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Forodesine

Forodesine is a potent, selective, transition state inhibitor (i) of the enzyme purine nucleoside phosphorylase (PNP). It's mechanisms of action is distinct from other purine nucleoside analogues in that forodesine does not act through interaction with nucleic acid. Selective PNPi leads to intracellular accumulation of dGTP in target lymphocytes and subsequent apoptosis. *In vitro*, T-cell lymphocytes are sensitive to forodesine. Based on these observations, a series of studies in subjects with cutaneous T-cell lymphoma were performed with single agent forodesine.

Using the intravenous formulation administered Q12H for 5 days on and 9 days off repeated as a 14-day course, no maximum tolerated dose (MTD) was reached up to 135 mg/m^2 Q12H in this dose-escalation phase 1 study (BCX1777-103). At study entry, 12/13 subjects with relapsed CTCL were ≥ Stage IIb. There were 4/13 (31%) observed responses, all partial as defined as a weighted score of skin, lymph nodes and Sezary cell count assessments. Because of the convenience of an oral formulation, a phase 1/2 study of the oral formation was performed (BCX1777-105) in relapsed CTCL. No MTD was reached up to 320 mg/m^2 using oral capsules on a QD schedule in the phase 1 portion (n=14). A phase 2 extension was performed using a dose of 200 mg QD (cohort 1, n=30) or 300 mg (cohort 2, n=15). For 200 mg, there were 2 CRs and 9 PRs (RR 11/30=37%). For 300 mg, there were 2 PRs (2/15=13%). Responses were defined by mSWAT scores and confirmation of response 28 days later was required in this analysis. The most common related adverse events in the Phase 2 study were edema (22%), fatigue, nausea (each 17%), pruritis (13%), diarrhea, headache (each 8%). 19% of subjects experienced a related grade 3 adverse event. There no related grade 4 adverse events. Grade 3 or higher lymphopenia was observed in 67% of subjects and CD4 counts <200 were observed in 27% of subjects.

Based on these data, a pivotal trial was planned and a Special Protocol Assessment with the FDA gained agreement. BCX1777-203 was initiated 10 October 2007 as a single arm study of single agent forodesine 200 mg QD administered to subjects with CTCL who have failed at least 3 prior systemic therapies. Response rate is the primary end point and enrollment is proceeding.