Methods: The primary objective of this phase 1 study is to evaluate the safety and tolerability of ACE-041. Secondary objectives include identifying MTD, PK, preliminary activity on PD markers and antitumor activity by RECIST, PET-CT and DCE-MRI. Cohorts of 3−6 patients are being enrolled at escalating dose levels. ACE-041 is administered SC every 3 weeks for a total of 4 doses or until disease progression. Patients with confirmed stable or responding disease may continue treatment for up to 12 months.
Results: 19 patients (11M, 8F) have been enrolled. Five dose levels (0.1 to 1.6 mg/kg) have been completed; the sixth cohort (3.2 mg/kg) is ongoing. The t1/2 is approximately 10−15 days and the Tmax is 4−7 days. ACE-041 is well tolerated with no DLTs reported thus far. Common to this population, preliminary AEs included nausea, fatigue, anorexia, headache, fever and vomiting, which were generally of low grade toxicity. Stable disease was observed in 3 patients having previously progressed on chemo- and/or anti-VEGF therapy lasting at least 6 cycles; one aggressive carcinoid patient (6 cycles before progressing) and 2 patients still on treatment (NSCLC and head and neck) after 7 cycles. Additionally, in a heavily pre-treated NSCLC patient with an adrenal metastasis enrolled at the 1.6 mg/kg dose level, a positive major response on 18-FDG-PET was observed with a significant decrease in metabolic activity 2 weeks following the first dose.
Conclusions: ACE-041 is a first-in-class inhibitor of angiogenesis targeting ALK-1. Treatment thus far has been well tolerated and preliminary evidence of antitumor activity has now been observed in this first-in-human study. The study is ongoing and final results will be presented at the meeting.

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PI3K inhibition is necessary and sufficient to induce an anti-angiogenic response in vivo based on suppression of tumor vascular structure

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Background: Vascular endothelial growth factor (VEGF) is a validated target for tumor angiogenesis and the PI3K pathway acts as a central mediator of VEGF driven endothelial cell survival and vascular permeability. While it has been demonstrated that a dual PI3K/mTOR inhibitor can suppress eNOS-induced vascular permeability and vasodilatation resulting in a reduction in the dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) parameter K^{trans}, the effects on vascular structure has not been elucidated [1]. Therefore, our aims were to further ascertain the role of PI3K pathway signaling on vascular structure and physiology by utilizing small molecule inhibitors that target PI3K (GDC-0941 and GNE-490), mTOR (rapamycin) or both (GDC-0980).
Methods: An array of in vivo imaging techniques were employed to evaluate the vascular response in human HM7 colorectal cancer xenografts: ex-vivo micro-computed tomography angiography (μCT-angio), DCE-MRI, vessel size imaging (VSI) by MRI and dynamic contrast-enhanced ultrasound (DCE-U/S) perfusion imaging.
Results: GDC-0980 strongly suppressed both tumor physiological and structural vascular parameters. The DCE-MRI parameter, K^{trans}, was reduced by 24% relative to the control group. DCE-U/S imaging showed that GDC-0980 reduced blood flow within the enhancement region by 8% and reduced the enhancement fraction (Ef) by 55%. GDC-0980 reduced μCT-angio vascular density (VD) by 57% relative to control. In-vivo VSI demonstrated a significant reduction in blood volume, the vessel density related parameter Q and increased vessel size; all changes consistent with a loss of small vessels. DCE-MRI and DCE-US demonstrate that GDC-0980 can suppress permeability and perfusion while uCT-angio, VSI and DCE-U/S Ef data indicates a strong effect on vascular structure. In addition, GDC-0941 also caused a significant decrease in VD while rapamycin did not. Interestingly, GNE-490, a pan-PI3K inhibitor that has similar pharmacokinetic parameters to GDC-0980, produced similar uCT-angio VD results as GDC-0980, suggesting that mTOR inhibition is not required for maintenance of vascular structural effects.
Conclusion: Inhibition of PI3K alone is necessary and sufficient to generate the dramatic physiological and structural changes in tumor vasculature that is characteristic of an anti-angiogenic response in vivo.

References

[1] Schnell et al., Cancer Res. 2008, p. 6598–6607.

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Updated efficacy and safety results for a randomized phase 2 trial of a tumor vascular disrupting agent fosbretabulin tromethamine (CA4P) with carboplatin (C), paclitaxel (P) and bevacizumab (B) in stage IIIB/IV non-squamous non-small cell lung cancer (NSCLC): The FALCON trial

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Background: CA4P is a reversible tubulin-binding tumor vascular disrupting agent (VDA) that has previously shown clinical activity in combination with chemotherapy and antiangiogenic therapy. Enrollment of a phase 2 study evaluating CA4P in combination with C (Carboplatin) + P (Paclitaxel) + B (Bevacizumab) in advanced non-squamous NSCLC was recently completed.
Methods: In an open-label, randomized controlled study for patients with untreated, histologically-confirmed, stage IIIb or IV, non-squamous, NSCLC 60 patients were randomized to receive up to 6 cycles of C + P + B with (CA4P arm) or without CA4P (control arm). After 6 cycles of therapy, patients without progression continued to receive their randomized treatment B or B + CA4P until progression. The primary endpoint is progression-free survival (PFS). Secondary endpoints include response rate and overall survival.
Results: As of June, 2010, the target enrollment of 60 patients was completed. Of these, 53 patients (safety population) received treatment (26 in CA4P arm and 27 in control arm) by the most recent data analysis (May 6, 2010). 30 patients enrolled at least 12 months prior to the data analysis, and these patients composed the efficacy population. For this group, PFS was 6.9 months in the CA4P arm vs. 6.2 months in the control arm with a HR and 95%CI of 0.70 (0.27, 1.82). Partial responses were seen in 60% of patients for the CA4P arm vs. 40% for the control arm. Safety profiles in both treatment arms were comparable. Hypertension, mostly grade 1 and 2, and neutropenia were more frequent in the CA4P arm. Toxicities were manageable and did not result in differences in dose intensity between the two treatment arms. There were three reversible cardiac ischemia events in the CA4P arm, none of which required hospitalization. Updated safety and efficacy data will be presented.
Conclusions: The addition of CA4P to standard doses of C + P + B continues to be well tolerated with trends towards improved outcomes in the CA4P arm.

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Anti-tumoral and anti-metastatic activity of a tetravalent bispecific antibody (TAvi6) targeting VEGF and Angiopoietin-2

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Background: VEGF blockade has been validated clinically as a treatment for human cancers. Angiopoietin-2 (Ang-2) expression has been shown to function as a key regulator of blood vessel remodeling and tumor angiogenesis. In tumors Ang-2 is up-regulated and a bad prognostic factor. Recent data demonstrated that Ang-2 inhibition mediates antitumoral effects. We have generated TAvi6, a novel bispecific antibody targeting VEGF-A and Ang-2 and tested its anti-tumor efficacy. TAvi6 is a tetravalent IgG-like bispecific antibody based on bevacizumab and targets Ang-2 with 2 disulfide-stabilized scFvs (LC06) fused to the C-terminus of the heavy chain.
Material and Methods: TAvi 6 was profiled in biochemical and cellular (angiogenesis) assays. Antitumoral efficacy was assessed in established s.c. Colo205, s.c. Calu-3 and orthotopic i.m.f.p. KPL-4 xenografts in SCID beige mice. Mice were treated with bevacizumab or <Ang-2> antibody LC06 (10 mg/kg), the respective combination (each 10 mg/kg) and TAvi6 (13.3 mg/kg). In addition, TAvi6 was evaluated in tumors progressing after 1st-line treatment with Avastin, for inhibition of metastasis to the lung quantified by Alu-PCR and for inhibition of angiogenesis in the cornea micropocket assay. Tumors were explanted for histological analysis.
Results: In biochemical assays (affinity, Tie2-Ang-2 interaction) and cellular assays (Tie2 phosphorylation, HUVEC proliferation, tube formation) TAvi6 shows properties identical to the parental antibodies bevacizumab and LC06. In the orthotopic KPL-4–003 xenograft tumor growth inhibition was 79% for bevacizumab; 39% for LC06; 90% for the combination and 91% for TAvi6. In the s.c. Colo205–009 xenograft TGI was 66% for