RXRγ were constitutively expressed in the ovaries. 4-HPR and OCP used alone had a small induction of retinoid receptor expression. However, the combination of 4-HPR with OCP had a stronger effect on induction of all retinoid receptors except RXRβ expression. OCP induced expression of ERβ, but the combination had a stronger effect, suggesting that there was a synergistic effect between the two drugs on hormone receptor expression. 4-HPR alone at the equivalent of 200mg/day induced apoptosis in monkey ovaries. Overall the combination showed more modulation on all the markers than the other 3 groups ($p<0.004$). Erβ was upregulated in the combination group ($p<0.04$), EGF was also upregulated and approached statistical significance ($p<0.06$). ERβ, but not ERα was upregulated in the combination group, but did not reach statistical significance.
This primate study suggests that the combination of 4-HPR and the oral contraceptive can induce apoptosis and upregulate some retinoid receptors and ERβ more than either drug alone, providing some clues to their mechanism. Although 4-HPR is thought to be receptor independent, in combination with OCP may in fact, act through the retinoid receptors and may be more effective in combination than either drug alone.
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583 POSTER

Serum proteomic biomarkers of a natural product in a prospective randomized placebo-controlled clinical trial in patients at risk for lung cancer

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Smoking, asthma, and chronic obstructive pulmonary disease (COPD) are known risk factors for lung cancer. The disease may be preventable, but many potential chemopreventive agents have not shown clinical activity in individuals at risk for lung cancer (Van Zandvijk et al, Lung Cancer 2003, 42:S71). A novel natural product LP01 demonstrated preclinical preventive and anticancer activities, and induced time-and dose-dependent changes in serum kallikreins and proteomic patterns in human lung cancer xenograft models (Baek et al, Proc AACR/NCI/EORTC 2003). The present study evaluated LP01 in a prospective, randomized, triple-masked, placebo-controlled, parallel-group clinical trial. In this study, lung cancer risk (1–5) was assessed based on length of addiction, asthma, and COPD, for a group of former long-term smokers (smoked >20 years, quit >1 year). This group, comprised of sixty men and women ages 35–70, received oral daily doses of 3,650 mg LP01 or placebo for 6 months. Peripheral blood serum specimens were obtained at the baseline and after drug treatment for 2 weeks, 1 month, 2 months, 4 and 6 months. Serum proteins were resolved on IMAC3/Cu metal affinity ProteinChip arrays and analyzed by surface-enhanced ligand desorption/ionization (SELDI). There were no adverse clinical effects of the therapy. The patients were stratified by the low risk (1 to <3) and high risk for lung cancer (⩾3), both in the drug and placebo groups for the analysis of SELDI proteomic patterns. Statistically significant differences ($p<0.05$) were observed between the drug and placebo groups in the cluster of small proteins <10,000 mass/charge (M/Z). The drug effects on select biomarkers were similar in the low and high risk for lung cancer. The findings warrant identification and characterization of potential biomarkers of risk for lung cancer and the efficacy of LP01.
Supported by Jiang Jing, Inc.

Clinical methodology

584 POSTER

Phase II trial design for radiation (XRT) modifiers: Efficient evaluation of safety, XRT modifier effect, post-XRT cytostatic effect and relevant molecular markers

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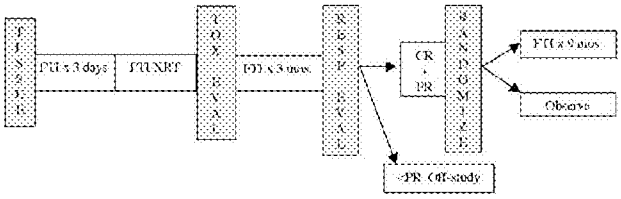
The appropriate design of trials that incorporate targeted agents with radiotherapy is critical to the development of these treatments. The principles of investigating XRT modifiers in trials have been previously reviewed (Colevas et al. JNCI, 2003). The goals of combining targeted agents with XRT are to improve efficacy and reduce combined modality toxicities, as compared to conventional chemoradiotherapy regimens. Recent preclinical studies have suggested that activation of the Ras-PI3K-Akt pathway affects XRT sensitivity, which has led to investigations of farnesyltransferase inhibitors (FTI) with XRT.
A novel bivariate phase II trial design has been proposed to evaluate FTI R115777 (NSC# 702818) and XRT in locally advanced NSCLC patients (pts). This design is well-suited to the dual aims of the trial, which are to demonstrate a reduced esophagitis toxicity (TOX) rate and similar clinical response (RESP) rate, as compared to conventional paclitaxel/carboplatin/XRT. R11577 is taken orally for 3 days pre-XRT, daily during XRT and for 3 mos. post-XRT. Randomized discontinuation in responders at 3 mos. post-XRT allows for evaluation of cytostatic effects based on time to progression (TTP) from randomization. Relevant molecular markers (*ras*, Akt, EGFr, MAPK) are examined in tumor tissue.



The Bayesian approach (MULTC99 software courtesy of P. Thall) quantifies pre-trial TOX and RESP probabilities (prob) and repeatedly updates these probs as TOX and RESP data accumulate during the trial. Early stopping rules for TOX and RESP are defined with the updated probs. FTI/XRT regimen is considered acceptable if the probs of TOX and RESP are ⩽0.25 and ⩾0.65, respectively. The trial terminates early if it is either likely (>95% chance) that the TOX goal cannot be achieved or unlikely (<10% chance) that the RESP goal can be achieved. Excellent stopping properties are demonstrated. If the true TOX and RESP probs are 0.46 (unacceptable; same as paclitaxel/carboplatin/XRT) and 0.78, respectively, then the prob of early stopping is 0.88, while for true probs of 0.25 and 0.65 (acceptable), respectively, then the prob of early stopping is <0.10.
This 80 pt trial provides precise estimates of TOX and RESP rates (posterior interval * width is 10%), 30 pts per randomized group for TTP analyses and abundant marker data for correlative analyses. Moreover, since pts are not pre-selected based on marker status, a rich co-variation in molecular markers is expected. The trial design (prior probs, stopping rules and properties) and power for correlative and TTP analyses will be fully described.

585 POSTER

Analytical and multi-center clinical performance evaluation of a diagnostic device designed to analyze the expression of 11q23/MLL abnormal fusion transcripts in acute leukemia

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Background: 11q23 abnormalities involving the *MLL* gene are highly heterogeneous. Over 50 partner genes have been described to date, and t hese molecular rearrangements are collectively associated with unfavorable prognosis in acute lymphoblastic leukemia (ALL) and an intermediate risk in acute myeloid leukemia (AML). However, the functional role and the prognostic significance of specific fusion transcripts on the progression and outcome of disease remain to be elucidated. Diagnostic testing of patients with acute leukemia includes cytogenetic analysis confirmed by FISH, RT-PCR, and/or Southern blotting. Molecular screening can be cumbersome, since identification of the fusion partner involves multiple and time-consuming analysis. We present analytical and clinical performance evaluation data for a new biochip based molecular device (*MLL* Fusion*Chip*™) designed to confirm the presence of 11q23 abnormality and identify the *MLL* fusion gene partner.
Methods: An analytical study was performed to address the robustness, precision, limit of detection, and analytical sensitivity and specificity of the *MLL* Fusion*Chip* ™ using RNA from 4 cell lines and 2 clinical samples. Clinical performance was then evaluated on a range of ALL and AML samples with known *MLL* rearrangements, identified by cytogenetics, FISH, and/or RT-PCR, in nine laboratories from seven countries. Following assessment of RNA quality, 127 *MLL* positive and 23 control samples were analysed with the *MLL* Fusion*Chip* ™. Each laboratory ran four sets of five assays including a control (positive cell line), 2 negative, and 2 positive samples.
Results: Technical validation results were: success rate 98.3%, r epeatability 100%, reproducibility 97.7%, limit of detection ⩽1%, analytical sensitivity 100%, and analytical specificity 92.3%. Nine different partners, including the rare partners AF17, AF10, MSF, and P300 were accurately identified in the clinical performance study. Furthermore, in two cases, the *MLL* Fusion*Chip*™ detected partners for which RT-PCR failed. The overall agreement between prior diagnostic analysis and the *MLL* Fusion*Chip*™ was >90%.