Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML

Authors: Naval Daver, Marina Konopleva, Abhishek Maiti, Tapan M. Kadia, Courtney D. DiNardo, Sanam Loghavi, Naveen Pemmaraju, Elias J. Jabbour, Guillermo Montalban-Bravo, Guilin Tang, Koji Sasaki, Gautam Borthakur, Musa Yilmaz, Joie Alvarez, Michelle Golez, Sherry A. Pierce, Graciela M. Nogueras González, Jing Ning, Hussein A Abbas, Farhad Ravandi, Guillermo Garcia-Manero, Hagop Kantarjian

Introduction:

In spite of frontline response rates of 65-70% with AZA-VEN a majority of pts relapse, with only 35-40% alive at 3+ years. Outcomes in R/R AML are poor with median overall survival (mOS) 5 - 7months (m). Magro, an anti-CD47 antibody that blocks the "don't eat me signal" on macrophages, demonstrated efficacy with AZA in ND TP53wt (ORR: 63%, mOS 18.9m) and TP53mut AML (ORR 69%, mOS 12.9m). Combined blockade of CD47-SIRPa axis by Magro with AZA-VEN increased phagocytosis in AML cell lines in vitro regardless of TP53 mut status, and prolonged survival in vivo in both AZA-VEN sensitive and refractory AML PDXs (Jia Y et al, ASH 2021). We designed a phase Ib/II trial to evaluate this triplet (NCT04435691).

Methods:

Pts ≥18 years with ECOG PS ≤2 and WBC <15x10 9/L with adequate organ function were eligible. The initial phase Ib enrolled R/R AML pts only. Once the RP2D was established the Phase II enrolled pts in 3 arms - frontline, VEN-naïve R/R AML, and VEN-exposed R/R AML. The frontline cohort enrolled pts ≥75yrs, or pts with documented comorbidities conferring ineligibility for intensive therapy; or pts with adverse risk karyotype and/or TP53mut regardless of age/fitness.

Pts received AZA 75 mg/m 2 on D1-7, VEN 400 mg (or equivalent per VEN label) on D1-28. Magro was dosed on cycle 1 D1, 4, 8, 11, 15, 22; weekly in cycle 2, and every 2 weeks in cycle 3+ (Fig. 1). At the end of the phase Ib (n=6 pts) no DLTs were noted and the Magro RP2D dose was established as 1 mg/kg on C1D1 and C1D4, 15 mg/kg on C1D8, and 30 mg/kg on C1D11 and subsequent doses.

Primary objective were safety, maximum tolerated dose (MTD), and RP2D of the triplet. Secondary objectives included CR/CRi rate, DOR and OS. Responses were per ELN2017.

Results:

Between Aug 2020 and July 1 2021 38 pts with newly diagnosed (ND) (n=17), R/R VEN-naïve (n=8), and R/R-post-VEN failure (n=13) were enrolled. An additional 6 ND pts were enrolled after July 1. Pt characteristics are in Table 1. In the ND pts the median (med) age was 70 yrs (range 33 - 84). Most pts had high-risk features: 14 (82%) pts ELN adverse risk, 45% ECOG PS≥2, and 8 (47%) were TP53m (VAF med 32%, range 5 - 94%).

Pts were evaluated for response and toxicity per intent to treat. 1 pt was still in cycle 1 and too early. The CR/CRi rate in the remaining ND pts was 94% (15/16) with a CR rate of 81% (Table 2). The 8-week mortality was 0. All pts achieved response after cycle 1. The med time to ANC recovery >0.5 and platelet recovery >50 among the CR/CRi pts was 28 (range 20 - 41) days and 24 (range 18- 41) days, respectively. Complete cytogenetic CR was achieved in 9 of 12 (75%) evaluable and MRD negativity by MFC <0.01% in 7 of 13 (55%) evaluable CR/CRi pts, with MRD monitoring ongoing. After a med follow-up of 3.4m, one of 17 frontline pts (a TP53 m pt) died after 7.6m from disease relapse, and one relapsed (the only MLFS pt) and is on alternate therapy (Fig 2). The other 15 pts continue on protocol. 7 of 8 ND pts with TP53m were evaluable (1 still in cycle 1) with a CR/CRi in 100% (7/7), CR in 86% pts (6/7), MRD negativity by MFC in 57% (4/7), CCyR in 3/4 evaluable pts, and 6/7 remain in remission.

In R/R prior VEN-naïve AML the CR/CRi rate was 63% (5/8) with med OS not reached (range 1.2-9.7). In R/R prior VEN failure AML the CR/CRi rate was 27% (3/13) with med OS 3.1 (range 0.9-6.5; Table 2).

Among all 38 pts the 4 wk and 8 wk mortality were 0 and 9.7% (n=4): these 4 deaths occurred in R/R pts. Frequent treatment-emergent non-hematologic adverse events regardless of attribution, of all grades included hypokalemia (58%), hypophosphatemia (55%), hyperbilirubinemia (53%), hyponatremia (53%) and sinus tachycardia (47%), and of Grade 3/4 included pneumonia (32%), febrile neutropenia (32%), hyperbilirubinemia (11%), elevated ALT (11), and skin infection (11%). Among 17 ND AML the med hemoglobin drop after magro 1 st dose was 1.1 g/dL (0.0 - 3.9) and after 2 nd dose was 0.8 g/dL (0.0 - 2.0). With close monitoring anemia was manageable with no SAEs, treatment interruptions or discontinuations due to anemia.

5 pts, all ND AML, have transitioned to allo-SCT and are alive.

Conclusion:

The combination of AZA VEN Magro was safe. High CR/CRi (94%) rates and CR rates (81%) were noted in ND pts, with majority (82%) ELN adverse risk. ANC and platelet recovery were robust (<28 days) in ND pts likely due to the lack of cumulative neutropenia or thrombocytopenia with Magro. Anemia occurs early on and should be monitored. Enrollment is ongoing and pivotal registration approaches with this combination are planned.