A Phase I/II Study of Venetoclax in combination with ASTX727 (Decitabine/Cedazuridine) in Treatment-Naïve High-risk Myelodysplastic Syndrome (MDS) or Chronic Myelomonocytic Leukemia (CMML)

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Background

•ASTX727, an oral formulation of the fixed dose combination of the HMA decitabine and cytidine deaminase inhibitor cedazuridine recently approved for the treatment of MDS and CMML[1]

•Venetoclax (VEN), an orally bioavailable BCL-2 inhibitor in combination with azacitidine has shown clinical activity in treatment-naïve HR MDS[2]

•We designed a total oral therapy with VEN+ASTX727 combination to improve the clinical outcomes and quality of life in pts with HR MDS or CMML

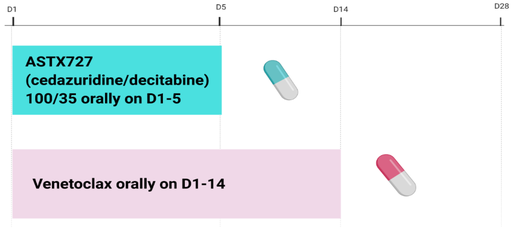
Materials & Methods

Study design – Single center open label non-randomized phase I/II study designed to evaluate the safety and efficacy of Ven+ASTX727 combination

Study eligibility criteria - patients ≥18 years with treatment-naïve, higher risk MDS (intermediate-2- or high-risk categories) per IPSS or CMML with excess blasts ≥5%.

Objectives - to determine the safety and tolerability (phase I) and overall response rate (ORR) (phase 2) of Ven+ASTX727 combination

Primary safety endpoint - The overall incidence and severity of all adverse events using Common Toxicity Criteria v 5.0.



Materials & Methods

Dose Level	ASTX727 (mg daily D1-5), oral	Venetoclax (mg daily D-14), oral
+1	100/35	400 x 14 days
0	100/35	200 x 14 days
-1	100/35	100 x 14 days

- Response assessment by bone marrow examination was done on D28
- Venetoclax dose was adjusted for concurrent azole/CYP3A4 inhibitor administration, if any.
- To mitigate tumor lysis syndrome, pretreatment white blood cell count should be less than 10 × 10^9/L.
- Cytoreduction was allowed

Results

Baseline characteristics	N=19
Age (years), median [range]	72 (54-94)
Disease Subtype Higher risk MDS (IPSS) CMML	 16 (84%) 3 (16%)
Hematological parameters Hemoglobin (g/dL) Platelets (x 10^9/L) Absolute Neutrophil Count (x 10^9/L)	 9.2 (7.1-12.4) 57 (19-171) 1.1 (0.1-7.8)
Bone marrow blasts (%), median [range]	12 (6-18)

•The median age is 72 years (range 54-94) with 16 pts (84%) aged ≥65 years.

•This high-risk cohort had baseline anemia and thrombocytopenia with a median bone marrow blast count of 12% (range 6-18%)

- They harbored a median number of 4 (range 1-9) mutations with most of them being adverse risk -*ASXL1* (58%) and *RUNX1* (42%).

Safety outcomes

Adverse events occurring in ≥2 patients	N (percentage)
Hematological AEs grade 3-4 Thrombocytopenia Neutropenia	 15 (83) 12 (67)
Infection/Febrile neutropenia grade ≤3	5 (28)
Other grade 1-2 non-hematological AEs Increased creatine Increased AST/ALT Increased bilirubin Nausea Constipation Fatigue Hyperuricemia	 4(22) 5 (28) 3 (17) 3(17) 5 (28) 6 (33) 2 (11)

- At baseline, most patients had grade 3 thrombocytopenia and neutropenia
- Regardless of attribution most common grade 3-4 hematological adverse events observed were thrombocytopenia and neutropenia
- Most common grade 1-2 non-hematological AEs were fatigue (33%),Increased liver enzymes (28%) and constipation (28%)
- No tumor lysis syndrome was observed
- 30-day and 60-day mortality were 0% each

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Response outcomes

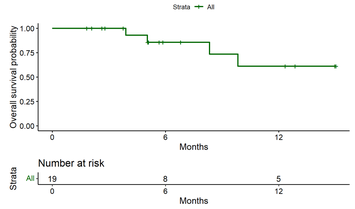
Response	N=19
Overall response rate (ORR) Complete remission (CR) Marrow complete remission (mCR)	18 (95) 3 (16) 15 (79)
Number of pts who underwent stem cell transplantation (SCT)	7 (37)

•The overall response rate in this cohort was 95% with mostly marrow complete remission (79%) of which 37% received curative intent SCT

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All patients who responded achieved their response within their first cycle

Survival outcomes



•At a median follow up of 5.9 months, median OS was not reached, and 1-year OS survival probability is 61%

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Median event free survival(EFS) was not reached and 1-year median EFS probability is 56%

Conclusion(s)

•Ven+ASTX727 combination appears safe and demonstrates preliminary efficacy in pts with higher risk MDS or CMML with excess blasts

•Total-oral regimen of Ven+ASTX727 combination appears to be a promising strategy for high-risk MDS or CMML pts and may alleviate the burden of chronic, long-term parenteral HMA treatment

References

1. Guillermo Garcia-Manero, James McCloskey, Elizabeth A. Griffiths, Karen W.L. Yee, Amer M. Zeidan, Aref Al-Kali et al. Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross over Phase 3 Study (ASCERTAIN study) of an Oral Hypomethylating Agent ASTX727 (cedazuridine/decitabine) Compared to IV Decitabine. Blood 2019; 134 (Supplement_1): 846

2. Wei,AH et al, *Blood* (2019) 134 (Supplement_1): 568.