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POSTER ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

A Phase I/II Study of Combination of ASTX727, Gilteritinib and Venetoclax in Patients with Relapsed/Refractory *FLT3* Mutated Acute Myeloid Leukemia (AML)

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Background

Activating mutations in *FLT3* occur in approximately 30% of patients (pts) with AML. Gilteritinib (GILT), a second-generation type I oral *FLT3* inhibitor, has been approved in pts with relapsed/refractory (R/R) *FLT3*-mutated AML. We conducted a phase I/II study to evaluate the combination of decitabine/cedazuridine (ASTX727), venetoclax (VEN), and GILT in pts with *FLT3*-mutated R/R AML or intermediate-2/high risk MDS/CMML.

Methods

This phase I/II study included pts with 1) R/R *FLT3*-mutated AML or R/R intermediate-2/high risk MDS/CMML or 2) newly diagnosed *FLT3*-mutated AML unfit for intensive chemotherapy (eligible for phase II only). Here we report the initial data from the R/R cohort. In the phase I portion there was no restriction to the number of prior therapies received; however, in the phase II portion pts who had received ≥3 prior therapies were excluded. Pts with *FLT3*-ITD and/or TKD mutations were eligible. Pts were required to have a performance status ≤3, total bilirubin ≤2.5 x ULN, ALT/AST ≤3 x ULN, and creatinine clearance ≥30 mL/min. In cycle 1 (C1), pts received decitabine/cedazuridine (35mg/100mg) orally on days 1-5, VEN (ramp-up to 400mg with adjustment for concomitant azole) orally on days 1-28, and GILT orally continuously. The GILT dose ranged from 80mg to 120mg daily during the phase I dose escalation (3+3 design). A bone marrow biopsy was performed on day 14, and if blasts were <5% or the marrow was insufficient/aplastic, the VEN was held. For C2 and beyond, ASTX727 was given for 5 days, VEN was given for 14-21 days and GILT was given continuously. The primary endpoint for the phase I was the MTD; and for the phase II, the overall response (defined as CR, CRh, CRi, or MLFS within 2 cycles of therapy).

Results

The phase I portion is complete with 12 pts enrolled (11 AML, and 1 high-risk CMML). Nine pts received GILT 80mg and 3 received 120mg. No DLTs at either dose level were observed. However, 80mg of GILT was selected for the phase II portion of this study based on the more favorable safety/efficacy profile and better count recovery observed in a parallel study of azacitidine combined with VEN and GILT in AML.

In the combined phase I/II cohort of pts with R/R AML or MDS/CMML, 15 pts have been treated. The median age was 65 years (range 38-83 years). Thirteen pts had a *FLT3*-ITD mutation (including 2 with a concomitant TKD mutation), and 1 pt had a *FLT3*-TKDmutation alone. Among pts with a *FLT3*-ITD, the median allelic ratio was 0.21 (range, 0.09 - 10.6). Among pts with a *FLT3*-TKD, the median allelic ratio was 0.05 (range, 0.02-0.09). Nine pts had diploid karyotype, 2 had adverse risk karyotype, and 4 had miscellaneous, intermediate-risk cytogenetic findings. The median number of prior therapies was 1 (range 1-9).

Among the 15 pts treated, 8 (53%) responded: 1 (6%) with CRh, 3 (20%) with CRi, and 4 (27%) with MLFS. The pt with an isolated *FLT3*-TKD mutation (along with del7q) did not respond. The pt with high-risk CMML achieved a CRi. Six of 12 pts who received prior HMA + VEN responded (2 CRi and 4 MLFS), and 2 of 3 pts without prior HMA + VEN responded (1 CRh and 1 CRi).

The median number of cycles received by pts was 2 (range 1-8). Best response was achieved by the end of C1 in 50% of responders, and by the end of C2 in the other 50% of responders. Of the 8 responders, 1 proceeded to alloSCT (with flow positive MRD at 0.3% but *FLT3* negative by PCR), 1 is still receiving treatment on protocol with continued response, 5 relapsed without HSCT (median time to relapse 2 months [range, 0.5-7 months]), and 1 died in MLFS. The transplanted pt remains in MRD-negative remission 5 months after alloSCT and is receiving maintenance GILT off protocol. With a median follow-up of 3.8 months (range, 1-18 months), the median overall survival for the cohort was 6.1 months.

There were 3 pts with grade 1-2 toxicities (1 with elevated liver enzymes, 2 with skin rash), 9 pts with grade 3 toxicities (9 with neutropenic fever, 4 of which became septic), no pts with grade 4 toxicities, and 2 patients with grade 5 toxicities (both had neutropenia and died from sepsis while on trial).

Conclusion

In this poor-risk population of pts with R/R *FLT3*-mutated AML or MDS/CMML, many of whom received prior HMA + VEN, the combination of ASTX727, VEN, and GILT was active, with an ORR of 53%. The trial continues to enroll to the R/R cohort, and is now open for patients with newly diagnosed *FLT3*-mutated AML who are unsuitable for intensive chemotherapy.

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