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Safety, pharmacokinetics and preliminary activity of the anti-IGF-IR antibody CP-751,871 in patients with sarcoma

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Background: CP-751,871 is a fully human IgG2 monoclonal antibody targeting the insulin-like growth factor-1 receptor (IGF-1R). IGF-1R inhibition is a promising novel therapy for sarcoma. IGF-1R is implicated in both autocrine and paracrine control of sarcoma growth; its blockade increases apoptosis and decreases migration, invasion, metastasis, and angiogenesis in sarcoma models.
Methods: Two expansion cohorts of sarcoma and Ewing's patients (pts) >9 years of age were opened within the dose-escalation Phase I study. CP-751,871 was administered at a dose of 20 mg/kg q21 days in the sarcoma cohort and q28 days in the Ewing's cohort. The primary objective was to investigate safety and tolerability of CP-751,871 in this population. Secondary objectives included evaluating pharmacokinetics and preliminary efficacy (RECIST).
Results: Twenty-six pts were enrolled. Sarcoma subtypes treated were Ewing's (n = 13), synovial (n = 5), desmoplastic round cell tumors (DSRCT, n = 3), rhabdomyosarcoma (n = 2), fibrosarcoma (n = 2), and chondrosarcoma (n = 1). The median pt age was 35 years (range 12−63); 58% had an ECOG PS1. The median number of previous regimens was 3 (range 1−5). Pts received a median of 2 treatment cycles (range 1−16). Grade $\geqslant$3 treatment-related adverse events (CTCAE 3.0) reported included Grade 4 uric acid increase (n = 1) and Grade 3 bilateral deep-vein thrombosis (n = 1). Pharmacokinetics of CP-751,871 in sarcoma pts were comparable to those in other patient populations, with a half-life supporting the q21 and q28 days schedules. Among 20 pts evaluable for response, we observed one confirmed and ongoing PR (to date 8 months) in a 12-year-old Ewing's sarcoma, and disease stabilization of $\geqslant$ 6 months in 4 pts (1 fibrosarcoma, 1 synovial and 2 Ewing's sarcoma). In addition, 4 pts experienced disease stabilization for $\geqslant$ 3 months (2 Ewing's sarcoma, 1 DSRCT and 1 chondrosarcoma). Seven Ewing's sarcoma pts remain on study.
Conclusion: CP-751,871 given q21 days or q28 days was well tolerated in pts with relapsed and/or refractory sarcoma. Promising preliminary activity in Ewing's sarcoma warrants further investigation in Phase II trials.

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Phase I study of the ribosome inactivating protein prodrug TST10088 (TST88) in patients with advanced solid tumors

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Background: Ricin is a ribosome inactivating protein that inhibits protein synthesis through depurination of a single adenosine in ribosomal RNA. TST88 is a novel recombinant ricin-based prodrug activated by matrix metalloproteinases (MMPs). TST88 is activated through an MMP-specific recognition sequence, selectively targeting tumor cells where high levels of MMPs are expressed. This study aimed to determine the maximum tolerated dose (MTD) and the recommended phase II dose (RPTD) of TST88 when given intravenously on days 1, 8 and 15 every 4 weeks. Secondary endpoints include pharmacokinetics (PK), immunogenicity, safety and antitumor activity.
Methods: Dose escalation was conducted in two stages. In the initial phase, single patients received increasing (2x) doses of TST88 from 0.01 mg/m^2 to 0.64 mg/m^2. Thereafter, a modified Fibonacci scheme was used with sequential cohorts of 3−6 patients to escalate doses from 1.1 mg/m^2 to 5 mg/m^2.
Results: Forty patients have been enrolled to date: median age=59 (range: 21−78); F:M = 18:22; ECOG 0:1:2 = 8:28:4. Primary tumor sites were colorectal (7), lung (5), breast (4), pancreas (4) and others (20). Seventy-eight cycles of TST88 have been administered (median 2; range: 1−8). Adverse events (AEs) at least possibly related to TST88 in over 15% of the patients included fatigue, fever, chills, nausea, anorexia, vomiting, anemia, hypophosphatemia and flu-like symptoms. AEs were generally CTCAE grades 1−2 and reversible. At 3.8 mg/m^2, pre-medications were prescribed to prevent or ameliorate dose-dependent acute infusion reactions. A combination of acetaminophen, histamine antagonists and corticosteroids was found to be ineffective, whereas the COX-2 inhibitor celecoxib given alone at 200 mg for 3 doses during the night before, 1 hour prior to TST88 dosing and the evening of dosing significantly reduced and attenuated this toxicity. One DLT of grade 3 flu-like symptoms was encountered at 5 mg/m^2 among 3 patients, however long-term administration of this dose was felt to be intolerable despite celecoxib pre-medication. The RPTD is 3.8 mg/m^2 with celecoxib pre-medication. PK curves were biphasic with an initial half-life of 2 hours and a terminal drug half-life of approximately 8 hours. Cmax and AUC correlated well with dose. Anti-TST88 antibody titers typically rose between days 22 and 36 and plateaued during cycle 2. In the presence of antibodies, Cmax was unchanged, however initial and terminal half-lives were decreased to about 1 and 5 hours, respectively. Response data are available for 35 evaluable patients, with 7 patients achieving stable disease as best response. Expansion is ongoing at 3.8 mg/m^2 with celecoxib pre-medication.
Conclusions: TST88 is tolerable with celecoxib pre-medication and exhibits favorable PK profiles. Disease stabilization has been observed, and further development of TST88 in combination with cytotoxic agents is being planned.

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A Phase I dose-escalation study of XL228, a potent IGF1R / Src inhibitor, in patients with advanced malignancies

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Background: XL228 is a small molecule inhibitor of IGF1R and Src, protein kinases known to promote survival, proliferation, and migration of cancer cells. A Phase 1 dose escalation study was initiated to identify the maximum tolerated dose (MTD) and characterize the safety, pharmacokinetics (PK), and pharmacodynamics of XL228 when administered to patients (pts) with advanced malignancies.
Methods: XL228 is administered as a weekly one-hour IV infusion in pts with solid tumors, multiple myeloma, or lymphoma for whom there are no approved therapies to prolong survival. The study treatment period consists of a 4-week cycle, followed by an optional treatment extension period consisting of 4-week cycles. Four cohorts (13 pts) have been enrolled as of 15 May 2008.
Results: XL228 has been dosed at 0.45, 0.9, 1.8 and 3.6 mg/kg. Eight of 12 evaluable pts remain active and continue to receive XL228 weekly; the longest time on study has been experienced by pts with small cell lung cancer (7+ cycles) and perirectal leiomyosarcoma (4+ cycles). There have been no dose-limiting toxicities or drug-related serious adverse events in this study reported to date. Grade 1 or 2 adverse events (preliminary, unaudited safety data) which are possibly related to study drug include the following: irritation at the infusion site, fatigue, nausea, and post-infusion hyperglycemia. Post-infusion asymptomatic AV block with PVCs was detected in a single pt, and subsequently found to be present both pre- and post-infusion after a 48-hour Holter monitor study. PK analysis of the first 3 cohorts has demonstrated a slightly greater than dose-proportional increase in exposure, with the mean terminal half life of the first three cohorts ranging from 47 to 55 hours, and marked tissue distribution. There were substantial changes in phosphorylation of Src kinase substrates in PBMC after XL228 infusion; decreases of up to 78%-100% were measured in Pyk2 Y402, Src Y416, and p56Dok2 Y351 phospho-epitopes. Rapid and transient increases in plasma glucose and insulin levels after infusion suggest on-target inhibition of the IGF1R/IR pathways. Additional pharmacodynamic studies evaluating the effects of XL228 on IGF1R and Src signaling pathways in hair and skin will be presented.
Conclusions: XL228 has thus far been generally well tolerated and has demonstrated favorable PK and target modulation. Several pts remain on study with stable disease. The MTD has not yet been defined, and dose escalation is ongoing.