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# POSTER ABSTRACTS

## 637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

### Phase II Study Assessing Safety and Preliminary Efficacy of High Dose Intravenous Ascorbic Acid in Patients with *TET2* Mutant Clonal Cytopenias

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**Background**: Clonal cytopenia(s) of undetermined significance ( **CCUS**) is defined as persistent cytopenias arising in the context of myeloid neoplasm ( **MN**)-associated somatic mutations ( **MT**) in hematopoietic stem cells. Patients ( **PTs**) with ***TET2*** **MT** CCUS have a high probability of progression to MN. To date, no FDA-approved therapies exist for CCUS, and PTs often have similar cytopenias/transfusion needs as those with myelodysplastic syndromes ( **MDS**). TET2 is an ascorbic acid (AA)-dependent dioxygenase that catalyzes the conversion of 5-methylcytosine ( **5mC**) to 5-hydroxymethylcytosine ( **5hmC**), providing rationale to study high-dose IV (HI)-AA in *TET2* MT CCUS. Here we report the final results of this pilot trial.
**Methods:** This is an investigator-initiated, single-institutional, phase II trial assessing the safety and efficacy of HI-AA in PTs with *TET2* MT CCUS (NCT03418038). PTs≥ 18 years with ≥1 *TET2* MT with or without additional somatic MTs, without prior treatment, and with any of the following laboratory criteria: (1) hemoglobin ( **Hb**) ≤10g/dL, (2) absolute neutrophil count ( **ANC**) ≤1(10^9/L), (3) platelet count ( **PLT**)≤100 (10^9/L) were eligible. HI-AA (1g/kg, maximum 100g) was given 3 times weekly for 12 weeks. The primary endpoint was hematologic response rates determined by MDS IWG 2018 criteria at week 20. (Platzbecker *Blood* 2018) and reported as hematologic improvement ( **HI**)- erythropoietic ( **HI-E**), platelets ( **HI-P**), neutrophils ( **HI-N**). Secondary endpoints include safety and adverse events ( **AEs**), graded by NCI-CTCAE v4.03. Correlative studies include changes in *TET2* MT variant allele fraction ( **VAF**), *in vitro* colony formation and differentiation, global and sequence-specific DNA methylation/hydroxymethylation, and quantitative 5hmC estimated by IHC in bone marrow biopsy specimens.
**Results:** Ten patients were enrolled, with a median age of 71.4 (range: 65, 79) years, 8 (80%) males. The median number of mutations was 3, with 9 (90%) having co-mutations. All PTs but one [-Y] had normal karyotype. Baseline Hb levels were normal in all but one who was red blood transfusion dependent. Five (50%) PTs were thrombocytopenic, and 5 (50%) PTs had ANC<1 (10^9/L). ( ***Table***).
HI-AA was well tolerated with the most common AEs being infusion-related polyuria (40%) and polydipsia (40%, 3 Grade 1, 1 Grade 2). One (10%) PT had constipation and headaches (both Grade 1), and 1 (10%) experienced dyspepsia. No treatment-related Grade 3 or 4 AEs' or deaths were reported.
The median follow-up duration was 16.8 months (range: 9.4, 24.1). Overall, no PTs met the criteria for HI. There were no significant differences with regards to median Hb, PLT, and ANC values at baseline, week 20, and 1-year (median Hb: 13.3, 12.5, and 12.7 g/dL, p=0.93; PLT: 97 vs. 120 vs. 92.5X10^9/L, p>0.99, and ANC: 0.9 vs. 1.2 vs. 1.3X10^9/L, p=0.99). By CTCAE grading criteria for cytopenias, 3 (30%) PTs had an improvement in severity of cytopenias, while 2 had worsening. One (10%) PT had an improvement in PLT (baseline vs. week 20: 62 vs 192X10^9/L) but was morphologically deemed to meet criteria for CMML-1 at week 20.
Four (40%) PTs met criteria for disease progression (PT_4, 7,8,10); CMML-1- 2 and MDS-2. The median time to progression was 5 months (95% CI: 4.9, unreached). Two PTs had mutational clonal evolution, with 1 (PT_8) acquiring a *RUNX1* (VAF: 20%) and 1 (PT_9) acquiring 2 *CBL* mutations (both VAF:4%) at one-year follow-up. There were no significant differences regarding the clinical characteristics or the *TET2* variants between PTs who had stable disease vs. progression. There were no significant

differences in *TET2* VAF at baseline, week 20, and 1-year (median: 39% vs. 43% vs. 42%, p=0.54). We profiled changes in 5-mC and 5-hmC (Illumina EpicArray) in PTs pre- and post-IV AA treatment and did not observe global changes. However, we were able to highlight site-specific changes in differentially methylated regions, largely resulting in hypomethylation at enhancer sites and affecting actively transcribed states in PTs with an improvement in cytopenia(s) severity by CTACE criteria ( **Figure**). **Conclusion:** We report the final safety and efficacy analysis of HI-AA in PTs with *TET2* $^{MT}$ CCUS. The trial data suggest that HI-AA is safe and well tolerated. Although there were no significant responses by IWG MDS criteria, alleviation in severity of cytopenias in a subset of PTs (n=3) along with correlative epigenetic changes in enhancer regions, needs further exploration.

**Disclosures Xie:** *Moffitt Cancer Center:* Current Employment; *Novartis:* Speakers Bureau. **Witzig:** *Kura Oncology:* Research Funding; *ADC:* Membership on an entity's Board of Directors or advisory committees; *Karyopharm:* Research Funding; *Salarius Pharma:* Membership on an entity's Board of Directors or advisory committees. **Patnaik:** *Epigenetix:* Research Funding; *Kura:* Research Funding; *CTI BioPharma:* Membership on an entity's Board of Directors or advisory committees; *StemLine:* Research Funding.

Table. Baseline characteristics for the entire cohort. AA: Ascorbic acid; ANC: absolute neutrophil count; AMC: absolute monocyte count; CG: cytogenetics; Hb: hemoglobin; PLT: platelet; PT: Patient. N: No; Y: Yes

| PT | Age at Rx (yrs.) | Sex | Baseline Hb | Baseline Plt | Baseline ANC | Baseline AMC | Baseline AA deficiency | Baseline mutation number | Molecular profile TET2 | Co-mutations | Baseline CG | Baseline atypia | Cellularity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PT_1 | 73.8 | M | 12.5 | 74.0 | 1.2 | 0.4 | N | 2 | Q1555V | *SRSF2* | 46, XY [20] | Slight | Hypercellularity |
| PT_2 | 69.1 | F | 13.5 | 141.5 | 0.7 | 0.6 | N | 1 | Y163L | - | 46, XX [20] | None | Normal cellularity |
| PT_3 | 77.4 | M | 12.1 | 133.0 | 0.8 | 0.2 | N | 3 | N275I | *ZRSR2* | 46, XY [20] | None | Hypercellularity |
| PT_4 | 64.7 | M | 13.1 | 28.5 | 0.8 | 0.4 | Y | 2 | R1808* | *SRSF2* | 46, XY, del(20)(q11.2q 13.3)[1]/46,XY[ 16] | Slight | Hypercellularity |
| PT_5 | 73.7 | M | 13.6 | 72.5 | 1.0 | 0.2 | N | 3 | N1743I R1214W | *SRSF2* | 46,XY [20] | Moderate | Normal cellularity |
| PT_6 | 67.4 | M | 7.8 | 390.5 | 4.9 | 0.4 | N | 2 | L1447R | *SRSF2* | 46, XY [20] | Slight | Hypercellularity |
| PT_7 | 66.1 | M | 13.7 | 67.0 | 8.4 | 2.1 | N | 4 | G1235* Q831T | *KRAS SRSF2* | 46, XY [20] | Moderate | Hypercellularity |
| PT_8 | 77.3 | M | 12.8 | 164.5 | 0.3 | 0.5 | N | 3 | R250* | *ASXL1 ZRSR2* | 46, XY [20] | Slight | Hypercellularity |
| PT_9 | 79.0 | F | 14.8 | 37.0 | 1.9 | 0.8 | Y | 2 | C1378Lfs*70 | *SRSF2* | 46, XX [20] | None | Hypercellularity |
| PT_10 | 64.9 | M | 12.1 | 120.5 | 0.3 | 0.7 | N | 3 | G259* c.3955-1G>A | *ZRSR2* | 45, X, -Y [20] | Slight | Hypercellularity |

Figure. Circos plot showing the genomic location and number of differentially methylated regions between patients pre- and post-treatment. Functional annotation of the hypomethylated regions using the ENCODE Epigenomics Roadmap peripheral blood mononuclear cell reference data.

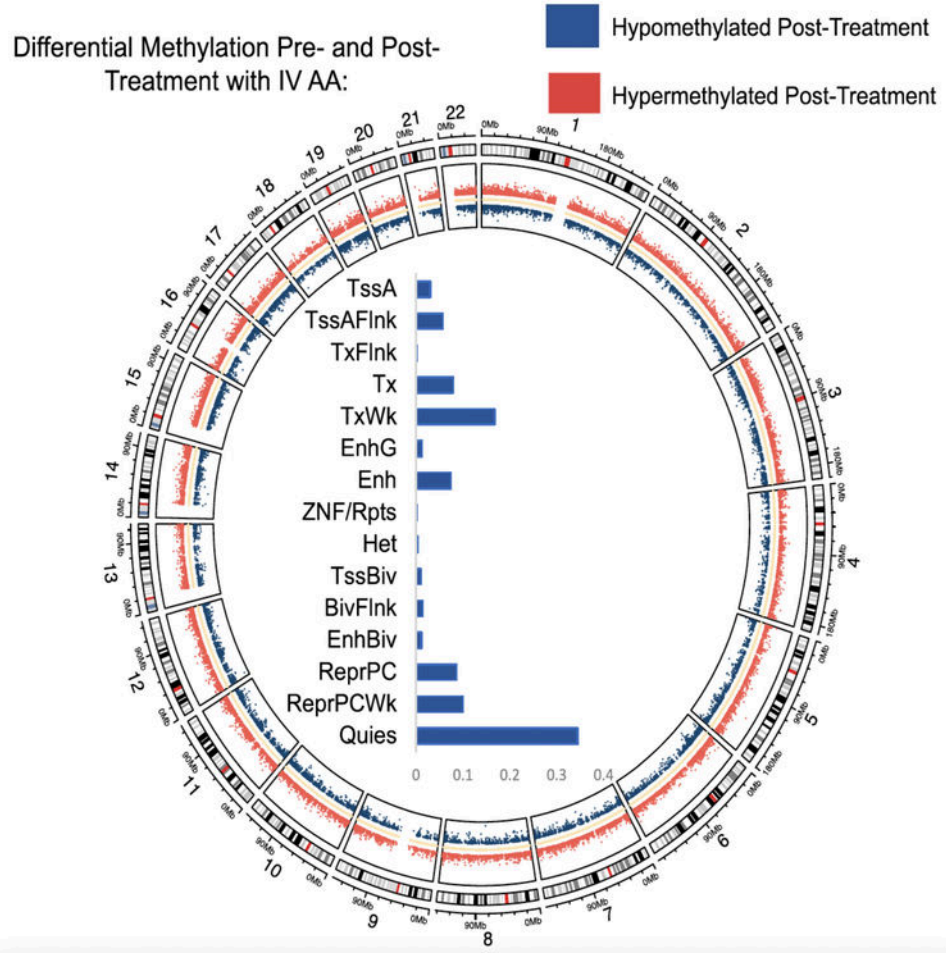


**Figure 1**

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