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EFFICACY AND SAFETY OF VENETOCLAX IN COMBINATION WITH GILTERITINIB FOR RELAPSED/REFRACTORY FLT3-MUTATED ACUTE MYELOID LEUKEMIA: UPDATED ANALYSES OF A PHASE 1B STUDY

Topic: 04. Acute myeloid leukemia - Clinical

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Background: The FMS-like tyrosine kinase 3 (*FLT3*) inhibitor gilteritinib (Gilt) improves survival compared with standard salvage chemotherapy in patients (pts) with *FLT3*-mutated (*FLT3*$^{mut+}$) acute myeloid leukemia (AML) who are relapsed/refractory (R/R) to standard chemotherapy. Interim analysis of an ongoing, multicenter, open-label, Phase 1b trial (NCT03625505) of Gilt + the B-cell lymphoma 2 (BCL-2) inhibitor venetoclax (Ven) in pts with R/R *FLT3*$^{mut+}$ AML reported high rates of marrow blast elimination and a modified composite complete remission (mCRc) rate of 84% (Daver et al. ASH 2020; Abstract 333).

Aims: To provide updated results from a Phase 1b trial of Ven + Gilt in R/R *FLT3*$^{mut+}$ AML.

Methods: The study design has been described previously (Daver et al. ASH 2020; Abstract 333). In brief, pts with R/R AML *FLT3*$^{mut+}$ received dosages up to Ven 400 mg daily with Gilt (80 mg or 120 mg) daily in 28-day cycles, following Ven ramp-up. The primary endpoint was mCRc (complete response [CR] + CR with incomplete platelet recovery + CR with incomplete blood count recovery [CRi] + morphologic leukemia-free state) to align with the Phase 3 ADMIRAL trial CRc responses. Duration of response (DOR) of mCRc was a secondary endpoint; overall survival (OS) and changes in FLT3 allelic burden were exploratory. Safety evaluation included adverse event (AE) monitoring.

Results: At the data cutoff of November 30, 2020, 43 pts with *FLT3*$^{mut+}$ had been enrolled. Median age (range) was 63 years (23–85). *FLT3* internal tandem duplications (ITD) were identified in 37 pts (86%) and 6 pts (14%) had only tyrosine kinase domain (TKD) mutations. Baseline cytogenetic risk was favorable in 2 pts (5%), intermediate in 23 pts (55%), poor in 13 pts (31%), and 5 pts (12%) had no mitoses/missing data. The median (range) prior lines of therapy was 2 (1–5), and 33 pts (77%) had 2 or more prior lines of therapy; 28 pts (65%) had received at least one prior *FLT3* inhibitor and 3 pts (7%) received prior Ven. Fourteen pts (33%) had prior transplant.

Grade 3/4 AEs were reported in 42 pts (98%). Grade ≥3 cytopenias occurred in 34 pts (79%) and were predominantly managed by Ven and/or Gilt dose interruptions and shorter Ven duration on subsequent cycles. The only grade 3/4 nonhematologic AE reported in >20% of pts was pneumonia (n=9; 21%). There was 1 instance of clinical tumor lysis syndrome. Serious AEs were reported in 32 pts (74%). Overall, 30- and 60-day mortality rates were 0% and 12%, respectively. AEs led to either Ven or Gilt interruptions in 24 pts (56%), reductions in 3 pts (7%), and discontinuations in 6 pts (14%).

mCRc was achieved by 86% of the *FLT3*$^{mut+}$ efficacy population (36/42) with a median time to first response of 1.0 month (range: 0.7–4.6), and by 86% of pts with prior *FLT3* tyrosine kinase inhibitor (TKI) exposure (24/28). *FLT3* molecular clearance ($<10^{-2}$) was observed in 69% of pts with mCRc who had PCR analyzed at baseline and at least one follow-up timepoint (18/26). DoR and OS are summarized in the **Table**.

Image:

Table: Summary of median DoR and OS in patients with *FLT3* mutations

	All *FLT3*$^{mut+}$ pts	All ITD pts	Prior TKI use	
	N=42	N=37	Yes	No
Median OS, months (95% CI)	N=42 10.5 (9.6–NE)	N=36 10.5 (8.0–NE)	N=28 10.5 (7.4–NE)	N=14 10.6 (6.6–NE)
Median DoR, months (95% CI)	N=36 5.6 (4.0–6.6)	N=32 5.6 (3.4–8.3)		

CI, confidence interval; DoR, duration of response; *FLT3*, FMS-like tyrosine kinase 3; *FLT3*$^{mut+}$, *FLT3*-mutated; ITD, internal tandem duplications; N, number of patients with data available for analysis; NE, not estimable; OS, overall survival; TKI, tyrosine kinase inhibitor.

Summary/Conclusion: These updated analyses show that Ven + Gilt achieved high rates of mCRc in pts with heavily pretreated and prior TKI-exposed R/R *FLT3*$^{mut+}$ AML with encouraging molecular clearance rates. Using similar response criteria to previously studied *FLT3*$^{mut+}$ populations, the high mCRc rate with Ven + Gilt reported here suggests strong antileukemic activity. Cytopenias were prominent but manageable. Updated follow-up and molecular data will be presented at the meeting.

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