

ENLIGHT-AML: A Phase 1 Study of GB3226, a Novel Dual Inhibitor of ENL-YEATS and FLT3, in Patients with Relapsed / Refractory Acute Myeloid Leukemia

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Background

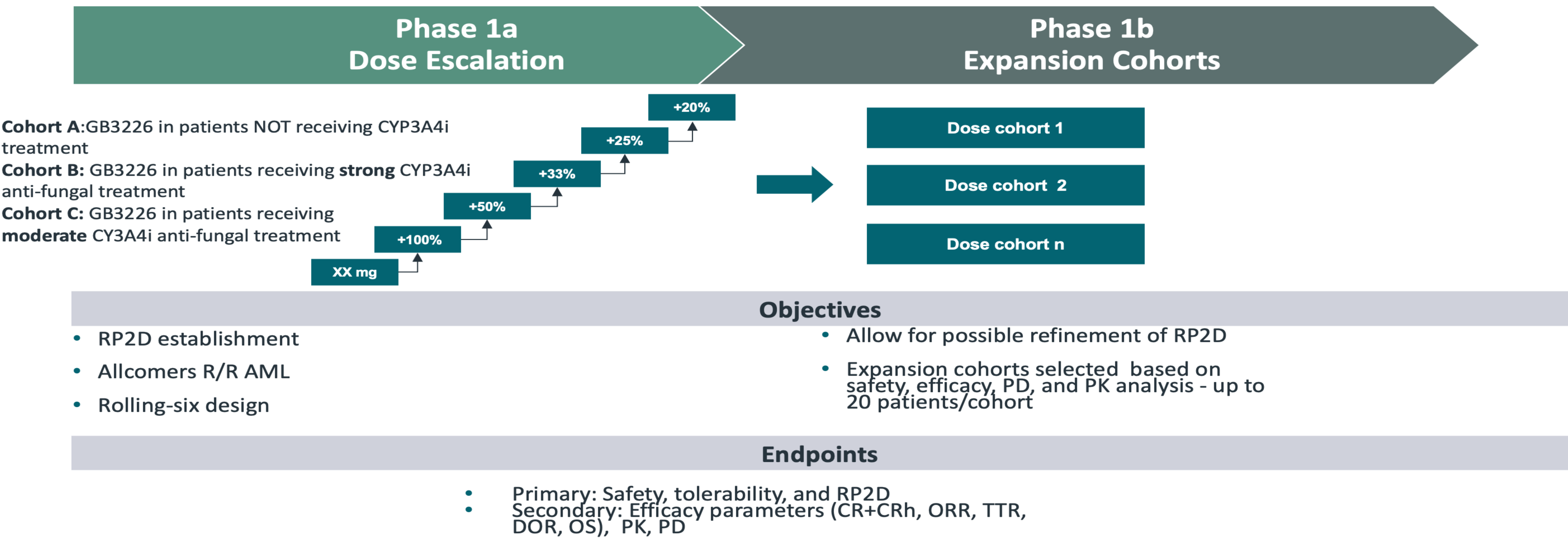
- Acute myeloid leukemia (AML) remains a formidable challenge in hematology, particularly for patients with relapsed or refractory (R/R) disease, where treatment options are limited and outcomes remain poor¹. Outcomes are dismal in patients with HOXA9/MEIS1 upregulated biology with co-mutations in FLT3²
- ENL (MLLT1), a chromatin reader protein, binds to acetylated histones through the YEATS domain and is crucial for sustaining oncogenic gene expression in leukemia³
- Genetic or pharmacological disruption of ENL-YEATS reduces leukemia burden³
- FLT3, a receptor tyrosine kinase overexpressed in most AML blasts, is mutated in approximately 30% of newly diagnosed adult AML^{4,5}
- Dual inhibition of ENL-YEATS and FLT3 may offer superior efficacy
- GB3226 is a first-in-class, oral dual inhibitor targeting the ENL-YEATS domain and FLT3, two key leukemic drivers
- Preclinical studies have demonstrated GB3226’s high-affinity binding to ENL-YEATS and FLT3. In relevant AML and patient-derived models, GB3226 induced sustainable tumor regression and HOXA9/MEIS1 transcriptional suppression - see also poster# 6106 presented at this meeting.

Methods

The ENLIGHT-AML study (ClinicalTrials.gov identifier: NCT07084584) is a Phase 1a/1b, open-label, dose-escalation and expansion study of GB3226 in relapsed or refractory AML with a nested DDI evaluation of the impact of CYP3A4 inhibitors (azole anti-fungals) on the pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of GB3226

Figure 1. ENLIGHT-AML study design

ENLIGHT-AML: GB3226 in Relapsed/Refractory AML – Phase 1a/1b



References

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- Andreeff et al. *Leukemia*. 2008 Nov;22(11):2041-7
- Wan et al. *Nature*. 2017 Mar 9;543(7644):265-269
- Small et al. *Hematology Am Soc Hematol Educ Program*. 2006:178-84
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Summary

GB3226: A First-in-Class Dual ENL-YEATS/FLT3 Inhibitor

Novel Mechanism: GB3226 is the first clinical-stage agent designed to inhibit both ENL-YEATS (MLLT1) and FLT3.

Preclinical Activity: Demonstrated high-affinity binding and sustained tumor regression in AML models, including patient-derived in vitro systems.

Dual-Targeting Rationale: Designed to overcome resistance mechanisms seen with single-pathway agents (e.g., menin or FLT3 inhibitors) and enhance suppression of leukemic stemness.

ENLIGHT-AML: Open-label, dose-escalation and expansion study evaluating safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy.

Potential Impact: GB3226 represents a novel, differentiated therapeutic approach for acute myeloid leukemia (AML) - an orphan disease with significant unmet medical need.



Methods – Cont’

Part 1a

- Patient sample:** This study employs a Rolling-six dose-escalation design across up to three cohorts to assess the safety, PK, PD and preliminary efficacy of GB3226 and the impact of CYP3A4 inhibitors on GB3226 . Cohort A and B will be launched simultaneously. Cohort C will be initiated if required.
 - Cohort A: No CYP3A4 modifiers. Anticipated starting dose: 100mg QD
 - Cohort B: Coadministration with strong CYP3A4 inhibitors (e.g., voriconazole, posaconazole). Anticipated starting dose: 25mg QD.
 - Cohort C: coadministration with moderate CYP3A4 inhibitors (e.g., isavuconazole)
- Administration:** GB3226 will be administered orally, once daily, in 28-days cycles
- Aim:** To identify dose levels and cohorts for Phase 1b expansion

Part 1b

- Patient sample:** Based on analysis of safety, PK, PD, and preliminary efficacy, cohorts from Phase 1a will be selected for expansion. Cohorts may be expanded up to a total of 20 patients.
- Aim:** Determine the recommended phase 2 dose, which may depend on concurrent CYP3A4 inhibitor use
- Enrollment:** Up to 140 patients may be enrolled in Phase 1a/1b, depending on number of dose levels and backfill cohorts.

Eligibility Criteria

- Principal Inclusion criteria**
 - ≥18 years of age
 - Relapsed/refractory AML with ≥5% blasts in the bone marrow and/or persistence or reappearance of peripheral blasts
 - Not eligible for other therapies known to provide clinical benefit
 - ECOG performance status 0-2
- Principal exclusion criteria**
 - APML or CML in blast crisis
 - Active CNS disease
 - Pregnant or breastfeeding women

Potential Extension

- The study is designed to allow potential expansion into a Phase 2 component following assessment of Phase 1a/b safety, PK, PD, and preliminary efficacy data. The Phase 2 component will be activated through a protocol amendment once the data support progression and regulatory/ethics approvals are obtained.

Study Status

- As of December 1st 2025, the study is in the preparatory phase with an IND submission planned for Q1 2026.

Acknowledgements

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