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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Long-Term Follow-up and T Cell Characteristics of Patients with *ASXL1*-Mutated Relapsed or Refractory MDS or CMML Treated with Guadecitabine and Atezolizumab

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Background
Treatment of patients with myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML) after failure of a hypomethylating agent (HMA) remains an unmet need. We and others demonstrated a modest overall response rate (ORR) to the combination of immune checkpoint inhibition (ICI) and an HMA in such patients; a promising overall survival (OS) compared to historical data (5-6 months) was seen in some, but not all, studies. Our study and that of Daver et al. suggested that patients with *ASXL1* mutations, in particular, may benefit from the addition of ICI.
We conducted a Phase I/II clinical trial evaluating the addition of a programmed death ligand 1 (PD-L1) inhibitor, atezolizumab, to a subcutaneous prodrug of the HMA decitabine, guadecitabine. We evaluated the presence of common driver mutations in CD3- bone marrow mononuclear cells (BMMC) and CD3+ T lymphocytes. Among 27 tested patients, 12 had the *ASXL1* mutations in the myeloid compartment and, of those, 5 patients' T cells carried the exact same mutation at a variant allele frequency (VAF) of >10%. Both patients with complete remission in the study (n=2) carried the mutation in both compartments (co-mutated) and median OS was significantly better for co-mutated patients (not reached) than for those with CD3- BMMC (myeloid) mutations (9.5 months) or wild type *ASXL1* (16.5 months). Herein we report long-term follow-up of this cohort of patients, along with T cell programmed death-1 (PD-1) expression analyzed based on mutational status.
Methods
Details of the trial design and correlative plan are published. In the published study we used a VAF cutoff of 2% (1% for *TP53*) for BMMC and 10% for CD3+ T lymphocytes for the panel of 40 commonly mutated genes. In the current study we also evaluated patients with a T cell *ASXL1* VAF of 5-10%. Patients have been followed for progression and survival every 6 months. Demographic and disease characteristics and outcome data were compared based on *ASXL1* mutation status. Previously obtained T lymphocyte PD-1 expression data from samples obtained pre-treatment (PRE), during cycle 2 (EARLY) and after cycle 3 or 4 (LATE) were analyzed based on *ASXL1* mutation status.
Results

Among 27 patients from 4 centers with DNA available for genetic analysis, 15 had no *ASXL1* mutation (*ASXL1* WT), 5 had *ASXL1* mutations restricted to the myeloid lineage, and 7 had *ASXL1* mutations in both the myeloid and T-cell populations (*ASXL1* co-mutated). Two co-mutated patients had T cell VAFs of 5-10% and 5 had VAFs>10% (Figure 1). No baseline characteristic by *ASXL1* mutational status was significantly associated with response to study treatment, though 6 of 7 co-mutated patients (vs 3/5 myeloid-only patients) had not responded to first-line HMA (refractory).

With a median follow-up time of 64.9 months, median survival times were 48.9 months (15.1, 64.9+) for co-mutated patients with T cell VAF >10%, 34.9 months (8.5, NR) for co-mutated patients including those with T cell VAF of >5%, 16.4 months (3.3, 27.3) for *ASXL1* WT patients, and 9.5 months (2.1, 35) for myeloid-only patients (Figure 2). This was statistically significant after adjusting for age and ECOG performance status at study entry, diagnosis, baseline bone marrow blast percentage, and number of prior chemotherapy regimens using the likelihood ratio test from multivariate analysis for overall survival ($P = 0.008$).

Early treatment-induced upregulation of $CD8^+$ T cell PD1 was observed in the *ASXL1* WT, before returning to baseline levels. This upregulation was more pronounced in the *ASXL1* co-mutated group beginning at a lower baseline and peaking at a higher MFI and was statistically significant ($P = 0.0098$). No significant treatment-induced change in PD-1 expression was noted in the myeloid-only subset.

Discussion

In patients with relapsed or refractory MDS or CMML, the presence of an *ASXL1* mutation in both myeloid and T lymphocyte compartments, as compared to WT or myeloid-only mutations, was associated with a significantly longer median OS when treated with the combination of ICI and HMA. Significant upregulation of PD-1 was noted in T lymphocytes from both wild-type and co-mutated patients. The effect of mutant *ASXL1* on T cell responsiveness to ICI deserves further investigation; patients with *ASXL1*-mutated HMA-refractory myeloid malignancies may benefit from ICI.

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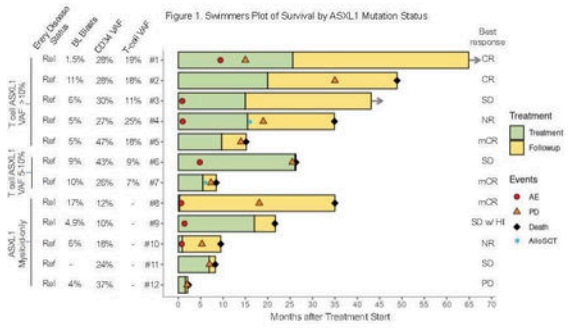

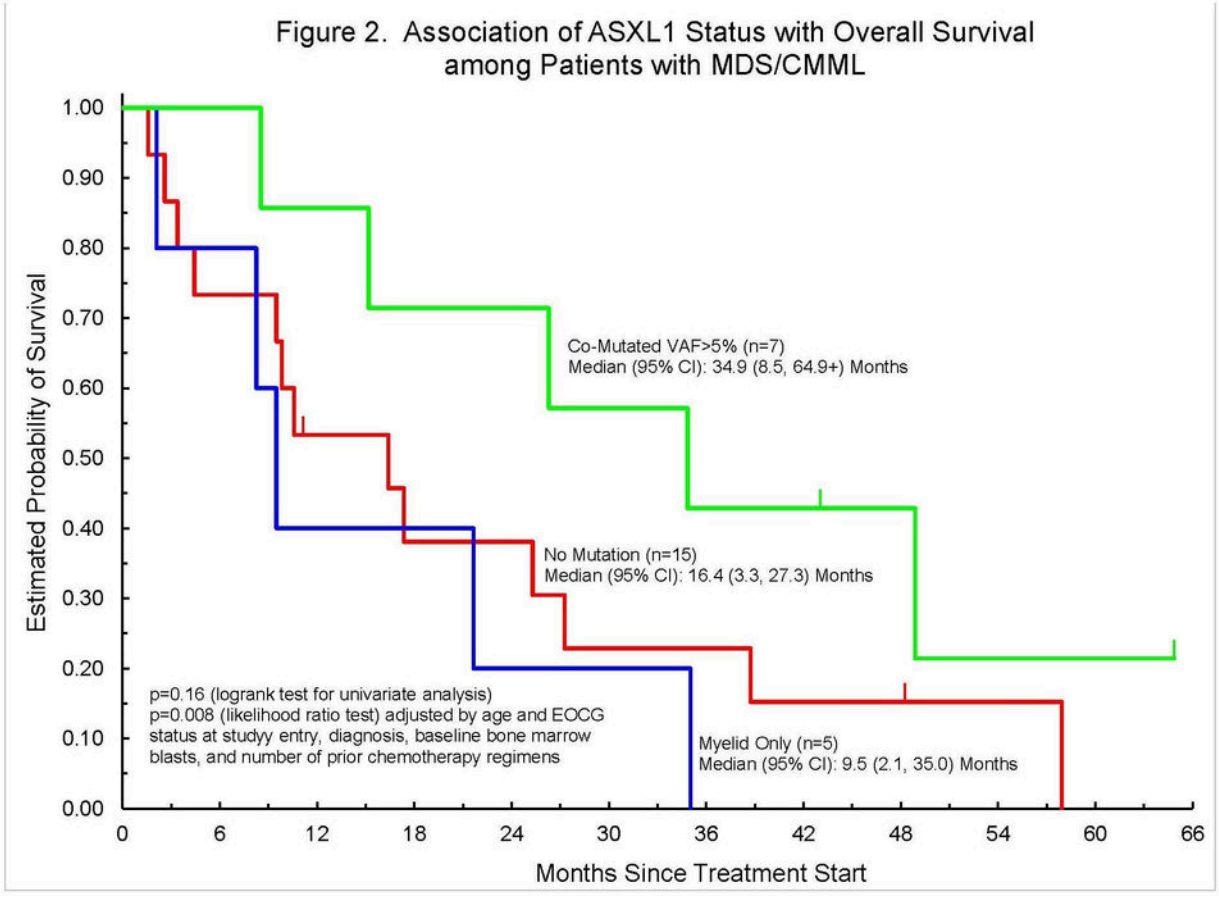

Figure 1

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