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Oral decitabine cedazuridine with and without venetoclax in higher-risk myelodysplastic syndromes or chronic myelomonocytic leukemia: a propensity score–matched study

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Hypomethylating agents (HMA) are indicated in the treatment of higher-risk myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML). The combination of hypomethylating agents with venetoclax (Ven) has demonstrated promising results in these diseases, although randomized clinical trials are needed for validation. In this retrospective study, we compared two matched cohorts of patients with MDS or CMML: one receiving oral decitabine-cedazuridine (DEC-C, $n = 73$) and one receiving DEC-C and Ven (DEC-C-Ven, $n = 51$), in three contemporary clinical trials. The aim is to determine the impact of the addition of Ven to HMA in MDS and CMML. Individuals were matched using a propensity score approach that was based on the IPSS-M score and age. All patients had excess blasts; 84% were diagnosed with MDS and 16% with CMML. Most patients had high- or very high-risk disease, according to the revised IPSS-R. The overall response rate was superior in the DEC-C-Ven cohort (90% vs 64%, $P = 0.002$). The median times to best response were 1.1 and 2.7 months for the DEC-C-Ven and DEC-C cohorts, respectively ($P < 0.001$). More patients underwent hematopoietic stem cell transplantation in the DEC-C-Ven cohort (47%) than in the DEC-C cohort (16%, $P < 0.001$). The 4- and 8-week mortality did not significantly differ between the DEC-C and DEC-C-Ven cohorts. Patients in the DEC-C-Ven cohort had a more profound neutropenia at days 15 and 21 of the first cycle. The median overall survival was 24 and 19 months for the DEC-C-Ven and DEC-C cohorts, respectively ($P = 0.89$), and the median event-free survival durations were 18 and 10 months ($P = 0.026$). In conclusion, the addition of Ven resulted in improved response rates and outcomes in specific subgroups; prospective clinical trials are needed to confirm these findings.

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INTRODUCTION

Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) are hematopoietic stem cell neoplasms characterized by ineffective hematopoiesis, cytopenias, and risk for transformation to acute myeloid leukemia (AML) [1]. The standard of care for most patients with higher-risk MDS and CMML is a hypomethylating agent (HMA), such as azacytidine or decitabine. In eligible patients, hematopoietic stem-cell transplantation (HSCT) is the sole curative therapy [2]. Higher-risk MDS is defined as a revised International Prognostic Scoring System (IPSS-R) score ≥3.5 [3], and more recently, an IPSS-molecular (IPSS-m) score >0 [4, 5]. According to a recent systematic review, patients with higher-risk MDS treated with single-agent azacytidine experienced a complete remission (CR) rate of 17% and a marrow CR (mCR) rate of 9%, with a median overall survival (OS) of 18.6 months [6]. Thus, novel combinations are warranted to improve the outcomes of patients with higher-risk MDS and CMML [7, 8].

Decitabine plus cedazuridine (DEC-C) is an oral, fixed-dose, HMA formulation. In a phase 2 clinical trial, DEC-C was demonstrated to produce similar systemic decitabine exposure and toxicity compared to intravenous decitabine and an overall response rate (ORR) of 60% [9]. These findings were followed by a phase 3 study that confirmed decitabine area under the curve equivalence between DEC-C and IV decitabine, with an ORR of 62% [10]. DEC-C is currently approved by the FDA for the treatment of patients with MDS [11].

Venetoclax (Ven) is a BH3-mimetic molecule that binds to BCL-2 and displaces proapoptotic proteins, promoting the mitochondrial apoptotic pathway in cancer cells [12, 13]. The combination of Ven with HMA is synergistic and has shown efficacy in vitro in AML and MDS models [13, 14]. In AML, the combination of azacytidine plus

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Ven is the standard of care for patients ineligible for intensive chemotherapy [15]. AML shares several clinical and biological characteristics with MDS and CMML, but the role of Ven with HMA in the latter conditions remains unclear. Previous studies exploring the combination of HMA plus Ven in MDS and CMML have shown encouraging results [16–22]. A recent meta-analysis reported a pooled ORR of 64% in treatment-naive MDS patients who receive HMA and Ven, which was superior to the response expected with HMA alone [6, 23]. Regardless, definitive conclusions regarding the role of Ven await the completion of the randomized phase 3 VERONA clinical trial (NCT04401748). We previously conducted a phase 1/2 clinical trial testing total oral combination of DEC-C with Ven in higher-risk MDS and CMML. The combination demonstrated both efficacy and tolerability, achieving an ORR of 95% [22]. In this retrospective study, we analyzed matched cohorts of patients treated with either DEC-C or DEC-C-Ven in 3 clinical trials to determine the impact of the addition of Ven on clinical outcomes.

METHODS

Study design and patient inclusion

This was a post-hoc, propensity score-matched analysis that included patients aged 18 years or older with MDS or CMML who were treated with frontline DEC-C as part of clinical trials. The characteristics of the 3 clinical trials are summarized in Supplementary Table 1. This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center and was performed in accordance with the Declaration of Helsinki. Each participant provided written informed consent for enrollment in the clinical trials of this study.

Patients treated with a combination of DEC-C and Ven between January 21, 2021, and November 13, 2023, comprised the DEC-C-Ven cohort. These patients were treated in a single-center, open-label, dose-escalation and -expansion, phase 1/2 clinical trial (NCT04655755) performed at The University of Texas MD Anderson Cancer Center (Houston, TX, USA). These patients had treatment-naïve MDS or CMML with International Prognostic Scoring System (IPSS) scores of intermediate-2 or higher. The study design included a dose escalation phase (fixed-dose DEC-C 35 mg/100 mg for 5 days and 2 dose levels of Ven, 200 or 400 mg for 14 days) and a dose expansion phase (fixed-dose DEC-C 35 mg/100 mg for 5 days and Ven 400 mg for 14 days).

Patients treated with DEC-C were part of two multicenter, open-label, randomized clinical trials. The first study (NCT02103478) was a phase 2 clinical trial that included a dose confirmation stage with two sequences: oral cedazuridine 100 mg and oral decitabine 35 mg for 5 days in cycle 1 (Sequence A) or 2 (Sequence B) or IV decitabine 20 mg/m^2 for 5 days in cycle 1 (Sequence B) or 2 (Sequence A). The oral treatment was continued from cycle 3 onwards. A subsequent stage continued the same design, but oral treatment was administered using a DEC-C fixed-dose combination tablet containing the 2 drugs at the same doses. The second study (NCT03306264, ASCERTAIN) was a registration phase 3 clinical trial with a crossover design using the same treatment sequences as in the prior study, patients received the DEC-C fixed-dose combination. Both clinical trials included patients who had been diagnosed with MDS and CMML with IPSS intermediate 1/2 or high; 1 prior cycle of HMA was permitted.

Cytogenetic and genomic assessment and outcome evaluation

A cytogenetic analysis was performed at diagnosis using conventional karyotype banding and fluorescence in situ hybridization, and a mutational analysis was performed using next-generation sequencing panels. Mutations in the DEC-C cohort were analyzed centrally by Genomic Testing Cooperative (Lake Forest, CA, US). Mutations in the DEC-C-Ven cohort were assessed using an 81-gene next-generation sequencing panel, as previously described [24]. The genetic coverage of both panels is detailed in Supplementary Tables 2 and 3.

Following protocol guidelines, treatment responses were assessed following the 2006 International Working Group (IWG) criteria [25]. The ORR was defined as the proportion of patients achieving CR or mCR. OS was calculated from diagnosis to death or last follow-up. Event-free survival (EFS) was calculated from diagnosis to failure to respond to therapy (not achieving a CR or mCR), disease relapse, or AML transformation after response, death, or last follow-up. Treatment-emergent adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 5.0).

Statistical methods

We performed propensity score matching using logistic regression with the nearest-neighbor method. The selected matching variables for the DEC-C and DEC-C-Ven cohorts were molecular International Prognostic Scoring System (IPSS-M) numeric score and patient age. A 2:1 matching ratio (DEC-C to DEC-C-Ven) without replacement was used, with a caliper value of 0.2 to limit the maximal distance between matched cases. A standardized mean difference threshold of 0.1 was applied to indicate bias reduction between both groups.

The baseline characteristics were analyzed using descriptive statistics. Student's t-test and Mann-Whitney U test were used to compare continuous variables with normal and non-normal distributions, respectively. For categorical variables, the χ^2 and Fisher's exact tests were used. The median follow-up time was calculated with the Kaplan–Meier estimate of potential follow-up. OS and EFS distributions were estimated with the Kaplan–Meier method and compared with the log-rank test. Cumulative incidence was calculated using competitive events, and comparisons were performed with Gray's test. Cox proportional hazards regression was used for the univariate analysis. All statistical analyses were performed using R statistics software version 4.4.1 (R core Team, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients baseline clinical characteristics

Of 56 patients screened in the phase 1/2 MD Anderson trial, 53 received DEC-C and Ven and constituted the initial cohort of patients treated with DEC-C-Ven. All patients had excess blasts, per the clinical trial inclusion criteria. One patient was diagnosed with atypical chronic myeloid leukemia and was excluded from this study, resulting in a total cohort of 52 patients.

A total of 138 and 173 patients were initially screened for eligibility in the DEC-C phase 2 and 3 trials, respectively. Among them, 213 (80 and 133) were treated with DEC-C and constituted the initial cohort of patients (Fig. 1). Eighty-five patients with MDS and 11 patients CMML with no excess blasts were excluded from this cohort, resulting in a total of 117. After propensity score matching, 45 were excluded for not meeting the matching criteria, leaving 73 in the DEC-C cohort and 51 in the DEC-C-Ven cohort. The baseline characteristics of the initial cohorts are detailed in Supplementary Table 4 and Supplementary Fig. 1. The propensity score matching results are detailed in Supplementary Fig. 2.

The baseline characteristics of the matched cohorts are detailed in Table 1. The median patient age was 71 and 70 years in the DEC-C and the DEC-C-Ven cohorts, respectively ($P = 0.653$). The DEC-C cohort had a higher proportion of patients in the IPSS Intermediate-1 risk group (43% vs 0%, $P < 0.001$) and a lower proportion of the IPSS Intermediate-2 risk group (33% vs 75%, $P < 0.001$) than the DEC-C-Ven cohort. The DEC-C-Ven cohort had a significantly higher median percentage of bone marrow blasts (12%) than did the DEC-C cohort (9%, $P < 0.001$). No other significant differences in clinical or laboratory parameters were found between the cohorts.

Cytogenetic abnormalities and mutations were well-balanced between the 2 matched cohorts (Fig. 2). A normal karyotype was found in 30 (41%) and 16 (31%) patients in the DEC-C and DEC-C-Ven cohorts, respectively ($P = 0.345$). Complex karyotypes were present in 14 (23.5%) and 12 (19%) patients ($P = 0.655$). The most common mutations in the DEC-C and DEC-C-Ven cohorts were *ASXL1* ($n = 30$ [41%] and $n = 20$ [39%], respectively), *RUNX1* ($n = 19$ [26%] and $n = 14$ [28%], respectively), and *TET2* ($n = 22$ [30%] and $n = 11$ [22%], respectively). There were no significant differences in mutation frequencies between the DEC-C and the DEC-C-Ven cohorts.

Treatment response

The ORRs by the IWG 2006 criteria [25] were 64% (47 of 73 patients) and 90% (46 of 51 patients) for the DEC-C and the DEC-C-Ven cohorts, respectively ($P = 0.002$) (Table 2). The CR rates were

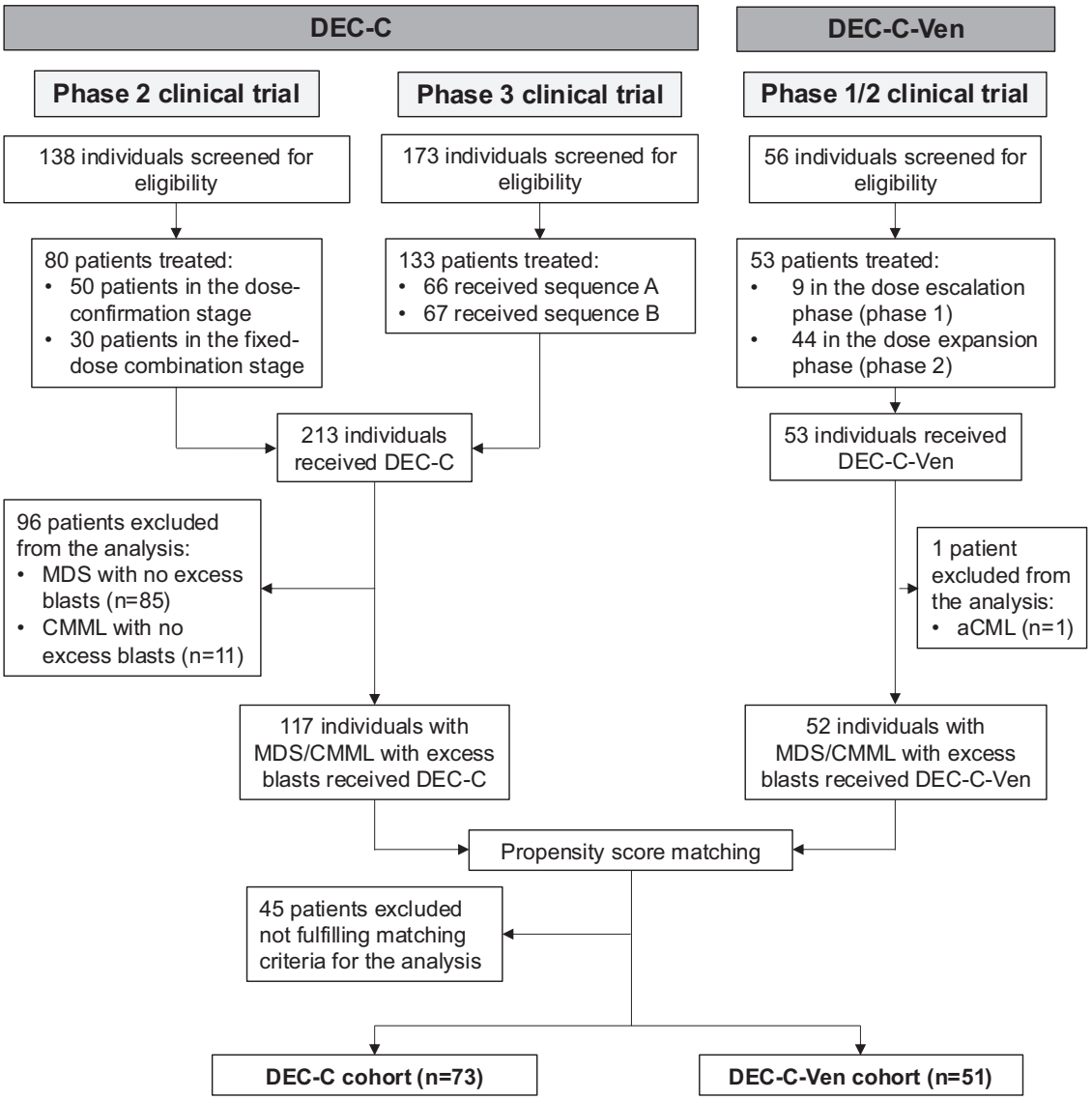

Fig. 1 Patient disposition in 3 clinical trials. aCML atypical chronic myelocytic leukemia.

22% and 43% and the mCR rates were 43% and 47% for the DEC-C and DEC-C-Ven cohorts, respectively. In a subgroup analysis, patients diagnosed with MDS had a higher ORR in the DEC-C-Ven cohort than those in the DEC-C cohort (89% vs 61%, respectively; $P = 0.002$). This difference was not observed in patients diagnosed with CMML (ORR = 100% vs 79% for patients treated in the DEC-C-Ven and DEC-C cohorts, respectively, $P = 0.521$). Patients with a bone marrow blast percentage ≥10 had a higher ORR in the DEC-C-Ven cohort (90%) than in the DEC-C cohort (70%, $P = 0.038$). Patients with a normal karyotype had a higher ORR in the DEC-C-Ven cohort (100%) than those in the DEC-C cohort (70%, $P = 0.018$). All patients with *ASXL1* mutation experienced a response to the DEC-C-Ven combination, compared to 73% for DEC-C ($P = 0.015$). Patients with *BCOR* and *STAG2* mutations had a significantly higher ORR in the DEC-C-Ven cohort than in the DEC-C cohort (Supplementary Fig. 3). We evaluated the response rates using the IWG 2023 criteria for the DEC-C-Ven cohort, detailed in Supplementary Table 5.

The median times to achieve the best response were 2.7 months (range, 1.6–18.8) and 1.2 months (0.7–4.1) in the DEC-C and DEC-C-Ven cohorts, respectively ($P < 0.001$). The median numbers of cycles were 9 (range, 1–29) and 2 (1–14) ($P < 0.001$).

Survival analysis

The median follow-up times were 29 months (95% confidence interval [CI], 28–32) and 16 months (95% CI, 13–21) for the DEC-C and DEC-C-Ven cohorts ($P < 0.001$). The median OS was 19 months (95% CI, 14–NR) for the DEC-C cohort and 24 months (95% CI, 11–NR) for the DEC-C-Ven cohort ($P = 0.89$). The 2-year OS rates were 43% and 58% in the DEC-C and DEC-C-Ven cohorts, respectively. The median EFS was 10 months (95% CI, 8–13) for the DEC-C cohort and 18 months (95% CI, 10–NR) for the DEC-C-Ven cohort ($P = 0.026$). The 2-year EFS rates were 14% and 44% for the DEC-C and DEC-C-Ven cohorts, respectively (Fig. 3). When censored at the time of HSCT, the median OS was 19 months (95% CI, 15–NR) for the DEC-C cohort and 31 months (95% CI, 10–NR) for the DEC-C-Ven cohort ($P = 0.923$). The median EFS, which was also censored at the time of HSCT, was 10 months (95% CI, 8–13) for the DEC-C cohort and 10 months (95% CI, 8–NR) for the DEC-C-Ven cohort ($P = 0.461$) (Supplementary Fig. 4).

A univariate analysis of OS showed no significant differences between the DEC-C and DEC-C-Ven cohort (hazard ratio [HR] = 1.04 [95% CI, 0.61–1.77], $P = 0.889$). An univariate analysis showed a significantly improved EFS in the DEC-C-Ven cohort than in the DEC-C cohort (HR = 0.6 [95% CI, 0.38–0.94], $P = 0.028$). Subgroup

Table 1. Baseline characteristics.

Characteristic	DEC-C cohort ($n = 73$)	DEC-C-Ven cohort ($n = 51$)	*P* value
Age, median (range) [years]	71 (40–90)	71 (27–94)	0.861
Age ≥75, *n* (%)	28 (38)	17 (33)	0.763
Race, *n* (%)			
Asian	0	3 (6)	0.544
Black	1 (1)	0	1
White	71 (97)	48 (94)	0.692
Not reported	1 (1)	0	1
Male sex, *n* (%)	45 (61)	36 (71)	0.402
ECOG performance status			
0	27 (37)	21 (41)	1
1	43 (59)	24 (47)	0.683
2	2 (3)	6 (12)	0.316
Not available	1 (1)	0	—
Hemoglobin, median (range) [g/L]	90 (64–142)	92 (62–144)	0.480
Neutrophil count, median (range) [x 10^9 cells/L]	1 (0.1–43.8)	0.9 (0.1–11.3)	0.357
Platelet count, median (range) [x 10^9 cells/L]	60 (8–570)	73 (19–407)	0.298
Bone marrow blasts, median (range) [%]	9 (5–19)	12 (6–18)	<0.001
ICC category[a], *n* (%)			
MDS with excess blasts	32 (44)	9 (18)	0.013
MDS/AML	27 (37)	36 (71)	0.001
CMML	14 (19)	6 (12)	1
Cytogenetic category, *n* (%)			
Very good	1 (1)	0	
Good	34 (47)	19 (37)	1
Intermediate	16 (22)	15 (29)	1
Poor	8 (11)	5 (10)	1
Very poor	14 (19)	12 (24)	1
IPSS			
Intermediate-1	31 (42)	0	<0.001
Intermediate-2	24 (33)	38 (75)	<0.001
High	18 (25)	13 (25)	1
IPSS-R, *n* (%)			
Very low	0	0	—
Low	2 (3)	0	1
Intermediate	17 (23)	6 (12)	0.832
High	25 (34)	16 (31)	1
Very high	29 (40)	29 (57)	0.447
IPSS-M, *n* (%)			
Very low	0	0	—
Low	3 (4)	0	1
Moderate low	2 (3)	1 (2)	1
Moderate high	5 (7)	3 (6)	1
High	17 (23)	17 (33)	1
Very high	46 (63)	30 (59)	1

[a]International Consensus Classification [32]: MDS with excess blasts defined as 5–9% or 2–9% blasts in the peripheral blood or bone marrow, respectively. MDS/AML defined as 10–19% of blasts in the peripheral blood or bone marrow.

analyses of ORR, OS, and EFS are detailed in Fig. 4 and Supplementary Figs. 3–6. Certain patient subgroups, including those with specific mutations (such as *ASXL1* or *RUNX1*) and those with high-risk disease (IPSS-R high or IPSS-M very high), had significantly longer EFS in the DEC-C-Ven cohort than in the DEC-C cohort.

During follow-up, 18 patients in the DEC-C cohort (25%) and 3 in the DEC-C-Ven cohort (6%) progressed to AML. The 2-year cumulative incidences of AML transformation were 24% for the DEC-C cohort and 9% for the DEC-C-Ven cohort ($P = 0.052$), and the 2-year cumulative incidences of death without AML transformation were 39% and 37% ($P = 0.428$). Twelve patients (16%) in the DEC-C cohort and 24 (47%) in the DEC-C-Ven cohort underwent HSCT ($P < 0.001$). The median times from treatment initiation to HSCT were 6 months (range, 2–13) and 4 months (range, 2–15) respectively ($P = 0.083$). We then calculated the cumulative incidence of death using HSCT as a competing event. The 2-year cumulative incidences of death without HSCT were 48% and 26% for the DEC-C and DEC-C-Ven cohorts, respectively ($P = 0.428$), and the 2-year cumulative incidences of HSCT were 17% and 54% ($P < 0.001$) (Supplementary Fig. 7).

After HSCT, the 1-year OS was 56% and 71% for the DEC-C and DEC-C-Ven cohorts, respectively ($P = 0.485$). The 1-year EFS was 33% and 65% for the DEC-C and DEC-C-Ven cohorts, respectively ($P = 0.062$). The 1-year cumulative incidence of death without relapse was 44% for the DEC-C cohort and 22% for the DEC-C-Ven cohort ($P = 0.259$). The 1-year cumulative incidence of relapse was 22% for the DEC-C and 6% for the DEC-C-Ven cohort ($P = 0.412$) (Supplementary Fig. 8)

Toxicity and count recovery

The 4- and 8-week mortality rates were 0% and 2% in the DEC-C cohort and 1% and 6% in the DEC-C-Ven cohort ($P = 0.407$; 0.302). In both cohorts, the absolute neutrophil count (ANC) and platelet count were recorded at baseline and days 8, 15, and 22 of the first course of treatment (Supplementary Fig. 9). As shown previously in Table 1, there were no differences in median baseline ANC and platelet count between patients in the DEC-C and DEC-C-Ven cohorts. The DEC-C-Ven cohort exhibited a more pronounced decline in the ANC count, with significantly lower median values at day 15 (0.3 vs 0.2 cells/10^9/L for the DEC-C and DEC-C-Ven cohort, $P = 0.013$) and 22 (0.3 vs 0.02 cells/10^9/L for the DEC-C and DEC-C-Ven cohort, $P < 0.001$). The platelet count showed a similar tendency in the DEC-C-Ven cohort, although differences in the counts at the established times were not statistically significant.

The most frequent treatment-emergent adverse events reported either with DEC-C or DEC-C with Ven were selected for analysis (Table 3). Patients in the DEC-C-Ven cohort had a significantly higher incidence of grade 3–4 neutropenia (75% vs 52%, $P = 0.019$) and thrombocytopenia (84% vs 58%, $P = 0.003$). Although cytopenias occurred more frequently in the DEC-C-Ven cohort, the incidence of major infectious complications (sepsis, pneumonia, skin infection, or febrile neutropenia) was not increased compared to the DEC-C cohort.

DISCUSSION

Combinations of HMA with novel drugs are being explored in high-risk MDS [26]. Ven combined with HMA is the standard of care for unfit patients with AML; therefore, this combination could be beneficial for patients with MDS. The phase 3 VERONA study, which is evaluating intravenous azacytidine, with or without the addition of Ven, is expected to provide more definitive conclusions about the effectiveness of Ven [27]. In this study, we evaluated patients who received DEC-C and DEC-C-Ven in three different clinical trials to elucidate the potential benefit of the addition of Ven, including analyses of specific subgroups of interest. To our knowledge, this is the first published head-to-head

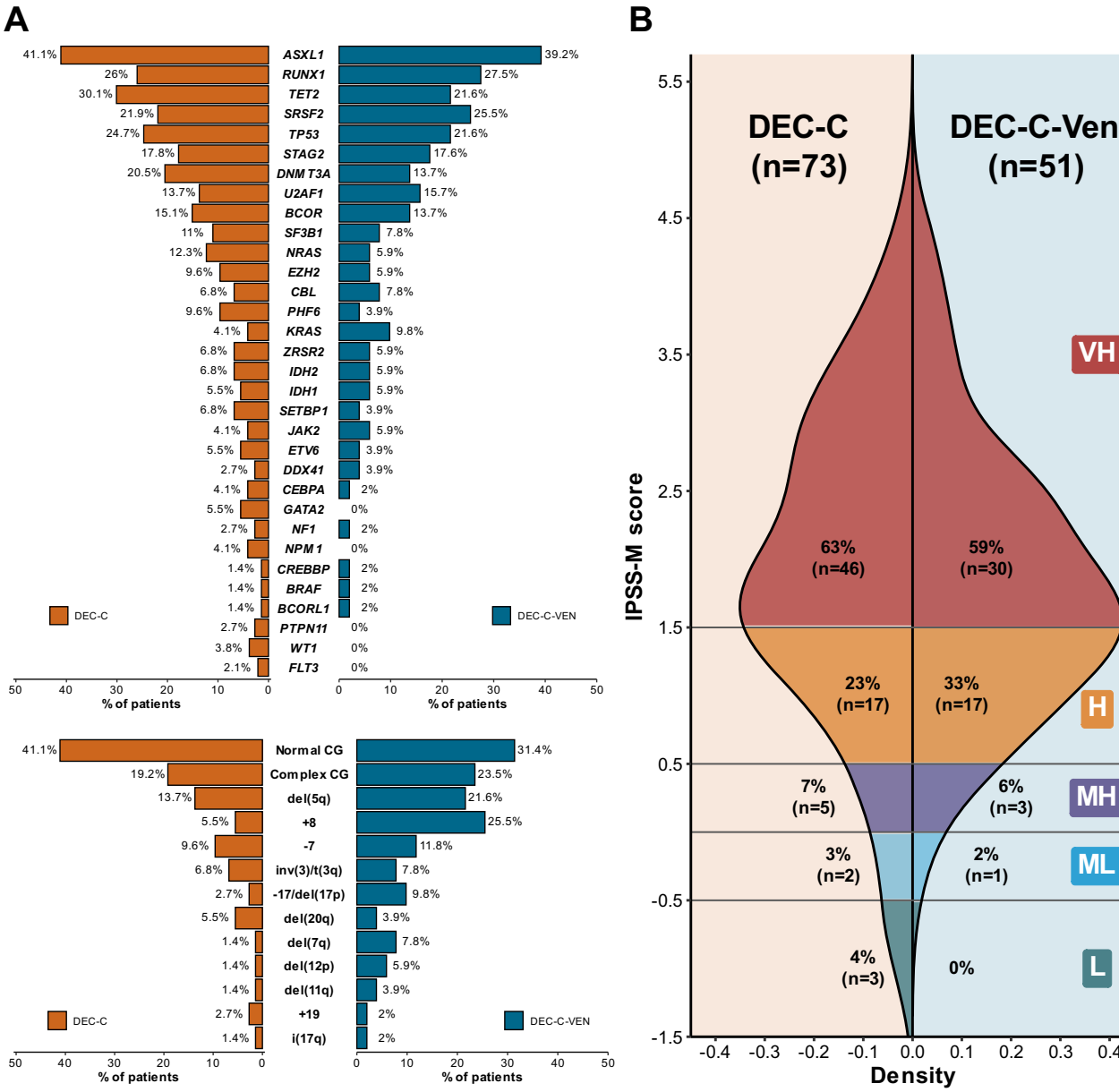

Fig. 2 Genetic characteristics of the matched cohorts. A Frequency of mutations and cytogenetic findings in each matched cohort. **B** Distribution of patients according to the IPSS-M score in each matched cohort. L low, ML moderate low, M moderate high, H high, VH very high.

comparison of patients with higher-risk MDS who were treated prospectively with HMA, with or without Ven.

The propensity score matching process generated two cohorts of patients treated with DEC-C and DEC-C-Ven, with evenly distributed clinical and biological characteristics. As a result, both cohorts were comparable, reducing the bias caused by relevant differences among patients. The ORR was higher in the DEC-C-Ven cohort (90%) than in the DEC-C cohort (64%; $P = 0.002$). Moreover, responses occurred earlier in the DEC-C-Ven cohort, requiring fewer treatment cycles. Given that HSCT is recommended for all eligible patients with higher-risk MDS, higher ORRs occurring earlier in treatment with DEC-C-Ven translated to more patients proceeding to HSCT (47.1% vs 16.4%; $P < 0.001$).

The median OS was longer in the DEC-C-Ven cohort (median OS = 24.0 months) than in the DEC-C cohort (OS = 18.8 months), although this difference was not statistically significant. However, the median EFS was statistically significantly longer in the DEC-C-Ven cohort (EFS = 17.6 months) than in the DEC-C cohort (EFS = 10 months; $P = 0.026$). We hypothesize that Ven provides additional benefits in patients treated with DEC-C. However, due to the shorter follow-up of the DEC-C-Ven cohort in this study (median = 16 months vs 29.4 months in the DEC-C cohort), potential differences in OS could not be demonstrated. Larger cohorts with longer follow-up times will provide crucial information regarding the OS benefit of Ven with HMAs. Additionally, the OS and EFS analyses, with censoring at the time of HSCT, showed a trend toward longer OS in the DEC-C-Ven cohort, although non statistically significant. This finding suggests that the benefits of adding Ven are related to a higher proportion of patients proceeding to HSCT, the only curative treatment for high-risk MDS.

A subgroup analysis showed that specific patient cohorts may be more likely to benefit from the addition of Ven. DEC-C-Ven-treated patients had a longer EFS duration than did DEC-C-treated patients in several subgroups. For example, patients with *ASXL1* mutation had a significant EFS benefit with the addition of Ven.

Table 2. Response analysis.

Response characteristic	DEC-C cohort ($n = 73$)	DEC-C-Ven cohort ($n = 51$)	*P* value
Response rate, *n* (%)			
ORR	47 (64)	46 (90)	0.002
CR	16 (22)	22 (43)	
mCR	31 (42)	24 (47)	
ORR by ICC [32] category, *n* (%)			
MDS with excess blasts	24 (60)	10 (91)	0.075
MDS/AML	23 (70)	36 (90)	0.038
CMML	11 (79)	6 (100)	0.521
Median time to best response, months (range)	2.7 (1.6–18.8)	1.2 (0.7–4.1)	<0.001
Number of cycles received, *n* (range)	9 (1–29)	2 (1–14)	<0.001
Number of patients proceeding to HSCT, *n* (%)	12 (16)	24 (47)	<0.001
Median time from treatment to HSCT, (range)	5.5 (2.2–12.7)	3.7 (2.3–15.3)	0.083

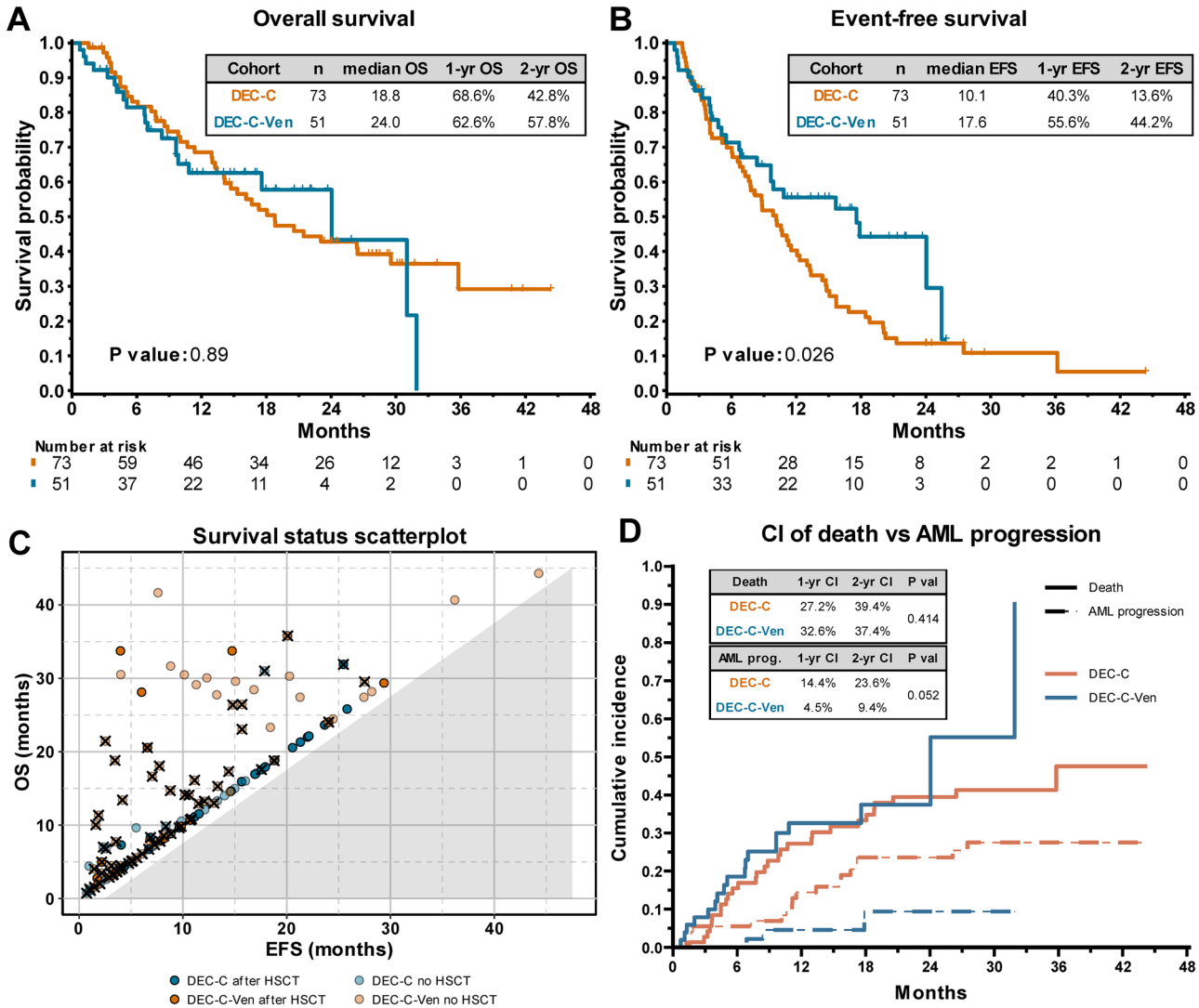

Fig. 3 Survival analysis. A OS of patients in the DEC-C and DEC-C-Ven cohorts. **B** EFS of patients in the DEC-C and DEC-C-Ven cohorts. **C** Survival scatterplot. Each point represents 1 patient, localized according to their OS and EFS durations. Crossed points represent deceased patients. **D** 95% CI of death vs AML progression.

This was reported in previous studies and indicates that *ASXL1* mutations increase Ven sensitivity through BCL-2 dependence in leukemic cells [17, 28, 29]. Moreover, patients with high-risk characteristics (such as high IPSS-R or very high IPSS-M) in the DEC-C-Ven cohort also exhibited longer EFS durations than did those in the DEC-C cohort. These patients benefit the most from early HSCT [30]. Likely, the high proportion of responses during the initial cycles of DEC-C-Ven enabled eligible patients to

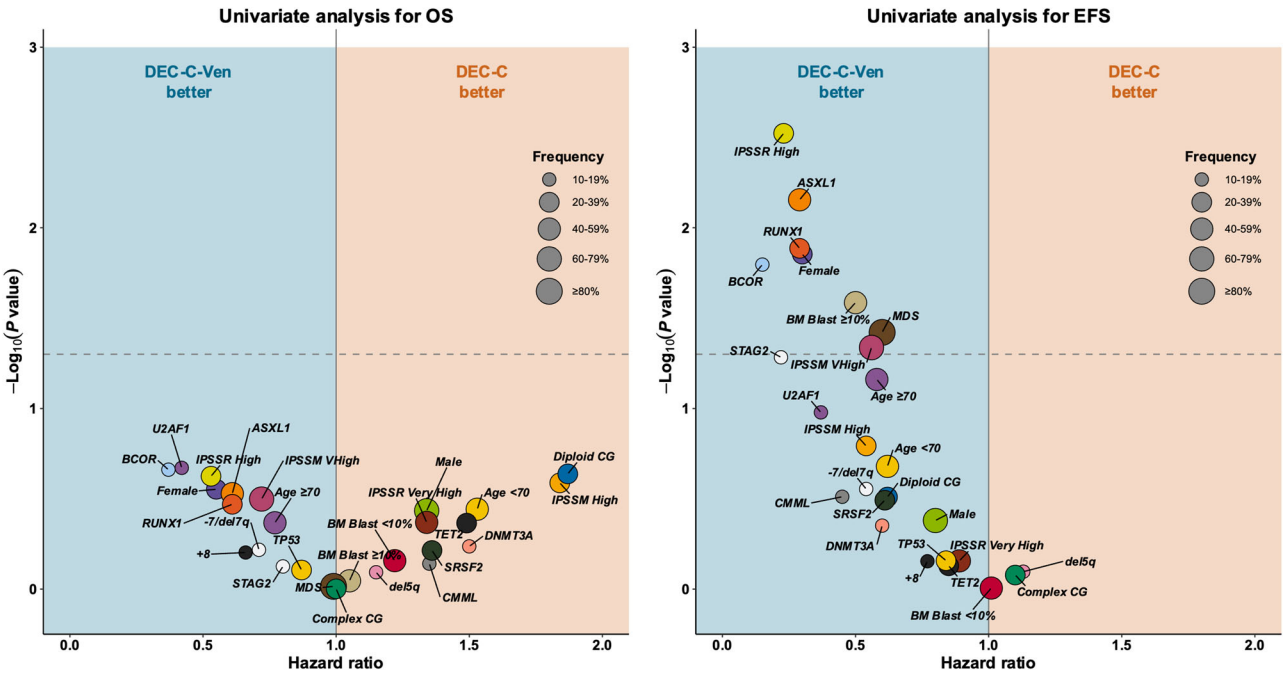

Fig. 4 Volcano plot representing the hazard ratio for OS and EFS, along with the *P* value of each univariate analysis (represented as the $-\mathbf{Log_{10}}$ of the *P* value). Dashed line represents $P = 0.05$. Point size is scaled to the frequency of each characteristic.

Table 3. Adverse events.

	DEC-C cohort ($n = 73$)				DEC-C-Ven cohort ($n = 51$)				*P* val G3–5
Adverse event	**3**	**4**	**5**	**3–5**	**3**	**4**	**5**	**3–5**	
Thrombocytopenia	9 (12)	33 (45)	0	42 (58)	9 (18)	34 (66)	0	43 (84)	0.003
Neutropenia	1 (1)	37 (51)	0	38 (52)	0	38 (75)	0	38 (75)	0.019
Anemia	34 (47)	1 (1)	0	35 (48)	18 (35)	1 (2)	0	19 (37)	0.318
Febrile neutropenia	22 (30)	4 (5)	0	26 (36)	11 (22)	0	0	11 (22)	0.138
Pneumonia	10 (14)	3 (4)	3 (4)	16 (22)	4 (8)	0	2 (4)	6 (12)	0.223
Sepsis	3 (4)	4 (5)	4 (5)	11 (15)	4 (8)	1 (2)	4 (8)	9 (18)	0.892
Skin infection	6 (8)	0	0	6 (8)	5 (10)	0	0	5 (10)	0.999
Dyspnea	6 (8)	0	0	6 (8)	1 (2)	1 (2)	0	2 (4)	0.468
Fatigue	2 (3)	0	0	2 (3)	0	0	0	0	0.511

undergo HSCT, thereby increasing their probability of long-term survival. Our observations align with a recent publication by Tremblay et al., in which a propensity score matching analysis was performed on a cohort of patients with CMML treated with HMA, with or without Ven [31]. Similar to our findings, the ORR and HSCT rates were higher in the Ven cohort, showing an EFS improvement but no significant differences in OS.

Toxicity analyses showed that the addition of Ven resulted in more profound significant, with a higher incidence of grade 3–4 neutropenia and thrombocytopenia. This is consistent with previous reports, in which the addition of Ven resulted in higher incidence of cytopenias, compared to single-agent HMA [15]. Nonetheless, this was not translated into more major infections in the DEC-C-Ven group. Mandatory antibiotic prophylaxis in the DEC-C-Ven cohort likely contributes to these findings, potentially preventing numerous high-grade infections.

A major limitation of this study is the post-hoc nature of the analyses performed, together with the limited number of patients analyzed. Moreover, the experimental cohort (DEC-C-Ven) had a significantly shorter follow-up time than did the DEC-C cohort, creating challenges in comparing long-term outcomes, such as OS. Although the characteristics of the clinical trials included in this study were very similar, there were some notable differences. Importantly, the DEC-C-Ven clinical trial was a single-center clinical trial, whereas the DEC-C cohort was generated from two multicenter clinical trials. This difference may have resulted in significant differences in clinical management or transplant eligibility criteria.

In conclusion, this is the first study that determined the effectiveness of DEC-C, with or without the addition of Ven, in two matched cohorts of MDS patients from three clinical trials. DEC-C-Ven led to higher response rates and HSCT rates and a significantly longer EFS duration. We found no evidence of a longer OS duration, although the follow-up time was too short to reach a definitive conclusion. Specific subgroups of patients with MDS (high-risk, according to IPSS-R or ISPSS-M, or those with *ASXL1* mutations) experienced survival benefits with this combination. These findings should be validated in larger randomized clinical trials of Ven in patients with MDS in combination with HMA (e.g., the ongoing VERONA phase 3 randomized clinical trial, NCT04401748).

Explanation of novelty

This is the first published head-to-head comparison of patients with higher-risk MDS who were treated prospectively with HMA,

with or without Ven. Patients treated with HMA and Ven had a superior response rate, and responses occurred faster, translating into more patients proceeding to hematopoietic stem cell transplantation. EFS was improved in patients receiving DEC-C-Ven, and there was a trend of improved OS although non-significant.

DATA AVAILABILITY

The data used for this study is not publicly available in order to protect patient confidentiality. Reasonable requests for de-identified data should be directed to the corresponding author.

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ABat: Study conception and design, data curation, analysis and interpretation, manuscript writing, review, and approval of the final version of the manuscript. KS: study conception and design, analysis interpretation, review, and approval of the final version of the manuscript. SU: data curation, review, and approval of the final version of the manuscript. GMB: study conception and design, data interpretation, review, and approval of the final version of the manuscript. ABaz**:** data analysis and interpretation, manuscript writing, review, and approval of the final version of the manuscript. KC: data interpretation, patient enrollment, data contribution, review, and approval of the final version of the manuscript. DH: data interpretation, patient enrollment, data contribution, review, and approval of the final version of the manuscript. IMB: data interpretation, data contribution, review, and approval of the final version of the manuscript. MS: data interpretation, patient enrollment, data contribution, review, and approval of the final version of the manuscript. GI: data contribution, review, and approval of the final version of the manuscript. NS: patient enrollment, data contribution, review, and approval of the final version of the

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