affect the process, and nonlinear regression is useful in defining curve characteristics. For example in PK, inflection points define different phases or "compartments" of drug disappearance, and segment slope defines the T1/2 for that compartment. We propose to apply similar analyses to survival data to assess if different "compartments" derived from semilog curves identify prognostically distinct subpopulations. If so, nonlinear regression analysis would permit characterization of each prognostic "compartment".
Materials and Methods: We reviewed the literature and replotted selected progression-free and overall Kaplan-Meier survival curves as semilog plots, then initiated curve-stripping/nonlinear regression analyses to assess the feasibility of this approach.
Results: In preliminary analyses, survival curves and progression-free survival (PFSC) curves for patients with non-small cell lung cancer (NSCLC) treated with erlotinib & gefitinib were at least biphasic, suggesting at least 2 prognostically-distinct subpopulations, while curves were uniphasic for placebo-treated patients. In other analyses, PFS curves for patients treated with surgery alone for stage I NSCLC were biphasic, while those for stage IIIA disease were triphasic, with an initial steep-slope compartment, then 2 "compartments" with slopes matching those of the stage I curve.
Conclusions: These preliminary analyses suggest converting Kaplan-Meier plots to semilog plots may potentially be useful in delineating prognostically distinct patient subpopulations. We will be applying this method widely to published clinical data to more fully assess its validity (eg, assessing relative impact on erlotinib on curves for patients with EGFR mutations vs others). Preliminary analyses of stages I vs III NSCLC suggest: (a) poor prognosis of stage III may be driven by a subpopulation with particularly rapid tumor growth, while other stage III prognostic "compartments" correspond to those seen in stage; (b) patients with stage I who relapse may come from a prognostically distinct stage I compartment in which tumor cell characteristics match those in the stage III intermediate "compartment".

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Validation of a histological sample transport medium preserving histoarchitecture and total and phospho-activated proteins

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Background: Biomarkers studies using precious tumor tissues is an essential part of oncology clinical trials. In preclinical studies, protocols providing high-quality samples preserving histoarchitecture, total and phospho-activated proteins exist. However, deviations from such protocols (eg delay in fixation, over fixation) can result in artifacts due to loss of immunoreactivity, in particular phospho-proteins. In the clinical setting, adherence to such protocols is challenging, particularly with multi-center studies. The clinical trial programme for the mTOR-inhibitor RAD001 (everolimus) uses centralized tissue/immunohistochemistry (IHC) analysis, thus requiring a reliable protocol for sample collection, preparation and transportation. We have validated a sample transport medium evaluating markers influencing the activity of mTOR, or being affected by mTOR activity, using tumor tissues from experimental animals.
Material and Methods: BT474 tumours, over expressing ErbB-2, grown subcutaneously in nude mice were excised and slices immediately placed into 4% phosphate buffered formaldehyde, pH 7.4, and fixed at 4ºC for 24h, allowing a range of $\pm$1h, prior to transfer of the samples to 70 % v/v ethanol transport medium. Slices were either directly processed into paraffin or stored in transport medium at 'room temperature' (20−27ºC) for 1, 2, and 4 weeks. Freshly cut sections from all samples were subjected to H&E staining and IHC for pAKT (S473, Cell Signaling Technology), HER-2 (Herceptest, Dako), pHER-2 (PN2A, Dako), pS6 (S235/236, and S240/244, Cell Signaling Technology), Ki-67 (Mib-1, Dako), and FISH-HER2 (PathVision, Vysis).
Results: No significant changes in either H&E or IHC/FISH-HER2 for any marker was observed when comparing stored versus immediately processed tissue. General architecture of the tumors was also maintained.
Conclusions: 70% ethanol provides a safe transport medium as compared with formaldehyde in that over fixation is prevented and stability of the sample architecture and immunoreactivity is maintained.

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Phase I dose escalation safety/tolerance study of PPI-2458 in subjects with Non-Hodgkin's lymphoma or solid tumors

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Methods: Patients with non-Hodgkin's lymphoma or solid tumors who failed prior treatments or are refractory to standard therapy are being enrolled in cohorts to receive escalating doses of PPI-2458. The treatment regimen being studied is an oral dose of PPI-2458 every other day (QOD) for 28 days. Subjects are enrolled for two 28 day cycles of PPI-2458. The first three cohorts studied 2, 3 and 5 mg QOD doses. Blood samples for pharmacokinetic (PK) and pharmacodynamic (PD) analyses were obtained during the first cycle of treatment on study days 1, 2, 3 and 15. The third cohort of this study is currently ongoing.
Results: To date 25 patients with a wide range of tumor types have been treated across three dose levels: 2 mg, 3 mg and 5 mg. One dose limiting toxicity (DLT) of grade 3 elevated liver transaminases was observed in Cohort 1 (2 mg). No additional DLTs have been observed to date. Preliminary PD data shows complete MetAP-2 inhibition (below lower limits of quantitation at any time point) in white blood cells in 76 % (13 out of 17) of the subjects treated to date. Preliminary PK data is being analyzed.
Conclusion: PPI-2458 administered orally QOD for 28-day cycles is safe and well tolerated at the doses tested to date. In addition PD data demonstrates MetAP-2 inhibition in white blood cells, even at initial dose levels evaluated. Tumor biopsies will be included in future cohorts to evaluate MetAP-2 inhibition in the target tissues.

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Morphologic assessments of tumor size: scan-rescan reproducibility of long- and short-axis measurements using manual and automated 3-dimensional assessments in liver and lung tumors using magnetic resonance imaging (MRI)

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Background: Current evaluations of therapeutic efficacy in solid tumors rely on assessments of changes in size, e.g., WHO and RECIST criteria. Conventional evaluations are limited to the plane of imaging. The aims of this study were to evaluate the differences in, and variability of, measurements of tumor size using manual and automated 2D and 3D methods.
Material and Methods: Scan-rescan MRIs were undertaken between 2 and 7 days apart, in 25 patients with malignant tumors in the liver or lung. The main inclusion criteria were: no preceding therapy >4 weeks, no inter-scan treatment, and lesions >3 cm. MRI included T_2 and T_1-weighted images without and with gadolinium, in 5 mm sections. Manual measurements of maximum inplane long- and short-axes were made from scan-rescan images and compared to automated inplane (2D) and 3D evaluations, which used a Geometrically Constrained Region Growth computer algorithm. The variances between visits were estimated using a statistical model and compared using Levene's test. *P*-values were adjusted by Tukey's method with α=0.1. The measurement methods were also compared by linear regression. Reproducibility was assessed using coefficients of variation.
Results: There were 24 evaluable patients (12 liver, 12 lung). Mean (SEM) long-axis measurements (cm) for manual, and automated 2D and 3D were: for lung lesions, 4.9 (0.43), 5.1 (0.49), and 5.8 (0.47); and for liver lesions, 4.9 (0.30), 5.1 (0.41) and 5.7 (0.48), respectively. 3D measurements were significantly longer than those obtained from 2D and manual inplane methods [$p_{adjusted} < 0.1$]. 3D and 2D automated measurements were correlated to the manual measurements, with a slopes significantly >1 for liver [$p < 0.05$], but not for lung [$p > 0.5$] (Figure 1). Short- and long-axis values were highly correlated [$p \approx 0.9$]. Scan-rescan reproducibility of long-axis measurements was not significantly different between the three methods [$p = 0.11-0.85$]: for liver and lung lesions, using