Poster P524

Phase 1b/2 Study on Safety, PK, PD and Preliminary Efficacy of the Selective SYK Inhibitor Lanraplenib in Combination with the FLT3 Inhibitor Gilteritinib in *FLT3*-mutated R/R AML (KB-LANRA 1001)

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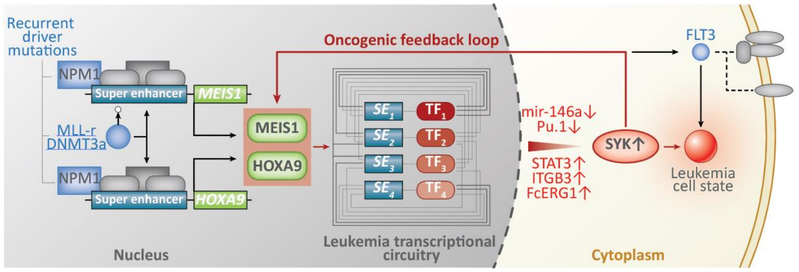
Background

- Spleen tyrosine kinase (SYK) is a key driver of lymphoid and myeloid cell signaling pathways and has been implicated in the pathogenesis of acute myeloid leukemias (AML) defined by dysregulated expression of *HOXA9* and *MEIS1* transcription factors.[1,2]
- SYK also cooperates with internal tandem duplication (ITD)–mutated *Fms-like tyrosine kinase 3* (*FLT3*) to drive leukemogenesis (**Figure 1**).[3]
- Combined pharmacologic inhibition of SYK and FLT3 results in robust antileukemic effects in preclinical models of *FLT3* ITD-driven AML.[3]
- Lanraplenib (LANRA), an oral, selective SYK inhibitor, dose-dependently reduces the viability of leukemic cells ex vivo from newly diagnosed, *FLT3* ITD-mutated AML patients and exhibits additive reductions in viability when combined with selective FLT3 inhibitor, gilteritinib.[4]
- Once-daily (QD) LANRA is well tolerated at doses up to 30 mg QD for up to 49 weeks in patients with autoimmune disorders.[5]
- The KB-LANRA 1001 trial (NCT05028751) is investigating the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antileukemic effects of LANRA when combined with gilteritinib in patients with relapsed or refractory (R/R) *FLT3*-mutated AML.

Figure 1: SYK Exhibits Cooperativity with *FLT3*-ITD to Drive Leukemogenesis[2]



Adapted from Mohr S, et al. *Cancer Cell*. 2017;31(4):549-562.e11.

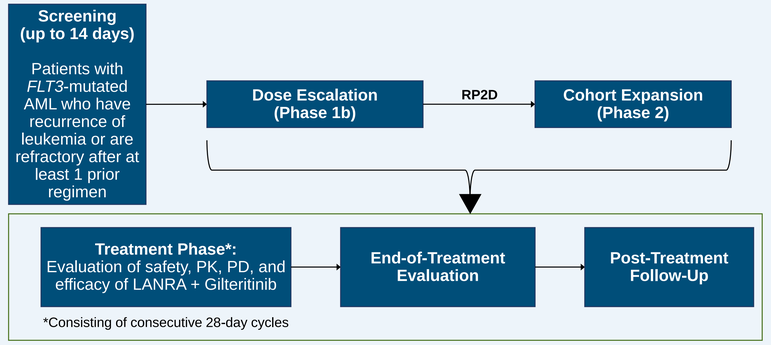
Objectives

- Evaluate the safety of LANRA in combination with gilteritinib in patients with R/R *FLT3*-mutated AML.
- Characterize the PK of LANRA alone and in combination with gilteritinib, as well as the PK of gilteritinib when administered in combination with LANRA.
- Evaluate preliminary antileukemic activity of LANRA in combination with gilteritinib in patients with R/R *FLT3*-mutated AML, including the rate of complete remission (CR)/complete remission with partial hematologic recovery (CRh) and the incidence of MRD negativity among patients who achieve a CR/CRh.
- Explore the predictive value of potential biomarker and characterize the PD properties of LANRA alone and in combination with gilteritinib.

Methods

- KB-LANRA 1001 is a multicenter, open-label, phase 1b/2 study to evaluate safety, PK, PD and preliminary anti-leukemic activity of LANRA plus gilteritinib in R/R *FLT3*-mutated AML patients.
- The study will be conducted in 2 parts:
  - **Phase 1b**: Patients will enroll into one of up to 4 dose cohorts based on a 3+3 dose escalation scheme for evaluations of safety, PK/PD, and determination of the maximally tolerated dose (MTD)/recommended phase 2 dose (RP2D) of LANRA in combination with standard dose gilteritinib.
  - **Phase 2**: Patients will enroll into an expansion cohort to further assess safety, PK, PD and antileukemic activity of the combination at the LANRA MTD/RP2D.

Study Design



- In both Phase 1b and Phase 2, patients will receive their assigned treatment until progression/relapse, failure to achieve at least a partial response (PR) after 6 months of study treatment, intolerance, or withdrawal from the study treatment.

Treatment

- Eligible patients will enroll sequentially into one of the following dose cohorts in phase 1b for PK/PD evaluations and determination of the MTD/RP2D of LANRA plus gilteritinib:

Dose Cohort (n)	LANRA Dose	Gilteritinib Dose
Cohort 1 (3–6 patients)	20 mg QD	120 mg QD
Cohort 2 (3–6 patients)	40 mg QD	
Cohort 3 (3–6 patients)	60 mg QD	
Cohort 4 (3–6 patients)	90 mg QD	

Patient Eligibility

Key Inclusion Criteria	Key Exclusion Criteria
• Adults ≥18 years with AML and at least 1 prior line of therapy • *FLT3*-mutated disease – Eligible patients may have either ITD or TKD mutations or both* • ECOG performance status 0–2 • Adequate hepatic and renal function • PT, aPTT, and INR ≤1.5× ULN unless receiving therapeutic anticoagulation • LVEF ≥50%	• Known CNS involvement with leukemia • Clinical signs/symptoms of leukostasis that has failed therapy including hydroxyurea and/or leukapheresis of at least 3 days duration • Active infection with hepatitis B, C, or HIV • Disseminated intravascular coagulation with active bleeding or signs of thrombosis • Known active COVID-19† • Administration of a live attenuated virus vaccine within 35 days before cycle 1, day 1 • History of nonmyeloid malignancy‡ • Clinically significant heart disease • Patients with a corrected QT interval >480 msec or long QT syndrome • Ongoing immunosuppressive therapy • Patients requiring treatment with strong CYP 3A4 inhibitors or inducers • Known hypersensitivity to LANRA, gilteritinib, their metabolites, or formulation excipient

aPTT = activated partial thromboplastin time; CNS = central nervous system; COVID-19 = coronavirus disease 2019; CYP = cytochrome P450; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; INR = international normalized ratio; LVEF = left ventricular ejection fraction; PT = prothrombin time; TKD = tyrosine kinase domain; ULN = upper limit of normal.
*Patients with a history of exposure to midostaurin, other multikinase inhibitors, and/or second-generation FLT3 inhibitors (including gilteritinib) for the treatment of AML are eligible. †Either symptomatic or asymptomatic, as determined by nasopharyngeal swab. ‡Except for treated localized basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer, or other cancer in complete remission for ≥3 years prior to enrollment.

Endpoints

Primary Endpoint

- Type, incidence, severity, causality, and outcome of adverse events (AEs), including serious and grade ≥3 AEs; DLTs; and MTD/RP2D of LANRA plus standard-dose gilteritinib

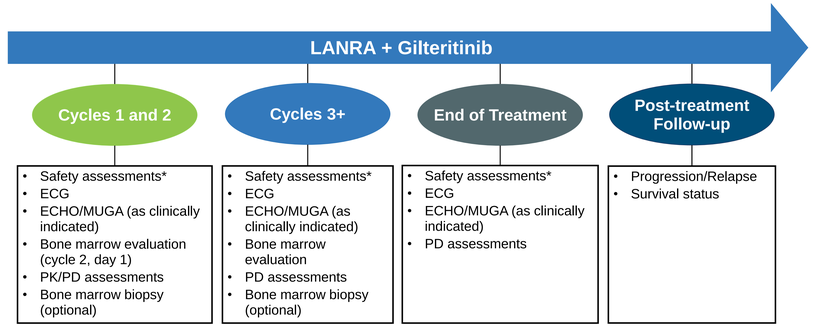
Secondary Endpoints	Exploratory Endpoints
• PK parameters (including C_{max}, T_{max}, and $AUC_{0\text{-last}}$; phase 1b) • Composite CR rate (CR, CRh), as defined by ELN 2017 criteria[6] • DoR • EFS • OS	• Assessment of MRD • Concordance of peripheral blood and bone marrow MRD in patients with CR/CRh • Baseline mutational profiling and gene-expression levels in leukemic cells for correlations with response and progression • Targeted protein/phosphoprotein-expression profiling • Changes from baseline in expression of genes of interest • Type(s) of prominent LANRA metabolites in plasma (phase 1b) • Sparse blood sampling for LANRA and gilteritinib plasma concentrations (phase 2)

$AUC_{0\text{-last}}$ = area under the concentration × time curve from time 0 until the last measurable plasma concentration; DLT = dose-limiting toxicity; C_{max} = maximal plasma concentration; DoR = duration of response; EFS = event-free survival; ELN = European LeukemiaNet; MRD = minimal residual disease; OS = overall survival; T_{max} = time to maximal plasma concentration.

Key Assessments and Timing

Screening

- ECOG PS
- ECHO/MUGA
- Hepatitis B/C/HIV serologies
- Bone marrow examination
- Safety assessments*
- PK/PD assessments



ECG = electrocardiogram; ECHO = echocardiogram; MUGA = multigated acquisition.
*Physical examination, vital signs, pulse oximetry, clinical chemistries/liver function studies, hematology (blood counts, coagulation parameters), and urinalysis.

Enrollment

- Four study sites in the U.S. are now open for recruitment, with additional sites planned to open in the EU. Approximately 55 patients are estimated to enroll.
- Additional information is available at ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT05028751

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Presented at the EHA 2022 Congress; June 9-12, 2022; Vienna, Austria.

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