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