Response to Comment on: "Clinical interrogation of *TP53* aberrations and its impact on survival in patients with myeloid neoplasms"

We thank the author for the valuable analysis of our work.[1,2] We understand the limitations associated with a retrospective study and this has been well described in the manuscript. However, this also allowed us to look at patients with *TP53*-mutated myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML) treated through different treatment approaches. Since most of the patients in our analysis were treated in clinical trials the genomics, responses and outcomes data were prospectively collected and annotated.

The author asks an important question about stratifying outcomes based on the type of mutation (missense and truncating) and further by different mutations in each group. While this could be interesting to discern the biological impact of *TP53* mutation/s, the clinical relevance might be limited in the context of MDS/AML.[3] Additionally, the majority of the patients had a missense mutation in our cohort (87%), limiting the power of a stratified outcomes analysis between missense and truncating mutations. However, this could become relevant in the future for clinical trials with agents that aim to reactivate mutant p53 protein.

With respect to the high frequency of patients treated on clinical trials in our dataset, at MD Anderson Cancer Center, clinical trials remain our priority in AML and other leukemia. This is especially relevant for *TP53*-mutated MDS/AML where standard-of-care treatment options rarely yield favorable results. Understandably eligibility criteria for clinical trials will limit patients with certain morbidities, functional status etc. Hence our analysis includes also the patients who were treated outside clinical trials.

Our data answered specific questions about the impact of *TP53* mutations and the burden of *TP53* mutations in MDS with excess blasts and AML. This defined the patient population and low-blast, MDS were excluded. Since cytogenetics is needed to capture the burden of *TP53* aberration, we had to exclude patients in whom baseline cytogenetics were not available. While this certainly excludes some patients, we doubt this would have affected the overall results. In any case we strongly support multicenter studies to evaluate and validate our results.

The author highlights an important issue with the use of venetoclax in the *TP53*-mutated AML. Indeed, this was one of the important questions we wanted to address in our analysis. While we report here higher rates of overall response and composite complete response with venetoclax added to low-intensity or intensive chemotherapy (than without venetoclax), this did not translate into higher rates of allogeneic hematopoietic stem cell transplantation (HSCT) or survival. This is especially true for high-burden *TP53* aberrations, and our study cohort was enriched with such patients. *Post hoc* analysis from the VIALE-a trial and other groups have showed no significant improvement in survival with venetoclax in *TP53*-mutated AML.[4,5] However, in patients where transplant is the immediate goal, the higher response rates can potentially make some of these patients eligible. We recently showed that even in responding patients with *TP53*-mutated AML, rates of HSCT remain low from several barriers beyond persistent leukemia.[6] Thus, the use of a venetoclax is often a personalized physician decision but is relevant in young, fit, eligible transplant patients who can be rapidly consolidated with an HSCT as soon as a bone marrow blast clearance is achieved. With respect to treatment intensity, the higher rates of HSCT in intensively treated patients could account for better survival compared to low-intensity therapy treated patients. In patients where HSCT is not feasible and *TP53* aberration burden is high it is prudent to treat them with low intensity venetoclax-free regimens, but certainly clinical trials remain the first choice.

Our analysis used an outcome-directed machine learning to identify *TP53* variant allele frequency in patients with a single *TP53* mutation and without *TP53* allelic loss, that clinically behaves like biallelic (high-risk) *TP53*. Several groups have attempted this. We do believe that dynamic monitoring of *TP53* clones at the time of remission, pre-HSCT and at later time points can enable better assessment of the depth of remission and prognosticate outcomes. This needs to be evaluated prospectively. Mutant-p53 re-activating drugs like eprentapopt failed to show survival benefit in a randomized phase III clinical trial (full data remains to be published), but newer small molecule activators (like rezatapopt) are being studied in *TP53* Y220C-mutated MDS/AML and solid organ malignancies.

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Disclosures

No conflicts of interest to disclose.

Contributions

Both authors wrote and reviewed the comment.

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