A phase I/II study of gilteritinib and momelotinib in adults with relapsed or refractory *FLT3*-mutated acute myeloid leukemia

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Background

- Outcomes of pts with relapsed/refractory (R/R) *FLT3*-mutated AML are poor
- Several mechanisms of resistance to FLT3 inhibitors (FLT3i) **(Figure 1):**
  - ~50% of pts lack a clear genomic driver of resistance
  - JAK/STAT pathways, such as GM-CSF and IL-3, may lead to resistance to FLT3i
  - *In vitro* and *in vivo* preclinical studies suggest a potential benefit of dual JAK/FLT3 inhibition in overcoming resistance to FLT3i
- **Momelotinib:**
  - JAK1/2 and activin A receptor type 1 (ACVR1) inhibitor
  - Approved for treatment of intermediate or high-risk myelofibrosis in adults with anemia
  - Inhibits in preclinical studies (Azhar M et al Blood Adv 2022;6(4):1186-92)
- Inhibition of ACVR1 may sensitize *FLT3*-mutated AML cells to FLT3i **(Figure 2)**

Figure 1. Mechanisms of Resistance to FLT3 Inhibitors

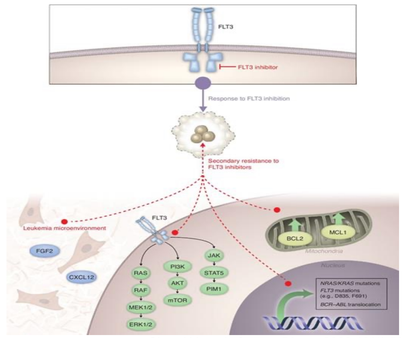
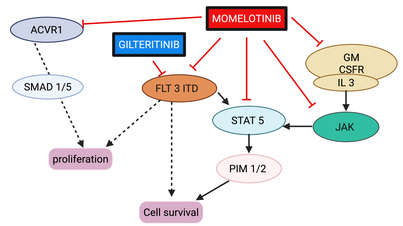


Figure 2. Mechanisms of Resistance and Synergy of Momelotinib + Gilteritinib in *FLT3*-ITD AML



Study Design

Inclusion Criteria:

- Adult pts with R/R *FLT3*-mutated AML
  - *FLT3-ITD or FLT3 D835/D836* mutations are eligible
- ECOG performance status ≤3
- Adequate organ function

Exclusion Criteria:

- Congenital long QT syndrome or QTcF >450 msec
- Active NYHA class III-V cardiac failure
- Active CNS leukemia
- Child-Turcotte-Pugh class C cirrhosis

Treatment regimen:

- **Cycle 1 (35-day cycle)**
  - Momelotinib orally daily on days 1-35 (doses as below)

Dose level	Momelotinib dose
Dose level 1 (starting dose)	200mg
Dose level 2	400mg
Dose level 3	600mg

  - Gilteritinib 120mg orally daily on days 8-35
  - The 7-day lead-in of momelotinib monotherapy in cycle 1 allows for early assessment of momelotinib activity and collection of PK and other correlative studies
- **Cycles 2-24 (28-day cycles)**
  - Momelotinib orally daily on days 1-28 (dose as above)
  - Gilteritinib 120mg orally daily on days 1-28

Study Objectives

Primary Objectives

***Phase I*:** To determine the minimum safe and biologically effective dose of momelotinib in combination with gilteritinib in R/R *FLT3*-mutated AML

Phase II: To determine the modified CRc rate (i.e., CR + CRi + MLFS) within 4 cycles of the combination regimen

Secondary Objectives

- To assess other efficacy endpoints (CR rate, MRD negativity by flow cytometry and FLT3 PCR, relapse-free survival, overall survival)
- To assess the proportion of patients proceeding to allogeneic hematopoietic stem cell transplantation
- To determine the safety of the combination regimen

Results

- As of May 2026, 13 pts were treated at MDA .
- Median number of cycles was 2 (range, 1-5)

Characteristic	Value, n (%)
Age (years), median [range]	67 [31-84]
***FLT3* mutation status**	
FLT3-ITD	11 (85)
FLT3-TKD (D835/D836)	2 (15)
Median *FLT3 ITD* VAF (%), median [range]	9 [3–59]
Prior therapies	
Number of prior therapies, median [range]	3 [1–6]
Venetoclax	12 (92)
Gilteritinib	12 (92)
Quizartinib	8 (62)
Co-mutations	
DNMT3A	6 (46)
WT1	5 (38)
RUNX1	4 (31)
Momelotinib dose level	
200 mg	3 (23)
400 mg	3 (23)
600 mg	7 (54)

Safety and Tolerability

- No dose-limiting toxicities (DLTs) observed at any dose level.
- Most common grade ≥3 non-hematologic AEs (regardless of causality)
  - Infection: 7 pts (54%)
  - Sepsis: 6 pts (46%)
  - Febrile neutropenia: 6 pts (46%)
  - Acute kidney injury: 4 pts (31%)
- One patient experienced transient grade 2 orthostatic hypotension within 24h of starting momelotinib 600 mg, a phenomenon previously described with higher doses of momelotinib

Efficacy

- 3/13 pts (23%) achieved CRc (CRi in 2 pts and MLFS in 1 pt)
  - All 3 pts with CRc had received prior gilteritinib and/or quizartinib
  - 2 additional pts (15%) had >50% BM blast reduction
  - 5/9 pts (56%) with baseline PB blasts had >50% PB blast reduction during the momelotinib lead-in phase, suggesting single-agent activity
    - 2 of these pts achieved a formal response (CRi and MLFS)

Characteristics of patients with evidence of clinical activity

Best Response	Dose Level	FLT3 Subtype	Prior FLT3 Inhibitor
CRi	400 mg	ITD	Gilteritinib + quizartinib
CRi	600 mg	ITD	Gilteritinib + quizartinib
MLFS	600 mg	ITD	Gilteritinib
>50% BM blast reduction	400 mg	ITD	Gilteritinib + quizartinib
>50% BM blast reduction	600 mg	ITD	Quizartinib

Conclusions

- Gilteritinib plus momelotinib was safe and had encouraging preliminary clinical activity in heavily pretreated patients with *FLT3*-mutated AML, including those previously exposed to gilteritinib and/or quizartinib
- No DLTs were observed at doses up to 600 mg daily
- Dose expansion is ongoing to further evaluate the safety, tolerability, and activity of the 400 mg and 600 mg dose levels and define the recommended phase II dose
- The study is expanding to additional sites, and future studies may evaluate the incorporation of venetoclax-based combinations
- Correlative studies are ongoing to evaluate mechanisms of response and resistance

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