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Outcomes of *TP53*-mutant Acute Myeloid Leukemia with Decitabine and Venetoclax

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Abstract

Background: *TP53* mutation (*TP53*^{mut}) confers adverse prognosis in acute myeloid leukemia (AML). Venetoclax with hypomethylating agents is a current standard for older patients, however recent reports suggest that *TP53*^{mut} confers resistance to venetoclax. We investigated outcomes of patients with *TP53*^{mut} AML treated with 10-day decitabine and venetoclax (DEC10-VEN, [NCT03404193](#)).

Methods: Patients with newly diagnosed AML received decitabine 20mg/m² for 10-days every 4–6 weeks for induction, followed by decitabine 5-days after response. Venetoclax dose was 400 mg daily. *TP53*^{mut} was identified in bone marrow samples using NGS with sensitivity of 5%. Outcomes were analyzed per ELN 2017 guidelines.

Results: Among 118 patients (median age: 72 years, range 49–89), 53% (n=63) had secondary AML, 33% (n=39) had AML with complex karyotype and 30% (n=35) had *TP53*^{mut} AML.

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The median *TP53* variant allele frequency was 32% (interquartile range 16%–65%), 23% (n=8) patients had only a single *TP53* mutation, 43% (n=15) had multiple mutations, and 34% (n=12) had mutation+deletion. Outcomes were significantly worse in *TP53*^{mut} compared to *TP53*^{WT} AML with overall response rate of 66% vs 89% (p=.002), CR/CRi of 57% vs 77% (p=.029) and 60-day mortality of 26% vs 4% (p<.001), respectively. Patients with *TP53*^{mut} vs *TP53*^{WT} had shorter overall survival at 5.2 vs. 19.4 months (hazard ratio [HR] 4.67, 95% CI 2.44–8.93, p<.0001), and shorter relapse-free survival at 3.4 vs 18.9 months (HR 4.80, 95% CI 1.97–11.69, p<.0001), respectively. Outcomes with DEC10-VEN in *TP53*^{mut} AML were comparable to historical results with 10-day decitabine alone.

Conclusion: Patients with *TP53*^{mut} AML have lower response rates and shorter survival with DEC10-VEN.

Keywords

TP53; AML; acute myeloid leukemia; decitabine; venetoclax; outcome

INTRODUCTION

TP53 is the most frequently mutated gene in human cancer. *TP53* functions as a tumor suppressor protecting against cellular stress and serves as the “guardian of the genome” preserving genomic integrity.¹ *TP53* mutations (*TP53*^{mut}) occur in 5–10% cases of de-novo AML, with higher frequency in older patients, and in 20–35% cases of therapy-related AML.^{2–4} AML with *TP53*^{mut} is associated with complex karyotype, poor response to intensive chemotherapy and has dismal outcomes with short median overall survival (OS) of 5 to 9 months.^{5,6}

Older patients are frequently unfit for intensive chemotherapy and epigenetic therapy with hypomethylating agents (HMA) offer modest advantage over chemotherapy in *TP53*^{mut} AML.⁷ The 10-day regimen of decitabine (DEC10) has been noted to be active in adverse-risk AML and those with relapsed/refractory disease.^{8–11} One study showed 100% response rate in *TP53*^{mut} AML and MDS and high mutation clearance with the 10-day regimen of decitabine.¹¹ Venetoclax in combination with low-intensity regimens is now a standard therapy for older or unfit patients with AML.^{12,13} Combining a 10-day regimen of decitabine with venetoclax (DEC10-VEN) showed high activity in adverse-risk AML.¹⁴ However, recent preclinical studies have suggested that *TP53*^{mut} may confer resistance to venetoclax.^{15–18}

Hence, we investigated outcomes of patients with *TP53*^{mut} AML treated on a prospective clinical trial of DEC10-VEN and compared outcomes to *TP53*^{WT} AML. Additionally, we evaluated the benefit of adding venetoclax to 10-day decitabine by comparing the results to a historical cohort of patients treated with 10-day decitabine alone from another prospective trial.

METHODOLOGY

Study design and participants

We conducted a post-hoc analysis of a phase 2 trial of 10-day decitabine and venetoclax (DEC10-VEN, [NCT03404193](#)). This trial enrolled patients who were 60 years of age and older with newly diagnosed AML who were unfit for intensive chemotherapy, or had secondary AML; or relapsed or refractory (R/R) AML. Patients were eligible if they had an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or less, white blood cell count less than $10 \times 10^9/L$, and adequate end-organ function. Patients with European Leukemia Net (ELN) favorable risk cytogenetics and prior exposure to BCL2 inhibitor were excluded.

Patients received decitabine 20 mg/m^2 for 10 days every 4 to 6 weeks for induction followed by decitabine for 5 days after CR/CRi. Venetoclax dose was 400 mg daily or equivalent with concomitant azole antifungal. Reduction of venetoclax duration was allowed in cases of prolonged myelosuppression. The full protocol of the study has been published previously.¹⁴ In this analysis, we included patients receiving frontline therapy for AML. Additionally, we compared outcomes of these patients treated with DEC10-VEN with individual patient level data of older patients with newly diagnosed *TP53*^{mut} AML treated with 10-day decitabine alone from another prospective trial at our institution ([NCT01786343](#)).⁸

TP53 sequencing was performed on DNA obtained from bone marrow aspirate using a next generation sequencing (NGS) panel targeting the entire coding or hot spot regions of 81 genes, or *TP53* alone, as described previously.¹⁹ The covered regions of *TP53* included the following exons and (codons): 2 (1–25), 4–11 (80–394). Bidirectional paired-end sequencing was performed using an Illumina MiSeq NGS platform (Illumina, San Diego, CA, USA) to screen for single nucleotide variants, and insertions/deletions (up to 52 base-pairs). The analytical sensitivity of the platform is variable for different genes but is generally 1–3% mutant reads in a background of wild type reads (supplemental methods). Measurable residual disease (MRD) was assessed using bone marrow aspirate samples using multiparametric flow cytometry (FCM) validated to a sensitivity level of 0.01–0.1%.²⁰ All cytogenetic and molecular analyses were conducted in a CLIA-certified laboratory.

Outcomes

The studied outcomes included response, relapse free survival (RFS) and overall survival (OS) defined per the ELN 2017 criteria.²¹ Overall response rate (ORR) included complete response (CR), CR with incomplete hematologic recovery (CRi), and morphologic leukemia-free state (MLFS). OS was defined from time from treatment initiation until death or censored at the last follow-up. RFS was defined from the time from achievement of CR or CRi until relapse or death or censored at last follow-up. In patients with *TP53*^{mut} AML outcomes were compared between responding patients without relapse until last follow-up; relapse after response, defined as morphologic relapse in bone marrow or peripheral blood after achieving a response; and primary refractory disease, defined as no response by four cycles of therapy.

Statistical Analysis

Chi-square test or Fisher's exact test was used to compare distribution of categorical variables between groups. Wilcoxon-Rank sum test was used for continuous variables between groups as appropriate. The distributions of time-to-event endpoints including RFS and OS were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard model was used to determine the hazard ratio for outcome related to *TP53* mutation status. Univariate and multivariate logistic and Cox-regression models were used to evaluate the association between patient characteristics and outcomes. For multivariate regression, variables were selected using a backward selection with a p-value cut-off at 0.05. *TP53* variant allelic frequencies (VAF) at screening and after cycle 1 were compared using paired t-test. All analyses were conducted using STATA version 13.0 (StataCorp, College Station, TX), Prism v 8.4 (GraphPad software, San Diego, California), and R v3.4.3 (R Core Team, Vienna, Austria).

RESULTS

Between January 20, 2018 and April 15, 2020, 118 patients received frontline therapy with DEC10-VEN and 35 (30%) patients had *TP53*^{mut} AML. The median age was 72 years (range 49–89). Eighty (68%) patients were older than 70 years, 32 (27%) patients had ECOG performance status of 2 or higher, 63 (53%) patients had secondary AML including 25 (21%) patients with therapy-related AML. Seventy-eight (66%) patients had ELN adverse risk AML and 39 (33%) patients had AML with complex karyotype (Table 1). Patients with *TP53*^{mut} AML were more likely to have therapy-related AML (t-AML) in 46% (n=16/35) patients compared to 11% (n=9/83) in patients with *TP53*^{WT} AML (p<.001). Patients with *TP53*^{mut} AML were less likely to have co-mutations compared to patients with *TP53*^{WT} AML including *NPM1* (3% vs 33%, p=.001), *RUNX1* (2% vs 22%, p=.035), *ASXL1* (3% vs 23%, p=.008) and *K/NRAS* (11% vs 28%, p=.005) and were more likely to have AML with complex karyotype compared to patients with *TP53*^{WT} AML (89% vs 10%, p<.001). The proportion of prior therapies for antecedent hematological disorder including hypomethylating agents, intensive chemotherapy, and stem-cell transplantation were comparable among patients with *TP53*^{mut} and *TP53*^{WT} AML (Table 1).

The most frequent co-mutations in *TP53*^{mut} AML included *DNMT3A* in 29% patients (Fig. 1a), *NF1*, *NRAS*, *TET2* (11% each) and *CBL*, *RUNX1*, *SF3B1* or *SRSF2* (9%, each). The median variant allele frequency (VAF) of *TP53*^{mut} was 32% (IQR 16–65%). At least one mutation per case involved the DNA binding domain of *TP53* in all *TP53*^{mut} AML. *TP53*-altered subgroups included single mutation only without deletion of *TP53* (n = 8/35, 23%) and multi-hit alterations (n=27/35, 77%) including multiple mutations without chromosomal deletion involving the *TP53* locus (n =12/35, 34%), or *TP53* mutation(s) with concomitant deletion noted on karyotype, array CGH or FISH (n = 15/35, 43%). Copy neutral loss of heterozygosity data was not available in this study.

Mutations in patients with response without relapse (n=7, 20%) vs. relapse (n=16, 48%) vs. primary refractory disease (n=10, 30%) are shown in Fig. 1b. Proportion of multi-hit *TP53* alterations were noted in 4/7 (57%) of responding patients without relapse vs. 13/16 (81%) in patients with relapse after response vs. 10/10 (100%) in refractory AML with

statistical significance ($p = .049$). Median baseline VAF was similar in these populations with median VAF of 27% in patients with response without relapse vs. 36% in patients with relapse after response vs. 44% in refractory AML, ($p = .918$). Twenty-five (76%) patients with $TP53^{mut}$ AML had follow-up NGS testing at the end of cycle 1 (EOC1) including 20 responders (with or without relapse) and 5 refractory patients. Responding patients had significant reduction of mutant $TP53$ VAF (mean change -28.5% , 95% CI $-15.4, -41.6\%$, $p < .001$). Among 5 patients who had refractory disease, the VAF change was not significant (mean change -21.4% , 95% CI $-9.5, 52.2\%$, $p = .126$), and none obtained a $TP53$ VAF $< 5\%$ at EOC1. Thirteen patients with relapsed disease after response had NGS at time of progression; there was significant increase in $TP53^{mut}$ VAF compared to VAF after the end of cycle 1 (mean change $+22.6\%$, 95% CI $4.8, 40.5\%$, $p = .018$).

The number of co-mutations were comparable among 3 groups with a median of one co-mutation in each of the 3 aforementioned groups. There were no identifiable differences in characteristics of $TP53$ mutation between patients without relapse vs. those experiencing relapse including multi-hit alterations vs single mutation only ($p = .312$), VAF ($p = .806$), co-mutations ($p = .830$) or complex karyotypes ($p = .791$). Nine out of 10 (90%) patients with refractory disease had secondary AML, compared to 60% of responding patients (with or without relapse, $p = .084$). History of antecedent hematological disorder was present in 7 out of 10 patients (70%) with refractory disease compared to 4 out of 23 of patients (17%) with responsive disease ($p = .006$). Five out of 10 (50%) patients with refractory disease had prior HMA exposure, compared to 1 out of 23 (4%) patients with responsive disease ($p = .005$). Patients with response without relapse had longer OS compared to patients with primary refractory disease (9.6 vs 1.9 months, HR 4.81, 95% CI 1.45–15.96, $p = .010$) but their OS was not significantly different compared to patients with relapsed disease (9.6 vs 6.9 months, HR 0.95, 95% CI 0.30–2.96, $p = .928$; Fig. S1).

Patients with $TP53^{mut}$ AML had significantly lower response rates compared to patients with $TP53^{WT}$ AML (Table 2). The ORR in patients with $TP53^{mut}$ compared to $TP53^{WT}$ AML was 66% vs 89% ($p = .002$), with CR/CRi in 57% vs 77% ($p = .029$) with lower rates of MRD negativity by FCM at 29% compared to 59% ($p = .012$). Incidence of primary refractory disease was 34% in patients with $TP53^{mut}$ AML versus 11% in patients with $TP53^{WT}$ AML ($p = .002$). On univariate and multivariate analysis, $TP53^{mut}$ AML conferred significantly lower odds ratio of achieving CR (odds ratio [OR] 0.17, $p < .001$) and CR/CRi (OR 0.22, $p = .003$; Table 3, S1, S2, S3). Compared to patients with $TP53^{WT}$ AML, those with $TP53^{mut}$ AML had a higher 30-day mortality (1% vs 3%, $p = .525$) and higher 60-day mortality (4% vs 26%, $p < .001$). All early deaths ($n = 9$) in patients with $TP53^{mut}$ AML within 60 days occurred in those who had refractory disease. Mortality due to uncontrolled infection or sepsis was not statistically significant in patients with $TP53^{mut}$ AML compared to $TP53^{WT}$ AML patients (21% vs. 17%, $p = .586$). Patients with response MLFS or better had lower infection-related mortality (6% vs. 4%, $p = .230$). Six (67%) patients had sepsis and 3 (33%) patients transitioned to hospice. Sixteen patients (19%) with $TP53^{WT}$ AML and only 1 patient (3%) with $TP53^{mut}$ AML underwent stem-cell transplantation (SCT) after response.

After a median follow-up of 20.2 months (95% CI 15.6, 22.9), the median OS in patients with *TP53*^{mut} AML was inferior compared to patients with *TP53*^{WT} AML (5.2 vs 19.4 months, HR 4.67, 95% CI 2.44–8.93, $p < .0001$, Fig. 2a). Similarly, median RFS in patients with *TP53*^{mut} AML was significantly shorter compared to patients with *TP53*^{WT} AML (3.4 vs 18.9 months, HR 4.80, 95% CI 3.26–14.99, $p < .001$, Fig. 2b). Patients with *TP53*^{mut} AML patients achieving CR had a median OS of 9.6 months compared to patients with CRi who had a median OS of 5.6 months vs non-responding patients who had a median OS of 1.9 months (Fig. 2c). Patients with *TP53*^{mut} AML who achieved negative MRD status by FCM had numerically higher median OS at 9.9 months, compared to patients with persistent MRD who had a median OS at 6.9 months, however this analysis was limited by the small sample size (HR 0.55, 95% CI 0.22–1.37, $p = .21$, Fig. 2d). Patients with *TP53*^{mut} AML had significantly shorter duration of response compared to *TP53*^{WT} AML (3.5 months vs NR, HR 7.21, 95% CI 3.34–15.56, $p < .001$, Fig. S2).

TP53 VAF cut-offs ranging from 20% to 40% did not have prognostic value for OS or RFS with DEC10-VEN. Patients with multi-hit alterations did not have significant survival difference compared to patients with single mutation only in OS (HR 1.24, 95% CI 0.50–3.05, $p = .643$; Fig. S3) or RFS (HR 1.65, 95% CI 0.37–7.34, $p = .512$). Fifteen patients with *TP53* mutation with noted deletion on karyotype, array CGH or FISH did not show difference in OS compared to *TP53*^{mut} patients without noted deletion (HR 0.95, 95% CI 0.46–1.93, $p = .876$).

Other independent adverse prognostic factors for achievement of CR included ECOG PS 2, *RUNX1*^{mut}, *ASXL1*^{mut}, and prior therapy for antecedent hematological disorder (Table 3). Univariate and multivariate analyses for OS confirmed that *TP53*^{mut} was associated with significantly higher risk of death (HR 6.96, 95% CI 3.76–12.88), along with secondary AML with antecedent hematologic disorder, *K/NRAS* and *DNMT3A* mutations (Table S5, 3). Similarly, univariate and multivariate analyses of RFS confirmed that *TP53*^{mut} was independently associated with high risk of relapse for patients with CR/CRi (HR 5.52, 95% CI 2.70–11.28, $p < .001$, Table S6, S7).

Finally, we compared outcomes of patients with newly diagnosed *TP53*^{mut} AML treated with DEC10-VEN ($n=35$) versus 10-day decitabine alone ($n=17$) treated on a separate prospective clinical trial (NCT01786343). The baseline characteristics of these patients were comparable (Table S4). Overall response rate was numerically higher at 66% with DEC10-VEN compared to 53% with 10-day decitabine. Negative MRD status was achieved in 29% ($n=6/20$) with DEC10-VEN compared to 25% ($n=2/8$) patients with 10-day decitabine. Time to morphologic response was comparable with DEC10-VEN vs 10-day decitabine at 1.2 months (IQR 1.1–1.4) vs. 1.3 months (IQR 1.2–2.4), respectively ($p = .197$). There was no significant difference in OS or RFS (Fig. 3). None of the patients who received 10-day decitabine underwent SCT. 7 patients with *TP53*^{mut} AML treated with 5-day decitabine alone in same trial had lower response rate at 43% including 1 CR, 1 CRi and 1 MLFS. 2 patients achieved MRD negative status (66%). While the sample size is very limited, there was no significant difference in OS or RFS compared to DEC10-VEN trial (Fig. S4).

DISCUSSION

Development of venetoclax has been an important breakthrough for the field of AML therapy, however primary and acquired resistance to venetoclax-based regimens continues to be a major problem. To our knowledge, this report represents the largest analysis to date which validates pre-clinical findings and smaller prior reports on the adverse impact of *TP53*^{mut} with venetoclax and HMA. Our study showed that patients with *TP53*^{mut} AML experienced significantly lower response rates and survival with DEC10-VEN compared to patients with *TP53*^{WT} AML despite reasonable response rates. Patients with *TP53*^{mut} AML with prior HMA exposure were significantly less likely to respond to DEC10-VEN. This is in contrast to our previous findings where patients failing frontline HMA for AML are still likely to respond to DEC10-VEN compared to salvage intensive chemotherapy.²²

Patients who achieved a CR or CRi had modestly better survival compared to patients who had refractory disease, however the number of patients in these sub-analyses were small. Achieving negative MRD status did not show significant benefit in our study. Overall, these results were comparable to prior reports of HMA with venetoclax showing ORR of 14 to 62% in *TP53*^{mut} AML and short overall survival.^{16–18} Previous reports have shown median OS of 2.1 to 10.1 months in *TP53*^{mut} AML with HMA or low-intensity therapy.^{5,11,23,24} No *TP53* VAF cut-off showed prognostic value for OS with DEC10-VEN in our study, consistent with prior studies investigating HMA or HMA with venetoclax in AML.^{8,17,25} Interestingly, there was no direct therapy-related mortality in patients with *TP53*^{mut}, yet these patients had significantly higher early mortality due to refractory disease and infections (66%).

In our study, only 1 (3%) patient with *TP53*^{mut} underwent SCT; the majority of patients were ineligible for SCT due to co-morbidities, development of complications including infections, or refractory disease. It is debatable if outcomes would have been different if more patients could have received SCT as patients with *TP53*^{mut} AML are at significant risk of relapse following SCT with long-term survival of less than 10%.^{6,11} Pre-clinical studies have suggested that *TP53*^{mut} confers intrinsic resistance to venetoclax through perturbation of mitochondrial homeostasis and cellular metabolism including increased oxidative phosphorylation.¹⁵ This study along with prior reports provide clinical validation of these pre-clinical findings and highlight the urgent need for novel therapies for *TP53*^{mut} AML. *TP53*^{mut} AML remains a therapeutic challenge and optimal backbone for combination with novel therapies remains to be evaluated in prospective trials. Potential approaches to overcome such mutant p53 mediated resistance include tropomyosin receptor kinase (TRK) inhibition, targeting oxidative phosphorylation or glutamine metabolism, p53 reactivators and harnessing other p53 independent mechanisms.^{6,15,26} Novel immunotherapeutic approaches including magrolimab, flotetuzumab, cusatuzumab are currently advancing in clinical trials and offer hope for patients with *TP53*^{mut} AML.

This was a post-hoc analysis which has inherent limitations. Detailed comparisons within subgroups of *TP53*^{mut} AML were limited by the small number of patients. *TP53* mutation analysis was conducted in a clinical laboratory and detailed information beyond standard clinical testing were not available, e.g., allelic status, copy neutral loss of heterozygosity,

single-cell level data, etc.²⁷ We only had three patients with responses lasting beyond six months. Consequently, we could not evaluate patients with *TP53*^{mut} AML who may have truly durable responses to venetoclax, and some patients without relapse had short follow-up and may relapse with longer follow-up. There was no preferential *TP53* mutations that we identified specific to responders or non-responders in the study. Further larger cohort study with *TP53*^{mut} AML patients with venetoclax-based therapy would provide insight in the role of specific *TP53* mutations in treatment response. Our exploratory comparison of DEC10-VEN vs 10-day decitabine alone should be interpreted with caution due to the small number of patients and ineluctable differences between the two trial populations. The backbone of 10-day decitabine offers a different risk-benefit ratio compared to the more widely adopted 5-day regimen, or the 7-day regimen of azacitidine used with venetoclax, thus limiting cross-trial comparisons.

In summary, we report the largest series of patients with *TP53*^{mut} treated on a prospective trial of DEC10-VEN and show that outcomes in these patients are significantly worse compared to patients with *TP53*^{WT} AML. These results highlight the urgent need for novel therapies for *TP53*^{mut} AML.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interests

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Data sharing:

At this time, we will not be able to share individual patient level data outside of our institution.

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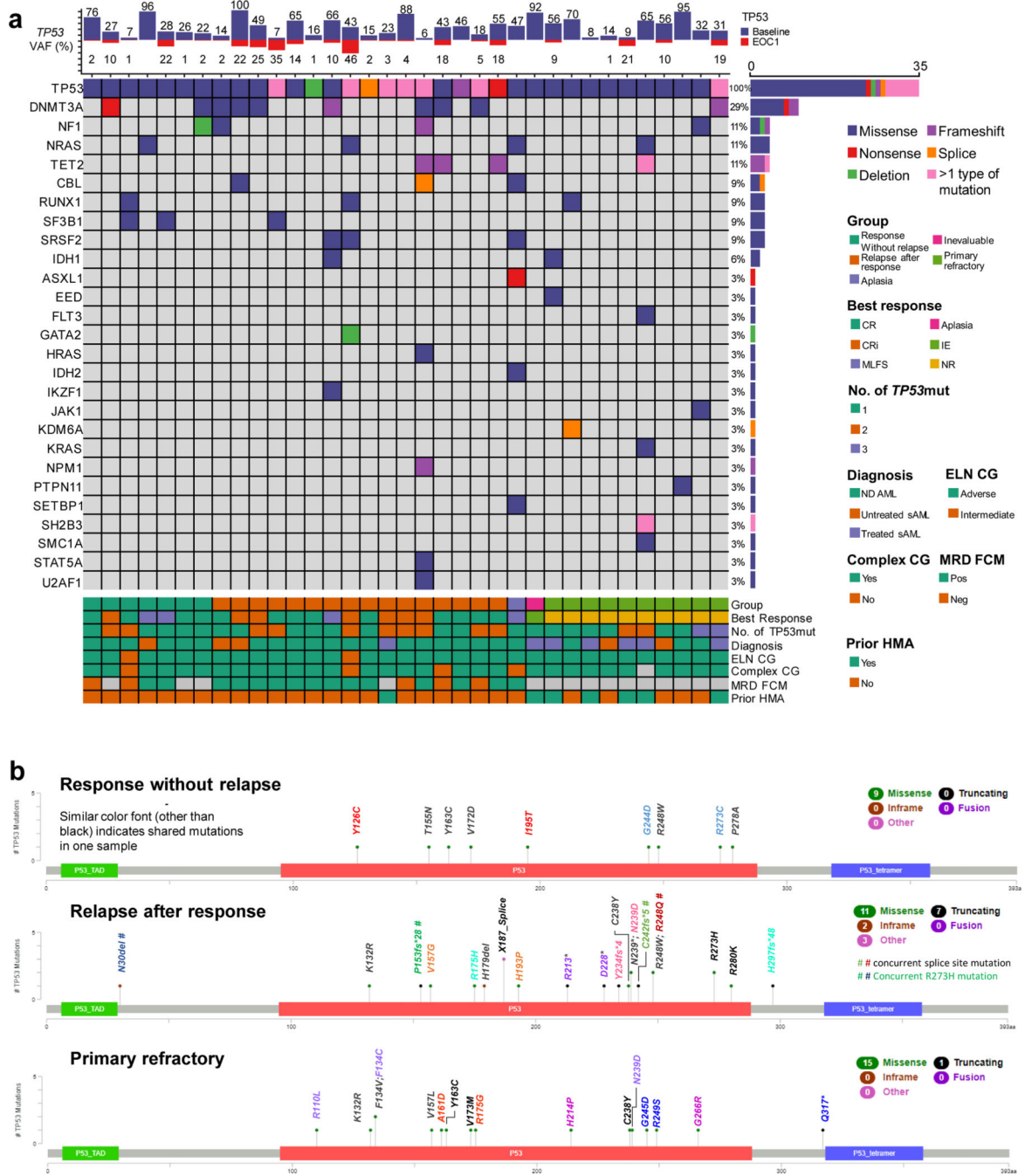


Fig 1.
a. *TP53* mutations mapped according to response **b.** mutational landscape of *TP53* mutated acute myeloid leukemia treated with 10-day decitabine and venetoclax.
 >1 type of mutation refers to patients with a missense and frameshift mutation or missense and nonsense mutation, etc.

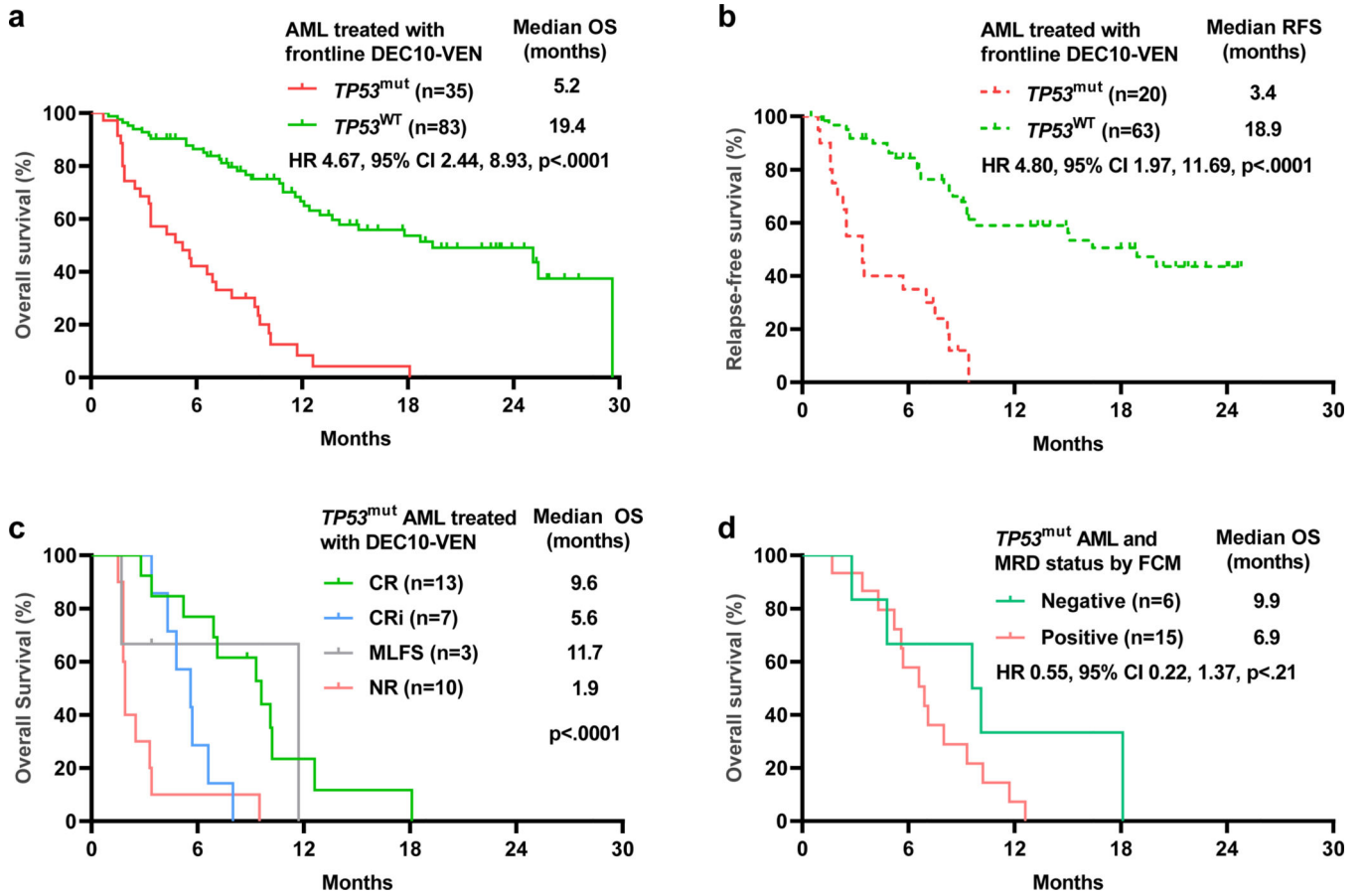


Fig 2.
a. Overall survival (OS) by *TP53* mutation status. **b.** Relapse Free Survival (RFS) by *TP53* mutation status. **c.** OS by response in *TP53* mutated acute myeloid leukemia (AML). **d.** OS in *TP53* mutated AML patients by measurable residual disease (MRD) status.

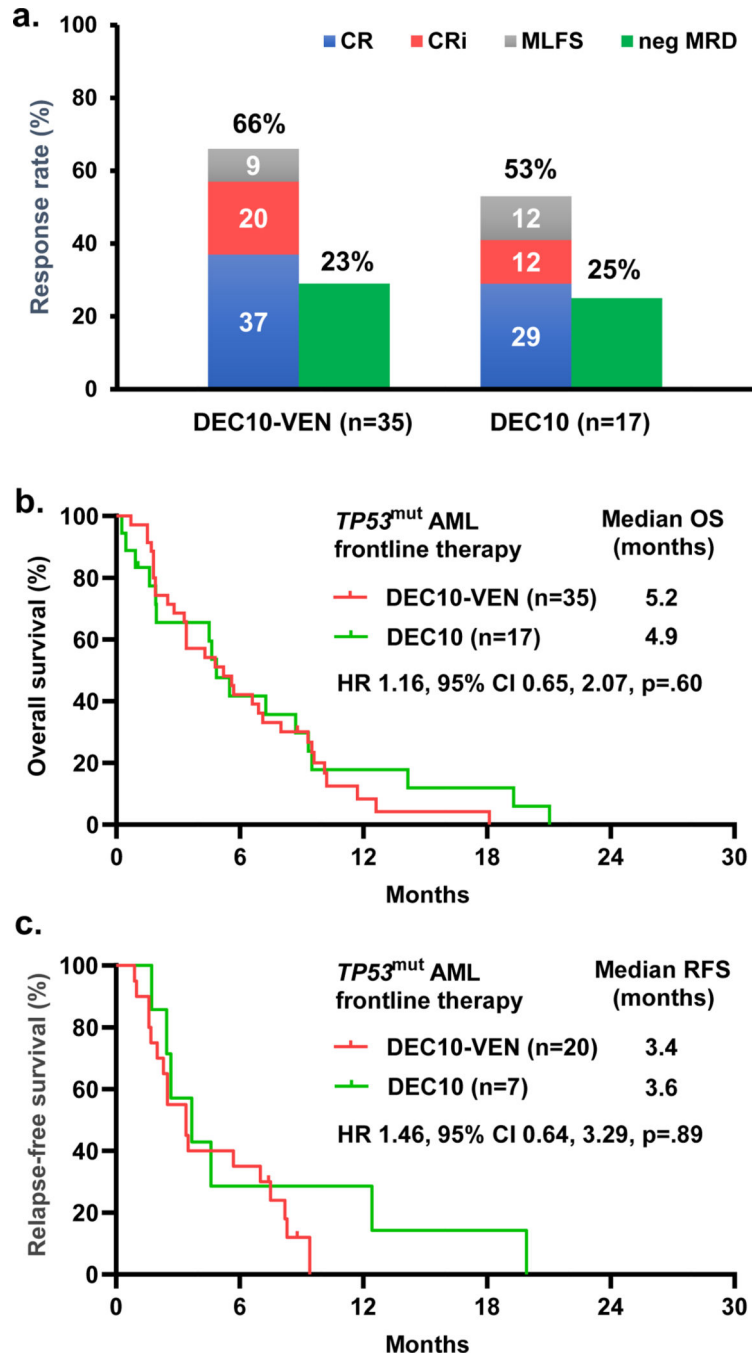


Fig 3. Outcomes in patients with newly diagnosed *TP53*^{mut} AML with 10-day decitabine with venetoclax vs 10-day decitabine alone, **a.** morphologic response and measurable residual disease (MRD) status, **b.** overall survival, and **c.** relapse-free survival. CR = complete response, CRi = CR with incomplete hematologic response, MLFS = morphologic leukemia-free state

Table 1.

Baseline characteristics of patients with acute myeloid leukemia with and without *TP53* mutation treated with 10-day decitabine and venetoclax.

Patient characteristics	<i>TP53</i> mutated AML (N= 35)	<i>TP53</i> wild type AML (N= 83)	<i>P</i>
Age, years	74 [69–78]	71 [68–77]	
70 years	25 (71)	55 (66)	.583
Male sex	18 (51)	46 (55)	.691
ECOG Performance Status			
0–1	25 (71)	61 (73)	.818
2	10 (29)	22 (27)	
Peripheral blood blasts, %	5 [0–17]	10 [0–37]	.247
Bone marrow blasts, %	28 [14–54]	40 [23–62]	.056
Diagnosis			
De novo AML	11 (31)	44 (53)	.032
sAML with AHD	12 (34)	32 (39)	.661
Therapy-related AML	16 (46)	9(11)	<.001
ELN 2017 cytogenetic risk			
Favorable	0 (0)	0 (0)	
Intermediate	2 (6)	58 (70)	
Adverse	33 (94)	25 (30) ¹	<.001
Complex cytogenetics	31 (89)	8 (10)	<.001
Co-mutations			
<i>NPM1</i>	1 (3)	27 (33)	.001
<i>FLT3</i> -ITD/TKD	0 (0)	18 (22)	.001
<i>IDH1/2</i>	4 (11)	21 (25)	.092
<i>RUNX1</i>	2 (6)	18 (22)	.035
<i>ASXL1</i>	1 (3)	19 (23)	.008
<i>K/NRAS</i>	4 (11)	23 (28)	.005
ELN 2017 risk group			
Favorable	0 (0)	26 (31)	
Intermediate	0 (0)	14 (17)	<.001
Adverse	35 (100)	43 (52)	
Prior therapy for AHD	7 (20)	21 (25)	.536
Hypomethylating agent (HMA)	7 (20)	18 (22)	.838
Intensive chemotherapy (IC)	0 (0)	4 (5)	.186
HMA and IC	0 (0)	2 (2)	.354
Stem-cell transplantation	3 (9)	5 (6)	.615

All results expressed as no. (%) or median [interquartile range], unless specified. ECOG: Eastern Cooperative Oncology Group; sAML: secondary acute myeloid leukemia; AHD: antecedent hematological disorder; ELN: European Leukemia Net.

Table 2.

Outcomes of patients with acute myeloid leukemia with and without *TP53* mutation treated with 10-day decitabine and venetoclax.

Outcome	<i>TP53</i> mutated AML (N= 35)	<i>TP53</i> wild type AML (N= 83)	<i>p</i>
Overall response rate	23 (66)	74 (89)	.002
CR	13 (37)	48 (58)	.040
CRi	7 (20)	16 (19)	.928
CR/CRi	20 (57)	64 (77)	.029
Morphologic leukemia-free state	3 (9)	10 (12)	.582
MRD negative by FCM	6 (29)	44 (59)	.012
No response	10 (29)	9 (11)	.017
Inevaluable/Aplasia ^I	2 (6)	0 (0)	.028
30-day mortality	1 (3)	1 (1)	.525
60-day mortality	9 (26)	3 (4)	< .001

All results expressed as no. (%). CR=complete remission, CRi = CR with incomplete hematologic recovery; MRD = minimal residual disease FCM = flow cytometry.

^I. One patient had early death before first evaluation and one patient with aplasia on initial evaluation passed away prior to repeat bone marrow evaluation.

Table 3.

Multivariate analysis for achievement of CR and overall survival

Parameter	OR (95% CI)	<i>p</i>
Achievement of CR		
<i>TP53</i> mutated vs wild type	0.17 (0.06–0.47)	<.001
ECOG PS 2 vs 0–1	0.24 (0.08–0.71)	.010
Prior HMA for AHD vs none	0.15 (0.01–0.24)	.002
<i>RUNX1</i> mutated vs wild type	0.23 (0.06–0.88)	.031
<i>ASXL1</i> mutated vs wild type	0.05 (0.12–0.24)	<.001
Overall survival		
<i>TP53</i> mutated vs wild type	6.96 (3.76–12.88)	<0.001
sAML with AHD vs <i>de novo</i> AML	2.97 (1.78–4.94)	<0.001
<i>DNMT3A</i> mutated vs wild type	0.44 (0.24–0.81)	0.009
<i>K/NRAS</i> mutated vs wild type	2.82 (1.58–5.02)	<0.001

PS = performance status, HMA = hypomethylating agent, AHD = antecedent hematological disorder, sAML = secondary AML

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