Abstract: P735

Title: EFFICACY AND SAFETY OF ORAL DECITABINE/CEDAZURIDINE (ASTX727) IN THE CMML SUBPOPULATION FROM PHASE 2 AND ASCERTAIN PHASE 3 STUDIES

Abstract Type: Poster Presentation

Session Title: Myeloproliferative neoplasms - Clinical

Background:

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disease characterized by persistent monocytosis, splenomegaly, and both dysplastic and myeloproliferative changes in the bone marrow. Hypomethylating agents are approved for CMML treatment as they have historically been included in pivotal studies, however only account for ~10% of trial patients. ASTX727, an orally available fixed dose combination (FDC) of 35 mg decitabine (DEC) and 100 mg cedazuridine (CED), a cytidine deaminase inhibitor, produces comparable PK AUC exposure compared to intravenous decitabine (Garcia-Manero, et al, 2019).

Aims:

We present the combined clinical experience of patients with CMML in the critical studies leading to FDA approval of oral DEC/CED (ClinicalTrilas.gov NCT02103478 and NCT03306264, respectively) with additional analysis of genetic profiles for the subset.

Methods:

33 CMML patients (16 from phase 2, and 17 from phase 3) who were candidates for parenteral decitabine with PS 0-2 were enrolled and received standard oral decitabine/cedazuridine FDC for 5 days. Clinical endpoints were best response according to International Working Group (IWG) 2006 response criteria, transfusion independence for at least 8 or 16 consecutive weeks, leukemia free survival (LFS), overall survival (OS), and safety. Peripheral blood collected prior to treatment was used for DNA isolation from leukocytes, and molecular abnormalities identified using a NGS hematologic malignancy panel, including 8 genes frequently associated with CMML. Cox-regression analysis on the various factors (eg binary mutational status, CR, etc.) was used for analyses of risk-factors for OS.

Results:

Median age was 71 years, with 55% patients with ECOG PS of 1. One-third of patients were RBC transfusion-dependent at baseline. 70% of patients were subtyped as CMML-1 based on the 2022 WHO classification, and 76% patients had MD-CMML. The median number of mutations in CMML patients was 3 (range 0-5) among 8 commonly mutated genes (see Figure 1). 85% of patients had received no prior anticancer therapy for CMML. Patients received a median of 10 cycles of therapy (range 2-36).

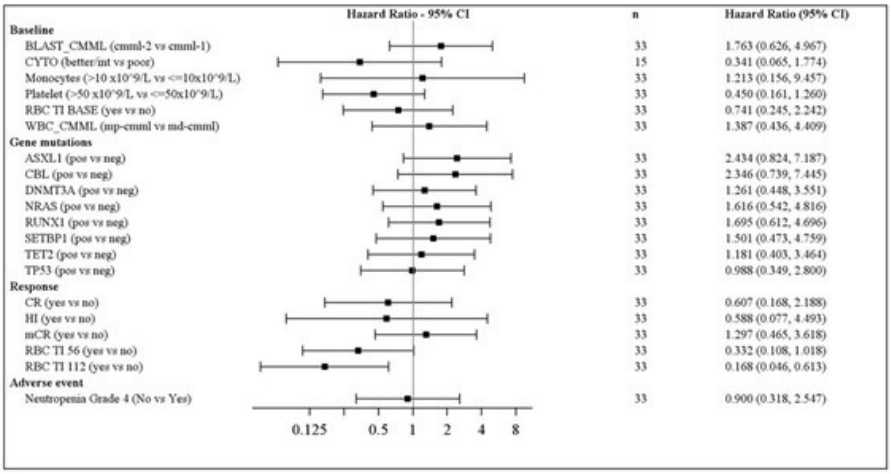
Seven patients (21.2%) had Complete Responses (CR), 14 (42.4%) had marrow CR (mCR), including 5 (15.2%) who also had hematologic improvement (HI). Overall response rate (ORR) [CR + PR+ mCR + HI] was 75.8%. 63.6% of those dependent on red blood cell (RBC) transfusions at baseline became transfusion independent (TI) for at least 8 weeks and 45.5% for 16 weeks. Median LFS was 28.3 months and median OS was 35.7 months. Safety profile is consistent with decitabine, with most grade 3 or higher events related to myelosuppression; Treatment-emergent adverse events of CTCAE Grade 3 or higher in > 10% of patients, independent of relationship to ASTX727, were cytopenias (neutropenia [61%], thrombocytopenia [55%], anemia [36%], febrile neutropenia [27%], and leukopenia [24%]). Given the advanced age of the CMML cohort, only 3 (9%) went on to Hematopoietic Stem Cell Transplant. Cox regression analysis suggested that post-treatment RBC TI seemed to be associated with survival; no apparent effect on OS was observed for other baseline or response-related factors, including baseline genetic variants, such as ASXL1 among others (Figure 1) though the sensitivity of such analysis is limited by the number of patients.

Summary/Conclusion:

DEC/CED has a well-tolerated safety profile with clinical benefit in CMML patients. Preliminary analysis suggests an association between TI and longer survival.

Figure 1

Forrest plot of factors affecting overall survival of oral DEC/CED treated CMML patients in Proportional Hazard Model Analysis of Maximum Likelihood Estimates



Keywords: Oral, Chronic myelomonocytic leukemia, CMML, Hypomethylating agents