> grade 2 occurs. From this DL, the dose will increase with 66%, 50%, 33% and 25% successively. Standard haematological, biological and clinical dose limiting toxicity (DLT) definitions are used. Activity is assessed at the end of every 2nd cycle (cy). PK is determined at d 1 of cy 1.
Results: 11 pts with solid tumours have been included (4 colorectal, 2 hepatocarcinoma and one each of NSCLC, cholangiocarcinoma, leiomyosarcoma, malignant melanoma, pancreas) with 1 pt/DL from 30 to 240 mg/m^2/d. One grade 2 adverse event (AE), neutropenia, was reported at 480 mg/m^2/d. A total of 4 patients were included at this DL. Accrual is ongoing at 800 mg/m^2/d (DL6). One DLT is reported at 800 mg/m^2/d; d 8 treatment postponed with more than 2 weeks due to reduction in Hb and platelets (CTCAE grade 3) after d 1 treatment. A total of 18 cycles (1 to 4/pt) of treatment have been administered. The main treatment-related AEs have been nausea and vomiting. No significant unexpected AEs occurred. Seven pts have been withdrawn: five due to progressive disease, one due to performance status, and one due to prolonged myelosuppression (DLT). Four pts are ongoing: one with stable disease after 3 cy (at 480 mg/m^2/d).
Conclusions: MTD is not reached. No unexpected AEs have occurred. CP-4126 is well tolerated by pts with solid tumours up to 800 mg/m^2/d in a d1, 8, 15 q4w schedule. Accrual is ongoing. Updated results including PK will be presented.

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Antitumor activity and reversal of multidrug resistance by the newly synthesised oleanolic acid derivative – methyl-3,11-dioxoolean-12-en-28-oate

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The aim of this study was to compare the cytotoxic effect of the newly synthesised oleanolic acid-derivative methyl 3,11-dioxoolean-12-en-28-oate (BB.136) in tumor and normal cells with its parent compound oleanolic acid. We also investigated the ability of the compound to reverse multidrug resistance, inhibit P-gp activity, arrest the cell cycle and to induce apoptosis. We used 7 cancer cell lines (MCF7, MCF7/ADR, HL-60, HL-60/AR, CCRF-CEM and CCRF-VCR1000) and one normal cell line (MCF10A). The growth inhibitory activity of BB.136 was assessed using MTT and SRB assays. Cell cycle analysis and induction of apoptosis were determined with propidium iodide.
We observed stronger cytotoxic activity of BB.136 comparing to the control compound oleanolic acid. The antiproliferative efficiency of the tested compound was similar in MCF7 and its resistant subline MCF7/ADR. The IC_{50} values were 4.53 μM and 3.77 μM, respectively (oleanolic acid: 5.38 μM and 37.02 μM). A similar result was obtained in CCRF-CEM and multidrug resistant CCRF-VCR1000 cells. It suggests that MDR1 expressing cells are not resistant to the tested oleanolic acid derivative. The most sensitive of the tumor cell lines to BB.136 were CCRF-CEM and CCRF-VCR1000 (IC_{50} 1.69 μM and 1.56 μM, respectively). MCF10A cells were more resistant (IC_{50} 18.36 μM) to BB.136 than the cancer cells. Additionally the tested compound enhanced the activity of Adriamycin in CCRF-VCR1000 cells, indicating a reversal of resistance. Flow cytometer analysis showed that treatment of HL-60 cells with a 4-fold IC_{50} concentration of the tested compound for 48 hours induced apoptosis in 36.2% of cells.
BB.136 is more potent than the parent compound and is able to induce apoptosis in HL-60 cell. Its lower cytotoxic activity against normal cells and its multidrug resistance reversing ability indicates that it is an interesting compound for further development.

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PEGylation governs the disposition and metabolism of irinotecan following administration of a novel PEG–Irinotecan conjugate

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NKTR-102, a novel PEG-Irinotecan conjugate, is currently in Phase I clinical development. PEGylation dominated the disposition kinetics of NKTR-102 as demonstrated in rat studies where the plasma kinetics of NKTR-102 mimicked that of the 14C-PEG itself used in NKTR-102.
PEGylation of irinotecan enhanced the pharmacokinetic and pharmacodynamic behavior of the active metabolite SN38. Prolonged systemic SN38 exposure resulted in slow disposition and metabolism of NKTR-102. Intravenous administration of 260 mg/kg of 14C-PEG to rats resulted in distribution primarily within the circulatory system. The main route of excretion of the 14C-PEG was via urine where 61.1% of the administered radioactivity was recovered over ten days. Fecal excretion and other elimination routes accounted for 22.7% of the administered radioactivity over the same period.
Intravenous administration of either the 14C-PEG alone or NKTR-102 showed prolonged plasma exposure. At equivalent doses, the plasma clearances of the 14C-PEG alone or NKTR-102 were similarly small, 2.5 mL/hr·kg and 9−30 mL/hr·kg, respectively. In contrast, plasma clearance of irinotecan following irinotecan administration was 2320 mL/hr·kg, 100–300 times greater than that following NKTR-102 administration. Unlike NKTR-102, irinotecan distributed extensively in the tissue compartment and minimally in the plasma compartment.
In the rat, NKTR-102 volume of distribution was comparable to the vascular compartment volume, which contributed to the observed high plasma exposure of NKTR-102. These results, combined with a lower clearance of SN38 derived from NKTR-102, resulted in notably greater exposure to SN38.
In summary, the PEG component of NKTR-102 dominated its disposition kinetics, resulting in greater and sustained systemic exposure to irinotecan and SN38.

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Differential inhibitory effects of epigallocatechin-3-gallate (EGCG) and C75 in cancer fatty acid metabolism

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Background: Endogenous fatty acid metabolism is crucial to maintain the cancer cell malignant phenotype. Lipogenesis is regulated by the enzyme fatty acid synthase (FASN); and fatty acid oxidation pathway is regulated by carnitine palmitoyltransferase-1 (CPT-1). Inhibition of FASN has been shown to induce apoptosis in a variety of cancer cells, and consequently to be a potential therapeutic target for the treatment of cancer. To date, only a few inhibitors of FASN have been reported (cerulenin, C75, EGCG, orlistat, triclosan), although the degree of specificity of this inhibition has not been addressed.
Material and Methods: We have evaluated the effects of C75 and (−)-epigallocatechin-3-gallate (EGCG) on fatty acid metabolism pathways (FASN and CPT-1 activities), cellular proliferation, induction of apoptosis and cell signalling (HER2, ERK1/2 and AKT cascades) in breast cancer cells and the effect of reduced FASN activity on adipocyte differentiation of 3T3-L1 cells.
Results: C75 and EGCG had comparable effects in blocking FASN activity. Treating cancer cells with C75 or EGCG induced apoptosis and caused a decrease in the active forms of oncoprotein HER2, AKT and ERK1/2 to a similar degree. In addition, C75 and EGCG reduced dramatically visible lipid droplet accumulation during preadypocite differentiation. We observed, in contrast, marked differential effects between C75 and EGCG on fatty acid oxidation pathway. While EGCG had either no effect or a moderate reduction in CPT-1 activity, C75 stimulated CPT-1 activity (up to 129%), even in presence of inhibitory levels of malonyl-CoA, a potent inhibitor of the CPT-1 enzyme.
Conclusions: In cancer cells, pharmacological inhibition of FASN occurs uncoupled from the stimulation of CPT-1 with EGCG but not with C75, suggesting that EGCG might be free of the CPT-I related in vivo weight-loss that has been associated with C75. Our results establish EGCG as a potent and specific natural inhibitor of fatty acid synthesis (FASN), which may hold promise as a target-directed anticaner drug.

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Safety, maximum tolerated dose and pharmacokinetics of a novel micellar formulation of paclitaxel in the treatment of recurrent solid tumours – a phase I/II study

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Background: Paclitaxel (Taxol®) treatment requires extensive premedication, slow infusion (3−24 h) and a close monitoring mainly due to effects caused by the solvent castor oil (Cremophor EL®). Paclitaxel,