CPX-351: A Randomized Phase 2b Study of CPX-351 v. Intensive Salvage Therapy in ≤65 Yo First Relapse AML Patients: Initial Efficacy and Safety Report

Background
CPX-351 is a liposomal formulation containing a 5:1 molar ratio of cytarabine (Ara-C) and daunorubicin (DNR) shown to maximize anti-tumor synergy. Preclinical studies demonstrated accumulation of CPX-351 within bone marrow with preferential uptake of liposomes by leukemia cells. A Phase 1 study using 90-minute I.V. infusions on Days 1, 3, and 5 found the MTD to be 101 u/m2 (1 u = 1 mg Ara-C + 0.44 mg DNR) and demonstrated marked prolongation of plasma Ara-C and DNR half-life. Eighteen of the 45 AML patients were in 1st relapse with 8 patients <65 years of age. All 8 achieved aplasia and 4/8 achieved CR after CPX-351. (Feldman E, et al. Blood 2008;112:Abst 2984). On this basis, a randomized Phase 2b study was initiated in first relapse AML patients comparing CPX-351 against investigator’s choice of salvage regimen. This report summarizes initial safety and response data for patients randomized and followed >60 days.

Methods
Patients ≤65yo with AML in 1st relapse after an initial CR lasting >1 month with ECOG PS= 0-2, SCr < 2.0 mg/dL, total bilirubin < 2.0 mg/dL, ALT/AST < 3 x ULN, and LVEF > 50% were eligible. Patients were randomized 2:1 to receive CPX-351 (100 u/m2; D 1, 3, 5) or investigators choice of intensive salvage treatment. Up to 2 inductions and 2 consolidation courses were allowed. Post remission treatment with hematopoietic stem cell transplantation (HSCT) was permitted. Patients were stratified using the European Prognostic Index (EPI) (Breems DA, et al. J Clin Oncol, 2005 Mar 20;23:1969-1978). The primary efficacy endpoint is % survival at 1-year and 2nd efficacy endpoints include CR+ CRi rate, CR+ CRi duration, EFS, aplasia rate (<5% blasts + <20% cellularity), and % referred for HSCT. Deaths at Day 30 and 60 and SAE frequency were monitored.

Results
As of November 12, 2010, 126 patients were accrued at 35 of 46 sites in the US, Canada, France and Poland. 94% had received prior anthracycline therapy. Most patients had a single induction (88% v. 93%) and salvage consisted mostly of MEC (51%) or 7+3 (16%). Demographic and EPI risk factors were well balanced except for prior HSCT (27% (CPX-351) vs. 18% (7+3)).
Compared to control, CPX-351 had greater anti-leukemia activity based on rate of aplasia (90% vs. 60%) and CR + CRi rate (51% vs. 42%). A greater response improvement with CPX-351 vs. control was observed in the EPI unfavorable group (23/56 (41.1%) vs. 9/30 (30%)) as well as in patients with no history of prior HSCT (56% vs. 41%).

Early deaths (<Day 60) were equivalent in the CPX-351 (12/81 (15%)) and salvage (7/45 (16%)) arms with progressive leukemia the cause in 9/19 patients. Patients with prior HSCT accounted for a disproportionate number of early deaths on the CPX-351 arm (6/12) compared to only 1/7 early deaths on salvage. Among the 126 patients, 1 or more SAEs were reported in 53/81 (65%) CPX-351 patients and 22/46 (49%) salvage patients. Serious infections and bleeding accounted for the majority of the SAEs in both arms. Grade 3-5 sepsis was reported more frequently on the CPX-351 arm than on salvage therapy.

**Conclusion**

In this Phase 2b randomized trial, CPX-351 has substantial clinical activity and is safe compared to salvage therapy. Improved efficacy was observed in patients with unfavorable EPI scores and in those with no history of HSCT. Longer myelosuppression with CPX-351 led to increased febrile neutropenia and infections. These initial data support further investigation of CPX-351 in first relapse AML patients. This study is expected to be completed in November 2011 and final results (including EFS + OS analyses) will be available at that time.