421 POSTER

A Phase Ib study to evaluate the pan-PI3K inhibitor GDC-0941 with paclitaxel and carboplatin with and without bevacizumab in non-small cell lung cancer patients

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Background: The PI3K-PTEN-AKT signaling pathway is deregulated in many cancer types. Increase in copy number of the PIK3CA gene is seen in up to 10% of non-squamous and 40% of squamous non-small cell lung cancer (NSCLC). Additionally, approximately 25% of NSCLC tumors show PTEN loss, and up to 33% harbor *KRAS* mutations. GDC-0941 has activity in NSCLC xenograft models of all genotypes including KRAS mutant models, and produces in vitro synergism with chemotherapy.
Methods: This study is designed to evaluate the pharmacokinetics, safety, and combination of GDC-0941 and a standard chemotherapy regimen used in NSCLC. Patients with NSCLC having received 0−1 prior chemotherapy regimens for advanced disease were eligible for this dose escalation study using a 3 + 3 design. GDC-0941 was given by mouth daily for 14 consecutive days in 21-day cycles. Paclitaxel (200 mg/m^2) and carboplatin (AUC 6 mg/mL min) with or without bevacizumab (15 mg/kg) were given intravenously on Day 1 of each cycle. In Cycle 1, GDC-0941 was given alone on Day 1 prior to initiation of chemotherapy with GDC-0941 on Day 2 for a total cycle length of 22 days.
Results: Ten patients were enrolled in 3 successive cohorts of 60, 100, and 165 mg of GDC-0941 in combination with paclitaxel and carboplatin in Arm A. The initial dose level of GDC-0941 in combination with paclitaxel, carboplatin and bevacizumab in Arm B was 100 mg. The most frequently reported adverse events related to study drugs were Grade 1 and 2 nausea, rash, anorexia, alopecia and vomiting consistent with the known safety profiles of GDC-0941, paclitaxel and carboplatin. Three patients had Grade 3 neutrophil counts that were not considered dose-limiting. No other Grade $\geqslant$3 related adverse events or dose-limiting toxicities were reported, and dose escalation continues in both arms. PK characteristics of GDC-0941, paclitaxel, 6-hydroxypaclitaxel and carboplatin were similar to historical single-agent profiles. One patient each at the 60 and 100 mg dose levels of GDC-0941 in Arm A experienced a confirmed partial response.
Conclusions: The combination of GDC-0941, paclitaxel and carboplatin is generally well tolerated, both with and without bevacizumab. Based on preliminary PK analysis, no PK interactions have been detected. The maximum tolerated dose of GDC-0941 for these combinations has not yet been identified, and dose escalation is ongoing. Antitumor activity has been observed.

Nanotechnology, drug delivery, new formulations, prodrugs

422 POSTER

Targeting the SH2 domain of Stat3 with phosphopeptide mimetic prodrugs leads to tumor growth inhibition and down-regulation of phosphoTyr705 Stat3 and angiogenic pathways

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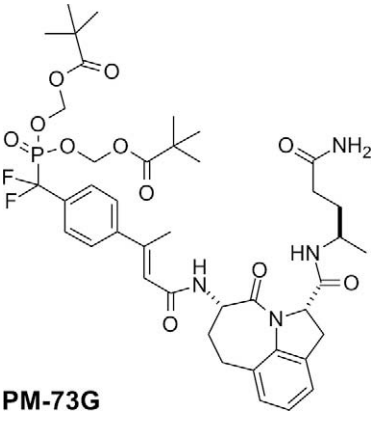
Background: Signal transducer and activator of transcription 3 (Stat3) transmits signals from IL-6 family cytokines, and growth factors such as EGF, VEGF, and PDGF. Stat3 is constitutively activated in cancers of the lung, head and neck, breast, prostate, AML, and others, and plays key roles in proliferation, survival, angiogenesis, and invasion. To uncouple Stat3 from its aberrant roles in cancer, we are targeting its SH2 domain with phosphopeptide mimetics derived from the recognition sequence, pTyr-Leu-Pro-Gln. Reported SH2 domain peptides targeted to Stat3, Grb2, and Src required >50 μM concentrations to inhibit their targets. Several small molecules such as resveratrol and sorafenib, have been shown to inhibit Stat3 phosphorylation in tumor cells. These are typically not selective for Stat3 and inhibit multiple pathways. Therefore a need exists for more selective and potent inhibitors of Stat3.
Material and Methods: A panel of cell-permeable, phosphatase-stable, peptidomimetic prodrugs such as PM-73G (Figure) were tested for inhibition of phosphorylation of Stat3 Tyr705, selectivity for the target versus other SH2 domains and signaling pathways, and for the ability to inhibit tumor cell growth *in vitro* and *in vivo*.
Results: A panel of prodrugs completely inhibited constitutive Stat3 phosphorylation at concentrations of ~500 nM in intact cultured tumor cells as judged by western blots. They were selective for Stat3 over Stat5, Src, and p85 (PI3K), and were 10-fold less potent for Stat1 phosphorylation. MAPK phosphorylation was not affected. Interestingly, very little growth inhibition in a panel of tumor cell lines was observed at concentrations that completely inhibit pStat3. Conversely, administration of PM-73G to MDA-MB-468 tumor xenografts *in vivo* resulted in reduced Stat3 pTyr705 and VEGF, determined by IHC and Western analyses of tumor tissue; tumor growth inhibition was also observed, and was accompanied by reduction in vascularization, as judged by reduced CD31 staining. Of note, neither survivin nor cyclinD1, both downstream of Stat3, were affected by treatment with PM-73G.
Conclusions: Selective Stat3 inhibition by targeting the SH2 domain *in vivo* appears to result in primarily a cytostatic, rather than cytotoxic mechanism, likely mediated through reduced angiogenesis. Further preclinical pre-clinical development of these novel, first-in-class prodrugs underway.



PM-73G

423 POSTER

Phase 1 dose escalation, safety and pharmacokinetic study of IT-101 (CRLX101), a novel nanopharmaceutical containing camptothecin, in advanced solid tumor cancer patients

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Background: IT-101 (CRLX101) is a novel polymeric nanoparticle comprised of biocompatible cyclodextrin-polyethylene glycol co-polymer conjugated to camptothecin (CPT). CPT is a potent, broad-spectrum antitumor agent that inhibits type I DNA topoisomerase. The polymeric nanoparticle formulation of the drug conjugate is specifically designed to (a) enhance delivery of active CPT to tumor tissue, (b) augment efficacy by prolonging therapeutic drug exposure to cancer cells, and (c) minimize toxicity by maintaining low systemic free drug level in circulation. IT-101 has demonstrated all three of these properties in pre-clinical animal model studies. A Phase 1 dose escalation study of IT-101 was conducted to assess safety, to characterize pharmacokinetics (PK), and to establish the maximum tolerated dose (MTD) in patients with advanced solid tumors.
Material and Methods: Patients with advanced solid tumors received IT-101 on a weekly x3 or an every-other-week schedule in a 28-day cycle. IT-101 was administered by intravenous infusion over 90 minutes. Serial plasma samples were analyzed for IT-101 and unbound CPT. Biological activity measurements were taken after every two cycles of therapy by CAT scan.
Results: Twenty-four (24) patients received IT-101 at 5 dose levels and on the 2 dosing schedules, ranging from 6 mg/m^2 to 18 mg/m^2 of CPT per dose. The every-other-week schedule was well-tolerated and an MTD was defined. The weekly $\times$3 schedule was found to have a less acceptable safety profile. Stable disease for greater than six (6) cycles of therapy was observed in four (4) patients, including two (2) with advanced non-small cell lung cancer (NSCLC). Safety and PK data will be presented along with a clinical data review from both dosing schedules.