In Vivo Assessment of the Next Generation Microtubule-Destabilizing Agent AB8939 in Patient-derived Xenograft Models of Acute Myeloid Leukemia

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AB8939 is a novel, synthesized, small-molecule microtubule-destabilizer drug with proven prolific and potent *in vitro* activity against numerous cancer cell lines. *In vitro* and *ex vivo* studies (reported separately) have determined that AB8939 is well-suited for the treatment of hematopoietic tumors, in particular relapsed/refractory or poor-prognosis acute myeloid leukemia (AML), notably being able to circumvent two major resistance mechanisms associated with AML (i.e. P-glycoprotein and myeloperoxidase-mediated resistance).

The therapeutic potential of AB8939 was investigated further through a series of *in vivo* experiments using three patient derived xenograft (PDX) mouse models and a cytarabine (Ara-C) resistant mouse model (MOLM14). MOLM14 cells and selected PDX primary cells were transduced to constitutively express luciferase for bioluminescence monitoring of tumor growth.

In an Ara-C-sensitive AML PDX mouse model (*ex vivo* IC_{50} response to Ara-C in survival/proliferation assays was 0.82 µM), AB8939 (6 mg/kg in weekly cycles of 5 consecutive days) showed a statistically significant, 10-fold decrease in the amount of blasts detected in blood following 14 days of treatment compared with control, and a superior treatment effect compared with Ara-C (single cycle of 10 mg/kg twice per day for 4 consecutive days) in terms of decreased blasts in blood.

In an Ara-C-refractory AML PDX mouse model (*ex vivo* IC_{50} response to Ara-C in survival/proliferation assays was 6.4 µM), animals treated with single agent AB8939 (6 mg/kg in weekly cycles of 5 consecutive days) showed reduced disease progression compared with control and Ara-C (single cycle of 10 mg/kg twice per day for 4 consecutive days) as evidenced from at least 10-times fewer blasts in blood, spleen and bone marrow following 28 days of treatment. This effect was even more pronounced for the combination treatment of AB8939 and

Ara-C, suggesting a synergistic response.

In a PDX mouse model that is highly resistant to Ara-C (*ex vivo* IC_{50} response to Ara-C in survival/proliferation assays was 8.3 µM), AB8939 as a single agent or in combination with Ara-C showed a significant ($P < 0.001$) decrease in tumor growth and reduction of blasts in blood with respect to Ara-C and control, following 27 days of treatment (8 animals per group). This improvement translated to survival benefit, with the single agent AB8939 cohort having a median survival of 89 days compared with 69 days and 65.5 days in the control and Ara-C cohorts, respectively. Indeed, all animals treated with single agent AB8939 were still alive at D83 post injection, which was 30 days after treatment was stopped. AB8939 as a single agent was well-tolerated with no toxicity-related deaths or impact on body weight. A greater treatment effect was again observed for the AB8939 plus Ara-C combination; however, clear signs of higher toxicity mean it will be imperative to optimize dosage of both AB8939 and Ara-C if used in combination.

For the well-established xenografted MOLM14 mouse model, immune-deficient NSG (NOD scid gamma) mice (5 animals per group) were injected intravenously with MOLM14-luciferase cells and treated over a period of 21 days with single agent AB8939 (subcutaneous injection) at a dosage of 6 mg/kg every day or 12 mg/kg every other day; Ara-C (intraperitoneal injection, single cycle of 10 mg/kg twice per day for 4 consecutive days); or vehicle. AB8939 caused a significant dose-dependent reduction in tumor volume ($p=0.001$) and increased survival with respect to control or single agent Ara-C (median survival at 6 and 12 mg/kg was 39 and 42 days, respectively, corresponding to a 60% improvement compared with the control and Ara-C groups). A similar dosing schedule study showed single agent AB8939 at 6 mg/kg administered over 6 consecutive days (6 ON/1 OFF) was optimal with this cohort having a median survival of 59 days, corresponding to a 100% improvement over control.

Overall, these *in vivo* data provide compelling proof-of-concept for AB8939 as a treatment of AML. AB8939 administered alone or in combination with Ara-C was demonstrated to significantly increase survival and reduce tumor growth as compared with single agent Ara-C in relevant animal models of AML. A first in human, phase 1 trial evaluating AB8939 in AML patients unfit to receive intensive chemotherapy in second and third-line has been initiated.