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Treatment of *TP53*-mutated myelodysplastic syndrome and acute myeloid leukemia with low-intensity metronomic decitabine and venetoclax

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M.G. designed and performed research and collected, analyzed, and interpreted data and wrote the manuscript; **I.M.** and **Y. Saunthararajah** designed and performed research, analyzed and interpreted data, and reviewed and edited the manuscript; **A.S., S.Y., D.L.C., M.K**., and **A.V.** performed research, analyzed and interpreted data, and reviewed and edited the manuscript; **B.R., D.L., N.K., K.G., R.A.S., L.C.S., R.G., S.P., N.S., M.C., Y. Shi,** and **B.A.J.** performed research and analyzed and interpreted data; **K.P.** contributed analytical tools, collected, analyzed, and interpreted data, and performed statistical analysis; **A.M., A.D., J.A.V., K.F. and L.S.** performed research and collected, analyzed, and interpreted data; **E.J.F.** designed and performed research and reviewed and edited the manuscript.

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Abstract:

Venetoclax (Ven) in combination with hypomethylating agents (HMA) (azacitidine or decitabine) is the standard of care for elderly or unfit patients with acute myeloid leukemia (AML) and is being explored in high-risk myelodysplastic syndrome (HR-MDS). However, currently approved dosing of HMA/Ven is associated with prolonged cytopenias, without a clear improvement in survival for *TP53*-mutated myeloid malignancies. In order to reduce hospitalizations during COVID, a once-weekly, metronomic schedule of decitabine (0.2 mg/Kg) and venetoclax (400 mg) was developed for patients with MDS and AML. Based on encouraging results, a phase 2 trial was performed. In the current study, we analyzed response rates and survival for all patients with TP53-mutated disease treated on the metronomic schedule. In total, 40 patients with *TP53*-mutated MDS and AML (26 in a prospective trial and 14 in the retrospective cohort) were included; 26 had HR-MDS and 14 had AML. The median age was 76.5 years, 70% had complex cytogenetics and 82% had bi-allelic *TP53* mutations. The ORR for AML (CR+Cri) was 70% and 57% (CR+mCR) for MDS. With a median follow-up of 12.9 months, the median OS for the entire cohort was 11.3 months (11.6 months for AML, 9.9 months for MDS), and median OS in the 31 patients with bi-allelic mutated *TP53* was 10.4 months. Transfusion independence was achieved in 58%. Neutropenic fever occurred in 15%, there were no therapy-related fatalities, and the 100-day mortality was 7.5%. A non-cytotoxic metronomic dosing schedule of decitabine/Ven has a low toxicity profile in *TP53*-mutated myeloid malignancies

Introduction:

TP53 is a tumor suppressor gene with pivotal roles in DNA damage response, genome stability, and apoptosis. It is mutated in 10-15% of de novo acute myeloid leukemias (AMLs), ~20% of elderly myelodysplastic syndromes (MDS)/AML, and >30% of therapy-related MDS/AMLs.[1,2] Inactivation of the *TP53* gene by mutation or deletion is often correlated with complex cytogenetics, resistance to conventional chemotherapeutic DNA-damaging agents and confers a very poor prognosis. *TP53*-mutated AML may initially respond to cytotoxic chemotherapy, but responses are typically short-lived due to selective pressure from chemotherapy, promoting the expansion of *TP53*-mutated clones.[3] Recent studies suggest that *TP53*-mutated MDS and AML have similarly poor survival, irrespective of blast counts, and have equally poor outcomes, mainly driven by homogeneity in their distinct molecular characteristics. [4-7] Venetoclax (Ven) added to the hypomethylating agents (HMA) of decitabine or azacitidine is the current standard of care for elderly patients with AML and is often used in high-risk MDS (HR-MDS) based on apparent synergism in early phase trials.[8] However, despite the robust activity of HMA/VEN in AML, the addition of Ven has not improved overall survival (OS) in the *TP53* mutant subgroup.[9] As many patients with TP53-mutated myeloid malignancies are elderly and have an incurable disease with a short life expectancy, therapies causing prolonged cytopenias may be undesirable if they compromise quality of life or cause prolonged hospitalizations. Recent data suggests that the vast majority of older adults with AML, prioritize quality of life over survival, with many opting to decline treatments that cause significant toxicities.[10] Moreover, many express a clear preference for spending time at home rather than undergoing therapies that require prolonged hospitalizations and emerging evidence suggests that the addition of Ven to HMA has not translated into more time spent at home.[11,12] For younger patients eligible for allogeneic stem cell transplantation, an important goal for induction therapy is to minimize toxicity and preserve transplant eligibility. Therefore, optimizing regimens that balance efficacy and tolerability remains a critical unmet need in this high-risk population.

The efficacy and improved tolerability of HMA/Ven when used in a metronomic once-weekly low-dose schedule of decitabine and Ven were previously described in a small cohort of HR-MDS and AML.[13,14] Although the mechanism of activity for this combination is not fully established, it is thought that the once-weekly HMA maintains S-phase-dependent DNMT1-targeting while minimizing myelosuppression.[15] Similarly, the addition of a single weekly dose of venetoclax also reduces myelosuppression while effectively inhibiting de novo pyrimidine synthesis, a major mechanism of resistance to HMAs.[16-18] This combination's lack of severe myelotoxicity makes it

a potentially attractive regimen for TP53-mutant myeloid diseases, particularly in an elderly population. In a previous retrospective report that included a heterogeneous group of myeloid malignancies, we observed a favorable side effect profile and a signal of efficacy that included a small subset of patients with TP53-mutated disease. In the current study, we focus our analysis in TP53-mutated AML and HR-MDS pooled from the retrospective and prospective cohort.

Methods:

This pooled analysis included patients enrolled in a single-arm phase II study (NCT05184842) and patients from a retrospective cohort treated at Montefiore Medical Center, with enrollment and treatment occurring between April 2020 and January 2025. The study design and eligibility criteria have been previously described.[14] Eligible patients had a confirmed diagnosis of AML or MDS (WHO 2016 criteria), an ECOG performance status of 0–3, and had not received prior HMA or venetoclax therapy. AML patients were either ≥75 years old or had comorbidities, making them ineligible for standard induction chemotherapy. The retrospective cohort consisted of all patients with TP53-mutated MDS or AML who were treated with metronomic decitabine/venetoclax beginning in April 2020, when the COVID-19 pandemic prompted adoption of this outpatient regimen to minimize myelosuppressive toxicity and reduce associated hospitalizations and clinic visits. All patients had no prior exposure to a hypomethylating agent/venetoclax combination. Patients received decitabine 0.2 mg/kg SQ weekly and venetoclax 400 mg PO on days 1, 8, 15, and 22 of a 28-day cycle, with three induction cycles followed by maintenance until progression or discontinuation. Cytoreduction with hydroxyurea was permitted before treatment initiation. Therapy began once the white blood cell count decreased to below 25,000/μL. Venetoclax dosing was adjusted for patients receiving concomitant azole antifungals or other strong CYP3A4 inhibitors.[19]

The Montefiore Einstein Institutional Review Board approved the study protocols and related documents. All patients in the prospective trial provided written informed consent. The study was conducted per the International Conference on Harmonization, Good Clinical Practice Guidelines, and the Declaration of Helsinki.

Assessment of outcomes:

Response was assessed per IWG 2006 (MDS) and ELN 2022 (AML) criteria. Efficacy for AML was assessed as the rate of objective response (complete remission [CR] + CR with incomplete blood count recovery [CRi]) and OS. For patients who achieved a response, the duration of response (DOR) was defined as the time of the first response (CR, CRi, marrow CR [mCR] or stable disease [SD]) until the earliest evidence of confirmed disease progression, or

death due to disease progression. For ongoing responses, data was censored at the time of last follow-up. OS was defined as the time from the first dose of decitabine/Ven to the date of death from any cause. Red cell and platelet transfusion independence was defined as a period of 56 days without transfusions.[20]

Mutations associated with AML were detected by a next-generation myeloid sequencing panel. MRD was assessed in bone marrow (BM) aspirates using a multiparameter flow cytometry assay performed by Hematologics Inc. (Seattle, WA), with a standardized panel of monoclonal antibodies, allowing for the detection of leukemia down to 0.02% of total nucleated cells in a specimen of adequate quality. Patients who had one negative sample for MRD value below this cutoff at any time while on study treatment were defined as patients with an MRD-negative response. Samples were collected at baseline from BM aspirates during the clinical assessment and at the end of every three cycles. Investigator-assessed adverse events (AEs) were summarized according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0. Baseline cytogenetic risk was determined locally and was evaluated using National Comprehensive Cancer Network (NCCN) criteria.

Statistical analysis:

Median times to event were calculated with standard Kaplan-Meier estimates, and confidence intervals were based on cumulative hazard, as implemented by the default parameters of the survfit function of the survival R package. The Kaplan–Meier method was used to estimate OS. The statistical analyses and figures were generated in R (version 4.2.2). Demographics were summarized using descriptive statistics. Response rates were summarized in counts and proportions. The phase II study is registered on ClinicalTrials.gov (NCT05184842).

Results:

Between April 2020 and January 2025, 40 patients with *TP53*-mutated myeloid malignancies (14 AML and 26 HR-MDS) were treated with metronomic, weekly low-dose decitabine and Ven, including 22 in the prospective trial cohort and 18 in the retrospective cohort (Table 1). The median age for the total population was 76.5 years (52-89) and 13 (32%) were from non-White minority backgrounds. ECOG performance status was 2-3 in 11 (27%) patients. All AML patients were ELN-poor risk and 21 MDS patients (81%) were R-IPSS high or very high risk. Four patients (29%) had secondary AML (2/4 were post-MPN), one patient had erythroid leukemia and 4 MDS patients (15%) were therapy-related. Thirty-nine patients had *TP53*-mutated disease, and one patient without available NGS testing had complex cytogenetic changes, including a 17p deletion. By NGS, *TP53* was the sole mutation identified in 18 patients (46%), including 15 with MDS and 3 with AML. The median *TP53* VAF was 36%. Thirty-eight of the

patients were evaluable for biallelic status. By ICC criteria, 31 (82%) had biallelic *TP53* mutation, and 30 (79%) were biallelic by WHO classification. Twenty-eight (70%) had complex cytogenetics; 11 AML (79%) and 17 (65%) MDS. At the start of therapy, 26 patients (65%) were transfusion-dependent (25[63%] red blood cells and 15[38%] platelets). 4 patients in the AML and 5 patients in the MDS cohorts were not evaluable for best response (2 withdrew consent, 1 lost to follow-up and 6 in the retrospective cohort did not have a BM biopsy done after starting therapy). All 40 patients were evaluated for OS.

Among response-evaluable patients in the AML cohort, 7 of 10 (70%) achieved a complete remission (CR), and 3 of 10 (30%) had no response. In the MDS cohort, 9 of 21 (43%) achieved a CR, 3 (15%) achieved a marrow CR (mCR), 4 (19%) had stable disease, and 5 (24%) had no response (Table 2). Using an intention-to-treat approach in which non-evaluable patients were considered non-responders, the CR rate was 50% (7/14) in AML and 35% (9/26) in MDS.

Among responding patients with adequate samples for MRD assessment, 10 of 21 (48%) achieved MRD negativity by multiparameter flow cytometry at the time of best morphologic response, including 4 of 7 (57%) in AML and 6 of 14 (43%) in MDS. When considering all patients who underwent bone marrow evaluation, 31% (10/32) achieved MRD negativity. The median time on therapy for the entire cohort was 5.1 months (3.3-7.7), with 10 (25%) patients remaining on treatment at the time of data cut-off. The median time to best response was 85 days. The median DOR in patients achieving a response (CR, CRi or mCR) was not reached (11.5–NR) for the entire cohort, not reached for AML, and was 11.5 months for the MDS patients. Of the 26 patients who were transfusion-dependent at the start of therapy, 15 (58%) became transfusion-independent, with 12 of 25 (48%) and 10 of 15 (67%) achieving red cell and platelet transfusion independence, respectively. Any hematological improvement (HI) was achieved in 60% of MDS patients (HI in neutrophils was 10 [42%]; platelets was 13 [52%]; and erythroid was 9 [36%]). Reasons for treatment discontinuation included disease progression (21 [52.5%]), lack of optimal response (6 [15%]), stem cell transplant (3 [7.5%]), withdrawal of consent (2 [5%]), recurrence of ovarian cancer (1 [2.5%]), death in CR (1 [2.5%]), lost to follow-up (1 [2.5%]), and removal from the study due to non-adherence to study therapy (1 [2.5%]); therapy was ongoing at the data cut-off date for four patients (10%). Nineteen patients (47.5%) received subsequent treatment for their myeloid disease.

With a median follow-up time of 12.9 months (10.1-NR), the median OS for the entire cohort was 11.3 months (8.8-NR) (Figure 1). The median OS for AML (≥20% blasts) was 11.6 months (10.4- NR), MDS 9.9 months (8.5-NR),

and for the 25 patients with ≥10% blasts, the median OS was 11.3 months (8.8-NR). When stratified by bi-allelic status, the median OS in the bi-allelic group (n=31) was 10.4 months (8.7-NR) and was not reached in the monoallelic group (6.9-NR) (Figure 2). Patients with complex cytogenetics (n=29) had an OS of 10.4 months (8.7-NR) compared to patients without complex cytogenetics (n=11) who had an OS of 15.2 months (8.5-NR). OS was not significantly different when evaluated by age (9.6 vs 11.6 months for age <75 and age ≥75, respectively; p= 0.79). For the six patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) (n=6), the median OS was 16 months (16-NR).

Safety:

During the first eight weeks of starting therapy, there was one death (1 [2.5%] of 40). Three patients died within the first 100 days of starting therapy, all due to disease progression. During this period, patients spent a mean of 89 days alive and out of the hospital, with a median of 100 days (range, 0–100). The majority (38 [95%] of 40) of patients had at least one non-heme treatment emergent adverse event (TEAE); grade 3 hematologic adverse events occurred in 11 patients (27.5%) for neutrophils, 35 (87.5%) for hemoglobin, and 7 (17.5%) for platelets, while grade 4 events occurred in 28 patients (70%) for neutrophils and 23 (57.5%) for platelets, with no grade 4 hemoglobin events observed (Table 3). 21 (53%) patients had grade 3 TEAEs, and no patients experienced a grade 4 TEAE. The most common TEAEs of any grade were fatigue (50%), bilirubin elevation (50%) pain (38%), nausea (38%), anorexia (32.5%) and creatinine elevation (32.5%). The most common grade 3 TEAEs were pneumonia (10 [25%]), neutropenic fever (6 [15%]), non-neutropenic fever (5 [13%]), hypoxia (3 [7.5%]), covid-19 infection with hypoxia (3 [7.5%]), and dyspnea hypoxia (3 [7.5%]). There were no therapy-related fatalities.

Discussion:

In this study, metronomic HMA/venetoclax demonstrated low treatment-related toxicity, very low early mortality, and appears to improve the time patients are able to spend at home. Reports using standard dose HMA/Ven in patients with complex cytogenetics and *TP53* mutations, the 30-day mortality has been reported at 17%, compared to a 30-day mortality of 5-10% in *TP53* WT patients.[9,21] Comparatively, in our cohort, the 30- and 100-day mortality were 2.5% and 7.5%, respectively. While the cause of early mortality may be multifactorial, as the *TP53* population tends to be elderly with higher comorbidities and worse performance status, a growing body of evidence suggests that *TP53* mutation is inherently immunosuppressive, leading to life-threatening infections and early mortality.[22] Although the exact mechanism for this has not yet been elucidated, *TP53* mutations appear to be enriched with an

immune-privileged microenvironment.[23] In this context, the frequent occurrence of severe infections and performance-status decline after upfront therapy represents a critical obstacle in bridging patients to allogenic stem cell transplantation, which remains the only potentially curative option for this population. In a retrospective review of TP53-mutated MDS and AML from MD Anderson, <20% of patients proceeded to transplant (20% MDS and 11% AML).[24] Similarly, in the COMMAND consortium that included 370 patients with TP53-mutated AML, only 13% were transplanted in first remission.[25] These results are particularly striking as one multicenter study showed that transplant was the only factor associated with survival on multivariate analysis.[26] The attrition of transplant-eligible patients from pre-transplant therapy may be mitigated by a less toxic metronomic dosing schedule, potentially expanding transplant eligibility in this frail population. The low early mortality in our study may also reflect the favorable hematologic profile of the regimen, as evidenced by a 58% transfusion independence rate. In contrast, transfusion independence in TP53-mutated patients receiving standard-dose HMA/venetoclax has been reported at 29.6%.[9] Although indirect, this comparison suggests that non-cytotoxic dosing may offer a potential advantage in this high-risk population by reducing toxicity to functioning hematopoietic cells and potentially enabling transfusion independence in more patients. Nevertheless, as cross-trial comparisons are subject to bias, a randomized trial between standard dosing and the low-dose, metronomic schedule is indicated. The favorable tolerability profile observed with our regimen may also create opportunities to explore rational triplet combinations. In contrast, efforts to combine additional novel agents with standard-dose HMA/venetoclax have frequently been constrained by substantial myelosuppression, hindering further progress.[27,28] Similarly, although not yet formally tested, this regimen may be better tolerated than other programs that have been tested for maintenance therapy after transplant.[29]

Although confirmatory studies are needed, the current data suggest that a less aggressive program did not compromise efficacy. Specifically, the metronomic schedule using non-cytotoxic dosing of decitabine and venetoclax resulted in a median OS of 11.3 months in TP53-mutated MDS and AML. This finding is noteworthy given that, despite extensive efforts over the past two decades that included cytotoxic chemotherapy, HMA, and Ven-based combinations, the OS in TP53-mutated AML and MDS has remained largely unchanged. A median OS of 5–6 months has been reported in prior TP53-mutated AML trials using standard-dose HMA/Ven, [9,30,31] and a dismal OS of 1.7 to 2.5 months was reported in some recent real-world experiences.[32,33] Similarly, in HR-MDS, the median OS of 9.9 months observed in a population in which the majority harbored biallelic TP53 alterations appears

consistent with outcomes reported with single-agent HMA therapy, where median OS estimates reported in the literature remain imprecise but are often reported at approximately 8-10 months.[34,35] Notably, recent attempts to improve outcomes in HR-MDS with standard dosing of VEN/HMA have to date not demonstrated an OS benefit, with excess myelosuppression-related toxicity considered a possible contributing factor.[36] In a preliminary report of the Phase 3 VERONA trial, which compared HMA/Ven versus HMA alone in HR-MDS, increased toxicity may have offset the OS benefit of the combination, as serious adverse events leading to treatment discontinuation were seen in 55% and 41% of patients in the HMA and HMA/Ven arms, respectively.[36]

An unexpected observation within our cohort was the inferior OS in MDS (9.9 vs. 11.6 months). However, in *TP53*-mutated disease, the traditional distinction between AML and MDS, purely based on a bone marrow blast count exceeding 20%, has recently been called into question. In a large-scale review, Grob et al assessed 2,200 cases of *TP53*-mutated MDS and AML and demonstrated that mutant *TP53* AML and MDS with excess blasts do not differ by molecular characteristics or survival and suggested that mutant *TP53* AML/MDS should be considered a single molecular disease entity.[5] Phenotypically, P53-mutated myeloid disease often presents with a lower blast count, and multiple reports have now shown it to be a unique poor-risk phenotype characterized by molecular features rather than blast count.[4,22,37]

A limitation of many studies to date has been the reporting of all *TP53* mutant patients as a homogeneous group. A growing body of literature suggests that the adverse prognosis of *TP53*-mutated MDS and AML is mainly driven by bi-allelic status. The vast majority of patients in our cohort were bi-allelic, and the percentage may be even higher as we did not have the capability to study loss of heterozygosity (LOH) or copy-neutral LOH. In one of the few studies to date that reported outcomes of AML by allelic status, AML with bi-allelic status had a median OS of 46 days.[6] In our cohort, the 31 patients with bi-allelic mutated P53 had an OS of 10.4 months. In patients with mono-allelic P53 (n=7), the median OS was not reached, consistent with recent reports showing that a single allele mutation does not predict poor outcomes.

Major limitations of our study include its single-center design, the relatively small number of patients, and the inclusion of both prospective and retrospective cohorts, which may introduce selection and reporting biases. In addition, a substantial proportion of patients lacked formal response assessment because post-treatment bone marrow evaluation was not performed, potentially affecting the robustness of the reported response rates and limiting definitive conclusions. Clearly, this data requires confirmation in a larger comparator study and should also

include the proportion of patients who proceed to transplant. Despite these limitations, this study provides experience supporting the safety of this approach and a signal of clinical activity in a heterogeneous population with TP53-mutated disease.

This promising regimen should be further explored in multi-center prospective trials in patients with *TP53*-mutated myeloid malignancies.

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Table 1. Baseline Demographics and Clinical Characteristics of the Patients

Characteristics	Cohort				Total (n = 40)
	AML (n = 14)		MDS (n = 26)		
	Prospective (n = 10)	Retrospective (n = 4)	Prospective (n = 14)	Retrospective (n = 12)	
Median age (range), y	77 (59 – 82)	80 (75 – 81)	73 (52 – 87)	79 (53 – 89)	76.5 (52 – 89)
Age >75 y, n (%)	6 (60)	3 (75)	6 (43)	8 (67)	23 (57.5)
Sex, n (%)					
Male	6 (60)	1 (25)	7 (50)	6 (50)	20 (50)
Female	4 (40)	3 (75)	7 (50)	6 (50)	20 (50)
ECOG PS, n (%)					
0	4 (40)	2 (50)	4 (29)	1 (8)	11 (28)
1	3 (30)	1 (25)	7 (50)	7 (58)	18 (45)
2	3 (30)	1 (25)	2 (14)	3 (25)	9 (22)
3	0	0	1 (7)	1 (8)	2 (5)
Complex CG, n (%)	9 (90)	2 (50)	11 (79)	6 (50)	28 (70)
Biallelic TP53, n (%) *	12 (100) †		19 (73)		31 (82)
TP53 mutation allelic frequency, n (%)					
<10	0	0	3 (21)	1 (8)	4 (10)
10-50	6 (60)	2 (50)	6 (43)	8 (67)	22 (55)
>50	3 (30)	2 (50)	2 (14)	3 (25)	10 (25)
n/a	1 (10)	0	3 (21)	0	4 (10)
Bone marrow blast %, median (range)	27.5 (20 – 90)	35 (23 – 90)	7 (0 – 17)	7 (0 – 17)	15 (0 – 90)
ELN, n (%)					
Adverse Risk	10 (100)	4 (100)			
Intermediate Risk	0	0			
Favorable Risk	0	0			
R-IPSS, n (%)					
Low			0	1 (8)	
Intermediate			1 (7)	3 (25)	
High			1 (7)	2 (17)	
Very High			12 (86)	6 (50)	

Baseline transfusion dependence, n (%)					
Red cells and/or Platelets	7 (70)	1 (25)	12 (86)	6 (50)	26 (65)
Race, n (%)					
White	5 (50)	2 (50)	11 (79)	9 (75)	27 (68)
Black	2 (20)	0	2 (14)	1 (8)	5 (12)
Hispanic	3 (30)	2 (50)	1 (7)	2 (17)	8 (20)

*ICC and WHO criteria

†Two AML were not evaluable

Table 2. Response Rate for Patients with MDS and AML and TP53 mutations

Characteristics	Cohort		Total (n = 40) n (%)
	AML (n = 14) n (%)	MDS (n = 26) n (%)	
Overall Survival	11.6 months (10.4-NR)	9.9 months (8.5-NR)	11.3 months (8.8-NR)
ORR			19/31 (62)
ORR (CR + CRi)	7/10 (70)		
ORR (CR + mCR)		12/21 (57)	
Best Response			
CR	7/10 (70)	9/21 (43)	16/31 (52)
mCR		3/21 (15)	
CRi	0		
MLFS	0		
No Response	3/10 (30)	5/21 (24)	8/31 (26)
SD		4/21 (19)	
Transfusion Independence	6/8 (75)	9/18 (50)	15/26 (58)
MRD Negative (Hematologics Flow)	4/7 (57)	6/14 (43)	10/21 (48)
HI Erythroid		9/25 (36)	
HI Platelets		13/25 (52)	
HI Neutrophils		10/24 (42)	

Table 3. Adverse Events for Entire Cohort

Event	Adverse Events by Grade (n = 40)		
	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)
All Non-Hematologic Adverse Events	38 (95)	21 (52.5)	0
Alkaline Phosphatase Elevation	12 (30)	0	0
ALT Elevation	10 (25)	3 (7.5)	0
AST Elevation	12 (30)	2 (5)	0
Anorexia	13 (32.5)	0	0
Atrial Fibrillation/Atrial Flutter	3 (7.5)	1 (2.5)	0
Bilirubin Elevation	20 (50)	0	0
Chills	4 (10)	0	0
Constipation	9 (22.5)	0	0
COVID-19	3 (7.5)	3 (7.5)	0
Creatinine Elevation	13 (32.5)	1 (2.5)	0
Diarrhea	7 (17.5)	0	0
Dizziness	7 (17.5)	0	0
Dyspnea	14 (35)	3 (7.5)	0
Dysuria	5 (12.5)	0	0
Edema, Lower Extremity	7 (17.5)	0	0
Fatigue	20 (50)	0	0
Fever, Neutropenic	6 (15)	6 (15)	0
Fever, Non-neutropenic	5 (12.5)	5 (12.5)	0
Headache	3 (7.5)	0	0
Hypoxia	5 (12.5)	3 (7.5)	0
Nausea	15 (37.5)	0	0
Pain	15 (37.5)	0	0
Pneumonia	10 (25)	10 (25)	0
Pruritus	3 (7.5)	0	0

Rash	6 (15)	0	0
Sinus Tachycardia	2 (5)	0	0
Upper Respiratory Infection	3 (7.5)	1 (2.5)	0
Vomiting	7 (17.5)	0	0
Weakness	10 (25)	0	0
Neutrophil Count Decreased	40 (100)	11 (27.5)	28 (70)
Platelet Count Decreased	36 (90)	7 (17.5)	23 (57.5)
Hemoglobin Decreased	40 (100)	35 (87.5)	0

*Adverse Events that were reported in at least 5% of patients in both cohorts are listed

Figure Legends:

Figure 1. Analysis of Median OS

Kaplan–Meier plot of OS and 95% confidence interval (CI) estimates are reported.

a, The OS estimate of the entire cohort of 40 patients.

b, OS for the six patients who underwent allogeneic stem cell transplant.

c, OS for the AML cohort

d, OS for the HR-MDS cohort

Figure 2. Median OS – Mono vs Bi-allelic TP53

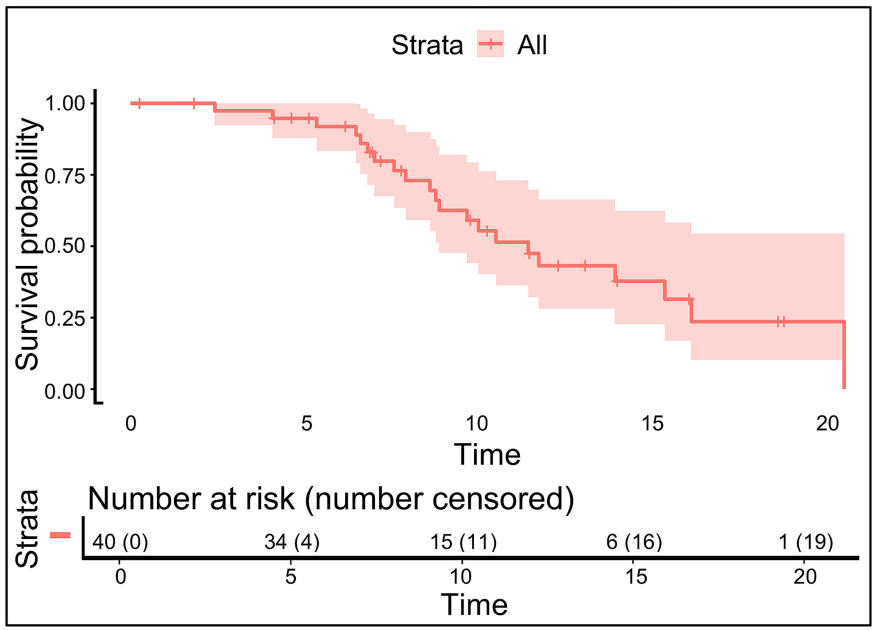
Kaplan-Meier survival analysis of overall survival in patients with monoallelic versus bi-allelic TP53 mutated AML and MDS

Figure 1. Analysis of Median OS

A

Entire Cohort (n=40)

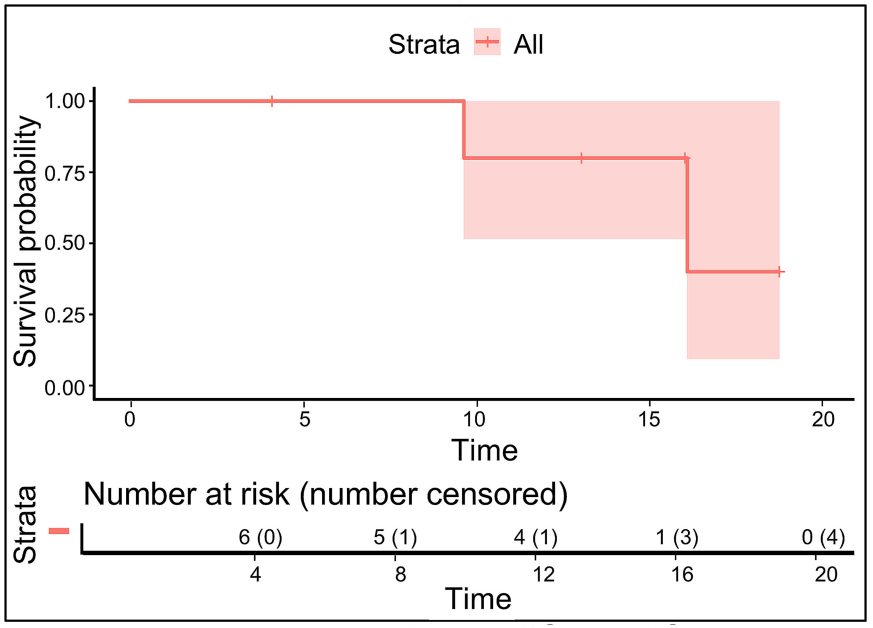
11.3 months (8.8 – NR)



B

Patients Transplanted (n=6)

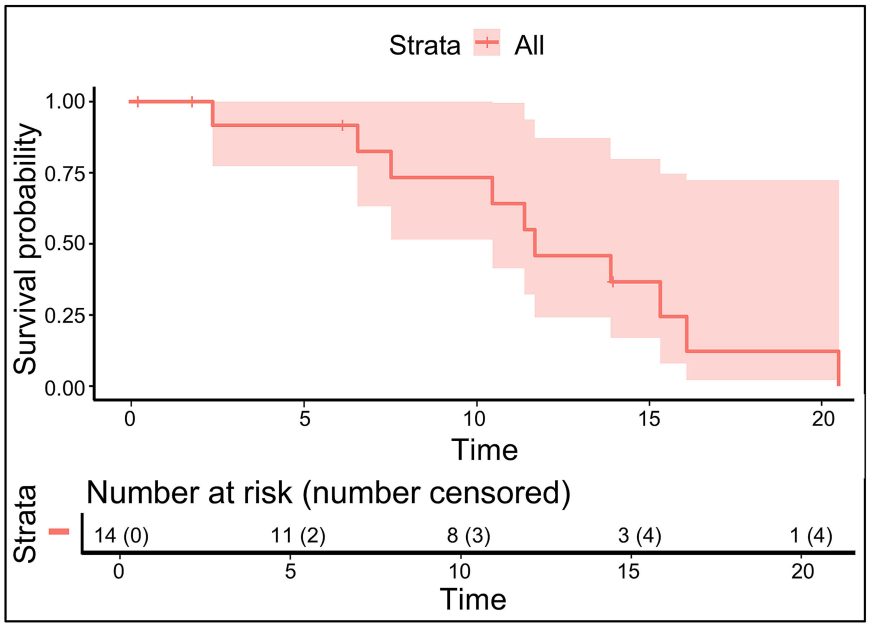
16 months (16 – NR)



C

AML Cohort (n=14)

11.6 months (10.4 – NR)



D

HR-MDS Cohort (n=26)

9.9 months (8.5 – NR)

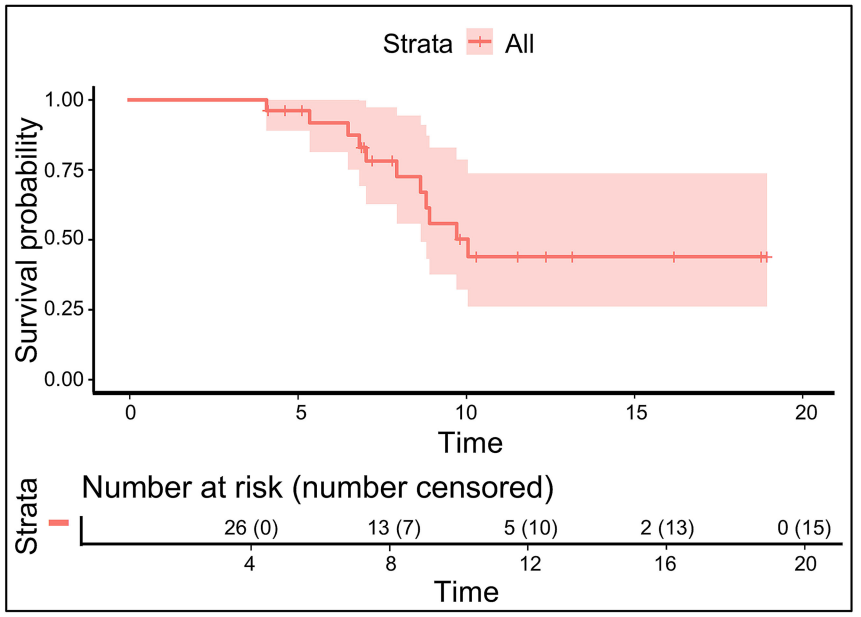


Figure 2. Median OS – Mono vs Bi-allelic TP53