AB8939, A NOVEL MICROTUBULE-DESTABILIZING AGENT FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA

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INTRODUCTION

➢ Compound AB8939 is a structurally novel, small chemical molecule, synthesized tubulin inhibitor
➢ AB8939 directly inhibits tubulin polymerization (µM range) in a dose-dependent manner
➢ AB8939 produces strong mitotic arrest via destabilization of the microtubule network by binding to the colchicine site

OBJECTIVES

➢ In vivo and ex vivo studies to evaluate anti-proliferative action of AB8939 against AML blasts isolated from patient samples (n=99) and its therapeutic potential in PDX mouse models
➢ In vitro studies characterize AB8939 mechanism of action in AML

RESULTS: ASSESSMENT OF AB8939 IN ACUTE MYELOID LEUKEMIA

➢ AB8939 overcomes multidrug resistance
  ○ AB8939 blocks proliferation of the Pgp-overexpressing, drug-resistant MEG-01/M2 cell line in a 6-day proliferation/survival assay
  ○ Stimulation of Pgp ATPase activity by AB8939 compared with substrates of Pgp (doxorubicin and verapamil) show that AB8939 is not a substrate of Pgp (CA-4 is Pgp-negative control)

➢ AB8939 substantially decreased the concentration of blasts in blood (38d post-graft), bone marrow (BM) and spleen (52d post-graft) relative to azacitidine (Vidaza®), a widely used hypomethylating agent for AML.

➢ AB8939 eradicates blasts from marrow in an AML126 PDX model
  ○ 3-week AB8939 treatment period (2 mg/kg 1x. 3d ON / 4d OFF for 2 weeks, then 5 mg/kg 3d ON / 4d OFF for 4 weeks)
  ○ AB8939 showed strong anti-leukemic activity with near eradication of blasts
  ○ AB8939 was well-tolerated with no toxicity-related deaths and no impact on body weight or behavior
  ○ No blasts could be detected in 6 / 8 mice treated with AB8939

○ The potential of AB8939 to overcome Ara-C resistance (IC50 > 5 µM) was demonstrated in proliferation assays (99 AML patient samples)
  ○ 66% of Ara-C-resistant blasts were sensitive to AB8939
  ○ 69% of blasts had nanomolar sensitivity (IC50 ≤ 500 nM)
  ○ 44% of blasts were very sensitive (IC50 ≤ 100 nM)

➢ AB8939 also showed broad anti-proliferative activity across the entire range (M0–M7) of AML subtypes

➢ Therapeutic potential of AB8939 in AML demonstrated in vivo using an Ara-C resistant (IC50=8 µM) PDX model
  ▶ Single agent AB8939: significant decrease in tumor growth, concentration of blasts in blood and bone marrow
  ▶ AB8939 plus Ara-C: significant decrease in disease burden (DSS post graft; D27 treatment)

CONCLUSIONS

➢ AB8939 overcomes P-glycoprotein (Pgp) and myeloperoxidase (MPO) mediated resistance
➢ AB8939 is active in Ara-C resistant/refractory AML
➢ AB8939 activity seen across all AML subtypes
➢ AB8939 alone or combined with Ara-C, improved survival and reduced disease burden relative to Ara-C
➢ AB8939 is active in azacitidine resistant AML, with greatly reduced hematotoxicity
➢ Findings support development of AB8939 as a treatment of relapsed/refractory AML patients unable to receive intensive chemotherapy

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