



## The 65th ASH Annual Meeting Abstracts

## POSTER ABSTRACTS

## 613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

**TP53 Y220C Mutations in Patients with Myeloid Malignancies**

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**Background:** *TP53* gene mutations lead to inactivation of the protein p53, causing genome instability, oncogenesis, and treatment resistance conferring an unfavorable prognosis. *TP53* Y220C missense mutations in exon 6 (p.659A>G) are described as a frequent 'hot spot' mutation in solid tumors. A novel Y220C-targeted small molecule (PC14586) has shown preliminary efficacy and safety in patients with solid tumors (Dumbrava, E., ASCO 2022). No data has been reported about *TP53* Y220C in hematologic malignancies to date. We set out to evaluate the clinicopathologic characteristics of *TP53* Y220C in hematologic malignancies and particularly, myeloid neoplasms.

**Methods:** We identified all patients with hematologic neoplasms with *TP53* Y220C mutations at University of Texas MD Anderson Cancer Center and Memorial Sloan-Kettering Cancer Center, detected by standard next generation sequencing assays, and focused on patients with myeloid malignancies; summarizing the patient characteristics, disease features and outcomes for patients with this specific *TP53* mutation. Overall survival (OS) was assessed by the Kaplan-Meier method from date of diagnosis to date of death from any cause or date of last follow-up. Leukemia-free survival (LFS) was calculated from time to diagnosis of *TP53* Y220C mutated myelodysplastic syndrome (MDS) to date of transformation to acute myeloid leukemia (AML) or death. Survival analysis was conducted only for newly diagnosed patients with available follow-up data.

**Results:** We identified 143 patients (pts) with hematologic malignancies harboring a *TP53* Y220C mutation. MDS and AML were the most frequent diagnoses (MDS, n=66; AML, n=48). Median age was 69 years (range, 32-92) and 56% of patients were male (Table 1). We then analyzed in more detail patients with MNs, including CHIP/CCUS, MDS, AML and MDS/MPN. Among those, in 76 (64%) pts the *TP53* Y220C mutation was detected at initial diagnosis and in 43 (36%) pts, *TP53* Y220C was identified in the relapsed/refractory setting. Therapy-related myeloid neoplasms (MNs) accounted for 51 of 119 pts (41%). Complex karyotype was frequent (n=88/119, 74%) in the setting of *TP53* Y220C. Median *TP53* Y220C variant allele frequency (VAF) was 32% (range, 1%-96%). Eighty-two patients (69%) had additional co-mutations: 24 (20%) pts had additional (non-Y220C) *TP53* mutations only; 34 (29%) pts had only non- *TP53* co-mutations (most frequently *DNMT3A* and *TET2*) and 24 (20%) pts had additional *TP53* mutations in the setting of other co-mutations. With a median follow-up of 9 months, median OS for patients with newly diagnosed *TP53* Y220C MDS (n=39) and AML (n=23) was 13.1 months (95% CI, 7.6 to 18.7) and 8 months (95% CI, 5.6 to 13.4), respectively ( $p=0.06$ ) (Figure 2). For the *TP53* Y220C MDS cohort, AML transformation occurred in 13 (33%) patients, after a median of 14.3 months. Median LFS for these patients was 12.2 months (95% CI, 7.9 to 16.5). Modest and non-statistically significant differences in median LFS for MDS patients who did and did not receive stem cell transplant (SCT) were identified; MDS+SCT (n=12) 14.5 months (95% CI, 4 to 25) vs MDS+no-SCT (n=27) 9.3 months (95% CI, 4.6 to 14),  $p=0.18$ . Interestingly, four patients diagnosed with *TP53* Y220C mutated CHIP/CCUS with a median VAF of 2% were identified, and with a median follow-up of 34.6 months, none have developed dysplastic changes or progression to MDS or AML at the time of cut off. Additional outcomes data will be forthcoming in the analysis of this cohort of patients with *TP53* Y220C mutated myeloid neoplasms.

**Conclusions:** TP53 Y220C mutations are present in malignant blood disorders and are particularly more common in myelodysplastic syndromes and acute myeloid leukemia, with associated poor outcomes. Novel targeted therapies for this TP53 variant (Y220C) would be of interest for this patient population.

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**Table 1.** Baseline Patient Characteristics (n = 143)

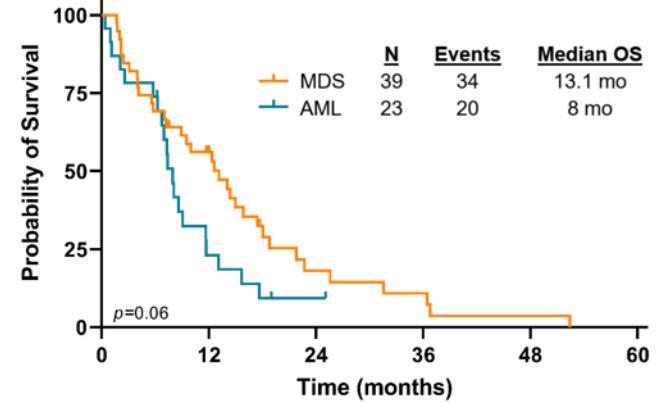
Parameter	Value
<b>Age, median [range], y</b>	69 [32-92]
<b>Male sex, No. (%)</b>	80 (56)
<b>Hematologic Malignancy, No. (%)</b>	
CLL	12 (8)
B-ALL	3 (2)
CHIP/CCUS	4 (3)
MDS	66 (46)
AML	48 (33)
MDS/MPN	1 (1)
MPN	6 (5)
Other	3 (2)
<b>Diagnosed <i>de novo</i> / relapsed-refractory MNs, No. (%) *</b>	76 (64) / 43 (36)
<b>Therapy-related MNs, No. (%) *</b>	51/119 (43)
<b>Cytogenetics, No. (%) *</b>	
Normal	13 (11)
Complex	88 (74)
Other <sup>§</sup>	12 (10)
Missing data	6 (5)
<b>Variant allele frequency (VAF), median [range] *</b>	0.32 [0.01-0.96]
<b>Molecular genetics co-mutations, No (%) *</b>	
No co-mutations	35/119 (29)
Additional co-mutations; No (%), median number [range]	82/119 (69)
Non-Y220C <i>TP53</i> mutations only	24 (20), 1 [1-5]
Other mutations only	34 (29), 1 [0-5]
Additional non-Y220C <i>TP53</i> + other	24 (20), 4 [2-8]
Missing data	2/119 (2)

Abbreviations: AML, acute myeloid leukemia, B-ALL, B-cell acute lymphoblastic leukemia; CHIP/CCUS, clonal hematopoiesis of indeterminate potential/clonal cytopenia of undetermined significance; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; MNs, myeloid neoplasms; MPN, myeloproliferative syndrome

\*Myeloid neoplasms included: CHIP/CCUS, MDS, AML, MDS/MPN

<sup>§</sup>Other include 5 of 12 patients with isolated del(5q) karyotype

**Figure 2.** Overall survival (OS) for patients with newly diagnosed MDS and AML with *TP53* Y220C mutated



**Figure 1**