Conclusion: In this ongoing study, ABT-510 can be administered safely at 200 mg/day SC. Plasma concentrations exceed efficacious concentrations in preclinical models.

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A novel anti-angiogenic/anti-metastatic peptide, ATN-161 (Ac-PHSCN-NH2), which targets multiple fully activated integrins including alpha-5 beta-1 and alpha-v beta-3, leads to increased anti-tumor activity and increased survival in multiple tumor models when combined with chemotherapy

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ATN-161, a novel anti-angiogenic/anti-metastatic peptide [Livant et al. (2000) Cancer Res 60: 309], is scheduled to enter into phase I clinical trials in October, 2002. We have hypothesized that one of the ways ATN-161 would be most effective in the clinical setting would be in combination with chemotherapy. Thus, we evaluated ATN-161 in combination with several chemotherapeutic agents in various models of tumor growth. ATN-161 (1-10 mg/kg, q3d)+ cyclophosphamide (160 mg/kg, day 1, 3, 5 after initiating treatment) synergistically reduced tumor growth rate of staged 3LL tumors resulting in increased survival of the combination therapy group as compared to vehicle controls or either drug alone. A similar result was obtained in the adjuvant setting in a DU145 tumor growth model. DU145 tumors were staged to ~1000 mm3 then surgically resected. Treatment with either ATN-161, taxol or the combination was initiated the day after surgery. The combination treatment group had the longest time to tumor recurrence. Some of the mice in this group had no recurrence and those tumors that did recur grew much more slowly than the tumors in the other treatment groups. The scheduling of ATN-161 treatment relative to chemotherapy was critical to the activity of the drugs in the combination regimen. Results in several other xenograft models (CWR22R, MDA-MB-231) using different combination regimens will also be presented.

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Pharmacokinetic/pharmacodynamic (PK/PD) relationships for the angiogenesis inhibitor ABT-510 in preclinical efficacy models

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ABT-510 is a subcutaneously (SC) administered nonapeptide thrombospondin analogue entering Phase II clinical development for treatment of advanced malignancies. The correlation of pre-clinical efficacy *in vivo* and pharmacokinetics was analyzed to help determine a PK target for human studies. Data were available from 11 murine models (melanoma B16F10, orthotopic (OT) bladder 253J B-V, OT bladder EJ-1, OT bladder HT-1376, OT breast MDA-MB-435, flank breast MDA-MB-435, flank breast MDA-435-LM, corneal micropocket assay, flank colon HC-T15, flank lung LX-1 and flank lung NCI-H460). ABT-510 was dosed SC by bolus (BID, QD, or QOD) or osmotic pump. Doses ranged from 0.1 to 200 mg/kg/day. Efficacy measures varied by model and included tumor volume, tumor weight, number of metastases, and VEGF or bFGF-stimulated new vessel density. PK were measured in satellite animals of the same strain or estimated from similar doses. For each model, a simple Emax equation was fitted to the efficacy and PK data. PK variables included Cmax, AUC, time/day where plasma concentration (Cp) > 10, 50, 100 or 200 ng/mL, as well as unit dose and dose/day. Selection of the best overall PK predictor of efficacy (time/day Cp>100 ng/mL) was made based on standard goodness-of-fit criteria. Results: Across all models where estimates were obtained, the mean Emax was 43% (ranging from 90% in melanoma to 6% in OT bladder 253J B-V). The Emax equation could not be fitted to data from four of the eleven models: flank colon, both flank lung and OT bladder HT-1376 models. The mean E50 was 1.1 h (ranging from 0.4 h in orthotopic bladder 253J B-V to 1.8 h in orthotopic breast). A target for clinical PK was defined as Cp>100 ng/mL for 3 h/day, which, on average, achieved 75% of Emax in the murine efficacy models. For comparison, in companion dogs with spontaneous solid tumors treated with ABT-510 SC 12.5 mg BID, Cp >100 ng/mL for >3 h/day was observed in all 10 animals for which PK data are available. Objective responses and disease stabilization have been observed in these pets. In humans, ABT-510 SC bolus doses of 100 mg QD achieve the target PK (Cp>100 ng/mL for >3 h/day) in both healthy subjects and patients with cancer.

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Minimization of the anti-angiogenic Histidine-Proline Rich Glycoprotein (HPRG) protein

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The potent anti-angiogenic activity of the abundant multi-domain plasma protein HPRG has recently been reported and localized to its Histidine-Proline Rich (H/P) domain (Juarez et al. Cancer Research; in press). HPRG is evolutionarily, functionally and structurally related to activated kininogen (HKa) which is also an anti-angiogenic molecule that stimulates endothelial cell apoptosis through binding to cell-surface tropomyosin (J-C. Zhang et al. Submitted). HPRG and the H/P domain, but not other domains of HPRG, also bind specifically and with high affinity to tropomyosin *in vitro*. The H/P domain of HPRG is composed of repetitions of the consensus sequence [H/P][H/P]PHG and using the *in vitro* tropomyosin binding assay, we have identified a 5-mer sequence that inhibits the binding of HKa to tropomyosin in the μM range. This pentapeptide also has moderate anti-angiogenic and anti-tumor activities in a Matrigel Plug model *in vivo*. The optimization of this 5-mer has been initiated and studies are currently underway to evaluate the activity of several of these optimized peptides *in vivo*. In addition, we have also prepared multimers of this sequence (4x, 3x, 2x). These peptides have increasing affinities for tropomyosin *in vitro* (4x>3x>2x) that correlate with increasing activities in a Matrigel Plug model *in vivo*. In conclusion, we report the identification of an active 5-mer consensus sequence and the development of several peptide lead series derived from the H/P domain of HPRG.

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A phase I study of TNP-470 continuous infusion alone or in combination with paclitaxel and carboplatin in adult patients with non small cell lung cancer (NSCLC) and other solid tumors

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TNP-470 (TNP) is a synthetic analog of fumagillin that demonstrates potent antiangiogenic properties. Previous studies suggest that the combination of TNP 60 mg/m^2 3 times per wk and paclitaxel (P) 225 mg/m^2 with or without carboplatin (C) AUC 5 is well-tolerated (ASCO 2000 and 2001). However, preclinical data suggest that TNP infused continuously (CI) may enhance antiangiogenic effects with manageable toxicity. This study was designed to determine the safety and MTD of TNP CI alone and with chemotherapy with or without a bolus of TNP. Single-agent TNP was administered in 28-day cycles and combination regimens in 21-day cycles.

Cohort	Patients (n)	P (mg/m^2)	TNP 1-hr (mg/m^2)	C (AUC)	TNP CI (mg/m^2/day)
A	6	–	–	–	10/28 days
C	7	–	–	–	10/5 days/wk
D	5	225	–	6	10/5 days/wk
F	6	200	–	6	2.5/5 days/wk
G	9	200	60	5	2.5/5 days/wk
H	6	200	60	6	2.5/5 days/wk

Thirty-nine subjects enrolled; 64% were chemonaive and 72% had NSCLC. Regimens in Cohorts A, C and D were not well-tolerated due to neurotoxicities and myelosuppression (80% grade 4 neutropenia in Cohort D). P and TNP were reduced in Cohort F resulting in improved tolerability. A TNP bolus was added in Cohorts G and H, with 55% and 66% of patients respectively completing * 4 cycles. Response rates in NSCLC patients in arms D-H was 47%. TNP CI 2.5 mg/m^2/day, with or without TNP 60 mg/m^2 1-hr infusion, appears to be well-tolerated when given in combination with P 200 mg/m^2 and C AUC 5-6, warranting further evaluation in NSCLC in a randomized setting.