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SMALL MOLECULE PAN-BCL2 FAMILY INHIBITOR OBATOCLAX (GX15-070): OVERVIEW OF CLINICAL PHASE I STUDY RESULTS.

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BACKGROUND: Obatoclax (GX15-070) is a synthetic small molecule which inhibits the binding of the antiapoptotic proteins bcl-2, bcl-xl, bcl-w and mcl-1 to the proapoptotic proteins bax and bak. It shows broad single agent cytotoxicity in cancer cell lines in vitro and in vivo.

INDIVIDUAL PHASE I STUDIES:

STUDY 1: Bcl-2 family proteins are universally overexpressed in Chronic Lymphocytic Leukemia (CLL) in which accumulation of malignant cells is thought to be the direct result of the consequent inability to undergo apoptosis. Obatoclax was shown to induce apoptosis in human B-CLL cells ex vivo. This completed study used accelerated dose escalation of 1-3 h infusions every 3 weeks with single intra-patient dose escalation allowed in patients with CLL. To assess obatoclax's direct effect on the release of proapoptotic proteins, the relative levels of activated bak/bax hetero oligomers were monitored serially in PBMNCs following dosing. Induction of apoptosis was monitored quantitatively with serial determinations of plasma concentration of histone-oligonucleosomal DNA (ODNA) complexes. 12 patients enrolled at doses ranging from 3.5-14 mg/m² administered using a 1 hr infusion and 13 patients at 20-40 mg/m² using a 3 hr infusion. Median age was 61 (range 46-76), Rai stage was III-IV in 19 and median number of prior therapies was 4 (range 2-10). The most frequent adverse events (AE) have been somnolence grade 1 (40%) or 2 (19%) and euphoria grade 1 (47%) or 2 (9%) occurring during or shortly following the infusion. Other AE's reported in ≥25% of patients were transient O₂ desaturation (25%), AST increase (34%) and fatigue (34%). Dose-limiting toxicities have been Grade 3 infusional neurological events such as somnolence, ataxia and dysphoria. Doses ≥10 mg/m² were associated with a significant increase in activated bak/bax hetero oligomers sustained for up to 8 hrs at the higher doses evaluated. An early release of ODNA occurred 1-6 hrs after the start of the infusion. A secondary increase occurred with a noticeable lag time from the peak plasma obatoclax concentration (24 to 168 hrs after the start of the infusion). There was a correlation between peak plasma ODNA concentration (median = 400 range 0-4358 AU/mL) and dose (threshold effect at 14 mg/m²) as well as AUC (max ODNA 2x baseline if AUC < 180 ng.hr/mL vs. 15 x baseline when AUC ≥ 180 ng.hr/mL; p < 0.015). 18/25 patients showed reduction of peripheral lymphocyte counts (mean of 29%). Best clinical responses assessed by CLL Workshop Criteria are unconfirmed PR in 1. In addition, 4/14 patients with baseline platelet count < 100,000/mm³ showed sustained elevations of platelet counts by ≥50% including two patients improving from 70,000 to

144,000/mm³ and 47,000 to 105,000/mm³; 3/11 patients who were anemic at baseline showed sustained elevations of Hb from 8.7 to 10.6 g/dL, 7.9 to 13.9 g/dL and 8.7 to 9.8 g/dL, the latter two achieving transfusion independence.

STUDY 2: In this ongoing study using a standard titration design, 5 cohorts of 3-6 patients with refractory solid tumors or lymphomas were treated with obatoclox at doses of 5mg/m² – 20 mg/m² IV infused over 3 hours, weekly. Each cycle of therapy consisted of 4 weekly infusions. N=18 pts were treated. Median age was 59 (range 24-71). A total of 180 infusions have been administered to date. Obatoclox underwent first order elimination kinetics with a short initial distribution phase (α t_{1/2}=0.6 h), followed by a longer elimination γ phase (t_{1/2}=43.8 h). C max and AUC were proportional to dose and at the 14 mg/m² dose level, median C max and AUC values were 98 ng/ml and 276 ng.hr/ml, respectively. The coefficient of variation was low at 38%. Adverse events have mostly been observed during or shortly after the infusion and have been transient. The most common pertain to the central nervous and gastro-intestinal systems (drowsiness, euphoria, ataxia, and abdominal pain). Most toxicities were mild to moderate, with the exception of grade 3 pain experienced by 2/2 pts with Hodgkin's disease, that resolved rapidly but resulted in treatment discontinuation in 1 patient. One episode of Grade 3 infusional CNS toxicity was reported at 14 mg/m² requiring the inclusion of 6 patients with no further DLT. No neutropenia, thrombocytopenia or lymphopenia have been reported. The MTD has not been reached. 6 Patients showed stable disease \geq 8 weeks, including a patient with refractory Non-Hodkin's lymphoma (NHL) with objective stabilization for 47+ weeks.

STUDY 3: In this ongoing study using a modified accelerated titration design, cohorts of 3-6 patients with refractory acute myeloid leukemia (AML), CLL or myelodysplastic syndromes (MDS) have been treated with obatoclox at doses of 7mg/m² – 40 mg/m² IV infused over 24 hours, every 2 weeks (N=14). Incidence and severity of nervous system and psychiatric AEs were less in this study using a 24-hour infusion than in studies using a shorter 3-hour infusion at the same dose levels. 3/8 patients with MDS experienced significant increases in cytopenias with suspension of platelet or red blood cell transfusional needs, including in 2 patients with secondary MDS. Reduction in bone marrow and peripheral blood blast counts have also been observed in MDS and refractory AML patients.

CONCLUSIONS: Single agent obatoclox produces relevant biological and clinical activity in patient with refractory malignancies. Clinical activity has been manifested by improvement in peripheral cytopenias and reduced red blood cell and platelet transfusion requirements in refractory CLL and MDS, regression or long term stabilization of adenopathy in refractory CLL and NHL, and reduction in marrow and peripheral blood counts in MDS and refractory AML. Common toxicities are neurological in nature (somnolence, euphoria), infusion related and mitigated by prolongation of the infusion duration. No myelosuppression, mucositis or cumulative toxicities have been noted. Single agent Phase II and combination Phase I studies are scheduled to start 3Q 2006.