZD4054) on CYP3A4 activity using midazolam as a probe in healthy male volunteers

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Background: Zibotentan (ZD4054) is a small-molecule, ET_A-receptor specific antagonist being investigated for the treatment of hormone-resistant prostate cancer. In this study, the known CYP3A4 substrate midazolam was used as a probe to evaluate the potential of zibotentan to inhibit the CYP3A4 metabolic pathway.
Methods: This was an open-label, randomized, single centre, two-period, crossover trial in healthy male volunteers. Subjects were randomized 1:1 to receive the following sequence or its opposite: 7 days' once-daily oral zibotentan 10 mg with a single oral dose of midazolam 7.5 mg on day 6; $\geqslant$7 days' washout; a single oral dose of midazolam 7.5 mg. Blood samples for midazolam pharmacokinetics (PK) were collected pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 and 30 hours post midazolam dose. Results of AUC and C_{max} were expressed as the ratio of geometric least square means (GLSMean) and 90% confidence intervals (CI) for midazolam + zibotentan:midazolam alone. An interaction between zibotentan and midazolam was predefined to have occurred if the upper 90% CI was greater than 1.5.
Results: A total of 12 subjects participated (mean age 49 years, range 32–59), with six subjects in each sequence cohort. All subjects completed the study and results from all subjects are included in the analysis. Steady-state levels of zibotentan were achieved over 7 days. Steady-state zibotentan

increased midazolam AUC by 1.2 fold compared with midazolam alone (Table). The upper limits of the 90% CIs for the AUC and C_{max} ratios were below 1.5, indicating no clinically relevant effect on midazolam exposure according to the predefined criteria. Zibotentan had no marked effect on the PK of 1-hydroxy and 4-hydroxy midazolam. Tolerability was as expected, with fatigue and headache being the most common adverse events associated with midazolam and zibotentan treatment, respectively.

Parameter	GLSMean		Ratio (90% CI)
	Midazolam + zibotentan	Midazolam	
AUC, ng×h/ml	109.5	91.5	1.20 (1.05–1.37)
AUC_{0-t}, ng×h/ml	107.9	89.8	1.20 (1.05–1.38)
C_{max}, ng/ml	39.4	37.5	1.05 (0.84–1.32)

Conclusion: These results indicate that zibotentan 10 mg once daily has no clinically relevant potential to inhibit CYP3A4.
Trial sponsored by AstraZeneca (AZ code D4320C00010).

1245 POSTER

Zoledronic acid and Taxotere (ZANTE) metronomic and sequential administration in patients with hormone refractory prostate cancer (HRPC) – final results of phase I study

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Background: Docetaxel (DTX) is an active agent for HRPC. Zoledronic acid (ZOL) has demonstrated efficacy in the treatment of bone metastases in patients with prostate cancer. In vitro data suggest that ZOL and DTX have a synergistic effect on growth inhibition of prostate cancer cells and that such synergism is sequence-dependent. On the basis of these considerations, a phase I clinical trial of ZOL and DTX administered in 2 different sequences was conducted in HRPC.
Patients and Methods: Inclusion criteria were: HRPC, bone metastases, ECOG PS 0−2, no previous chemotherapy, adequate organ function, written informed consent. Cohorts of three to six patients were sequentially enrolled to receive one of three escalated doses of docetaxel (30, 40 and 50 mg/m^2) in combination with a fixed dose of ZOL (2 mg), both administered every 14 days in two different sequences. Sequence A: DTX at the day 1 followed by ZOL at the day 2. Sequence B: ZOL at the day 1 followed by DTX at the day 2. DLT was defined as the occurrence during the first 3 cycles (6 weeks) of therapy of febrile or long lasting G4 neutropenia, G3−4 thrombocytopenia, G3−4 non hematologic toxicity (except nausea and vomiting), any toxicity inducing a delay of treatment longer than 2 weeks. Angiogenic factors, cytokines and T lymphocyte subpopulation distribution were evaluated prior and after treatment.
Results: The study enrolled 22 patients (median age 73 years; range 43−80). The MTD was not achieved with sequence A. Two patients at third level of sequence B developed DLT that consisted of G3 thromboflebitis and cardiac ischemia. A reduction ⩾50% of PSA levels was observed in four patients (levels 2A and 3A). Angiogenic factors, cytokines and T lymphocyte subpopulation distribution were evaluated in 19/22 patients. Data will be reported at the congress.
Conclusions: The recommended dose of docetaxel was 40 mg/m^2 for sequence ZOL → DTX and 50 mg/m^2 for sequence DTX → ZOL.

1246 POSTER

Oral oncology drugs: how do patients view their effectiveness?

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Background: While standard chemotherapeutic agents are usually administered intravenously, the growing number of oral agents is progressively gaining prominence. Many possess new mechanisms of action and specific targets that result in different adverse effect profiles from those associated with traditional chemotherapies. Oral administration of chemotherapy (CT) offers considerable advantages over the parenteral route. This study sets out to analyze patient opinion on different aspects of oral and intravenous (IV) treatment.
Material and Methods: This prospective study was carried out by means of a survey of patients to compare differences in preference, tolerance, effectiveness and security between oral and IV chemotherapy. 190 patients who had received both treatments were enrolled from September to November 2008.
Results: Seventy percent of the patients were women and the median age at diagnosis was 60 years (range, 28 to 91 years). Fifty percent had gynaecological tumours (mainly breast cancer); thirty percent, digestive tumours; eighteen percent, lung cancer and two percent, other neoplasm, with a median of 3 different CT schemes received (range, 1 to 9).
Patients preferred the oral route to the IV route (76% vs. 20% respectively; $P < 0.001$). Four percent had no preference. Tolerance was better with oral therapy (64%) than with IV chemotherapy (36%; $P < 0.001$) and became lower as the number of treatment cycles increased. With respect to effectiveness, sixty percent of patients considered the IV chemotherapy more effective, while eleven percent chose oral therapy and twenty nine percent found both equally effective ($p < 0.001$). Sixty one percent of patients felt more secure receiving intravenous CT, while eight percent felt more secure with oral therapy. Thirty one percent felt that there were no differences between the two routes of administration ($p < 0.001$).
Conclusions: Oral agents open up new possibilities with respect to convenience and patient satisfaction. Nonetheless, some aspects of the use of oral CT need to be examined. This study shows better tolerance of oral administration and a patient preference for oral therapy. However, when asked about important issues such as the effectiveness or security offered by the different treatment types, most patients expressed a preference for the IV route, irrespective of tolerance.

1247 POSTER

Phase I study of nimotuzumab, a humanized anti-epidermal growth factor receptor (EGFR) IgG1 monoclonal antibody in Japanese patients with solid tumors

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Background: Nimotuzumab is a humanized IgG1 monoclonal antibody to epidermal growth factor receptor (EGFR). The antibody has demonstrated absence of severe skin toxicity commonly caused by other EGFR-targeting antibodies. The primary objective of this phase I open-label dose escalation study was to evaluate safety of nimotuzumab in Japanese patients with solid tumors. Secondary endpoints included tumor response and human antibody against nimotuzumab (HAHA), and pharmacokinetics (PK), pharmacodynamics (PD) and biomarker.
Methods: Thirteen patients with advanced solid tumors who had failed in prior standard therapies were enrolled in two centers. Nimotuzumab was given intravenously weekly at the dose levels of 100, 200 and 400 mg/body. Skin biopsies and serum samples were collected for PD analysis before treatment and after fourth infusion. For biomarker analysis, blood and formalin fixed and paraffin embedded tumor samples before treatment were collected
Results: Twelve patients were treated except 1 patient who received other therapy. Median treatment cycle (4 weeks per cycle) was 4 (range 1−10) in these 12 patients. Neither dose limiting toxicity nor grade 3 drug-related adverse events including infusion reaction were observed, and maximum tolerated dose was not reached. Common drug-related adverse events were grade 1 or 2 skin rash (58%), which were localized and did not show relation to the dose levels. No HAHA appeared during the whole treatment course. AUC_{0-inf}, C_{max} and $t_{1/2}$ increased and the clearance decreased in a dose dependent manner. While neither complete nor partial response was obtained, 8 patients (67%) showed stable disease (⩾4 weeks). Median time to progression (TTP) was 14 weeks. Among 8 patients whose pre-treatment tumor samples were obtained, 5 patients with amplified gene copy number of EGFR showed longer TTP than the other 3 patients.
Conclusions: Nimotuzumab was well tolerated up to 400 mg/body weekly in Japanese patients with advanced solid tumors. Additional biomarker analysis is currently ongoing.