AB8939, a Microtubule-Destabilizing Agent with Potential to Overcome Multidrug Resistance, is Active Across the Range (M0–M7) of Acute Myeloid Leukemia Subtypes

Blood (2019) 134 (Supplement_1): 5154.

https://doi.org/10.1182/blood-2019-127021

Authors: Armelle Goubard[1,2,3], Martine Humbert[1], Colin Mansfield[1], *Olivier Hermine[1,4], Patrice Dubreuil[1,2], ON BEHALF OF THE AB8939 STUDY GROUP

[1] AB Science, Paris, France.

[2] Centre de Recherche en Cancérologie de Marseille (CRCM), INSERM, CNRS, Aix-Marseille Univ, Institut Paoli-Calmettes, Marseille, France.

[3] TrGET Platform, CRCM-U1068, Marseille, France.

[4] Imagine Institute, INSERM UMR 1163 and CNRS ERL 8254, Laboratory of Cellular and Molecular Mechanisms of Hematologic Disorders and Therapeutic Implications, Hopital Necker, Paris, France.

* Presenting author

Compound AB8939 is a structurally novel, small chemical molecule, synthesized tubulin inhibitor that can circumvent two of the major resistance mechanisms in acute myeloid leukemia (AML), namely P-glycoprotein (Pgp) and myeloperoxidase (MPO) mediated resistance, thereby conferring an important advantage over traditional tubulin inhibitors.

A series of *ex vivo* and *in vivo* studies provide proof-of-concept that AB8939 has broad anti-proliferative activity across the breath of acute myeloid leukemia (AML) subtypes, i.e. M0 through M7 of the French-American-British AML classification.

Acute myeloid leukemia blasts were isolated from patients' peripheral blood and/or bone marrow samples, collected either at the time of diagnosis or following relapse, and also from patient derived xenograft (PDX) models. After purification, mononuclear cells were treated for 48 hours with various concentrations of AB8939 or cytarabine (Ara-C) and analyzed in a cell proliferation/viability assay.

AB8939 produced a strong anti-proliferative action against blasts isolated from AML patients with a majority of IC_{50} values ranging from 1.4 nM to 1.0 µM. Two-thirds of AML patients had nanomolar sensitivity to AB8939 ($IC_{50} \leq 500$ nM), while 44% where very sensitive ($IC_{50} \leq 100$ nM) and 11% were highly sensitive ($IC_{50} \leq 10$ nM). The potential of AB8939 to overcome Ara-C-resistance was also evident with 66% of Ara-C-resistant blasts (i.e. IC_{50} >5 µM) being sensitive to AB8939.

Notably, AB8939 demonstrated activity across the entire spectrum of AML subtypes, according to the French-American-British (FAB) AML classification, with an IC_{50} of < 50 nM in M0, M1, M4, M5 and M6 subtypes, corresponding to over 90% of the AML patient population. A slightly lower sensitivity was observed for the M3 subtype (IC_{50} = 1.25 µM). Additionally, potent AB8939 activity was also seen in Ara-C-insensitive biphenotypic and mixed-phenotype acute leukemia samples.

All FAB categories other than M7 were tested in the abovementioned *ex vivo* assessment. Acute megakaryocytic leukemia (FAB AML subtype M7) is a rare form of adult AML, accounting for only 1% of cases, and is associated with resistance to standard treatment and poor prognosis. The effect of AB8939 in this subtype was assessed *in vivo* using an AMKL26 model, an NSG mouse model based on cells isolated from a patient with an aggressive acute megakaryocytic leukemia presenting the ETO2-GLIS2 fusion oncogene. Following post graft detection of blasts, single agent AB8939 was administered intravenously at a dose of 2 mg/kg for three consecutive days per week (3 ON / 4 OFF) for 2 weeks and then at 5 mg/kg for three consecutive days per week (3 ON / 4 OFF) for 1 week. At the end of the 3-week treatment period, blast detection in bone marrow was performed via bioluminescence imaging with comparison to vehicle-treated controls.

As seen in the figure below, single agent AB8939 showed strong anti-leukemic activity in this AMKL26 mouse model as evidenced by the near eradication of blasts. No blasts could be detected in 6 out of 8 mice treated with AB8939. At the described dosing schedule, AB8939 was well-tolerated with no toxicity-related deaths and no impact on animal body weight or behavior.

These findings provide preclinical proof of concept for the development of AB8939 as a next-generation tubulin inhibitor for AML, in particular for poor-prognosis AML subsets and relapse/refractory AML; i.e. patients that currently have very limited therapeutic options and represent the highest unmet medical need.

Figure: Detection of AMKL26 PDX blasts in mice following single agent AB8939 treatment. AB8939 eradicates blasts from bone marrow in an AMKL26 PDX mouse model (AML M7)