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AB Science (EURONEXT: AB)

Introduction

This report focuses on AB Science's second platform, AB8939, a promising Phase I/II asset that complements the company's flagship masitinib program. Following our coverage of masitinib's progress in March 2024 and its subsequent update in May 2024, we now turn to AB8939, an asset enabling a diversification of AB Science's pipeline.

Executive Summary

The development of AB8939 underscores AB Science's strategic shift toward pipeline diversification, reducing its reliance on masitinib, a single product applied across multiple indications. This approach effectively mitigates the company's previous binary risk profile.

AB8939 targets refractory/relapsed acute myeloid leukemia (R/R AML), a rare and aggressive blood cancer characterized by the proliferation of immature white blood cells, leading to rapid progression and poor prognosis. For patients who relapse or fail to respond to existing treatments, options are extremely limited, with supportive care often being the only alternative. AB9838's unique dual mechanism of action, supported by promising *in vivo* results, appears to address key resistance pathways in AML. AB Science is initially focusing on MECOM-rearranged patients, a genetically defined subset of AML patients representing approximately 5% of cases and known for their high resistance to current treatments.

Early Phase I/II clinical data, while based on a small cohort, demonstrated encouraging trends for AB8939 as a standalone therapy. Results showed reductions in leukemia biomarkers (blasts), a few cases of complete remission or improved overall survival in the broad R/R AML population, and a 50% response rate (2/4 patients) among MECOM-mutated patients (a subset presenting a specific mutation), surpassing current outcomes for this challenging population. Although preliminary, these results indicate a promising direction for future clinical trials. This Phase I/II trial is still ongoing to evaluate AB8939 in combination with standard-of-care therapies for R/R AML, with results expected soon, which could further strengthen its clinical profile.

AB Science plans to adopt a phased clinical development strategy, beginning with the MECOM-rearranged subgroup to establish proof of concept and access to accelerated regulatory registration pathways. Successful Phase II results in this subgroup could unlock a niche market estimated at $100 million worldwide before expanding into the broader relapsed/refractory AML (R/R AML) population, representing a $2 billion market.

Following the initial efficacy results, AB8939 stands out as a potential candidate for partnerships. In the oncology sector, collaborations are occurring increasingly early, sometimes even at the preclinical stage, making AB Science a potential target. Furthermore, a pharmaceutical partner could take over the broader development of AB8939 after Phase II MECOM results, with the possibility of expanding its use to additional R/R AML populations, positioning it as a standalone late-line therapy or in combination with existing treatments in earlier lines of treatment.

AB8939 also benefits from strong intellectual property protection, with patents valid until 2036 and potential extensions to 2044. Orphan Drug Designation ensures additional market exclusivity post-approval, further enhancing the asset's long-term revenue potential.

While less advanced than the masitinib program, AB8939 offers significant value to AB Science through diversification, a compelling underlying market, and strong partnership potential contingent on robust efficacy results. Investors should, however, remain mindful that AB8939 is still in the early clinical stages of development, with the inherent risks typical of this phase. The next major milestones for value creation will be Phase I/II efficacy results in combination therapy and then the Phase II trials in MECOM.

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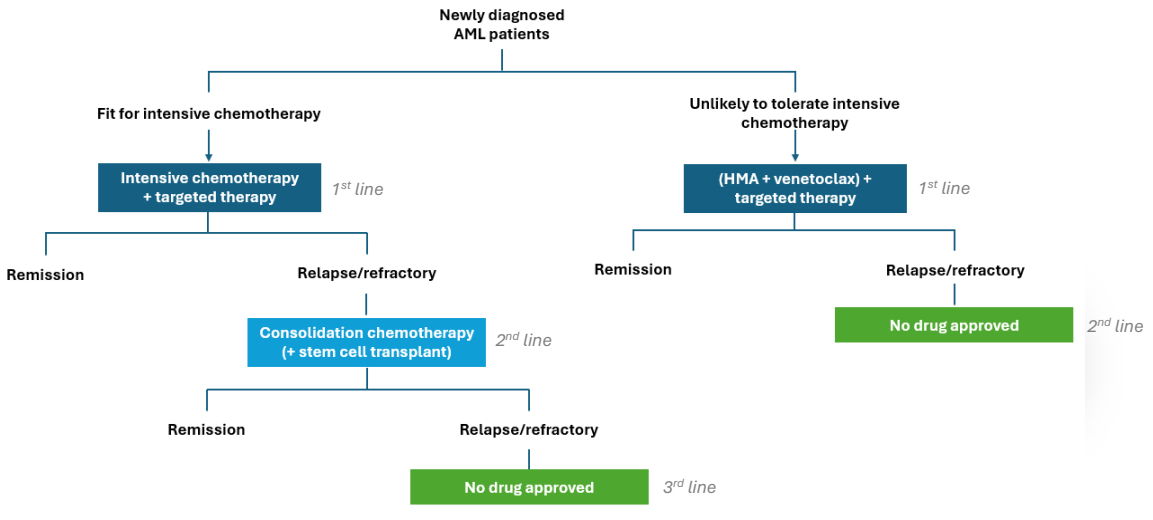
Despite recent promising therapeutic advancements, the urgent medical need for refractory and resistant AML patients remains

AML is a highly aggressive cancer of the blood and of the bone marrow characterized by the rapid and uncontrolled proliferation of abnormal myeloid cells, known as leukemic blasts. These cells originate from mutations or epigenetic alterations in hematopoietic stem cells, which disrupt normal differentiation and maturation processes. As a result, leukemic blasts accumulate in the bone marrow, crowding out healthy blood-forming cells and leading to deficiencies in red blood cells, platelets, and functional white blood cells. Risk factors for AML include advanced age, previous exposure to radiation and chemotherapy, smoking, as well as certain genetic and blood conditions. Over the past three decades, the number of AML patients has nearly doubled, currently reaching approximately 145,000 individuals globally.

Despite being one of the most common types of leukemia in adults, AML remains difficult to treat, particularly in its refractory and resistant forms. Refractory AML refers to cases where leukemia does not respond to initial treatments, while resistant AML describes cases where the disease relapses after achieving a response. Both forms present a significant challenge due to the failure of standard therapies to target leukemic stem cells, which are resistant to treatment and drive relapses and recurrence.

Treatment options for newly diagnosed AML patients typically involve intensive chemotherapy, such as the standard '7+3' cycle regimen combining 7 days of cytarabine and 3 days of anthracycline. This approach remains the cornerstone for patients capable of tolerating aggressive treatments, as it offers the best chance of achieving remission. However, for older patients or those unlikely to withstand such intensity (representing almost half of the patients), lower-dose regimens are used to achieve a balanced safety/efficacy profile suited to the patient medical status. The advancement of new therapies in the past decade has expanded treatment options, including the combination of hypomethylating agents (HMA) and venetoclax (VEN) for frail patients, as well as targeted therapies for subsets of patients with specific mutations such as IDH1/2 or FLT3. These new therapies mark a shift from traditional chemotherapy to more personalized and effective treatments.

FIGURE 1
Standard of treatment for AML patients



Despite promising therapies, R/R AML remains challenging. Around 40% of patients do not achieve remission with standard therapies, and 50-70% of those who achieve remission relapse within a few years. For R/R AML, the 5-year overall survival rate is only 10%, highlighting the urgent need for innovative therapies to improve long-term outcomes. Globally, the population of patients with R/R AML is estimated at 90,000 individuals, including approximately 50,000 in Europe and the United States.

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AB8939 has a dual mechanism of action to overcome current resistance mechanisms in AML treatment

AB8939 operates through two innovative mechanisms of action: as a next-generation microtubule destabilizer likely to kill highly dividing blasts and as a targeted stem cell ALDH1/2 inhibitor. Blasts are abnormal immature white blood cells, which multiply uncontrollably, filling up the bone marrow, and preventing production of other cells important for survival, such as red blood cells and platelets. Reducing blast levels helps prevent the disease from spreading to other organs, making it a key marker of treatment effectiveness. Additionally, lowering cancer stem cells is crucial in AML treatment, as these cells are often responsible for relapses and disease progression.

1. The microtubule destabilizer mechanism of action and interest against resistance

As a microtubule destabilizer, AB8939 disrupts the cancer cell's microtubule network, which is critical for cell division and survival. This well-established mechanism is widely used in oncology, especially in some types of chemotherapies, due to its ability to halt tumor growth and induce cell death. Its success in treating various cancers provides a strong rationale for applying this approach in AML treatment. Preclinical data show that AB8939 effectively eradicates both leukemic blasts and leukemia stem cells in standalone treatment, likely due to its microtubule disruption mechanism of action.

What sets AB8939 apart for R/R AML is its ability to bypass common resistance mechanisms. Unlike other microtubule-targeting agents, AB8939 is not affected by the multidrug resistance pathway, as it demonstrated in an *in vitro* assay that it does not bind to P-glycoprotein, the efflux pump that expels chemotherapy drugs from cells. This allows AB8939 to retain its effectiveness in resistant AML strains. Furthermore, the literature shows that AB8939 is not degraded by myeloperoxidase, an enzyme often overexpressed in AML cells and capable of breaking down many chemotherapy agents.

These unique properties make AB8939 a promising option for overcoming resistance and providing a more effective treatment for refractory AML.

2. A targeted stem cell ALDH1/2 inhibitor

According to management, AB8939 may also act as a targeted inhibitor of aldehyde dehydrogenase 1/2 (ALDH1/2), an enzyme essential for the survival of leukemia stem cells in AML. These resilient cells, highly resistant to standard chemotherapy, drive treatment failure and relapse, making them a critical target for innovative therapies.

Leukemia stem cells rely on ALDH1/2 activity to detoxify reactive oxygen species and harmful metabolites, protecting them from oxidative stress and supporting their regeneration and survival. By inhibiting ALDH1/2, AB8939 could weaken these defenses, making the leukemia stem cells more vulnerable to treatment and reducing their ability to repair. Preliminary *in vitro* studies confirm AB8939's sub-micromolar potency against recombinant ALDH1/2.

Moreover, a specific subset of AML patients carrying the MECOM mutation exhibit overexpression of ALDH, suggesting that AB8939's mechanism of action may be particularly effective in this subset of patients, who often demonstrate extreme resistance to chemotherapy and very low overall survival.

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Initial results demonstrate promising efficacy with standalone treatment

1. Promising Phase I/II results in standalone therapy for R/R AML

AB Science enrolled 28 patients in this Phase I/II trial to evaluate the compound's maximum tolerated dose (MTD) and safety profile, while also collecting preliminary data on its efficacy. This is standard practice for Phase 1 oncology studies.

It is important to note that patients in these trials are at the end of their treatment journey, having failed all available standard therapies, with no further treatment options. Demonstrating significant efficacy at this advanced stage of the disease is inherently challenging.

TABLE 1

Results of two particularly responding cases in Phase I/II

[1] Source: Outcomes of patients with relapsed or refractory acute myeloid leukemia: a population-based real-world study, American Journal of Blood

Case	Patient Profile	Treatment Details	Efficacy Results
Case 1	81-year-old R/R AML patient, non-responsive to standard care	Very low dose (0.9 mg/m^2), 28 days	• OS: 13.8 months vs. 5.3 months (untreated R/R AML OS median [1]) • Blast reduction in blood: 1.5% to 0.9% • Blast reduction in bone marrow: 15% to 9%
Case 2	Young but fragile patient with aggressive relapsed disease (55% blasts in bone marrow)	Maximum tolerated dose (21.3 mg/m^2), 14 days	• Achieved complete response • Blast reduction in bone marrow: 55% to 8%

While these two cases are not providing statistically significant conclusions, they highlight positive trends in R/R AML patients with no other treatment options, supporting the potential of AB8939 in this population.

2. A highly responsive subset of AML patients with MECOM mutation

MECOM-mutated AML represents a genetically defined subset of AML patients with a very poor prognosis. MECOM mutations often involve overexpression of the EVI1 gene. Patients with MECOM mutations tend to have a less favorable prognosis due to the aggressive nature of the disease. This mutation is often associated with a higher risk of disease relapse after initial treatment. A study analyzing 55 R/R AML patients with MECOM rearrangements reported a median overall survival of 5.9 months (study *PMC10483357*).

Research suggests that ALDH is a biomarker of poor prognosis in AML. AB Science hypothesizes that the MECOM mutation leads to EVI1 overexpression of ALDH1, contributing to high resistance in leukemia stem cells. AB8939 may target this ALDH1 in stem cells, decreasing the resistance of leukemia stem cells to treatment.

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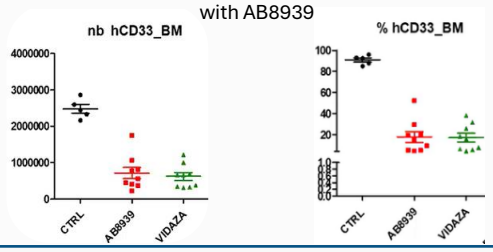
TABLE 2

AB8939's efficacy on AML patients with MECOM mutations

Study Type	Details on the study	Efficacy Results
In vitro	Efficacy of the treatment tested on 4 MECOM patient blasts	50% response rate (2/4 patient blasts)
In vivo	Efficacy of the treatment tested on 4 mouse models	Good efficacy on the destruction of blasts in the bone marrow with AB8939 
Phase I/II	4 patients with MECOM on the 38 R/R AML patients injected in Phase I/II Efficacy of the treatment tested on these 4 patients	50% response rate (2/4 MECOM patients): • **Case 1,** refractory to all treatments: ○ OS: 17.6 months vs 5.6 months ○ Blast reduction in bone marrow: 55% to 5% • **Case 2,** refractory to all treatments: ○ Complete response ○ Blast reduction in bone marrow: 13% to 3%

AB8939 shows excellent preliminary preclinical efficacy results in combination therapy

Both Vidaza (azacitidine) and Venetoclax are commonly used for elderly AML patients who are not candidates for intensive chemotherapy. AB Science conducted preclinical *in vivo* studies to assess the potential of combining its compound with these two standard treatments for newly diagnosed patients unlikely to tolerate intensive chemotherapy. As shown in **Fig. 2** and **Fig.3,** the results demonstrate that AB8939 performs effectively as a monotherapy and exhibits even greater efficacy when combined with Vidaza or Venetoclax.

FIGURE 2

Concentration of hCD33-positive cells, with AB8939 alone, Venetoclax alone or in combination

A reduction of hCD33 indicates that the therapy is targeting and eliminating leukemia cells

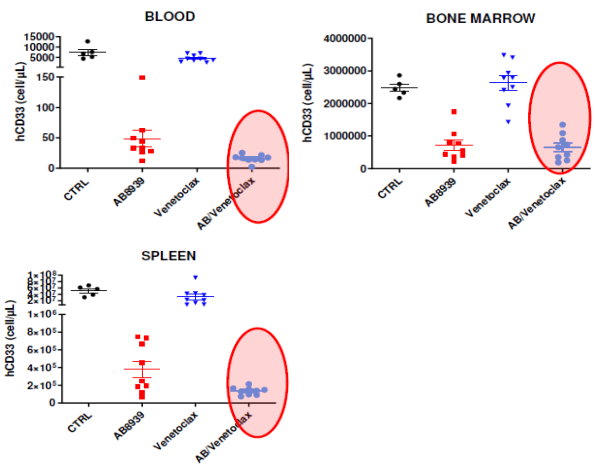
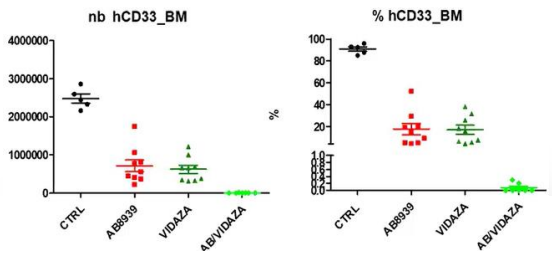


FIGURE 3

Concentration of hCD33-positive cells, with AB8939 alone, Vidaza alone or in combination on MECOM R/R AML patients



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AB8939 presents a good safety profile, which is crucial given the vulnerability of the R/R AML population

In AML patients, maintaining body weight and stable hematopoietic progenitors (mCD45) is critical, as current treatments often cause weight loss and mCD45 damage, leading to poor therapy tolerance and increased risks of anemia, immune suppression, and bleeding. Preclinical and Phase I data showed that AB8939 prevents weight loss, preserves mCD45 levels, and restores normal neutrophil and platelet counts, with no reported bleeding or infections, making it particularly suitable for fragile patients.

Competition in R/R AML patients is active and could be complemented by AB8939

The therapeutic landscape of R/R AML has evolved significantly, driven by advancements in genomic profiling technologies like next-generation sequencing, which have enabled the identification of genetic mutations involved in AML pathogenesis. On one side, approved targeted therapies include Gilteritinib (Astellas) and Quizartinib (Daiichi Sankyo) for FLT3-mutated AML, Ivosidenib (Servier) for IDH1 mutations, and Enasidenib (Bristol-Myers Squibb) for IDH2 mutations.

TABLE 3

Approved and late-stage clinical development targeted therapies for AML patient subsets with specific mutation

Target	% of AML patients	Approved Therapies	Median OS of patients with approved therapies	Emerging therapies
FLT3	25-30%	Gilteritinib, Quizartinib	~9.3 months (Gilteritinib ADMIRAL Trial)	Crenolanib (Phase III)
IDH1	~6-10%	Ivosidenib	~8.8 months (Ivosidenib trials)	FT-2102 (Phase II)
IDH2	~8-12%	Enasidenib	~8.3 months (Enasidenib trials)	Phase II combination trials with hypomethylating agents
TP53	~10-20%	/	/	Eprenetapopt (Phase III)

On the other side, therapies under clinical development are emerging: Crenolanib (Arog Pharmaceuticals, Phase III for FLT3), FT-2102 (Forma Therapeutics, Phase II for IDH1), and ongoing trials combining Enasidenib with hypomethylating agents for IDH2-mutated AML (Bristol-Myers Squibb, Phase II). For TP53-mutated AML, where no approved therapies exist, novel agents like APR-246 (Eprenetapopt, Aprea Therapeutics, Phase II) and Magrolimab (Gilead, Phase II) are being investigated.

Beyond targeted therapies, other therapeutic approaches are advancing for R/R AML, including immunotherapies such as Flotetuzumab (Macrogenics, Phase II), and CAR-T cells (various developers, Phase I/II), focused on AML-specific antigens.

Given the pathogenesis of the disease, AB Science targets, through its mechanism of action, a pathway that is both independently viable and easily combinable with other therapies, as they often focus on subsets of patients with specific mutations. This ensures no direct competition and allows AB Science's approach to complement both existing and emerging treatments.

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AB Science's management aims to get accelerated registration for AB8939 in MECOM-rearranged patients before expanding to broader R/R AML patients

The promising results of AB8939 in *in vivo* and Phase I/II studies for MECOM-rearranged AML patients, showing a 50% response rate in early trials, have guided AB Science's strategy to prioritize development in this subset of AML patients. This approach is advantageous as it leverages the potential for accelerated registration based solely on strong Phase II results. Similar regulatory pathways have been successfully utilized by other companies, such as Syndax with Revumenib, which obtained approval for a subset of AML population following a Phase I/II study — demonstrating the feasibility of this strategy.

Revumenib, targeting KMT2A-rearranged and NPM1-mutated AML, was approved after a trial involving 57 evaluable Phase II patients, achieving a 23% complete or near-complete response rate. AB Science plans to follow a similar pathway, enrolling approximately 60 R/R AML patients with MECOM rearrangements in its Phase II trial, aiming to surpass the 14% response rate reported in the literature.

This focused strategy allows AB Science to target MECOM-rearranged AML, a population representing 5% of all AML cases and an estimated $100 million market worldwide.

Success in this initial niche sub-market would provide a solid foundation for expanding AB8939's potential applications. The next step could involve targeting the broader R/R AML population, where AB8939 could be used as a monotherapy in last-line treatment, especially where there are no approved treatments. In the long term, AB Science could explore combination therapies with existing treatments for newly diagnosed patients who are not eligible for intensive chemotherapy. This gradual evolution from a focused or late-line indications to broader, earlier-line ones would significantly increase the overall market opportunity for AB8939 to $2 billion worldwide.

AB8939 benefits from strong Intellectual Property until at least 2036

AB8939 is protected by a Composition of Matter patent, one of the strongest forms of intellectual property in the pharmaceutical industry, until 2036 for AML. This protection could be extended to 2044 through a 'second medical use' patent (application filed), specifically for AML with chromosomal abnormalities, which represent approximately 50% of AML cases.

For MECOM-rearranged patients, the drug qualifies for Orphan Drug status, granting a 7-year protection period upon FDA approval (status already granted in the USA) and a 10-year protection period upon EMA approval (application to be filed with EMA).

This diversification strategy enhances AB Science's valuation and mitigates risks

The development of AB8939 marks an important step in AB Science's strategy, enhancing the company's valuation and diversifying its asset portfolio. Until now, AB Science has primarily relied on its flagship product, masitinib. The addition of AB8939 mitigates the risks associated with being a mono-product biotech, a key factor for reducing investor exposure to binary outcomes typical in the industry.

Although current results for AB8939 are based on a small sample (4 MECOM patients) and may not fully predict Phase II outcomes on a larger cohort, robust Phase II data should reveal the asset's true value. When the company reaches this stage, we expect the program to attract significant interest from potential partners. While the MECOM subset represents a niche market, its expansion into the broader R/R AML population offers an attractive opportunity for a pharmaceutical partner, increasing the market potential to $2 billion.

TABLE 4

Recent M&A acquisitions in the oncology field

Buyer	Acquired Company	Date	Transaction Value	Key Asset	Phase
Novartis	Mariana Oncology	May 2024	$1.3 billion	Radioligand therapies	Preclinical
BioNTech	Biotheus	November 2024	$950 million	Immunotherapies	Phase I/II
Merck	Harpoon Thx	January 2024	$680 million	Immunotherapies	Phase I/II
J&J	Ambrx	January 2024	$2 billion	ADC	Phase II

In the oncology sector, assets with positive Phase II results typically can lead to deals exceeding $500 million (**Tab. 4**). Even before obtaining these positive Phase II MECOM results, AB8939 already represents a compelling opportunity for a pharmaceutical partner and its appeal will grow further if Phase II MECOM results are positive.

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