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Venetoclax and hypomethylating agents in *TP53*-mutated acute myeloid leukaemia

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Keywords

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TP53 mutations occur in nearly 10% of adults with *de novo* acute myeloid leukaemia (AML); however, these mutations are encountered at higher frequency in therapy-related AML (t-AML) (~35%) and AML with complex cytogenetics (50–60%) (Ok, *et al* 2015, Rucker, *et al* 2012). The presence of the *TP53* mutation (*TP53m*) conveys an extremely poor prognosis (Grossmann, *et al* 2012, Rucker, *et al* 2012). Patients with *TP53m* AML are generally older in age (Rucker, *et al* 2012), and their physical fitness, especially in those with t-AML, is poor (Granfeldt Ostgard, *et al* 2015). The clinical response of *TP53m* AML to standard induction regimens has been disappointing, and if achieved, is usually short-lived (Grossmann, *et al* 2012, Rucker, *et al* 2012).

Venetoclax (VEN) has shown encouraging activity when combined with hypomethylating agents (HMAs) in both newly diagnosed and relapsed/refractory (r/r) AML (Aldoss, *et al* 2018, DiNardo, *et al* 2019). The combination is well-tolerated even in frail patients and is associated with low treatment-related mortality (TRM) (DiNardo, *et al* 2019). Apoptosis mediated by venetoclax appears to be *TP53*-independent (Anderson, *et al* 2016), and

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Authorship contributions

IA, RN, AS, SJF, GM, VP designed the research study; JZ, RP, GS, MM performed the research, IA, JZ, JFS analysed the data; IA, JFS, VP wrote the paper.

Disclosure and competing interests

IA serves on an advisory board with Agios and the speakers' bureau with Jazz Pharmaceuticals, and is a consultant Autolus Therapeutics. RN serves on advisory boards with Merck and Celgene and has a research collaboration with Jazz Pharmaceuticals. AS is on the speakers' bureau for Amgen, Celgene and Stemline. VP has served on the advisory boards for Abbvie and Jazz Pharmaceuticals and is member of speakers' bureau for Jazz Pharmaceuticals, Amgen, Novartis and Abbvie. GM is on the speakers' bureau for Abbvie. The remaining authors have no relevant conflicts of interest to declare.

VEN/HMA activity was observed across various high-risk leukaemia genetics (Aldoss, *et al* 2018, DiNardo, *et al* 2019).

We conducted a retrospective analysis of AML patients treated with the combination of VEN/HMA at our institution between June 2016 and April 2019. We identified *TP53m* utilizing an in-house next generation sequencing panel. The study was approved by the City of Hope Institutional Review Board. Response was defined as either complete remission (CR) or CR with incomplete count recovery (CRi). In univariate analysis, descriptive statistics were used to summarize the covariates for both response and non-response groups. The correlations between response to VEN/HMA and these covariates were assessed by the Pearson Chi-square test for categorical variables. A logistic multivariable regression model was applied to the three covariates with P values not exceeding 0.1; odds ratios and 95% confidence intervals (CI) are listed in Table SI. The median leukaemia-free survival (LFS) and overall survival (OS) were summarized for the response group only. All analyses were performed with R 3.5.1 (<http://www.R-project.org>) or SAS 9.4 (SAS Institute Inc, Cary, NC).

We identified 32 adults with *TP53m* AML who were treated with VEN/HMA. One patient with r/r AML was unevaluable for response because of death from sepsis 10 days after initiating therapy. The median age was 68 years (22–85). Sixteen (52%) patients had r/r AML while 15 (48%) patients were newly diagnosed. The majority of patients had complex cytogenetics ($n=24$, 77%). The median variant allele frequency (VAF) for *TP53m* was 56% (range, 3–95%), and 9 (29%) patients had more than one *TP53* mutation. Nineteen (61%) patients had additional somatic mutations. Decitabine was the HMA used in the majority of cases (90%) and was more frequently given as a 5-day schedule rather than a 10-day schedule (52% vs. 39%).

Among the 31 evaluable patients, 16 (52%) experienced a response, including 7 CR and 9 CRi. Response was achieved after a median of 2 (range, 1–3) cycles. Minimal residual disease (MRD), defined as $>0.01\%$ by multiparameter flow cytometry in a reference laboratory, was evaluated in 10 of the responders, and 7 (70%) achieved MRD negativity. Prior HMA monotherapy was the only factor observed to be associated with a lower response compared to that in patients who were HMA-naïve (14% vs. 63%, $P=0.025$). There was a trend toward a higher CR/CRi rate in patients with more than one *TP53* mutation (78% vs. 41%, $P=0.062$) and in those who were treated with VEN/HMA in the frontline setting (67% vs. 38%, $P=0.1$). Response was comparable across patient age, sex, AML type, receipt of prior allogeneic haematopoietic cell transplantation (alloHCT), cytogenetics, presence of additional mutations and type and duration of HMA therapy. Table I depicts patient characteristics and response rates. In multivariate analysis of response, prior exposure to HMA was associated with a non-significant trend toward lower response (odds ratio= 0.12; 95%CI: -1.69 – 1.27 ; $P=0.092$) (Table SII).

Response to VEN/HMA in *TP53m* AML according to associated additional mutations is shown in Table SI. The location and pattern of *TP53* mutations for responders and non-responders is depicted in Figure 1. The median *TP53* VAF was comparable for responders and non-responders (56% vs. 52%). The median LFS and OS for responders was 234 days

(95% CI: 101–329) and 329 days (95% CI: 284–not reached), respectively. Five responders (31%) underwent alloHCT in CR.

Consistent with previous reports (DiNardo, *et al* 2019), we illustrate that the response to this regimen in the frontline setting is encouraging for this high-risk group, especially considering the fact that the majority of patients with *TP53*m AML carried complex cytogenetics. Furthermore, we also show a promising CR/CRi rate (38%) in patients with *r/r TP53*m AML, which includes some patients relapsing after prior alloHCT. Deep responses were observed, and a proportion of responders underwent alloHCT.

Prior exposure to HMA predicted lower response to VEN/HMA in this cohort, in contrast to another report from our institution that did not restrict analysis to *TP53*m AML (Aldoss, *et al* 2018). Most patients in our cohort received decitabine as their HMA, and this preference may have been influenced by results of a study utilising 10-day courses of decitabine in *TP53*m myeloid neoplasms and yielding a 100% response rate (Welch, *et al* 2016). In our cohort, the response rate was comparable between patients treated with either a 5- or 10-day course of decitabine. The VAF of *TP53*m was comparable in responders and non-responders, in contrast to a myelodysplastic syndrome study which indicated an impact of *TP53* VAF on survival outcomes among patients treated with HMA (Sallman, *et al* 2016). The majority of *TP53* mutations were present in the DNA-binding domain in both groups, consistent with COSMIC data and in line with the fact that TP53 acts as a tumor suppressor primarily through its function as a DNA-binding transcription factor regulating the expression of genes that control cell cycle arrest and apoptosis (Tate, *et al* 2019).

Although our preliminary results with VEN/HMA appear favourable compared to the dismal outcomes reported in *TP53*m AML patients when treated with conventional combination chemotherapy (Grossmann, *et al* 2012, Kadia, *et al* 2016, Rucker, *et al* 2012), the median LFS was relatively short, and relapses occurred frequently. The combination of VEN/HMA may serve as a well-tolerated backbone to which other novel agents could be added in order to further improve response rates and remission duration in *TP53*m AML and thereby safely bridge more patients to transplantation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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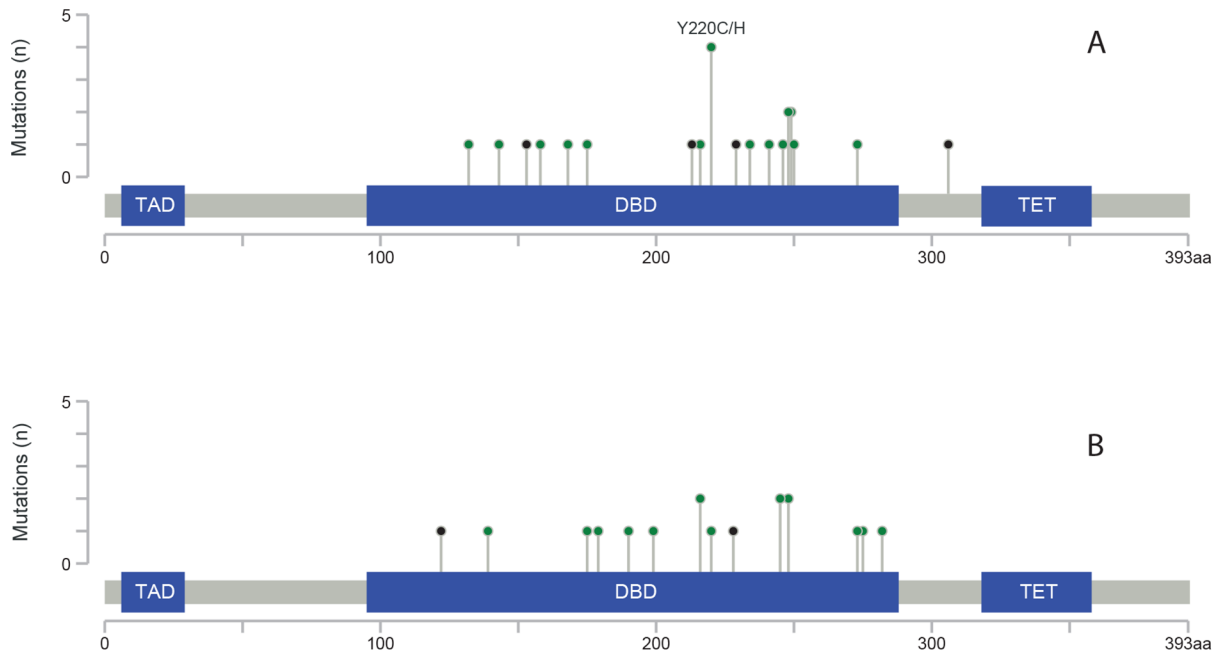


Figure 1. Location of *TP53* mutations in a) responders and b) non-responders.

DBD: DNA-binding domain; TAD: topologically associating domain; TET: tetramerization domain.m

Table 1.

Patient characteristics and response to VEN/HMA

	Evaluable patients	CR/CRi	P-value
Number	31	16 (50)	
Age, years; median (range)	68 (22–85)		0.376
65 years	14 (45)	6 (43)	
>65 years	17 (55)	10 (59)	
Sex			0.2
Male	14 (45)	9 (64)	
Female	17 (55)	7 (41)	
AML setting			0.104
Newly diagnosed	15 (48)	10 (67)	
R/R	16 (52)	6 (38)	
AML type			0.213
<i>De novo</i>	13 (42)	5 (38)	
Secondary/therapy-related	18 (58)	11 (61)	
Prior HMA treatment			0.025
Yes	7 (23)	1 (14)	
No	24 (77)	15 (63)	
Prior allogeneic HCT			0.571
Yes	5 (16)	2 (40)	
No	26 (84)	14 (54)	
Cytogenetics			0.562
Complex	24 (77)	13 (54)	
with MK	16 (52)	8 (50)	
without MK	8 (26)	5 (63)	
Normal karyotype	2 (6)	1 (50)	
Others	5 (16)	2 (40)	
Additional mutations			0.552
No	12 (39)	7 (58)	
Yes	19 (61)	9 (47)	
TP53 allele frequency, %; median (range)	56 (3–95)	56 (9–92)	
TP53 mutations (n)			0.062
1	22 (71)	9 (41)	
2	9 (29)	7 (78)	
HMA type/schedule			1
Decitabine	28 (90)	14 (50)	
5 days	16 (52)	8 (50)	
10 days	12 (39)	6 (50)	
Azacitadine	3 (10)	2 (67)	

Abbreviations: AML, acute myeloid leukaemia; CR, complete remission; CRi, complete remission with incomplete count recovery; HCT, haematopoietic cell transplantation; HMA, hypomethylating agent; MK, monosomal karyotype; N, number; VEN, venetoclax.