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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.

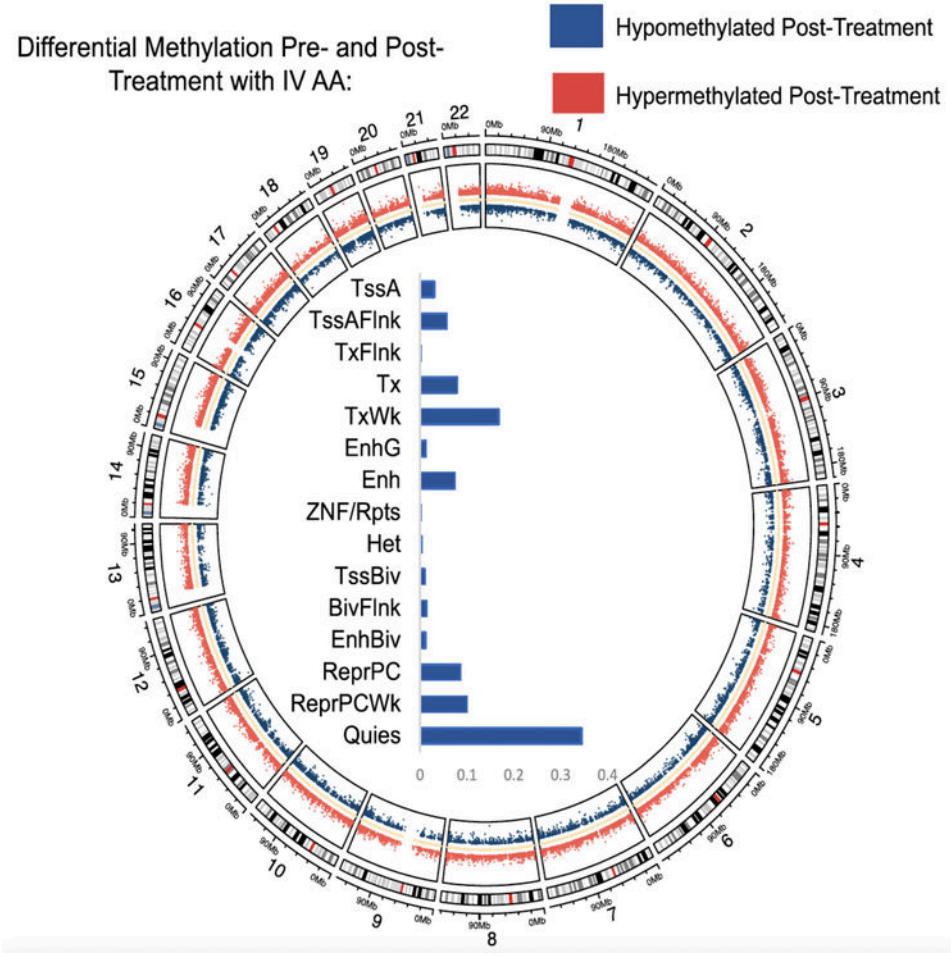

Figure 1

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