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Outcomes in Patients with Poor-Risk Cytogenetics with or without *TP53* Mutations Treated with Venetoclax and Azacitidine

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ABSTRACT

Purpose: To evaluate efficacy and safety of venetoclax + azacitidine in treatment-naïve patients with acute myeloid leukemia harboring poor-risk cytogenetics and $TP53^{mut}$ or $TP53^{wt}$.

Patients and Methods: We analyzed data from a phase III study (NCT02993523) comparing venetoclax (400 mg orally days 1–28) + azacitidine (75 mg/m^2 days 1–7) or placebo + azacitidine, and from a phase Ib study (NCT02203773) of venetoclax + azacitidine. Patients were ineligible for intensive therapy. *TP53* status was analyzed centrally; cytogenetic studies were performed locally.

Results: Patients ($n = 127$) with poor-risk cytogenetics receiving venetoclax + azacitidine ($TP53^{wt} = 50$; $TP53^{mut} = 54$) were compared with patients with poor-risk cytogenetics ($n = 56$) receiving azacitidine alone ($TP53^{wt} = 22$; $TP53^{mut} = 18$).

For poor-risk cytogenetics + $TP53^{wt}$ patients, venetoclax + azacitidine versus azacitidine alone resulted in composite remission rates (CRc) of 70% versus 23%, median duration of remission (DoR) of 18.4 versus 8.5 months, and median overall survival (OS) of 23.4 versus 11.3 months, respectively. Outcomes with venetoclax + azacitidine were comparable with similarly treated patients with intermediate-risk cytogenetics and $TP53^{wt}$.

For poor-risk cytogenetics + $TP53^{mut}$ patients, venetoclax + azacitidine versus azacitidine alone resulted in CRc of 41% versus 17%, median DoR of 6.5 versus 6.7 months, and median OS of 5.2 versus 4.9 months, respectively.

For poor-risk cytogenetics + $TP53^{mut}$ patients, predominant grade ≥3 adverse events (AE) for venetoclax + azacitidine versus azacitidine were febrile neutropenia (55%/39%), thrombocytopenia (28%/28%), neutropenia (26%/17%), anemia (13%/6%), and pneumonia (28%/33%). AEs were comparable between $TP53^{mut}$ and $TP53^{wt}$ patients.

Conclusions: In poor-risk cytogenetics + $TP53^{mut}$ patients, venetoclax + azacitidine improved remission rates but not DoR or OS compared with azacitidine alone. However, in poor-risk cytogenetics + $TP53^{wt}$ patients, venetoclax + azacitidine resulted in higher remission rates and longer DoR and OS than azacitidine alone, with outcomes comparable with similarly treated patients with intermediate-risk cytogenetics. Toxicities were similar in $TP53^{mut}$ and $TP53^{wt}$ patients.

See related commentary by Green and Zeidner, p. 5235

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Introduction

The biology of acute myeloid leukemia (AML) changes with age; older adults have a higher incidence of poor-risk cytogenetics, including partial or complete loss of chromosomes 5 or 7 and the presence of complex or monosomal karyotypes (1). Poor-risk cytogenetic profiles are associated with inadequate responses to conventional therapies, a high risk of relapse, and dismal overall survival (OS; refs. 1–6). The *TP53* gene plays a pivotal role in activating DNA repair and triggering cell-cycle arrest (2). *TP53* is mutated in over half of human cancers, and such mutations frequently occur in AML (2, 7). *TP53* mutations ($TP53^{mut}$) represent an important resistance mechanism to DNA-damaging chemotherapeutic agents (2, 7), resulting in poor treatment outcomes (3, 7–9). In addition, the *TP53* mutational burden, as measured by the variant allele frequency (VAF), is also linked to inferior OS (10, 11). Poor-risk cytogenetic profiles and $TP53^{mut}$ are highly correlated (12, 13), but both are considered independent adverse risk factors for AML (5).

Several novel targeted therapies have been approved to treat patients with AML (13). The prognostic significance of poor-risk cytogenetics with $TP53^{mut}$ or $TP53^{wt}$ has been defined in the context of conventional and typically intensive chemotherapeutic approaches, and currently, there is a lack of evidence regarding whether these prognostic classifications also apply to lower-intensity or targeted therapies that have distinct mechanisms of action.

Translational Relevance

Poor-risk cytogenetics are associated with inferior outcomes in patients with acute myeloid leukemia treated with conventional therapies. *TP53* mutations (*TP53*^{mut}) frequently co-occur with poor-risk cytogenetics. The phase III VIALE-A study showed that patients treated with venetoclax + azacitidine had higher remission rates and superior overall survival (OS) than patients treated with azacitidine alone. Herein, we evaluated the efficacy of venetoclax + azacitidine in patients with poor-risk cytogenetics and *TP53*^{mut} or *TP53* wild-type (*TP53*^{wt}). Patients with poor-risk cytogenetics and *TP53*^{mut} receiving venetoclax + azacitidine had higher response rates but similar durations of remission (DoR) and OS than treatment with azacitidine alone. However, patients with poor-risk cytogenetics and *TP53*^{wt} who received venetoclax + azacitidine had remission rates, DoR, and OS that were superior to patients receiving azacitidine alone and comparable with those of similarly treated patients with intermediate-risk cytogenetics. Thus, in the absence of *TP53*^{mut}, poor-risk cytogenetics may not be an adverse risk factor for venetoclax + azacitidine.

Venetoclax with azacitidine is the current standard of care for patients with treatment-naïve AML who are not eligible for intensive induction chemotherapy (14). Herein, we report the outcomes of treatment-naïve AML patients harboring poor-risk cytogenetics with or without *TP53*^{mut}, who were unfit for intensive chemotherapy due to age ≥ 75 years and/or comorbidities, and thus were treated with the venetoclax + azacitidine combination or azacitidine alone. We also compared treatment outcomes in this patient population with poor-risk cytogenetics with *TP53*^{mut} or *TP53*^{wt} to those of patients with intermediate-risk cytogenetics and *TP53*^{mut} or *TP53*^{wt}.

Patients and Methods

Patients and treatment

This pooled analysis included patients from the ongoing random-ized double-blind phase III study (NCT02993523, VIALE-A) and a prior non-randomized, single-arm phase Ib study (NCT02203773). The study designs and eligibility criteria have been previously reported (4, 14, 15). Patients received 400-mg venetoclax orally daily on days 3 to 28 (100 and 200 mg given on days 1 and 2 in cycle 1) and 75-mg/m^2 azacitidine intravenously or subcutaneously on days 1 to 7 every 28-day cycle, or azacitidine monotherapy. Individuals enrolled in both studies had a confirmed diagnosis of AML by the World Health Organization criteria, received no prior therapy, and were ineligible for standard induction chemotherapy due to age ≥75 years or the presence of comorbidities. A subset of patients in the phase Ib study were also treated with venetoclax 400 mg and decitabine intravenously at 20 mg/m^2 on days 1 to 5 every 28-day cycle and are reported separately.

The applicable internal review boards or ethics committees approved study protocols and related documents. The studies were conducted per the International Conference on Harmonization, Good Clinical Practice guidelines, and the Declaration of Helsinki. All patients provided written informed consent.

Assessment of outcomes

Response assessments [composite complete remission (CRc) = complete remission (CR) + CR with incomplete hematologic remis-sion (CRi)] were performed at the end of cycle 1 and every three cycles thereafter. They were evaluated per modified International Working Group (IWG) criteria (16). Duration of CRc (DoR) was defined as the number of days from the date of first response (CR or CRi) per the modified IWG criteria to the earliest evidence of confirmed morpho-logic relapse, disease progression, or death due to disease progression. OS was defined as the time from randomization (phase III study) or the number of days from the first dose of the study drug (phase Ib study) to the date of death from any cause. Rates of transfusion independence to red blood cells (RBCs) and platelets (≥56 consecutive days) were assessed. Measurable residual disease (MRD) was assessed centrally by flow cytometry [Labcorp Drug Development (formerly Covance), Princeton, NJ, USA] in patients who achieved CRc with MRD nega-tivity defined by European Leukemia Network guidelines (14, 17). MRD negativity was defined as one or fewer residual leukemic blasts per 1,000 leukocytes or 10^{-3}. Patients who had one negative sample for MRD value below this cutoff at any time in the study were defined as patients with an MRD-negative response. Samples were collected at baseline from bone marrow aspirates during the clinical assessment end of cycle one and after every three cycles thereafter (17). Adverse events (AE) were graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 (18).

Baseline cytogenetic risk was determined locally and was evaluated using National Comprehensive Cancer Network (NCCN) criteria (version 2.2016). DNA was isolated from bone marrow aspirates collected from patients prior to the first dose of the study drug and was analyzed centrally. The MyAML (next-generation sequencing, Invivoscribe, San Diego, CA, USA) assay was used to detect the presence of *TP53* variants in both phase Ib and phase III studies. The assay's limit of detection was a variant allelic frequency ≥ 2.5%.

Statistical analysis

Demographics were summarized by descriptive statistics. Remis-sion rates were summarized in counts and proportions. OS and DoR were evaluated by the Kaplan–Meier methodology. The 95% confi-dence intervals (CI) for time to event endpoints were estimated based on log-log transformation.

Data availability

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, indi-vidual, and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified research-ers who engage in rigorous, independent, scientific research and will be provided following review and approval of a research proposal, Statistical Analysis Plan, and execution of a Data Sharing Agreement. Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions con-sidered. For more information on the process or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.

Results

Patient disposition and baseline characteristics

The clinical data cutoff dates were January 4, 2020, for the phase III study, and July 19, 2019, for the phase Ib study. The pooled analysis
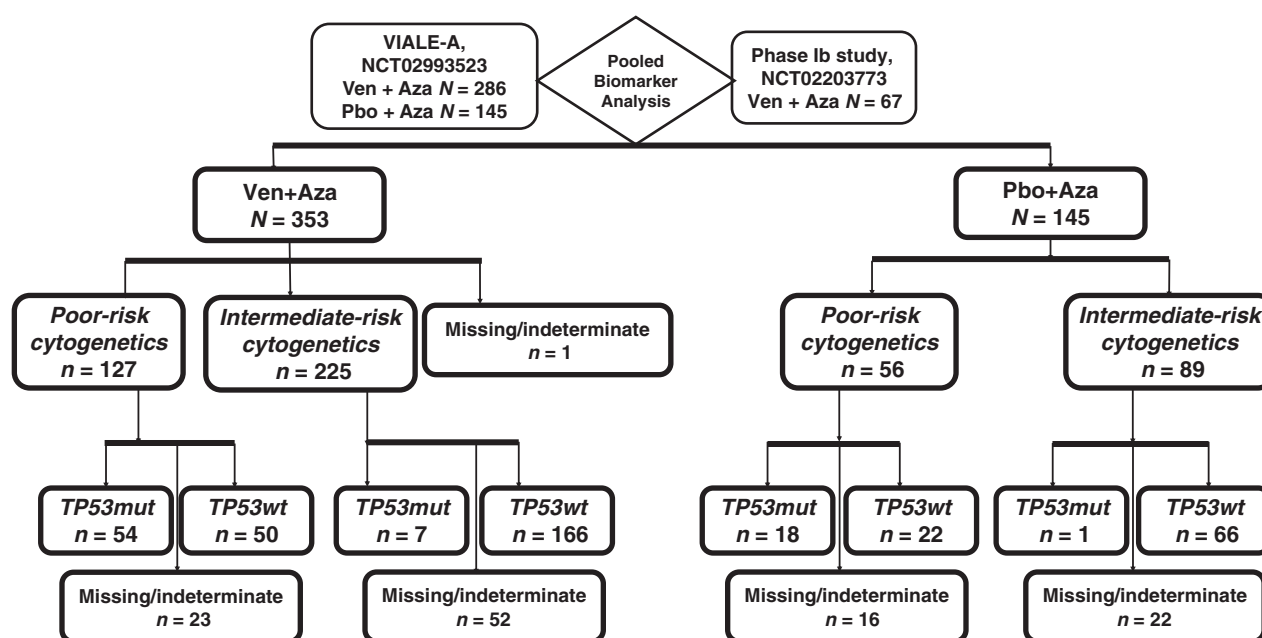
Figure 1.
Study design and molecular classification. Abbreviations: Aza, azacitidine; mut, mutated; Pbo, placebo; wt, wild-type; Ven, venetoclax.

included 353 patients treated with venetoclax + azacitidine (phase III, $n = 286$; phase Ib, $n = 67$) and 145 patients treated with azacitidine alone.

In the biomarker evaluable population, poor-risk cytogenetics were identified in 36% ($n = 127/353$) of patients in the venetoclax + azacitidine group and 39% ($n = 56/145$) in the azacitidine alone group. Among those with poor-risk cytogenetics, $TP53^{mut}$ was detected in 52% ($n = 54/104$) in the venetoclax + azacitidine group and 45% ($n = 18/40$) in the azacitidine alone group. Among patients with poor-risk cytogenetics, $TP53^{wt}$ was detected in 48% ($n = 50/104$) in the venetoclax + azacitidine group and 55% ($n = 22/40$) in the azacitidine alone group. The study design and overview of the molecular categorization of patients are shown in **Fig. 1**.

The key baseline demographic characteristics for patients with poor-risk and intermediate-risk cytogenetics are shown in **Table 1**. Patients with poor-risk cytogenetics with $TP53^{mut}$ exhibited del 5 or 7 abnormalities and complex karyotypes more frequently than patients with $TP53^{wt}$. In addition, *FLT3*, *IDH1/2*, and *NPM1* mutations were more frequently detected among patients in the intermediate-risk group.

Response to treatment

The response to treatments in the subgroups is shown in **Fig. 2A** and **B**. In all treatment groups, higher CRc rates were observed in patients with poor-risk cytogenetics and $TP53^{wt}$ than in those with poor-risk cytogenetics and $TP53^{mut}$. Among patients with poor-risk cytogenetics and $TP53^{wt}$, the CRc rate was 70.0% for those treated with venetoclax + azacitidine and 22.7% for those treated with azacitidine alone. In patients with poor-risk cytogenetics and $TP53^{wt}$, CRc rates with venetoclax + azacitidine were similar to those of intermediate-risk and $TP53^{wt}$ (70.0% vs. 71.7%, respectively). However, in patients with poor-risk cytogenetics and $TP53^{mut}$, the CRc rates in the venetoclax + azacitidine and azacitidine alone groups were 40.7% and 16.7%, respectively.

In patients with poor-risk cytogenetics and $TP53^{wt}$ treated with venetoclax + azacitidine, 60% achieved transfusion independence, similar to results observed in patients with intermediate-risk cytogenetics and $TP53^{wt}$ (71.4%; **Fig. 2C** and **D**). Among those with poor-risk cytogenetics and $TP53^{wt}$, the proportion of patients who achieved MRD negativity (MRD $<10^{-3}$) was also higher in the venetoclax + azacitidine group as compared with the azacitidine alone group (35.6% vs. 10.5%, **Fig. 2E**). Similarly, in patients with intermediate-risk cytogenetics and $TP53^{wt}$ treated with venetoclax + azacitidine, 44.8% achieved MRD negativity (**Fig. 2F**). Three (6%) patients with poor-risk cytogenetics and $TP53^{wt}$ treated with venetoclax + azacitidine underwent a transplant. In patients with poor-risk cytogenetics and $TP53^{mut}$ treated with venetoclax + azacitidine, 29.6% achieved transfusion independence, 17.5% achieved MRD negativity, and 22.2% of patients with poor-risk cytogenetics and $TP53^{mut}$ treated with azacitidine achieved transfusion independence, and none achieved MRD negativity.

The DoR in patients with poor-risk cytogenetics and $TP53^{wt}$ was also higher in the venetoclax + azacitidine group than in the azacitidine-only group (18.4 vs. 8.5 months; **Fig. 3A**); however, these conclusions are limited by the very few azacitidine-only patients who achieved a response. Similar to CRc, the DoR for patients with poor-risk cytogenetics and $TP53^{wt}$ who received venetoclax + azacitidine was comparable with that of patients with intermediate-risk cytogenetics and $TP53^{wt}$ who received the same regimen (18.4 vs. 21.9 months, respectively; **Fig. 3B**). Patients with poor-risk cytogenetics and $TP53^{mut}$ had a shorter DoR, with no appreciable differences seen between the venetoclax + azacitidine (6.5 months) and azacitidine alone (6.7 months) groups.

For OS, patients with poor-risk cytogenetics and $TP53^{wt}$ treated with venetoclax + azacitidine had a longer OS than patients treated with azacitidine alone (23.4 vs. 11.3 months; **Fig. 3C**). Once again, the outcome of patients treated with venetoclax + azacitidine was similar to that of patients with intermediate-risk cytogenetics and $TP53^{wt}$

Table 1. Patient demographics and baseline characteristics.

	Poor-risk cytogenetics				Intermediate-risk cytogenetics			
	Venetoclax + Azacitidine		Azacitidine		Venetoclax + Azacitidine		Azacitidine	
	$TP53^{mut}$ (n = 54)	$TP53^{wt}$ (n = 50)	$TP53^{mut}$ (n = 18)	$TP53^{wt}$ (n = 22)	$TP53^{mut}$ (n = 7)	$TP53^{wt}$ (n = 166)	$TP53^{mut}$ (n = 1)	$TP53^{wt}$ (n = 66)
Median age, years (range)	77.0 (53–86)	74.5 (66–86)	75.0 (60–86)	76.5 (62–90)	76.0 (67–84)	77.0 (49–91)	75 (75–75)	76.5 (64–86)
Age categories, n (%)								
<75y	21 (38.9)	25 (50.0)	10 (55.6)	7 (31.8)	2 (28.6)	60 (36.1)	0 (0)	27 (40.9)
≥75 y	33 (61.1)	25 (50.0)	8 (44.4)	15 (68.2)	5 (71.4)	106 (63.9)	1 (100)	39 (59.1)
AML types, n (%)								
De novo	42 (77.8)	30 (60.0)	14 (77.8)	13 (59.1)	3 (42.9)	128 (77.1)	1 (100)	52 (78.8)
Secondary	12 (22.2)	20 (40.0)	4 (22.2)	9 (40.9)	4 (57.1)	38 (22.9)	0 (0)	14 (21.2)
Blast count, n (%)								
<30%	24 (44.4)	14 (28.0)	8 (44.4)	6 (27.3)	4 (57.1)	38 (22.9)	0 (0)	16 (24.2)
≥30–<50%	12 (22.2)	12 (24.0)	5 (27.8)	6 (27.3)	1 (14.3)	36 (21.7)	0 (0)	14 (21.2)
≥50%	18 (33.3)	24 (48.0)	5 (27.8)	10 (45.5)	2 (28.6)	92 (55.4)	1 (100)	36 (54.5)
ECOG score, n (%)								
1–2	32 (59.3)	29 (58.0)	10 (55.6)	16 (72.7)	3 (42.9)	98 (59.0)	1 (100)	38 (57.6)
3–4	22 (40.7)	21 (42.0)	8 (44.4)	6 (27.3)	4 (57.1)	68 (41.0)	0 (0)	28 (42.4)
Molecular mutations, n (%)								
FLT3 detected	2 (3.7)	6 (12.0)	0 (0)	2 (9.1)	2 (28.6)	37 (22.3)	1 (100)	25 (37.9)
IDH1/2 detected	2 (3.7)	15 (30.0)	0 (0)	6 (27.3)	1 (14.3)	58 (34.9)	0 (0)	15 (22.7)
NPM1 detected	0 (0)	0 (0)	0 (0)	1 (4.5)	1 (14.3)	42 (25.3)	0 (0)	17 (25.8)
Cytogenetics[a], n (%)								
t11q23 detected	5 (9.3)	2 (4.0)	1 (5.6)	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)
t3_3 detected	1 (1.9)	5 (10.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
del 5 or 7 detected	45 (83.3)	34 (68.0)	16 (88.9)	16 (72.7)	0 (0)	0 (0)	0 (0)	0 (0)
Complex karyotype detected	49 (90.7)	25 (50.0)	17 (94.4)	7 (31.8)	0 (0)	1 (0.6)	0 (0)	0 (0)
del 17 detected	13 (24.1)	2 (4.0)	4 (22.2)	0 (0)	0(0)	0 (0)	0(0)	1 (1.5)

Note: Patients enrolled in the phase III VIALE-A study were stratified by cytogenetic risk (intermediate, poor).
Abbreviations: AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; mut, mutated; wt, wild-type.
[a]Cytogenetics were classified per NCCN (2016) criteria.

treated with venetoclax + azacitidine (19.1 months; **Fig. 3D**). In contrast, patients with poor-risk cytogenetics and $TP53^{mut}$ had an inferior OS, regardless of treatment approach (5.2 months for venetoclax + azacitidine and 4.9 months for azacitidine alone).

For patients who received venetoclax + azacitidine, CRc rates or OS did not differ on the basis of the VAF of the $TP53^{mut}$ (<20%, 20%–40%, or >40%; **Fig. 4A** and **B**). We also compared outcomes of venetoclax + azacitidine treatment in patients with poor-risk cytogenetics and $TP53^{mut}$ overall with those of patients with specific high-risk cytogenetic abnormalities, including abnormalities of t11q23, t3;3, complex karyotype, and del17p. The results are summarized in Supplementary Table S1. Patients with $TP53^{wt}$ consistently had better outcomes than their $TP53^{mut}$ counterparts, regardless of karyotype.

Fifteen patients with poor-risk cytogenetics and $TP53^{wt}$ had cooccurring $IDH1/2^{mut}$ (**Table 1**). It has been demonstrated that patients with an $IDH1/2^{mut}$ have superior responses to venetoclax + azacitidine (19). Therefore, we further evaluated the efficacy among patients with poor-risk cytogenetics and $TP53^{wt}$ who were also $IDH1/2^{wt}$; 70% (n = 35/50) treated with venetoclax + azacitidine, and 73% (n = 16/22) treated with azacitidine alone, respectively. The patients with poor-risk cytogenetics, $TP53^{wt}$, and $IDH1/2^{wt}$, and treated with venetoclax + azacitidine, had longer OS than patients with a similar profile treated with azacitidine alone (21.1 vs. 11.3 months; Supplementary Fig S1). The patients with intermediate-risk cytogenetics, $TP53^{wt}$, and $IDH1/2^{wt}$ treated with venetoclax + azacitidine had an OS of 18.3 months compared with those with poor-risk cytogenetics, $TP53^{wt}$, and $IDH1/2^{wt}$ treated with venetoclax + azacitidine.

Safety

All patients with poor-risk cytogenetics and $TP53^{mut}$ experienced at least one treatment-emergent AE with venetoclax + azacitidine or azacitidine alone. All grade ≥ 3 AEs with ≥ 20% occurrence are listed in Supplementary Table S2. Among patients with poor-risk cytogenetics and $TP53^{mut}$, the predominant grade ≥ 3 hematologic AEs for those treated with venetoclax + azacitidine versus azacitidine alone included febrile neutropenia (55% vs. 39%), thrombocytopenia (28% vs. 28%), neutropenia (26% vs. 17%), pneumonia (28% vs. 33%), and anemia (13% vs. 6%). Similar AE rates were observed in patients with poor-risk cytogenetics and $TP53^{wt}$.

In patients with poor-risk cytogenetics and $TP53^{mut}$, 9 (17%) deaths occurred within 30 days of treatment administration in the venetoclax + azacitidine group, and 2 (11%) in the azacitidine alone group.

Discussion

We analyzed a large dataset of newly diagnosed patients with AML unfit for intensive chemotherapy from two multicenter, international studies in which patients were treated uniformly. In patients with poor-risk cytogenetics and $TP53^{wt}$, treatment with venetoclax + azacitidine conferred better outcomes than patients treated with azacitidine alone. These outcomes were similar to patients with intermediate-risk cytogenetics and $TP53^{wt}$ treated with venetoclax + azacitidine. Historically, studies have shown that poor-risk cytogenetics are an independent poor prognostic factor for poor treatment outcomes (5, 20, 21). However, this association was observed in the
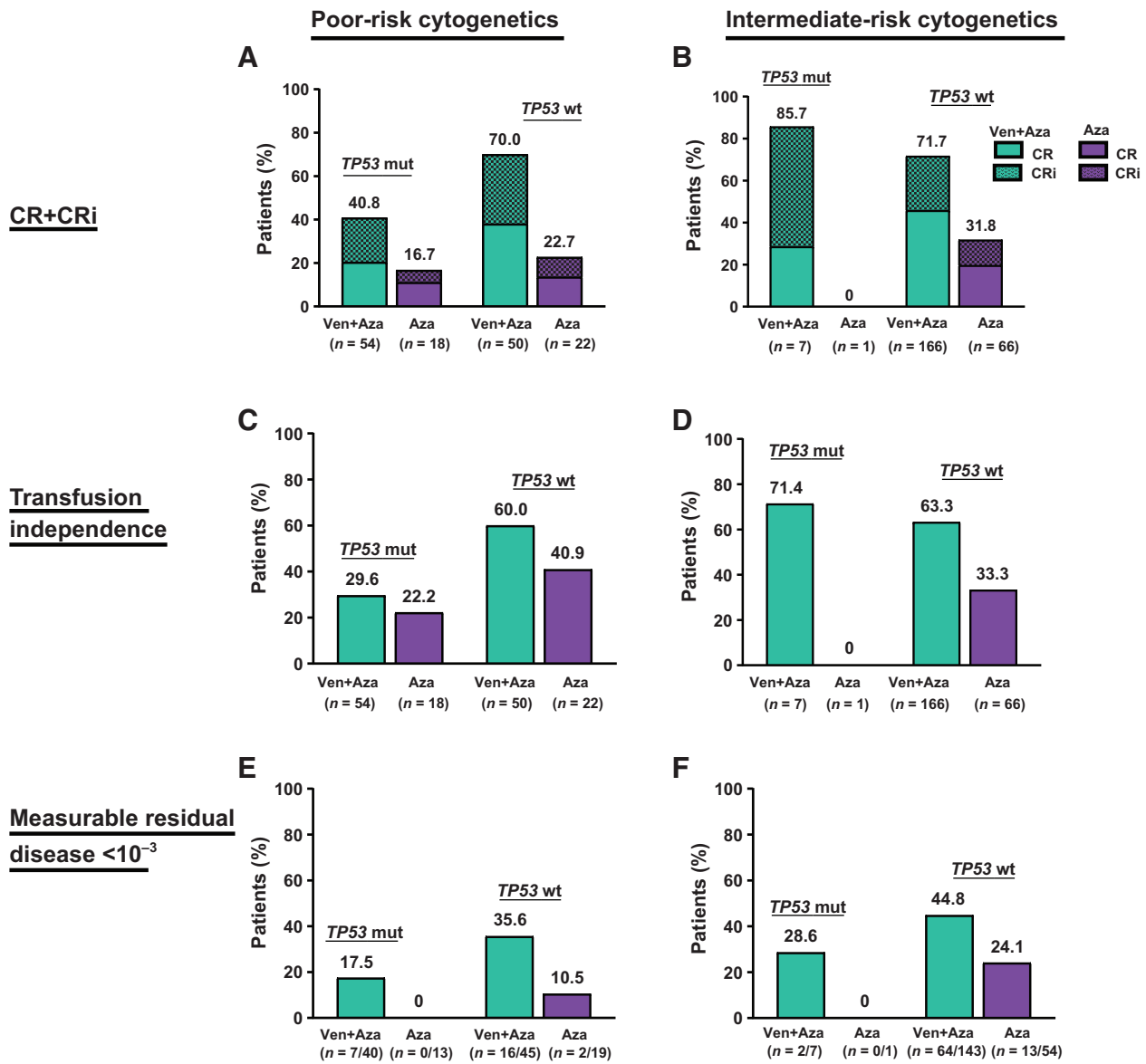
Figure 2.
Response rates. **A,** CR+CRi in patients with poor-risk cytogenetics. **B,** CR+CRi in patients with intermediate-risk cytogenetics. **C,** Transfusion independence in patients with poor-risk cytogenetics. **D,** Transfusion independence in patients with intermediate-risk cytogenetics. **E,** MRD $<10^{-3}$ in patients with poor-risk cytogenetics. **F,** MRD $<10^{-3}$ in patients with intermediate-risk cytogenetics. Abbreviations: Aza, azacitidine; CR, complete remission; CRi, CR with incomplete hematologic recovery; mut, mutated; wt, wild-type; Ven, venetoclax.

context of conventional treatments, typically intensive chemotherapy, which is frequently not a viable option for a disease in which most patients are ineligible for treatment due to advanced age.

As expected, among patients with poor-risk cytogenetics, the occurrence of $TP53^{mut}$ was high; 52% in the venetoclax + azacitidine group and 45% in the azacitidine alone group. While patients with these disease features demonstrated a higher response rate to venetoclax + azacitidine than azacitidine alone (including an 18% MRD < 10^{-3} negativity rate with venetoclax + azacitidine), the duration of response and OS remained poor and was not different between treatment groups. The OS among patients with $TP53^{mut}$ appeared to be similar to patients treated with intensive chemotherapy in both

clinical and real-world studies (22–24). Preclinical studies have shown that $TP53^{mut}$ can result in venetoclax resistance in AML cell lines. The expression levels of antiapoptotic proteins BCL2 and MCL1 are reduced in $TP53^{mut}$ cells, correlating inversely with increased BCLxL expression, resulting in higher ratios of BCLxL to BCL2 (25). Venetoclax binds directly to BCL2; therefore, a decrease in BCL2 expression contributes to the loss of drug sensitivity (26). DiNardo and colleagues have also demonstrated that $TP53^{mut}$ was associated with resistance to venetoclax, hypomethylating agents, and cytarabine, as single agents or in combination (27). $TP53^{mut}$ AML remains a challenging disease entity; novel therapies such as antiCD47 or $TP53^{mut}$ reactivators are being investigated with the hope that these
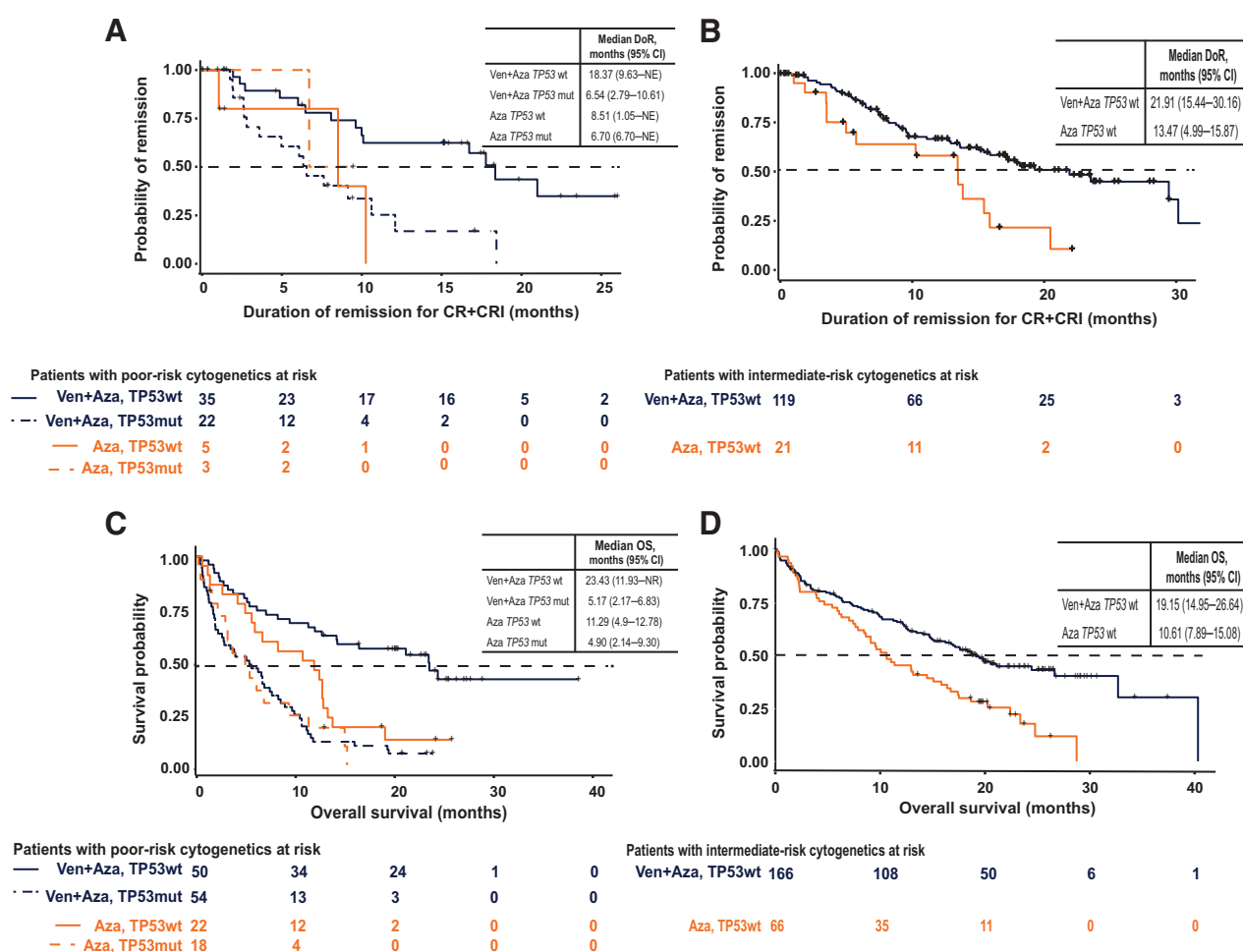
Figure 3.
Duration of response and OS. **A,** Duration of response among patients with poor-risk cytogenetics. **B,** Duration of response among patients with intermediate-risk cytogenetics. **C,** OS among patients with poor-risk cytogenetics. **D,** OS among patients with intermediate-risk cytogenetics. Abbreviations: Aza, azacitidine; mut, mutated; wt, wild-type; Ven, venetoclax.

novel approaches may overcome the treatment resistance associated with $TP53^{mut}$ (NCT04214860, NCT05079230, NCT04435691, NCT04778397 NCT04435691, NCT05079230; refs. 28, 29). Similarly, a triple combination of venetoclax + azacitidine with an antiCD47 agent is also under investigation (NCT04912063), intending to improve outcomes in this hard-to-treat subgroup of patients.

We also showed that the OS of patients with venetoclax and azacitidine treatment was not associated with VAF of the $TP53^{mut}$. This observation, the etiology of which is unclear, is consistent with the data reported by Short and colleagues, in which they showed that the VAF of the $TP53^{mut}$ was significant for patients treated with cytarabine-based regimens but not HMA or venetoclax-based therapies (11).

Our findings suggest that in the absence of a $TP53^{mut}$, the adverse prognostic implication of poor-risk cytogenetics might not apply to patients treated with venetoclax + azacitidine (Supplementary Fig. S2). The CRc, DoR, and OS for these patients were similar to the outcomes for patients treated with this regimen who had intermediate-risk cytogenetics. We recently reported that patients with poor-risk cytogenetics and $IDH1/2^{wt}$ had inferior outcomes (19). Here, we show that

the presence of a $TP53^{mut}$ drives inferior outcomes in the poor-risk cytogenetic group.

The safety and tolerability of venetoclax + azacitidine were similar, irrespective of $TP53^{mut}$ status. Observed toxicities were predominantly hematologic and were consistent with previously reported data (14, 15). No unusual toxicities or significant differences in neutropenia-related AEs were identified between similarly treated patients with $TP53^{mut}$ and $TP53^{wt}$. However, we observed a higher ≤ 60-day death rate among patients with a $TP53^{mut}$ (36%) as compared with $TP53^{wt}$ (8%) when treated with venetoclax + azacitidine, a reflection of the resistance to treatment associated with this adverse mutation.

There are limitations to this analysis. To increase the number of patients with poor-risk cytogenetics and $TP53^{mut}$, a pooled analysis of a prior phase III and a phase Ib study was conducted. However, this approach did not increase the number of patients in each subgroup treated with azacitidine alone due to the single-arm design of the phase Ib study. The small sample sizes in the azacitidine alone group limit the interpretation of the key findings between the two treatments.

In conclusion, our results demonstrate that the improved efficacy of the venetoclax + azacitidine combination in treatment-naïve patients
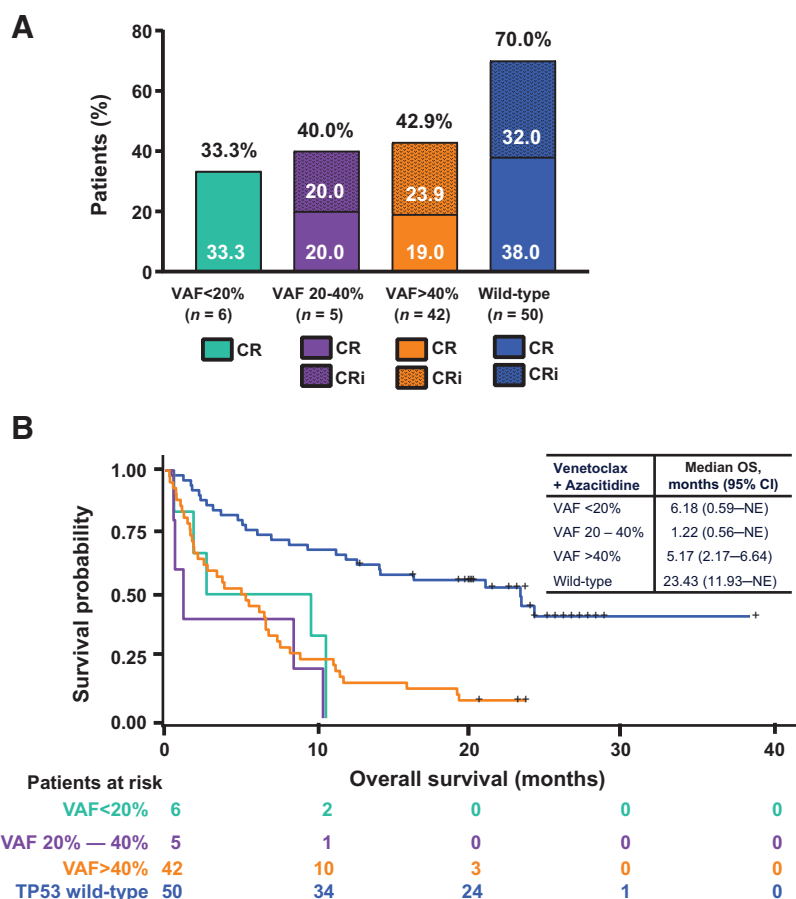
A

B

Figure 4.
Response rates and OS by VAF. **A,** Response rates by VAF among patients with poor-risk cytogenetics and *TP53*^mut treated with venetoclax + azacitidine. **B,** OS by variant allelic frequency among patients with poor-risk cytogenetics and *TP53*^mut treated with venetoclax + azacitidine. Abbreviations: CR, complete remission; CRi, CR with incomplete hematologic recovery; NE, not evaluable; VAF, variant allele frequency.

with AML unfit for intensive therapy and with poor-risk cytogenetics is restricted to patients without a *TP53*^mut. The status of this gene mutation could inform treatment decisions and would be useful information at diagnosis. This analysis also suggests that conventional prognostic factors in AML, defined mainly in the context of intensive therapeutic approaches, should be reanalyzed in the new setting of novel treatments.

Authors' Disclosures

Authors' Contributions

D.A. Pollyea: Conceptualization, writing–original draft, writing–review and editing. **K.W. Pratz:** Conceptualization, supervision, validation, visualization, methodology, writing–original draft, writing–review and editing. **A.H. Wei:** Conceptualization, supervision, validation, visualization, methodology, writing–original draft, writing–review and editing. **V. Pullarkat:** Conceptualization, supervision, validation, visualization, methodology, writing–original draft, writing–review and editing. **B.A. Jonas:** Writing–original draft, writing–review and editing. **C. Recher:** Writing–original draft, writing–review and editing. **S. Babu:** Conceptualization, methodology, writing–original draft, writing–review and editing. **A.C. Schuh:** Conceptualization, data curation, methodology, writing–original draft, writing–review and editing. **M. Dail:** Conceptualization, data curation, supervision, methodology, writing–original draft, writing–review and editing. **Y. Sun:** Conceptualization, data curation, supervision, validation, visualization, methodology, writing–original draft, writing–review and editing. **J. Potluri:** Conceptualization, data curation, supervision, validation, visualization, methodology, writing–original draft, writing–review and editing. **B. Chyla:** Conceptualization, data curation, supervision, validation, visualization, methodology, writing–original draft, writing–review and

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