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An Intravenous Phase I Trial of PV701, a Replication-Competent Virus, in the Treatment of Patients with Advanced Solid Cancers

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Late-stage cancer patients (N=79) were enrolled in a phase I trial of intravenous PV701, an oncolytic strain of Newcastle disease virus. The dose was escalated between cohorts to a dose intensification of >100-fold. The most common AEs were flu-like symptoms. These AEs occurred principally on the first dose (1.2E+10 PFU/m^2) and were reduced with each subsequent dose. First dose "desensitization" permitted a 10-fold increase for all subsequent doses. Tumor-site specific AEs [tumor inflammation, dyspnea only in patients with lung tumors, and elevated transaminases only in patients with liver metastasis] were also observed. One renal cancer patient, with an 8 cm lung tumor and baseline reduced pulmonary capacity, died of respiratory failure with severe edema/inflammation manifested predominately in the tumor-bearing lung. Signs of efficacy were observed, especially at the higher dose levels of PV701. These included two radiographic objective responses (CR-head and neck; PR-colon), 1 histologic PR (mesothelioma) and 6 cases of measurable tumor reductions. Progression-free survival of 4-30 months (ongoing) was observed in 13 patients. PV701 particles in tumor tissue obtained after 11 months of therapy were shown by EM. A lymphoplasmacytic infiltrate in that tumor tissue also was noted. Additional clinical studies (phase I and phase II) are planned.

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Preclinical Studies with PV701, a Replication-Competent Oncolytic Strain of Newcastle Disease Virus.

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PV701, a naturally attenuated, replication-competent isolate of a Newcastle disease virus vaccine strain exhibited potent and selective *in vitro* killing of eighty percent (43/54) of human tumor cells evaluated relative to normal cells. High rates of tumor regression were observed using human tumor xenografts implanted in athymic mice following a single intratumoral injection of PV701 (>75% complete and partial regression with 3E+8 PFU in five tumor lines tested). Efficacy in the treatment of ovarian tumors was also demonstrated by the intraperitoneal route. Intravenous administration of PV701 could elicit complete regression of subcutaneous fibrosarcoma xenografts at doses less than 1/100 of the IV MTD (6E+6 vs 8E+8 PFU). Three days following a single IV administration of PV701, high concentrations of infectious virus were recovered from tumor. By contrast, no infectious virus was recovered from normal heart, lung, brain, liver or kidney reflecting the *in vivo* tumor cell specificity of PV701 in this model. No tumor regressions were observed with UV-killed PV701, demonstrating that replication-competent virus is required for efficacy. A repeat IV dose regimen was more efficacious than a single dose regimen. In repeat dosing studies the initial dose lessened the toxicity of subsequent doses. Desensitization to toxicity is is consistent with the demonstrated role of pro-inflammatory cytokines like TNF-alpha in mediating PV701 toxicity. Thus, repeat dosing with PV701 increased efficacy without increased toxicity. These studies provided data to support an intravenous phase I clinical trial of PV701 for the treatment of patients with advanced solid cancers.

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Systemic administration of replication-selective adenoviruses.

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Replication-selective viruses and bacteria are being developed for the treatment of cancer. dl1520 (Onyx-015 or CI-1042, Pfizer) is an E1B-55kD gene-deleted replication-selective adenovirus (1-4) that was the first genetically-engineered, replication-selective virus to enter trials in humans. We used a staged clinical development approach that proceeded from intratumoral (i.t.) to intraperitoneal (i.p.), intra-arterial (i.a.) and eventually intravenous (i.v.) administration. Over 230 cancer patients have been treated to date, including 174 i.t. (head and neck, pancreatic, GI met. to liver), 16 i.p. (ovarian), 31 i.a. (hepatic artery for colorectal met. to liver), 10 i.v. (lung met., any carcinoma). dl1520 has been well-tolerated by all routes of administration, including doses of up to 2x1012 particles i.a. and 2x1013 particles i.v.. Common toxicities included fever (typically grade 2-3 i.a./ i.v.), asthenia and injection site pain (i.t.). Clinically-relevant hepatotoxicity due to dl1520 was not demonstrated, although transient grade 1-2 transaminitis was documented in some patients following i.v. infusion at doses >2x1012 particles. Reproducible evidence of viral replication was obtained (within <10 days) following 1) i.t., i.a. and i.v. administration, 2) in head and neck and colorectal cancer patients but not in pancreatic (i.t.) or ovarian (i.p.) carcinomas; no patient had replication documented >10 days after treatment. Single agent-induced objective tumor regressions were demonstrated in head and neck cancers (15-20%) but not in pancreatic, colorectal, ovarian or metastatic lung tumors. Evidence for potential synergy with chemotherapy has been obtained from head and neck (i.t.) and colorectal cancer patients (i.a.) (5) (6). IL-1, IL-6, IL-10, interferon-gamma and TNF levels all increased acutely following i.a. and/or i.v. administration (6) (7).

Given the clear documentation of safety and feasibility with this approach following intravascular administration, but the lack of significant single agent efficacy to date with dl1520, we carried out preclinical studies of intravenous treatment with a significantly more potent adenovirus dl922/947 (E1A mutant) in nude mouse-human tumor xenograft models; antitumoral effficacy was significantly supreior to dl1520 in all models, and equivalent to or even superior to wildtype adenovirus i.v. The replication-selective virus approach has promise as a systemic treatment for cancer.