3427: Preliminary Results of a Phase 1 Study of the Safety and Tolerability of the Combination of Revumenib (REV) with Gilteritinib (GILT) in Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML)

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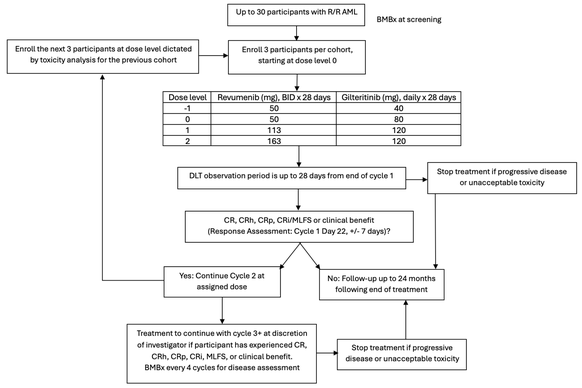
Background

- Menin inhibitors disrupt the interaction between menin and KMT2A, leading to downregulation of *HOXA*/*MEIS1* target genes and subsequent differentiation of leukemic blasts
- Revumenib is a menin inhibitor approved for the treatment of R/R acute leukemias with *KMT2A* translocation and *NPM1*-mutated (*NPM1*m) AML based on the AUGMENT-101 study[1,2]
- Gilteritinib is a FLT3 inhibitor approved for the treatment of R/R AML based on the ADMIRAL trial[3]
- *NPM1* mutations are present in approximately 30% of AML of which approximately half will have a concurrent *FLT3* mutation[4]
- Preclinical models have shown synergy of menin and FLT3 inhibition[5]
- Thus, there has been significant interest in co-targeting FLT3 and menin with concurrent *FLT3* mutations and genomic abnormalities leading to *HOXA/MEIS1* overexpression

Methods

- Phase 1, multi-center, dose-escalation study of concurrent REV + GILT
- Inclusion: adults with R/R AML with *FLT3* mutations and *KMT2A* translocation, *NPM1*m, or other genomic abnormality sensitivity to menin inhibition. Strong CYP3A4 inhibitor for antifungal prophylaxis was required for ≥24 hours prior to initiation.
- Exclusion: active CNS involvement, isolated extramedullary disease or baseline QTcF > 450ms
- Bayesian optimal interval design guided dose-escalation



Results

Table 1. Baseline characteristics.

Characteristic	Patients (n=7)
Age, median (range), y	57 (40-71)
Male, n (%)	3 (42.9%)
Prior lines of therapy, median (range)	1 (1-5)
Prior allogeneic stem cell transplant, n (%)	2 (28.6%)
FLT3 mutation type, n (%)	ITD: 5 (71.4%), TKD: 2 (28.6%)
Genomic abnormality with HOXA/MEIS1 overexpression, n (%)	*NPM1*m: 5 (71.4%), *KMT2A*-PTD: 1 (14.3%), *NUP98*r 1 (14.3%)
Prior menin inhibitor, n (%)	3 (42.9%) *(2 of 3 with prior revumenib)*
Prior FLT3 inhibitor, n (%)	2 (28.6%) *(no prior gilteritinib)*

Table 2. Most frequent grade ≥ 3 adverse events.

Grade ≥ 3 AEs	n (%), (n=7)
Febrile neutropenia	4 (57.1%)
Dyspnea	2 (28.6%)
Hypotension	2 (28.6%)
QTcF prolongation	2 (28.6%)

Other AEs of special interest:
- Differentiation syndrome: 1 (14.3%), grade 2 in setting of multifactorial shock
- No arrhythmias seen

Table 3. Dose limiting toxicities (DLTs) seen at treated dose levels to date.

Dose Level	Patients Treated, n (%)	DLT, n	Event(s)
0	3 (42.9%)	0	N/A
1	4 (57.1%)	2	Grade 3 QTc prolongation, both able to resume at dose reduction. One patient able to re-escalate dose after posaconazole discontinuation.

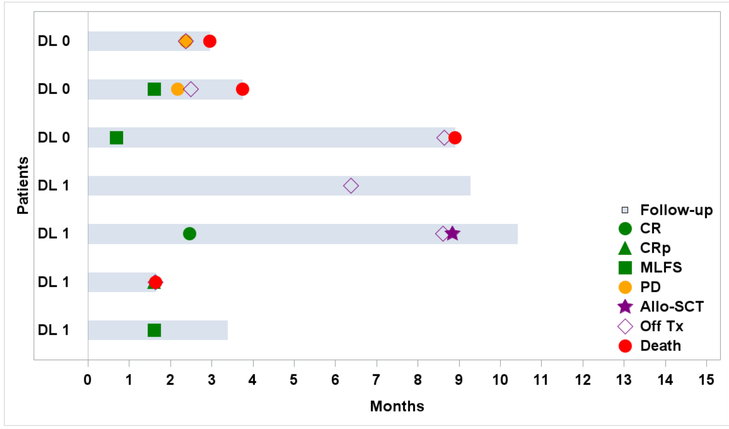
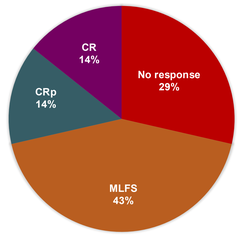


Figure 1. Swimmer plot with enrolled patients.

Results (continued)



- Median duration of treatment: 111 days (range: 72–262)
- 1 patient (14.3%) on active treatment
- 1 patient (14.3%) proceeded to allo-SCT
- 3 (42.9%) alive

Figure 2. Response rates of enrolled patients.

Conclusions

- REV + GILT combination appears well tolerated, demonstrated early signs of efficacy, and supports continued evaluation
- QTc prolongation identified as DLT in presence of strong CYP3A4 inhibitors
  - One patient successfully re-escalated after discontinuing posaconazole without recurrent QTc prolongation
- Overall safety profile consistent with known effects of REV and GILT
- DL0 expansion ongoing following two DLTs at DL1. Further dose optimization required to establish recommended phase 2 dose.
- Planned cohort without concurrent azoles to refine dosing strategy

References

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