Results: 52 patients (31 M, 21 F) median age 60 (range 40-77), median ECOG performance status 1 (range 0-1), prior chemotherapy regimens median 2 (range 1-4) have received 152+ treatments (mean 2.9 cycles, range 1-16+), with dose reductions required in 3% of doses. All patients were resistant to platinum and taxanes, 24% resistant to second line docetaxel, and 55% having failed additional 3rd line salvage therapy including gemcitabine (27%), and EGFR inhibitors (20%). No Grade 4 events were reported. Grade 3 events were infrequent. No myelosuppression, thrombocytopenia or cumulative toxicity was seen. Possibly drug-related toxicities were mild (Grade 1-2) fatigue (38%), nausea (38%), and vomiting (22%). At the interim analysis, 41/52 patients were evaluable for efficacy. Disease stabilization was seen in 21/41 (51%). The median duration of stable disease exceeds 39 weeks. Median survival for both 2nd and 3rd and 4th line patients exceeds 10 months, and requires further patient follow-up to reach median survival. The longest duration of TLK286 therapy was one year. Survival at one year requires further patient follow-up.
Conclusions: TLK286 is well tolerated in this heavily pretreated advanced NSCLC population. Efficacy in this heavily treated population that includes 55% 3rd and 4th line patients is encouraging. Median survival exceeds 10 months and has not yet been reached. Future studies of TLK286 in advanced NSCLC are warranted.

Tubulin interacting agents

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The seco-taxane IDN5390 is able to circumvent paclitaxel resistance in drug-resistant cells with overexpression of class III beta-tubulin

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A primary mechanism of drug resistance to taxanes is the overexpression of class III beta-tubulin isotype. The activity of newly developed taxanes has been assessed against a panel of human cancer cell lines showing inherent or acquired drug resistance and overexpression of such isotype and the seco-taxane IDN5390 has been selected. Levels of beta-tubulin isotypes have been determined by RT-PCR in cells treated with paclitaxel, IDN5390 and with their combination. In wt cells, paclitaxel raised the levels of class III beta-tubulin isotype, whereas IDN5390 induced the opposite effect, and combination of both compounds prevented paclitaxel-dependent class III overexpression. In paclitaxel-resistant cells showing high levels of class III beta-tubulin, paclitaxel treatment did not modulate further class III beta-tubulin, while IDN5390 alone or in combination diminished the expression of the class III isotype. Other beta-tubulin isotypes were unaffected by drug treatments. Starting from these findings, we tested the presence of a potential synergism between paclitaxel and IDN5390. Results indicated a synergism, particularly in class III overexpressing cells. Finally, the synergism has been confirmed in paclitaxel-resistant xenografts transplanted in nude mice: a significant activity was noticed in xenografts treated with combination of paclitaxel and IDN5390 (TWI 52%, LCK to 0.8), whereas as single agents paclitaxel and IDN5390 were devoid of relevant effects (TWI of 29 % LCK of 0.2 and TWI 36% and LCK of 0.4 for paclitaxel and IDN5390, respectively). At the end of the study, we assessed the class III beta-tubulin expression in the xenografts and we found that, in keeping with "*in vitro*" findings, paclitaxel induced the overexpression of class III, while IDN5390 did not and, when combined with paclitaxel, it prevented the class III overexpression. Our data indicates that IDN5390 is able to circumvent paclitaxel-resistance in cellular models with overexpression of class III beta-tubulin and that the combination between seco-analogues and paclitaxel could represent a novel strategy to overcome MDR-independent taxane resistance.

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Absence of vascular regrowth at 96hrs in response to the vascular-targeting agent ZD6126 demonstrated by dynamic-contrast enhanced (DCE) MRI

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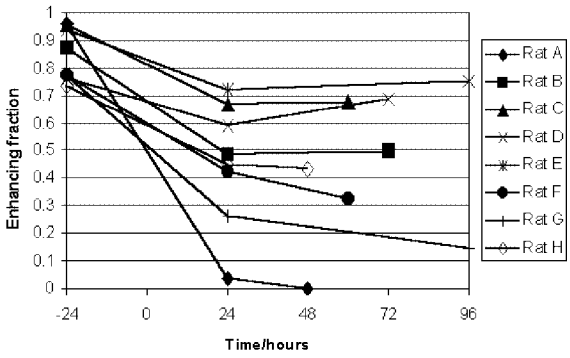
Tumour neovasculature is structurally distinct from normal vasculature and is therefore an attractive therapeutic target. The novel vascular-targeting agent ZD6126 is metabolised to the tubulin-binding agent ZD6126 phenol *in vivo*. Its action leads to the selective disruption of the cytoskeleton of newly divided endothelial cells, occlusion of tumour blood vessels and haemorrhagic tumour necrosis. We have previously shown the antivascular effect of 50 mg/kg ZD6126 on rat GH3 prolactinomas to be profound 24 h after administration [1]. This was consistent with the induction of massive central tumour necrosis with a residual viable rim of tumour cells, a common feature of the response to this agent. Tumour regrowth has been previously shown to occur from this viable rim after treatment with ZD6126 [2]. In this study we used DCE-MRI to assess regrowth of the tumour tissue up to 96 h post-treatment with ZD6126. GH3 prolactinomas were grown in the flanks of 8 Wistar Furth rats. DCE-MRI data were obtained 24 h pre-treatment using a 4.7T Varian Unity Inova. MRI was repeated 24 h post-treatment with 50 mg/kg ZD6126, followed by a final scan at 48, 60, 72 or 96 h post-treatment. Multislice dynamic data were obtained using a spin-echo sequence (TR = 120, TE = 10) for 10 min post gadopentetate injection. The gadopentetate concentration was calculated voxelwise and integrated over the first 10 images to give an IAUC. Tumour data were normalised to the median IAUC of muscle. Tumour IAUC values greater than the muscle median were defined as highly-enhancing. After the final scan tumours were excised and scored for necrosis. Post-treatment, all tumours showed a significant reduction (between 20-80%) in highly-enhancing voxels. Images of tumour IAUC implied that ZD6126 reduced the IAUC close to zero in certain areas, typically in the centre of the tumour. The fraction of highly-enhancing voxels at the final time point (48 - 96 h) remained similar to that at 24 h post-treatment for all tumours, independent of the time elapsed to the final time point.



Analysis of tumour necrosis supported this finding, indicating that, notably, there was no significant tumour regrowth up to 96 h post ZD6126 treatment in this model.
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References

[1] McIntyre, D.J.O. et al. Proc Intl Soc Mag Reson Med 2001;9:480.
[2] Blakey D.C. et al. Clin Cancer Res 2002;8:1974

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IDN-5390, an orally active, antiangiogenic taxoid with low toxicity, ideally suited for metronomic dosing

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Our goal is the development of new semisynthetic taxoids that both overcome Pgp-based multidrug resistance and are less toxic to the host. Use of metronomic dosing (i.e., long-term, low dosing) to lower host toxicity, may be feasible with a taxoid that targets both tumor and growth of tumor vasculature. Previous studies demonstrated that IDN-5390 actively inhibits endothelial cell migration, suggesting antiangiogenic specificity (Taraboletti et al., Cancer Res. 8: 1182, 2002). However, in these studies both MCF7 human breast tumor cells and human umbilical vein endothelial cells (HUVEC) were growth inhibited by IDN-5390 *in vitro* at similar concentrations (IC_{50} 15nM). In addition, IDN-5390 was found to be less potent than paclitaxel (2nM) and the taxoid IDN-5109 (0.4nM) selected for its ability to overcome Pgp multidrug resistance. Interestingly, IDN-5390 had a lower fold resistance (121x) than paclitaxel (647x) in Pgp positive multidrug resistant MCF7/Adr cells but higher than that (45x) for IDN-5109. *In vivo*, IDN-5390