of treatment) and in one patient at 70 mg (leucopenia grade 2 on 7th week of treatment). The 50 mg were the HMD. Objective antitumor response was documented in 8 among 52 evaluable cases and 32% of patients experienced disease stability for at least 6 months. High pretreatment levels of TSP-1 were associated with objective tumor response (p=. 0003). The steady-state of blood concentrations of vinorelbine (VRL) and 4-O-deacetyl-vinorelbine (DVRL) ranged around 1 ng/ml and were consistent with expected low accumulation.
Conclusions: Protracted administration of metronomic oral vinorelbine is feasible at doses up to 50 mg administered 3 times a week. The observed durable antitumor effects against chemo-resistant tumors at doses lacking of undesirable side effects taken together with pharmacokinetics and featured predictive biomarkers provide clinical evidence supporting that metronomic therapy with vinorelbine primarily targets the vascular network of tumors. A randomized phase II study is now recruiting patients to define the optimal metronomic dose of oral vinorelbine.

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Synergistic effect of nab-paclitaxel and anti-VEGF-A antibody (bevacizumab) against the metastasis of breast tumor xenografts

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Background: *nab*-Paclitaxel (Abraxane®; ABX) is a 130-nm, albumin-bound paclitaxel that has shown greater efficacy and less toxicity than solvent-based paclitaxel in several xenograft models and in clinical trials. This study was designed to determine the effects of ABX and anti-VEGF-A antibody (bevacizumab; Avastin®; AVA), as single or combined therapy, on the growth of orthotopically implanted MDA-MB-231 tumors and on metastatic spread to the lungs and lymph nodes (LNs).
Material and Methods: Luciferase-expressing MDA-MB-231 human breast carcinoma cells were implanted into mammary fatpads of female *nu/nu* mice and allowed to reach an average size of 230 mm^3 before treatment. Ten mice were treated with 1 or 2 cycles of ABX (10 mg/kg, qdx5), followed by injection of AVA (4 mg/kg, 2/wkx6). Additional groups received ABX alone, AVA alone, or saline. Mice were monitored for tumor growth and toxicity. Mice were sacrificed when mean tumor volume in the saline-treated group reached 2000 mm^3. Luciferase activity was measured in extracts prepared from the 10 axillary LNs and both lobes of the lungs of each mouse.
Results: No toxicity was observed in any group. Tumors reached an average size of 1000 mm^3/group on days 25, 30, 45, and 80 after treatment with saline, AVA, and 1 and 2 cycles of ABX, respectively. Combined AVA and ABX therapy, particularly with 2 cycles of ABX, yielded a significantly better outcome than either therapy alone (30% of mice had complete regression; tumors in the remaining mice were reduced by 90% compared with controls). Only the combined therapy reduced metastasis to the lungs and LNs, with 6 of the 20 mice in combination therapy having no metastases to lungs or LNs ($P = 0.03$ vs controls, Fisher exact test). Total metastatic burden to LNs was reduced in a dose-dependent manner, with 42%, 85%, and 82% suppression of LN metastasis burden at AVA doses of 2, 4, and 8 mg/kg, respectively. AVA alone suppressed LN metastasis by only 8%. Metastatic burden to the lungs was not sufficient for statistical analysis, although the same trend was observed.
Conclusions: As expected, AVA alone did not significantly inhibit primary tumors or metastasis. The efficacy of ABX was much higher than that of AVA and was substantially improved by adding a second cycle of the drug. However, only the combination of ABX and AVA eradicated primary tumors in 30% of the mice and completely eliminated regional and distant metastases in 70% of the treated animals.

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A dose escalation study of AMG 386, a selective inhibitor of angiopoietin-2, in adult patients with advanced solid tumors

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Background: Angiopoietin-2, is upregulated at sites of tumor angiogenesis, and promotes new vessel growth through interaction with its receptor, Tie2. AMG 386 is a peptide-Fc fusion protein (peptibody) that inhibits the interaction between angiopoietins and Tie2. In preclinical tumor models, AMG 386 treatment results in decreased endothelial proliferation, increased tumor necrosis and decreased tumor growth, supporting further evaluation of AMG 386 as a novel therapeutic in Phase 1 cancer trials either alone or in combination.
The objectives of this first in human Phase 1 study are to assess the safety and pharmacokinetics (PK) of AMG 386 in adult subjects with advanced solid tumors.
Methods: Adult subjects were sequentially enrolled into 5 dose cohorts and received weekly intravenous doses of AMG 386 at 0.3, 1, 3, 10, and 30 mg/kg. Safety assessments included adverse events (AEs), clinical laboratories, vital signs, ECG monitoring, and anti-AMG 386 antibody formation. Tumor response was also assessed.
Results: 22 subjects have been treated in this dose escalation Phase 1 study with safety data available to date for 21 [(10 M/12 F); median age (range): 55 (43–79)]. Tumor types included: non-small cell lung, pancreatic, colorectal, hemangio, sarcoma, ovarian, breast, thyroid, renal, pseudomyxoma, parotid, and adenocarcinoma of unknown primary origin. Treatment-related AEs were generally mild or moderate (most CTCAE grade 1 or 2), with only fatigue (n = 7), gastrointestinal disorder (n = 3), and peripheral edema (n = 2) reported in more than 1 pt. One dose limiting toxicity (DLT) at 30 mg/kg was observed. Dose-linear PK was observed and the half-life supports weekly dosing. Serum concentrations reached steady state by week 3. Minimal accumulation was observed after multiple doses. Neutralizing antibodies were not detected. Best RECIST responses include stable disease (n = 16, 76%) and progressive disease (n = 5, 24%).
Conclusions: Weekly administration of AMG 386 up to 30 mg/kg was safe and well tolerated. The maximum tolerated dose was not reached. Minor AEs do not appear to be dose-related; 1 DLT was observed. 76% of subjects experienced stable disease (SD). The observation of a significant number of patients with SD is encouraging and supports evaluation of AMG 386 in further clinical studies.

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Pigment Epithelial-Derived Factor: development of anti-angiogenic peptides

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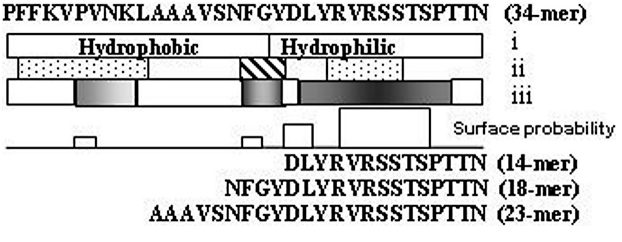
Background: Pigment epithelial-derived factor (PEDF) is a potent natural angiogenesis inhibitor. We have recently mapped PEDF anti-angiogenic activity to its 34-mer N terminal peptide (residues 24−57). This peptide retains PEDF anti-angiogenic properties: it reproduces signaling events in endothelial cell (EC), elicits EC apoptosis and blocks migration. Forced expression of 34-mer peptide delays the growth of prostate carcinoma. In this study we designed and screened short synthetic PEDF peptides for potential use as anti-angiogenic/anti-cancer therapeutics.
Material and Methods: The 3D structure of the 34-mer peptide was analyzed using Protean software in terms of relative hydrophobicity, charge distribution, and antigenic index. Short synthetic peptides covering the 34-mer fragment were generated (see figure) and tested for the ability to cause apoptosis and inhibit EC migration. Peptides were further tested for anti-angiogenic activity *in vivo* in matrigel plug and mouse corneal assays.



Results: The 34-mer C-terminus is strongly hydrophilic, with highly charged central area and high antigenic index, and is likely to interact with a target receptor. All screened peptides (14, 18 and 23-mer) demonstrated activity in EC apoptosis and migration assays. Dose-response curves were generated and the potency of the peptides compared to native PEDF and the 34-mer. Although all peptides showed anti-angiogenic activity *in vitro*, only one remained active *in vivo* due to stability differences. Neither of the peptides showed signs of toxicity at the doses tested.
Conclusion: We generated short peptides that reproduce the anti-angiogenic activity of PEDF in vitro and in vivo. These peptides will be tested in pre-clinical models of prostate cancer and melanoma and, if active, proposed for early stage clinical trials.