molecules of paclitaxel. In contrast to free paclitaxel, which is normally prevented from reaching the brain by the Pgp efflux pump, ANG1005 is efficiently transported across the BBB, with approx. 100 fold higher transport rate compared to free paclitaxel and 10 fold higher transport rate than Temozolomide measured using in-situ brain perfusion in rats. In addition, ANG1005 is homogenously distributed in rat brains. ANG1005 was detected by LC-MS-MS in both normal brain and brain tumors in mice 30 minutes after i.v. injection; detected brain levels of 2.1 μM are above the therapeutic concentrations of paclitaxel. The effect of ANG1005 was evaluated on glioblastoma (U87) xenograft tumor growth in immune deficient mice and resulted in a significant increase of survival of mice treated with ANG1005 of 27%. In a rat glioblastoma (U87) brain orthotopic model, administration of ANG1005 resulted in a shrinking of IC tumors measured by MRI.
Conclusion: The AngioPep peptide vector can be used to transport small drugs to the brain parenchyma for the treatment of brain cancers. ANG1005 is currently under evaluation in two phase 1 clinical trials for the treatment of primary and secondary brain tumors in humans.

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Comparative pharmacokinetic study of abiraterone acetate in a capsule and tablet formulation

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Abiraterone acetate is a novel 17-hydroxylase/c17−20 lyase inhibitor, blocking the conversion of pregnenolone to dehydroepiandrosterone (DHEA) and progesterone to androstenedione, thus inhibiting the production of testosterone and oestrogen precursors. Consistent with the continued androgen signalling in a substantial proportion of castration resistant or hormone refractory prostate cancer patients, this compound has shown impressive decrease in PSA levels associated with significant antitumour activity in Phase I and II studies. The present study was carried out to assess and compare the pharmacokinetic profile of abiraterone following administration of capsules or tablets of abiraterone acetate, under fed (after an experimental high fat-high caloric meal) and fasted conditions, in patients with progressive prostate cancer despite GnRH analogue treatment. The study was two armed (fed or fasted) with patients enrolled in either group 1 (Study Day [SD] 1 capsules, SD 2 tablets) or group 2 (SD 1 tablets, SD 2 capsules) at a dose of 1000 mg abiraterone acetate. Blood samples collected pre-dose and 1, 2, 4, 6, 8, 24, 48, 72 hours post dose were analysed by LCMSMS and pharmacokinetic parameters derived. A 2×2 crossover model was preformed with fixed effects for sequence, formulation and period, and random effect for subject nested within sequence, on AUC(0-t), AUC(0-∞) and Cmax, using capsule formulation as the reference in 27 evaluable patients. The confidence interval for fixed effect was 95%. Our study shows that the 90% confidence intervals for AUC and Cmax are between the 119–293% in fasted state, and in the fed state, 65–141%. The only significant difference in the two formulations was in the Tmax in the fasted state suggesting that the absorption is faster in the capsules compared with the tablets. As previously determined, high fat-high caloric meal significantly increased the exposure to abiraterone.

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The effects of treatment sequencing on the antitumor activity of vandetanib and paclitaxel in a model of ovarian carcinoma xenograft

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Background: We have previously shown (Cesca et al, AACR 2008) that vandetanib (ZACTIMA™), an inhibitor of VEGFR2, EGFR and RET signaling, induced vascular morphological and functional changes in human ovarian carcinoma xenografts grown in nude mice (reduced vessel area, increase in mature vessels and diminished vascular permeability). Furthermore, vandetanib pretreatment reduced tumor uptake of paclitaxel (PTX) at early timepoints after its injection. The purpose of this study was to use this information to guide the schedule of combination treatments.
Materials and Methods: PTX distribution, after continuous or intermittent (five days suspension) vandetanib pre-treatment, was analyzed by HPLC in plasma and tumors at 1 h and 24 h after PTX injection. In parallel tumors, tumor perfusion was assessed by determining Hoechst 33342 content by HPLC. The antitumor activity of combination treatment was examined by giving vandetanib (50 mg/kg/day p.o., five days time course), before or after PTX (20 mg/kg i.v.) in A2780−1A9 tumor bearing mice. Tumor growth was evaluated, and response expressed as the best T/C % and growth delay (T-C), compared with vandetanib alone.
Results: Pretreatment with vandetanib for five days resulted in a 30% decrease in tumor uptake of PTX measured one hour after PTX injection. However, after suspending vandetanib treatment for five days the PTX biodistribution in tumor was similar to that in controls not treated with vandetanib. Diminished H33342 levels in the tumor after vandetanib treatment (20% to 30%) suggested that the decrease in PTX biodistribution was associated with reduced tumor perfusion. The administration of PTX followed by vandetanib resulted in greater antitumor activity (T/C = 18%) compared with the reverse sequence (T/C = 40%). Repeating these treatments for 3 cycles, with five days break between cycles, further increased the growth delay (T-C = 21 days for PTX followed by vandetanib and T-C = 13 days for vandetanib followed by PTX).
Conclusions: These findings indicate that there is an improved antitumor activity of vandetanib plus PTX, compared with either agent alone. The data also suggest that, in this model, the combination of vandetanib and PTX had greater antitumor effects when vandetanib was given after PTX.

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Customized PEG linkers improve tumor delivery of RNA antagonist oligonucleotides

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Background: Locked Nucleic Acid (LNA) antisense oligonucleotides (LNA-ONs) are novel RNA antagonists capable of potently silencing mRNA targets in vitro (at low to sub-nanomolar concentrations) and in vivo. Nevertheless, systemic delivery of LNA-ONs may be further improved if more favorable pharmacokinetic profile, cell penetration, and specific tumor targeting were possible. We describe here the utility of Customized PEG linkers that enhance cellular uptake of LNA-ONs resulting in potent down-modulation of target mRNA in human tumor cells and improved tumor delivery of LNA-ONs in tumor-bearing mice.
Material and Methods: Customized PEG linkers were synthesized by incorporating either cell penetrating peptides (CPP) or folate into the PEG polymers, which were then converted to releasable linkers before being conjugated with anti-survivin or anti-ErbB3 LNA-ONs. Target gene down-modulation by PEG-LNA-ON conjugates was evaluated using Real-Time (RT)-PCR. The PEG conjugates were administered intravenously to tumor-bearing mice to study the biodistribution and target knockdown by hybridization methodology and RT-PCR, respectively.
Results: When CPPs or folate were attached to the PEG-LNA-ON conjugates, marked intracellular delivery of the PEG conjugates was demonstrated by fluorescence microscopy that was comparable to cells transfected with lipofectamine. CPP-PEG-LNA-ON conjugates have shown concentration-dependent and target-specific mRNA down-modulation in a panel of tumor cell lines. In contrast, folate conjugates did not improve down-modulation of the target mRNA in the absence of transfection and are trapped in intracellular vesicles. Both enhanced tumor accumulation of oligonucleotides and improved mRNA down-modulation in human tumor tissue implanted in mice was observed with PEG conjugates compared with naked LNA-ONs.
Conclusions: Customized PEG linkers have improved the in vitro cellular uptake of LNA-ONs. PEG-LNA-ON conjugates with CPP or folate can efficiently enter cancer cell without transfection. However, only CPP-PEG-LNA-ONs have improved knockdown of target mRNA without transfection. Both the enhanced permeation and retention effect and targeted delivery probably promote LNA-ON accumulation and modulation of gene expression in the tumor. Customized PEG linkers may provide a promising approach for more efficient in vivo delivery of oligonucleotides including LNA-ONs and siRNAs.