

**Title: A Phase II Pilot Study of Bortezomib (PS-341, Velcade, IND# 58,443) Combined with Reinduction Chemotherapy in Children and Young Adults with Recurrent, Refractory or Secondary Acute Myeloid Leukemia (AAML07P1)**

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**Synopsis:**

This study proposes to test the hypothesis that the addition of bortezomib to Acute Myeloid Leukemia (AML) relapse regimens (idarubicin/cytarabine or etoposide/cytarabine) will improve the overall response rate in children with relapsed/refractory/secondary AML without significantly increasing the toxicity. This study will combine bortezomib with two different regimens with proven efficacy in relapsed AML. For patients below a threshold cumulative anthracycline dose (400 mg/m<sup>2</sup>), bortezomib will be combined with a regimen containing idarubicin and cytarabine (Arm A; CIB). For patients with higher than the threshold cumulative anthracycline dose, bortezomib will be combined with etoposide and cytarabine (Arm B; CEB), a safe and efficacious non-anthracycline containing regimen.

Arm A will be opened groupwide in an Efficacy Phase. Arm B will initially be opened in a limited institution Dose-Finding Phase which will determine the dose of bortezomib that is safe and tolerable in combination with the Arm B chemotherapy regimen of high-dose cytarabine and etoposide. Arm B is not open at CHRCO currently.

The groupwide Efficacy Phase for both arms will determine 1) the toxicities and tolerability of bortezomib when added to these reinduction regimens, and 2) whether bortezomib increases the response rate (CR+CRp) in children and young adults with relapsed/refractory/secondary AML when added to the standard AML reinduction regimens. When the study is opened groupwide in the Efficacy Phase, both arms will have two stages, with enrollment temporarily suspended after completion of accrual to the first stage for interim assessment of tolerability and response. Secondary objectives will examine the effects of bortezomib on NF- $\kappa$ B binding activity, proteasome inhibition, and the feasibility of measuring the leukemia stem cell population before and after chemotherapy.