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

O. HERMINE[1,2], M. HUMBERT[2], A. GOUBARD[2,3,4], C. AUCLAIR[2,5], C. MANSFIELD[2], P. DUBREUIL[2,3], ON BEHALF OF THE AB8939 STUDY GROUP*

1: Imagine Institute, INSERM UMR 1163 and CNRS ERL 8254, Hopital Necker, Paris. 2: AB Science, Paris. 3: Centre de Recherche en Cancérologie de Marseille (CRCM), INSERM, CNRS, Aix-Marseille Univ, Institut Paoli-Calmettes, Marseille. 4: TrGET Platform, CRCM-U1068, Marseille, 5: Biology Department, ENS Paris-Saclay, Paris-Saclay University, Paris. France.

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

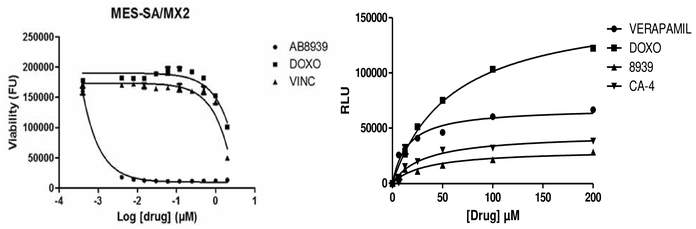
ACKNOWLEDGEMENTS

AB8939 STUDY GROUP*

Auclair C, Audebert S, Benjahad A, Castellano R, Casteran N, Collette Y, Gigant B, Goubard A, Gros L, Hajem B, Kinet J-P, Letard S, Lopez M, Mercher T, Montersino C, Moussy A, Neves M, Pez D, Rebuffet É, Siovashian S, Verdier Pinard P

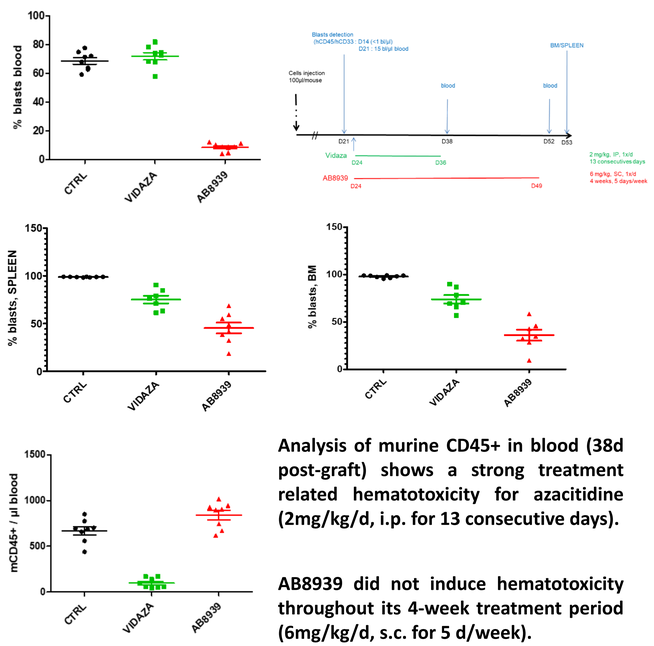
RESULTS: ASSESSMENT OF AB8939 IN ACUTE MYELOID LEUKEMIA

- 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 (IC_{50}~13 µM) PDX model (M1 subtype)

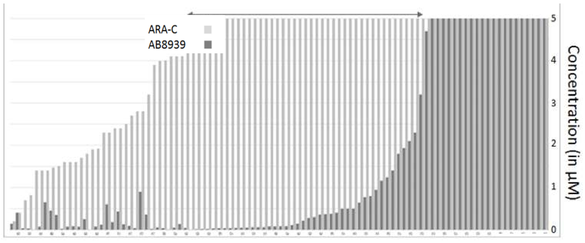
AB8939 substantially decreased the concentration of blasts in blood (38d post-graft), bone marrow (BM) and spleen (52d post-graft) relative to azacitidine (Vidaza®), a widely used hypomethylating agent for AML



Analysis of murine CD45+ in blood (38d post-graft) shows a strong treatment related hematotoxicity for azacitidine (2mg/kg/d, i.p. for 13 consecutive days).

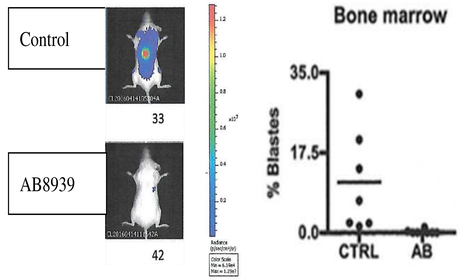
AB8939 did not induce hematotoxicity throughout its 4-week treatment period (6mg/kg/d, s.c. for 5 d/week).

- The potential of AB8939 to overcome Ara-C resistance (IC_{50} >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 (IC_{50} ≤ 500 nM)
  - 44% of blasts were very sensitive (IC_{50} ≤ 100 nM)
- AB8939 also showed broad anti-proliferative activity across the entire range (M0–M7) of AML subtypes



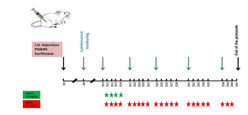
Sample cells from AML patients

- 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

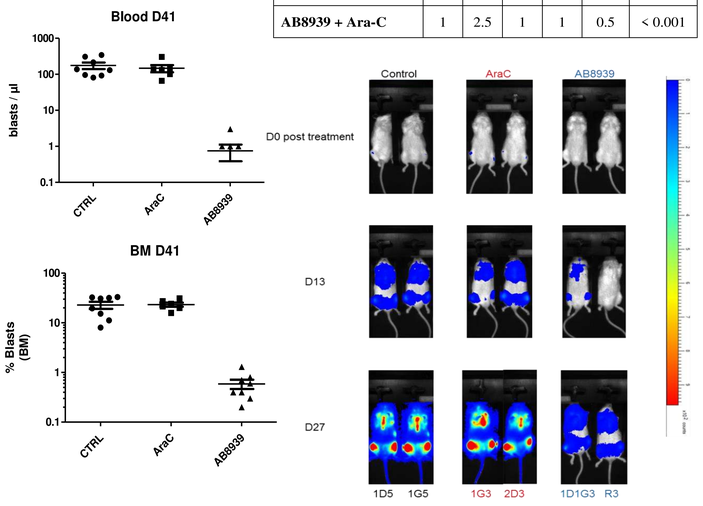


- Therapeutic potential of AB8939 in AML demonstrated *in vivo* using an Ara-C resistant (IC_{50}~8 µM) PDX model

Single agent AB8939: significant decrease in tumor growth, concentration of blasts in blood and bone marrow



Bioluminescence (days post graft)	D27	D34	D41	D49	D55	P value*
Control	1	9	44	113	133.5	-
Ara-C 10 mg/kg (bid)	1	5	17	73	64	NS
AB8939 6 mg/kg/day	1	3	3.5	6	6	< 0.001
AB8939 + Ara-C	1	2.5	1	1	0.5	< 0.001



AB8939 plus Ara-C: significant decrease in disease burden (D55 post graft; D27 treatment)

Bioluminescence (days post graft)	D10	D17	D24	D31	D38	P value*
Control	1	10.8	66.6	373.9	2191.6	-
Ara-C 10 mg/kg (bid)	1	11.6	49.6	659.5	2144.6	NS
AB8939 6 mg/kg/day	1	10.6	19.8	50.6	151.3	< 0.001