expression of endothelial markers, and the loss of tube-like formation ability. These effects were observed even with low dose of ZOL (1uM), but could be restored by co-treatment with GGOH. On the other hand, treatment of putative EPCs with ZOL at higher doses (>10uM) resulted apoptosis induction, as confirmed by annexinV/PI staining.
Conclusion: ZOL inhibited the differentiation of EPCs from PBMC, in a dose-dependent manner, the effect being observed even at low levels. Treatment with higher doses of ZOL resulted in apoptotic death of putative EPCs. Since GGOH could restore the inhibitory effect of ZOL on EPC differentiation, the effect of ZOL was speculated to be dependent on the inhibition of prenylation of small-G-proteins. From the present findings, we concluded that ZOL should be a potential anti-cancer agent, by inhibiting important steps of the angiogenic process.

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Antitumor activity and pharmacokinetics of a novel PEGylated irinotecan in irinotecan-resistant colorectal tumours implanted in mice

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NKTR-102, a novel PEG-Irinotecan conjugate, is currently in Phase I clinical development. Nonclinical studies examined the antitumor activity and pharmacokinetics in a mouse HT29 colorectal tumor model, which is moderately resistant to irinotecan treatment.
Intravenous administration of NKTR-102 at 40, 60 or 90 mg/kg (irinotecan equivalent dose) on days 1, 4 and 8 to tumor-bearing mice caused marked, statistically significant dose-related decreases in HT29 tumor growth (relative to saline control) that persisted until termination on day 60. Intravenous irinotecan at the same doses resulted in only modest suppression of tumor growth that was short lived and not statistically different from saline control. Tumor growth delay after NKTR-102 was significantly longer than that after irinotecan at all 3 dose levels ($p < 0.001$). Tumor regression was observed after NKTR-102 at 90 mg/kg, but not after irinotecan at any dose level.
A 40 mg/kg IV administration of NKTR-102 on days 1, 4 and 8 resulted in prolonged plasma and tumor exposure to active metabolites irinotecan and SN38 that correlated with marked suppression of tumor growth. Mean Tumor SN38 Cmax of 1100 ng/g occurred on day 15, and tumor SN38 concentration was maintained above 100 ng/g observed at termination on day 60. Apparent t1/2 values for SN38 in plasma and tumor after the first dose of NKTR-102 were 17 and 15 days, respectively, whereas, SN38 t1/2 values after 40 mg/kg irinotecan were in the expected range of 2−4 hr. SN38 AUC values in plasma and tumor after the first dose of NKTR-102 were 531- and 366-fold greater, respectively, than those after irinotecan dosing. Subsequent doses of NKTR-102 on days 4 and 8 resulted in even greater SN38 exposure relative to irinotecan dosing, resulting from accumulation in both plasma and tumor.
In summary, NKTR-102 resulted in marked, prolonged growth suppression of HT-29 tumor, which is otherwise modestly resistant to irinotecan. Pharmacokinetic results indicate that this suppression results from prolonged systemic and tumor SN38 exposure resulting from slow disposition and metabolism of NKTR-102.

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A phase I dose-escalation study of RAD001 administered daily to Japanese patients with advanced solid tumors

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Background: RAD001 (everolimus) is an oral rapamycin derivative targeting mTOR (mammalian target of rapamycin), a key downstream serine-threonine kinase in the PI3K/AKT/mTOR pathway regulating protein synthesis and ultimately cell growth, proliferation, and survival. 10 mg is considered safe and tolerable in Western pts; this is the first study conducted in Japan.
Methods: Pts with relapsed/refractory advanced solid tumors were treated at doses of 2.5, 5.0, and 10.0 mg qd. The primary objective was to confirm the tolerability of and assess the safety profile of single agent RAD001 in Japanese pts. Secondary objectives were to assess pharmacokinetics, inhibition of tumor p70 ^{S6K} activity, and preliminary anti-tumor activity.
Results: 9 (4M and 5F) pts with a median age of 64 y (range: 49−74) were treated, 3 at each dose level. No DLT has been observed and the drug has been generally well tolerated. The most frequently observed adverse events (in $\geqslant$2 pts) were thrombocytopenia, anorexia, rash, weight decrease, abdominal pain, diarrhea, fatigue, leucopenia, mucosal inflammation, nasopharyngitis, nausea, stomatitis. One pt developed grade 2 interstitial pulmonary disease. One PR was observed in a pt with esophageal CA (10 mg); this pt's response involved rapid regression of disease surrounding the major subclavicular vessels, which ultimately caused hemorrhage and death. Another pt with gastric CA (10 mg) having a response of PR at one assessment before progression of disease; One pt with colon CA (5 mg) had SD for $\geqslant$4 months by RECIST. Dose-exposure relationship in Japanese pts were similar to Western pts. Inhibition of p-S6K and p-Akt was achieved at the initial dose of 2.5 mg. A dose of 10 mg was selected for further development.
Conclusions: 10 mg qd of RAD001 is safe and generally well tolerated in Japanese pts with advanced solid tumors. RAD001 demonstrated pharmacodynamic and preliminary clinical activity. Further development is ongoing.

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Metabolism of [^{14}C]-ZD4054 in healthy volunteers

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Background: ZD4054 is a specific endothelin A receptor antagonist being developed for the treatment of cancer.
Patients and Methods: The metabolism, excretion, and pharmacokinetics of ZD4054 were studied following administration of a single oral dose of [^{14}C]-ZD4054 (15 mg, 90 μCi) to six healthy volunteers (three female; three male) aged 52–65 years.
Results: The total recovery of radioactivity over 5 days was high (mean 93.4$\pm$7.3%; range 80.6–99.0%), with 78% recovered within 24 hours. Most of the dose was eliminated in the urine (71–94%), in which the main component was unchanged ZD4054 (35–77% of the dose; mean 58%). Several metabolites were identified in the urine. Excretion into the feces accounted for 5–19% of the dose, and comprised a number of minor metabolites with little unchanged ZD4054. The concentrations of radioactivity in whole blood were generally lower than those in plasma (geometric mean blood:plasma ratio ranged from 0.67 at 2 hours after dosing to 0.75 at 24 hours), suggesting limited association of drug-related material with blood cells. Concentrations of ZD4054 and radioactivity in plasma were similar up to 12 hours post dose, indicating the absence of circulating metabolites, and diverged thereafter as radiolabeled metabolites appeared in the plasma. ZD4054 was the major radiolabeled plasma component over 24 hours (75–86% of plasma radioactivity), with one detectable metabolite accounting for 4% of plasma radioactivity. No other metabolites were detected in plasma over 24 hours. Results were similar for male and female subjects. The single oral dose of [^{14}C]-ZD4054 was well tolerated in these healthy volunteers aged >50 years; no adverse events (AEs) were serious or greater than CTC grade 2. Headache (five subjects) and nausea (two subjects) were the only AEs that occurred in more than one subject.
Conclusions: These results show that ZD4054 is predominantly eliminated unchanged in the urine and that concentrations of circulating metabolites are low.

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A multicenter phase I study of a novel nucleoside analogue, CP-4126, in patients with advanced solid tumours – preliminary results

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Background: CP-4126 (gemcitabine 5′-elaidic acid ester) is a novel optimized nucleoside analogue with a broad spectrum of preclinical antitumour activity. The intracellular uptake of CP-4126 is independent of nucleoside transporters and its antitumour activity is less affected by multidrug resistance than gemcitabine. The study aims to determine the maximum tolerated dose (MTD) and the recommended dose of CP-4126, to establish its safety profile and pharmacokinetic parameters (PK) characteristics, and to preliminary assess the antitumour activity.
Materials & Methods: 15 to 25 patients (pts) with confirmed solid tumour diagnosis are to be accrued in this dose escalation study [1 to 6 pts per dose level (DL)]. CP-4126 is administered on days (d) 1, 8 and 15 every 4 week (q4w) by a 30-min infusion. Dosing started at 30 mg/m^2/d and the dose is to increase with a 100% escalation factor until CTCAE toxicity