60 mg BID resulted in reductions of 80−90% in phosphorylation of AKT, 4EBP1 and S6, and was associated with a 54% reduction in proliferation as assessed by Ki67 in tumor cells. The pattern of inhibition of PI3K pathway phosphoepitopes suggests that XL765 inhibits PI3K and both mTOR/Raptor and mTOR/Rictor in pts.
Conclusions: In this Phase 1 study, XL765 has been generally well tolerated at doses up to 60 mg BID, and further exploration of this dose as well as a QD regimen is in progress. XL765 demonstrates robust pharmacodynamic activity, as assessed by analysis of multiple PI3K and mTOR dependent readouts in surrogate tissues and tumor.

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Pre-clinical evaluation of efficacy and PK/PD biomarkers of GDC-0941, a potent class 1 PI3K inhibitor

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Background: Constitutive activation of the phosphoinositide-3 kinase (PI3K)/Akt signaling pathway is a frequent event in many types of cancers and results in increased cell growth and survival. We recently discovered GDC-0941, a class 1 PI3K inhibitor currently in phase 1 clinical trials. Pre-clinically, we have demonstrated the potent anti-tumor activity of GDC-0941 *in vitro* and *in vivo*. (Folkes *et al.,* late breaking abstract-146, Friedman *et al.,* late breaking abstract 110, AACR 2008). In this study we evaluate the efficacy, pharmacokinetic (PK) and pharmcaodynamic (PD) markers of GDC-0941 *in vivo*.
Methods: GDC-0941 was dosed up to 200 mg/kg daily by oral gavage in mice bearing breast and prostate cancer xenografts. GDC-0941 plasma PK, tumor PK and tissue PD analysis of downstream PI3K biomarkers (pAKT, PRAS40, pS6, phospho-p70S6K) was evaluated after single dose and multiple daily dose efficacy studies. PD analysis was conducted on *ex vivo* xenograft tumour samples and normal murine tissues using a combination of luminex, mesocale, immunohistochemical and Western blot assays.
Results: GDC-0941 had significant dose dependent *in vivo* efficacy and was well tolerated. In single dose and multiple daily dose efficacy studies GDC-0941 caused rapid downregulation of pAKT, PRAS40, pS6 and phospho-p70S6K in the tumour, consistent with PI3K pathway inhibition. PK analysis of GDC-0941 showed that reduction of pAKT in the tumours was positively correlated to plasma and tumour drug concentrations. There were minimal effects on pAKT in normal murine tissue at 30 min. pAKT knockdown in the tumour was verified and found to be comparable using both luminex and mesocale assays. Imunohistochemical analysis of MDA-MB-361 breast tumours showed heterogenous expression of pAKT and pS6, which was significantly reduced 1hr post dose of GDC-0941. Highly efficacious doses of 75–150 mg/kg GDC-0941 gave prolonged biomarker knockdown, recovering by 24 hrs consistent with the drug exposure.
Conclusions: GDC-0941 had significant anti-tumour activity *in vivo* with concomitant reduction in PI3K signalling in xenograft tumour tissue. These pre-clinical data support the evaluation of pAKT, PRAS40, pS6 and phospho-p70S6K as potential PI3K pathway biomarkers in GDC-0941 clinical studies.

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A phase I dose-escalation study of the safety, pharmacokinetics and pharmacodynamics of XL147, a novel PI3K inhibitor administered orally to patients with advanced solid tumors

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Background: XL147 is a potent, selective, oral inhibitor of Class I PI3 kinases. Administration of XL147 leads to tumor growth inhibition or regression in preclinical cancer models and has been shown to enhance the anti-tumor activity of EGFR-targeted agents and cytotoxic drugs.
Methods: XL147–001 is a Phase 1, non-randomized, open label, dose escalation, safety and pharmacokinetics (PK) study. Patients (pts) with advanced solid tumors are enrolled in successive cohorts to receive XL147 daily on Days 1−21 of 28-day cycles (21on/7off schedule). In Cycle 1, clinical and laboratory data are obtained to assess safety and pharmacodynamics. Tumor response is evaluated by RECIST criteria every 8 wks.
Results: To date, 19 pts have been treated with XL147 across six dose levels from 30 mg to 600 mg daily. At 600 mg daily a DLT of Grade 3 skin rash was observed. At 400 mg daily, one Grade 1 gastritis, and one Grade 1 skin rash were reported possibly related to study drug. There were no SAEs related to XL147. Plasma PK analysis indicated exposure increased with dose. The mean terminal plasma half-life at steady state ranged from 3−6 days, with steady state plasma concentrations achieved between Days 15 and 20. Accumulation was evident, as plasma exposures were 5 to 10-fold higher on Day 21 than on Day 1. XL147 transiently augmented food-induced changes in plasma insulin with a trend suggesting dose- and exposure-dependence. Inhibition of PI3K pathway signaling was demonstrated in pts by reductions in phosphorylation of PI3K pathway components including AKT, PRAS40, and 4EBP1 in PBMCs and hair bulbs. In one example, administration of 120 mg daily resulted in reduced phosphorylation of AKT (32%), PRAS40 (74%), 4EBP1 (46%) and S6 (57%) in hair bulbs. Similar analyses are ongoing in skin and tumor samples from multiple pts. As of May 2008, one pt with basal cell carcinoma has remained on study >10 cycles; three pts with NSCLC and one pt with NHL remained on study >8 cycles; an additional two pts remained on study >4 cycles.
Conclusions: XL147 has been generally well tolerated at doses up to 400 mg daily on the 21on/7off dosing schedule. Inhibition of PI3K signaling has been demonstrated and there are preliminary signs of clinical benefit as assessed by time on study. Cohort expansion at the 600 mg dose level is ongoing to determine the MTD for the 21/7 dosing regimen. In parallel, pts are being enrolled on a continuous daily dosing schedule.

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NVP-BEZ235, a dual pan-PI3K/mTOR kinase inhibitor, is effective in human lung cancer models harboring EGFR mutations

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Background: Mutations in the intracellular kinase domain of the epidermal growth factor receptor (EGFR) are often found in a subset of patients with lung cancer and correlate with therapeutic response to EGFR kinase modulators. Resistance to these targeted anticancer agents invariable develops, and current treatments have limited long-term antitumor efficacy. In this study, we evaluated the effectiveness of a dual PI3K/mTOR kinase inhibitor, NVP-BEZ235, in the treatment of human lung cancer models harboring EGFR mutations.
Materials and Methods: To study the potential use of NVP-BEZ235, which is currently in Phase I clinical trials, in the treatment of lung adenocarcinomas, the compound was tested *in vitro* and *in vivo* in several human lung models that require a functional EGFR for tumor maintenance.
Results: NVP-BEZ235 significantly inhibits the proliferation (GI_{50} <50 nM) of lung tumor cell lines harboring EGFR-activating mutations as well as EGFR tyrosine kinase resistance somatic mutations by specifically blocking the biological function of PI3K signaling components. In animal models, oral treatment with NVP-BEZ235 (35 mg/kg qd) caused tumor stasis ($T/C = 0.04$, $p < 0.05$) in NCI-H1975 xenografts, an EGFR mutant model (Leu858Arg and Thr790Met), which has shown high levels of EGFR tyrosine kinase inhibitor resistance. Moreover, ex-vivo analysis of tumor samples treated with NVP-BEZ235 revealed significant inhibition of pS473-Akt and downstream targets with no inhibition of YP/TP-ERK1/2 at 1 h post last dose. NVP-BEZ235 was well tolerated at the efficacious doses when compared with vehicle treated animals, with no significant difference seen in the body weight. Significant antitumor activity was also observed in a mechanistic c-MET amplified gefitinib resistant model (Hcc827GR), and in an EGFR mutant model sensitive to EGFR kinase inhibitors (Hcc827, ex 19 del).
Conclusions: These preclinical evaluations suggest that NVP-BEZ235 may represent an effective therapeutic strategy for patients with lung cancers harboring drug-sensitive EGFR mutations or those with the novo and acquired resistance to EGFR tyrosine kinase inhibitors.

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Combination of class I PI3K inhibitor, GDC-0941, with standard of care therapeutics results in enhanced anti-tumor responses in human cancer models in vitro and in vivo

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Background: Phosphoinositide 3-kinases (PI3Ks) are lipid kinases that regulate tumor cell growth, migration and survival. We previously reported