



EUROPEAN
HEMATOLOGY
ASSOCIATION

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

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

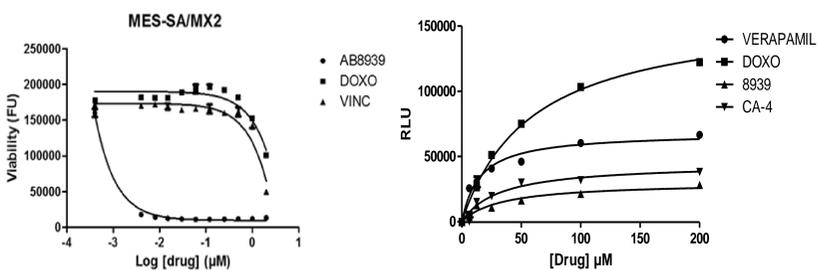
ACKNOWLEDGEMENTS

AB8939 STUDY GROUP*

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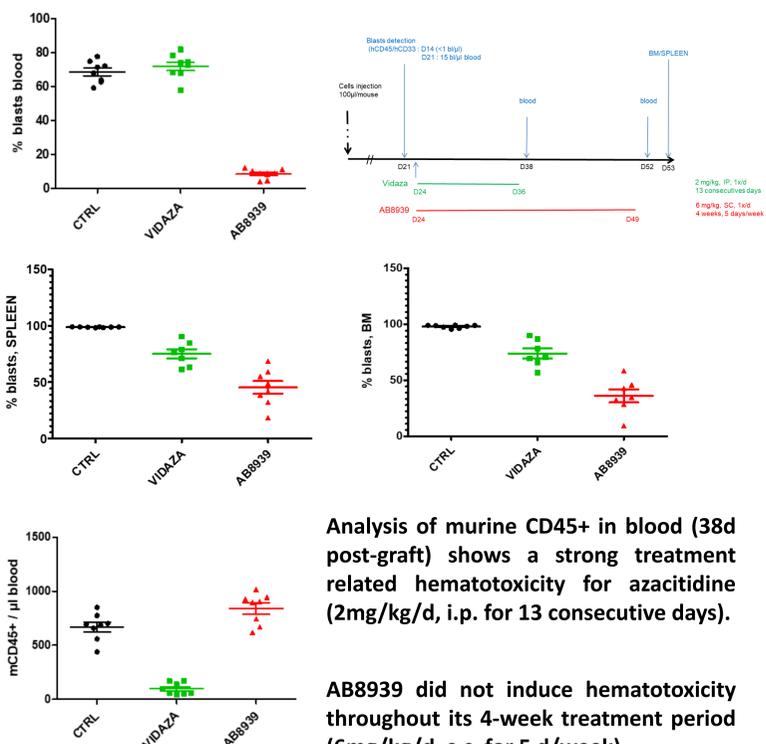
RESULTS: ASSESSMENT OF AB8939 IN ACUTE MYELOID LEUKEMIA

- AB8939 overcomes multidrug resistance
 - AB8939 blocks proliferation of the Pgp-overexpressing, drug-resistant MES-SA/MX2 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)

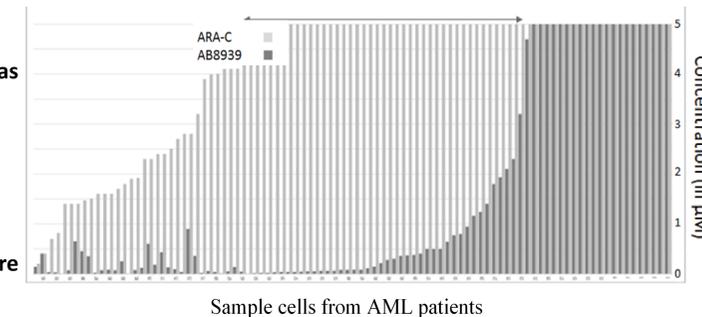


- Therapeutic potential of AB8939 in AML demonstrated *in vivo* using an azacitidine resistant ($\text{IC}_{50} \sim 13 \mu\text{M}$) PDX model (M1 subtype)

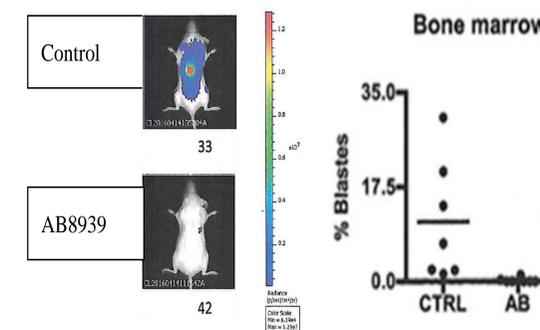
AB8939 substantially decreased the concentration of blasts in blood (38d post-graft), bone marrow (BM) and spleen (52d post-graft) relative to azacitidine (Vidaza®), a widely used hypomethylating agent for AML



- The potential of AB8939 to overcome Ara-C resistance ($\text{IC}_{50} > 5 \mu\text{M}$) 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 ($\text{IC}_{50} \leq 500 \text{ nM}$)
 - 44% of blasts were very sensitive ($\text{IC}_{50} \leq 100 \text{ nM}$)
- AB8939 also showed broad anti-proliferative activity across the entire range (M0–M7) of AML subtypes



- AB8939 eradicates blasts from marrow in an AMKL26 PDX model
 - 3-week AB8939 treatment period (2 mg/kg i.v. 3d ON / 4d OFF for 2 weeks, then 5 mg/kg 3d ON / 4d OFF for 1 week)
 - 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



- Therapeutic potential of AB8939 in AML demonstrated *in vivo* using an Ara-C resistant ($\text{IC}_{50} \sim 8 \mu\text{M}$) 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 (D55 post graft; D27 treatment)

