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Characteristics and clinical outcomes of patients with myeloid malignancies and *DDX41* variants

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Abstract

DDX41 is the most frequently mutated gene in myeloid neoplasms associated with germline predisposition including myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). We analyzed 3795 patients with myeloid neoplasms and identified 151 (4%) with DDX41 variants and a diagnosis of AML ($n = 96$), MDS ($n = 52$), and chronic myelomonocytic leukemia ($n = 3$). The most frequent *DDX41* variants were the somatic variant p.R525H, followed by the germline variants p.M1I and p.D140fs. Most neoplasms had a normal karyotype (59%) and the most frequent co-mutations were *TP53* (16%) and *ASXL1* (15%). 30% of patients had no concomitant mutations besides *DDX41* mutation. Patients with myeloid malignancies and *DDX41* variants responded well to therapy, with an overall response rate for patients with treatment naïve AML and MDS of 87% and 84%, respectively. The median overall survival (mOS) of patients with treatment-naïve AML or MDS was 49 and 71 months, respectively. Patients with AML treated with low-intensity regimens including venetoclax had an improved survival (2-year OS 91% vs. 60%, $p = .02$) and lower cumulative incidence of relapse compared to those treated without venetoclax (10% vs. 56%, $p = .03$). In the 33% of patients receiving hematopoietic stem cell transplantation, the 2-year OS was 80% and 85% for AML and MDS, respectively.

1 | INTRODUCTION

The identification of germline mutations predisposing to an increased risk of myeloid neoplasms is a growing field of interest.[1] A familial or personal history of cancer or pre-existing cytopenia(s), together with specific clinical findings and an early age of onset of a myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) are potentially suggestive of an inherited mutation in a gene predisposing to myeloid malignancies,[2] although these risk factors are not always apparent.[3] As a result of this increasing knowledge, the revised 4th edition of the World Health Organization (WHO) classification of hematopoietic and lymphoid tissues published in 2016 recognized myeloid neoplasms with germline predisposition as distinct disease entities.[4] Moreover, the latest WHO classification (2022) as well as the International Consensus Classification (ICC) have maintained this distinction with the additional description of new genes implicated in germline predisposition to myeloid neoplasms.[5,6] It is crucial to identify patients with germline mutations since this finding may directly impact treatment decisions, transplant donor options, and raises the potential for genetic counseling in potentially affected family members.

DEAD-box RNA Helicase 41 (*DDX41*) is the most frequently mutated gene in myeloid malignancies with germline predisposition.[7,8] *DDX41* is located on chromosome 5q35.3, with an approximate length of 5.3Kb and 17 exons.[9] The resulting DDX41 protein is widely expressed and is involved in multiple and diverse cellular functions. First, DDX41 has a role in innate immunity, acting as a pattern recognition receptor which can detect specific viral or bacterial nucleotide sequences in the cytoplasm and initiate an inflammatory pathway involving the activation of TANK-binding kinase 1 (TBK1) and the upregulation of type

I interferon.[10,11] Moreover, in the nucleus, DDX41 interacts with R-loops, which consist of three-stranded structures of RNA–DNA hybrids and a displaced strand of DNA. The downregulation of DDX41 in both zebrafish and human cells leads to the accumulation of R-loops and results in increased DNA breaks.[12,13] Finally, DDX41 has an important role in mRNA splicing and ribosome biogenesis. DDX41 interacts with many spliceosome proteins, and DDX41-knockdown cellular models display abnormalities in alternative splicing which entails altered ratios of different protein isoforms.[14] Finally, DDX41 is involved in processing of small nucleolar RNAs (snoRNA), which are necessary for ribosome generation.[15] Given these multiple functions, *DDX41* is crucial in hematopoietic stem cells, although the mechanism by which its mutation predisposes to neoplasia is incompletely understood.[16]

The prognostic impact of *DDX41* mutations in myeloid malignancies remains poorly defined. In a large study of patients with AML or MDS and *DDX41* mutations, Polprasert et al. reported a worse survival in this specific group.[9] However, other retrospective studies have shown either no impact on survival, or improved outcomes in patients with myeloid malignancies and *DDX41* mutations.[7,17,18] A recent study by Duployez et al. analyzed the outcomes of a large cohort of intensively-treated patients with *DDX41* germline mutations and suggested a better outcome in *DDX41*-mutated cases compared to wild-type cases.[19] Moreover, there is a unique concern regarding patients with *DDX41* mutations that undergo hematopoietic stem cell transplantation (HSCT), as recent publications suggest these patients may have an impaired survival due to an increased risk of severe acute graft versus host disease (GVHD).[20,21] In this study, we analyzed one of the largest cohorts of patients with *DDX41* variants, with special emphasis on response to therapy and clinical outcomes as well as the impact of HSCT.

2 | METHODS

2.1 | Study design, patients, and response assessment

We performed a single-center retrospective study at the University of Texas MD Anderson Cancer Center spanning 2010–2022 and included all patients diagnosed with myeloid neoplasm who had available next-generation sequencing (NGS) results. Patients were diagnosed according to the 2016 World Health Organization criteria.[4] Responses were assessed using the 2006 International Working Group (IWG) criteria for patients with MDS or CMML and by the 2017 European LeukemiaNet (ELN) criteria for patients with AML.[22,23] The overall response rate (ORR) for MDS and CMML included patients who achieved complete remission (CR), partial remission (PR), marrow CR (mCR) and hematological improvement. In AML, the ORR included patients with CR, CR with incomplete blood count recovery (CRi), PR or morphological leukemia-free state (MLFS).

2.2 | Genetic studies

DDX41 mutation analysis was performed using DNA extracted from fresh bone marrow samples. Targeted NGS testing was performed using an 81-gene panel in a Clinical Laboratory Improvement Amendments (CLIA) certified molecular diagnostics laboratory, as previously published.[24] The list of genes and specific coverage included in the panel

is described in the Supplementary material (Table S1). For patients undergoing germline mutation testing, *DDX41* mutation analysis was performed using DNA isolated from cultured skin fibroblasts obtained from a skin punch biopsy after counseling by a board-certified genetic counselor. In general, *DDX41* variants with a variant allele frequency (VAF) <40% were presumed to be somatic variants whereas those with VAF ≥40% or with confirmation in skin fibroblasts were presumed to be germline. *DDX41* germline variants were further classified as pathogenic/likely pathogenic (P/LP) according to the ACMG/AMP guidelines as described by Li P et al.[18] Variants not fulfilling criteria for P/LP were classified as variants of unknown significance (VUS) or benign/likely benign (B/LB) as appropriate.

2.3 | Statistical methods

Baseline patient characteristics were analyzed using descriptive statistics. Student's *t*-test and the Mann–Whitney *U*-test were used for comparison of continuous variables with normal and non-normal distributions, respectively. For categorical variables, the χ^2 and Fisher's exact test were used. The median follow-up time was calculated with the Kaplan–Meier estimate of potential follow-up. Overall survival (OS) was calculated from diagnosis to death. Survival distributions were estimated using the Kaplan–Meier method and were compared with the log-rank test. In patients receiving treatment, the cumulative incidence of relapse was calculated using relapse as the primary event and death without relapse as a competing event. Cumulative incidence comparison was performed using Gray's test.[25] A Cox proportional hazards regression was used for the univariate and multivariate analyses. All statistical analyses were performed using R statistics version 4.2.2 (R core Team, R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Baseline patient characteristics and *DDX41* mutations

A total of 3795 patients diagnosed with a myeloid malignancy and with available NGS testing were identified, with 151 (4%) patients harboring at least one *DDX41* variant. Specifically, the incidence of *DDX41* mutations was 96 out of 2204 (4.4%) patients with AML, 52 out of 1302 patients (4%) with MDS, and 3 out of 289 patients (1%) with CMML. The baseline characteristics are summarized in Table 1. Overall, most patients were males (n = 114, 75.5%) with a median age of 69 years (21–90). Most self-identified as non-Hispanic white (n = 129, 85.4%). Neoplasms preceding the myeloid malignancy diagnosis were frequent (n = 43, 28.5%); most commonly prostate cancer (n = 11, 7.3%), lymphoproliferative diseases (n = 11, 7.3%), gammopathies (n = 5, 3.3%) and bladder cancer (n = 5, 3.3%). A family history of cancer in 1st and 2nd degree relatives was frequent (n = 91, 60.2%). Thirty-three patients (21.9%) had a reported family history of MDS or leukemia. In patients with AML, the blast count was relatively low (median of 28%, range 8–91) and in patients with MDS the median was 10% (1–18), with 38 patients (73% of all patients with MDS) presenting with excess blasts. Regarding disease status, 112 patients (74.2%) were treatment-naïve at presentation, whereas 39 patients (25.8%) had received a previous treatment for the myeloid neoplasm (relapsed/refractory, R/R).

Among the 151 analyzed patients, 27 patients (17.8%) had one *DDX41* germline P/LP variant, 19 patients (12.5%) had only *DDX41* somatic P/LP variants, and 79 patients (52%) had a combination of a P/LP germline variant plus ≥1 somatic variant. Twenty-six patients (17.8%) had a germline *DDX41* variant identified which was classified as a VUS. Overall, there were 36 different P/LP *DDX41* germline variants, 35 different *DDX41* somatic variants and 19 different *DDX41* VUS. Forty-five out of the 106 patients (42.4%) with a presumed *DDX41* germline P/LP variant had a confirmed diagnosis in cultured skin fibroblasts. Eight patients (5.3%) presented with two somatic *DDX41* variants, four of them in combination with a germline *DDX41* variant. The different *DDX41* variants identified are detailed in Figure 1. Most somatic *DDX41* variants were missense (n = 101, 95.3%) and the most frequent were p.R525H (n = 63, 58.9%), p.G530D (n = 4, 3.7%, both located in the helicase domain), p.P321L (n = 4, 3.7%) and p.G228C (n = 3, 2.8%). Most germline P/LP *DDX41* variants corresponded to null variants (n = 83, 73.5%), including nonsense/frameshift variants (n = 48, 45.3%), first codon involvement (n = 25, 23.6%) or splicing site involvement (n = 8, 7.5%). The most frequent *DDX41* germline variants were p.M1I (n = 25, 23.6%), p.D140fs (n = 24, 22.6%), p.R369G (n = 5, 4.7%), p.Q41* (n = 5, 4.7%) and p.M316fs (n = 4, 3.8%). Most patients with p.M1I and p.D140fs germline variants had a concurrent *DDX41* somatic variant (n = 18 [69.2%] and n = 20 [83.3%], respectively), p.R525H being the most common. The p.R525H somatic variant was present with a germline P/LP *DDX41* variant in 58 patients (92%). The median *DDX41* germline and somatic variants VAFs were 49% (3–87) and 5% (1–29%), respectively (Supplementary material Figure S1). Two patients had a germline P/LP DDX41 variant with a low VAF, one due to a disease relapse with sustained donor chimerism and the other was considered a technical error. A comprehensive description of the *DDX41* variants is detailed in the Supplementary material (Table S2).

3.2 | Cytogenetic and molecular findings

Most patients with *DDX41* variants had a myeloid neoplasm with normal karyotype (n = 88, 58.2%). In patients with whose disease had cytogenetic abnormalities, there was no recurrent cytogenetic abnormalities (Table 1). Two patients with *DDX41* germline VUS presented with AML with a t(8;21)(q22;q22)/ *RUNX1::RUNX1T1* and two patients presented with acute promyelocytic leukemia (APL) with t(15;17)(q24;q21)/ *PML::RARA* (one with a *DDX41* germline VUS and the other with a somatic p.K134R *DDX41* variant).

Patients with *DDX41* variants frequently had concomitant mutations (n = 107, 70.9%, Figure 2). The median number of concomitant mutated genes per patient was 1 (0–12), being 1 (0–8) and 1 (0–5) for AML and MDS, respectively. The most common co-mutations were *TP53* (n = 25, 16.6%), *ASXL1* (n = 22, 14.6%), *SRSF2* (n = 17, 11.3%) and *DNMT3A* (n = 16, 10.6%). There was no significant difference in the incidence of specific mutations between patients with germline versus somatic *DDX41* variants. Focusing on patients with somatic-only *DDX41* P/LP variants, there was a higher incidence of *CBL* mutations (n = 3 vs. 1, 16% vs. 1%, p = .011) compared to those with germline *DDX41* variants. The median number of mutations per patient was higher in the *DDX41* VUS cohort (median of 2, 0–12) than in the P/LP *DDX41* variants cohort (median of 1, 0–8, p = .02). In the cohort of patients with P/LP *DDX41* variants there were fewer patients with *FLT3*-ITD (n = 1 [1%] vs. n = 3

[12%] *n, p* = .012), for patients with P/LP *DDX41* variants and *DDX41* VUS, respectively. *SF3B1* mutations were also less frequent in patients with P/LP *DDX41* variants (*n* = 2.2%) compared to patients with *DDX41* VUS (*n* = 4, 15%, *p* = .008).

Almost one third of the patients with *DDX41* variants did not have other concomitant mutations (*n* = 45, 29.8%). Regarding *DDX41* status, 25 patients (56%) had a combination of a germline P/LP *DDX41* variant with a somatic *DDX41* variant, 10 patients (22%) had only a germline P/LP *DDX41* variant, 6 patients (13%) had only a somatic *DDX41* variant, and 4 patients (9%) had a *DDX41* VUS. Most of these patients had a normal karyotype (*n* = 29, 64%), and other common abnormalities were chromosome Y deletion (*n* = 6, 13.3%) and chromosome 8 trisomy (*n* = 3, 6.7%). Information regarding characteristics of these patients is detailed in Supplementary Material (Table S3).

3.3 | Treatment responses and survival in patients with *DDX41* variants

Only patients with P/LP *DDX41* variants were included in the response and survival analyses (*n* = 124, 82.1%). Of these, 111 patients (89.5%) including 73 patients with AML and 38 with MDS received treatment for the myeloid neoplasm. Two patients diagnosed with CMML and APL, respectively, were excluded for this analysis. The different types of treatment as well as the disease status are detailed in Table 2 and in the Supplementary Material (Table S4). Among patients with AML treated in a frontline setting, the ORR was 89% (16/18 patients) for patients treated with intensive chemotherapy (+/− venetoclax) and 86% (31/36 patients) for patients treated with low-intensity therapy (+/− venetoclax). In patients with MDS treated in the frontline setting with low-intensity therapy, the ORR was 84%. As expected, responses in patients in a R/R status were lower and more heterogeneous.

The median follow-up for patients with AML and MDS was 26 (95% CI 12–44) and 52 (95% CI 21–77) months, respectively. The median OS for patients with previously untreated AML and MDS was 49 (27-NA) and 71 (63-NA) months, respectively. In patients with R/R AML and R/R MDS, the median OS was 11 (7-NA) and 20 (20-NA) months, respectively. In patients with treatment-naïve AML receiving intensive chemotherapy, the median OS was 27 months (20-NA), without significant differences related to venetoclax use (23 months vs. NA for patients treated without and with venetoclax, respectively, *p* = .3). However, in treatment-naïve AML patients receiving low-intensity therapy, the 2-year OS was 60% (±16) versus 91% (±6) for patients treated without or with venetoclax, respectively (*p* = .02). In line with the above, treatment-naïve patients with MDS treated with low-intensity therapy plus venetoclax showed an improved 2-year OS (100%), compared with those without venetoclax (86% [±7.4], although this was not statistically significant (*p* = .34) (Figure 3). Univariate and multivariate analysis were performed on patients with AML and MDS treated with low intensity regimens (Supplementary Material Table S5). The multivariate analysis for OS confirmed the independent prognostic value of venetoclax (HR 0.06 [0.01–0.53], *p* = .01) and age (HR 1.29 [1.06–1.58], *p* = .01) in patients with AML treated receiving low-intensity therapy. There was no significant impact of co-mutations in patients with *DDX41* variants, including *TP53*, although the number of patients was small.

For patients achieving a response, we analyzed the cumulative incidence of death and relapse as competing events. In patients with previously untreated AML, the 2-year

cumulative incidence of death and relapse were 10% (±4.8) and 34.6% (±9), respectively. In patients with previously untreated MDS, the 2-year cumulative incidence of death and progression/AML transformation were 8.3% (±5.8) and 37.7% (±10.3), respectively. Patients treated with AML receiving low-intensity therapy with venetoclax had a lower incidence of relapse (9.5%) compared to those treated with low-intensity therapy without venetoclax (55.6%, $p = .03$), without observed differences in mortality (5% vs. 22.2%, respectively, $p = .2$). Additional survival analyses are detailed in the Supplementary Material (Figures S2.1 to S2.3).

3.4 | Outcomes after HSCT

A total of 42 patients with P/LP *DDX41* variants with AML ($n = 27$, 34.2%) and MDS ($n = 15$, 34.1%) proceeded to HSCT. Baseline characteristics at HSCT are detailed in Supplementary Material Table S6. Overall, the median age at HSCT was 63 years old (41–75), 50% received a myeloablative conditioning, 62% were transplanted using a matched unrelated donor graft and 71% used post-transplant cyclophosphamide (PTCy) for GVHD prophylaxis. The median OS after HSCT for patients with AML and MDS was 57.2 (43.7-NA) and not achieved (NA-NA), respectively (Supplementary material Figure S3). The 2-year cumulative incidence of relapse and death without relapse for patients with AML was 15.6% (±8.7) and 8% (±5.5), respectively. For patients with MDS, there were only two deaths within the first year post-HSCT (CI of death at 2 years 15.2% ± 10.4) and one relapse after 3 years post-HSCT.

4 | DISCUSSION

This study provides a comprehensive analysis of patients with myeloid neoplasms with *DDX41* variants. The incidence of these variants was overall 4%, consistent with previous reports describing an incidence of 3%–5%.[19,26] We confirmed the male predominance of these myeloid neoplasms and the median age of presentation of around 70 years. We reported 28.5% of patients with a previous oncologic diagnosis (mostly prostate cancer or lymphoproliferative disorders) and 60% of patients with a family history of cancer (including leukemia in 21.9% of patients). It remains unclear if *DDX41* is associated with an increased incidence of solid neoplasms, and there is a need to better assess this issue. In our cohort, the incidence of solid neoplasms appears to be high, although we lack an age-matched control cohort as a true comparator.

In AML patients with *DDX41* mutations, most patients had no elevation in WBC count and the blast count was relatively low in AML, consistent with a more “hypoproliferative” presentation. This finding may be explained by the small number of patients with signaling mutations (such as *FLT3*), which often present with higher WBC counts. In addition, most AML patients were categorized as intermediate or high risk, mostly because of the absence of favorable risk abnormalities and/or the presence of high-risk mutations (such as *TP53* or *ASXL1*). Similarly, about 75% of patients with MDS had excess blasts, leading to higher risk.

In our analysis of the *DDX41* variants, we first segregated those with potential pathogenic impact (P/LP) from those of unknown significance (VUS) and excluded *DDX41* VUS from

outcome and survival analyses. This is important because VUS likely have no negative impact on *DDX41* function. This was recently well described by Li et al, in which patients with *DDX41* VUS behaved similarly to patients who had wild type *DDX41* alleles.[18] The most frequent *DDX41* P/LP variants in our cohort were p.R525H, p.M1I and p.D140fs, as expected from a cohort with a high proportion of Caucasian patients of North American ancestry. These mutations usually appeared in pairs (germline with somatic), although a single mutation (either somatic or germline) could also be identified. Overall, this study provides more data about known variants together with poorly or non-previously reported variants, which is crucial to better define the mutational landscape of *DDX41*.

It is furthermore important to characterize the cytogenetic and mutational landscape of patients with *DDX41* variants, as this can directly impact disease behavior and outcomes. There was a high proportion of patients with normal karyotype, and up to 30% of patients did not have any co-mutations. This could be the preliminary evidence that mono or bi-allelic *DDX41* gene truncations per se could initiate and maintain a leukemic clone, since no other genetic abnormality is detected. However, to date the specific steps and biology of this leukemogenic process remains unclear. This is further supported by the finding that patients with P/LP *DDX41* variants had lower numbers of mutations, including signaling pathway mutations, than those with *DDX41* VUS. Whole genome sequencing studies and epigenetic analyses are eagerly awaited to address this specific issue. The most frequent co-mutation in our cohort including both newly diagnosed and relapsed patients was *TP53* (16.6%), similarly to previous reports describing a frequency of 3%–30%.[27,28] When specifically evaluating previously untreated patients, we could not find any co-occurring mutation that independently impacted outcomes. This was also reported recently by Makishima et al,[29] although larger datasets are needed to better define if any specific genetic subtype could impact the outcomes of patients with *DDX41* variants.

One of the key strengths of this study was the ability to analyze different types of therapy in this genetically defined subset of patients, as detailed clinical data regarding treatment outcomes in patients with *DDX41* mutations has not been widely explored. Overall, we identified that response rates in previously untreated patients with MDS and AML were high, suggesting that malignancies with *DDX41* variants are sensitive to current therapies. When we analyzed specific treatments, ineligible patients for intensive chemotherapy that received low-intensity therapy plus venetoclax had a better OS and a lower CI of relapse. The addition of venetoclax has been shown to improve survival in patients treated with hypomethylating agents in AML and is also being evaluated in HR-MDS.[30,31] However, this study is the first to specifically identify the favorable impact of venetoclax in patients with *DDX41* variants, with a high ORR and a 2-year OS of 91% and 100%, for patients with AML and MDS, respectively.

HSCT outcomes in patients with *DDX41* is a key recent issue due to the high reported incidence of severe GVHD, with one study reporting grade 3–4 acute GVHD in 38% of transplanted patients with *DDX41* mutations.[20,21] Our study did not specifically assess the rates and severity of GVHD. However, the outcomes reported after HSCT in our cohort appear favorable. In our cohort, 71% of patients received GVHD prophylaxis including PTCy, which has been associated with a lower incidence of severe forms of acute GVHD.[21]

This finding could explain our favorable outcomes after HSCT, although studies focused specifically in HSCT and GVHD are warranted in patients with DDX41 mutations.

In conclusion, in this large cohort of patients with *DDX41* germline and somatic variants, we detail genetic characteristics and clinical outcomes and highlight the encouraging and improved outcomes of patients receiving venetoclax-based therapies and the safety of HSCT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

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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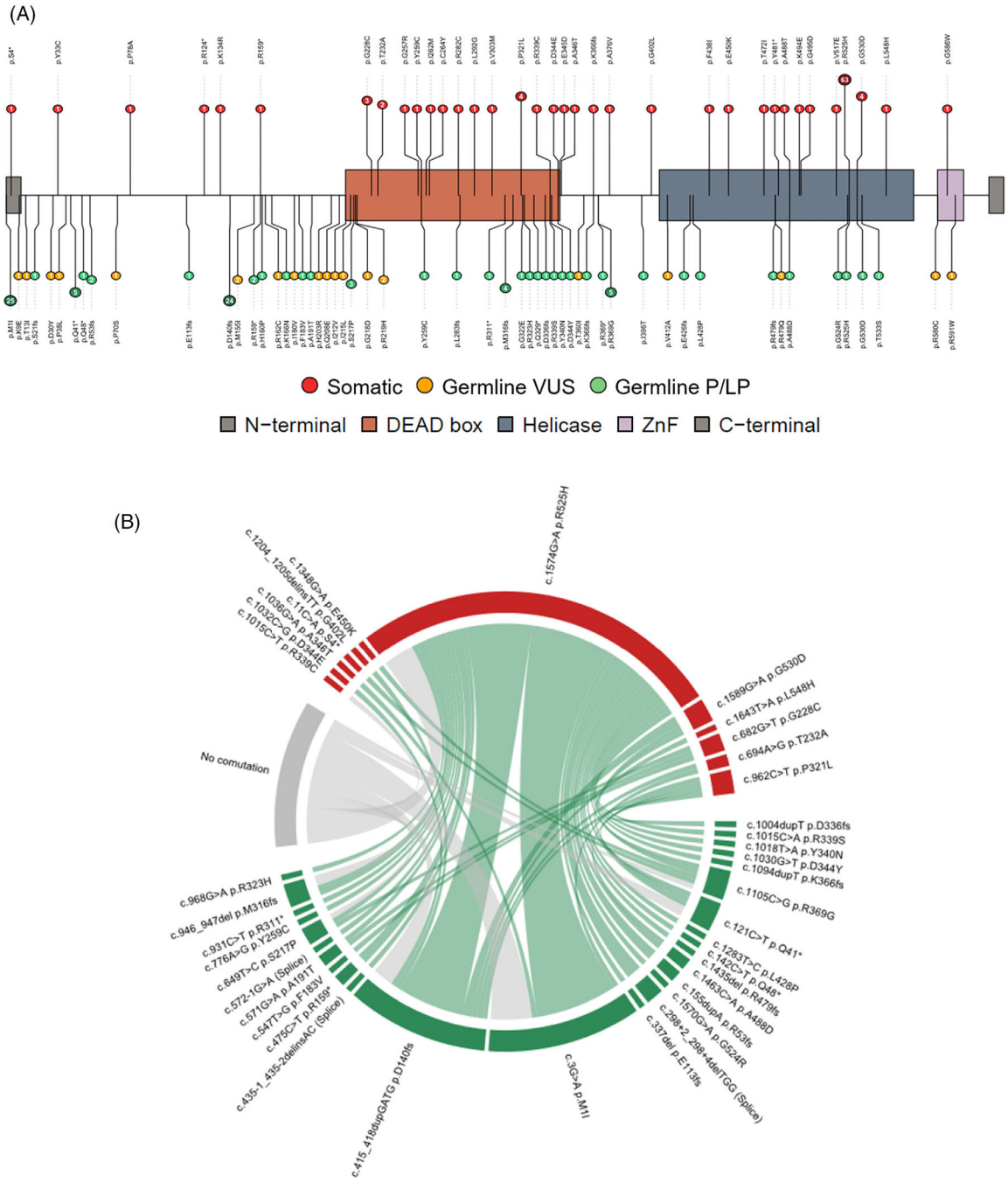

FIGURE 1.

(A) Lollipop plot of the *DDX41* variants identified. Splicing mutations are not represented.

(B) Relationship between germline (dark green) and somatic (red) *DDX41* variants.

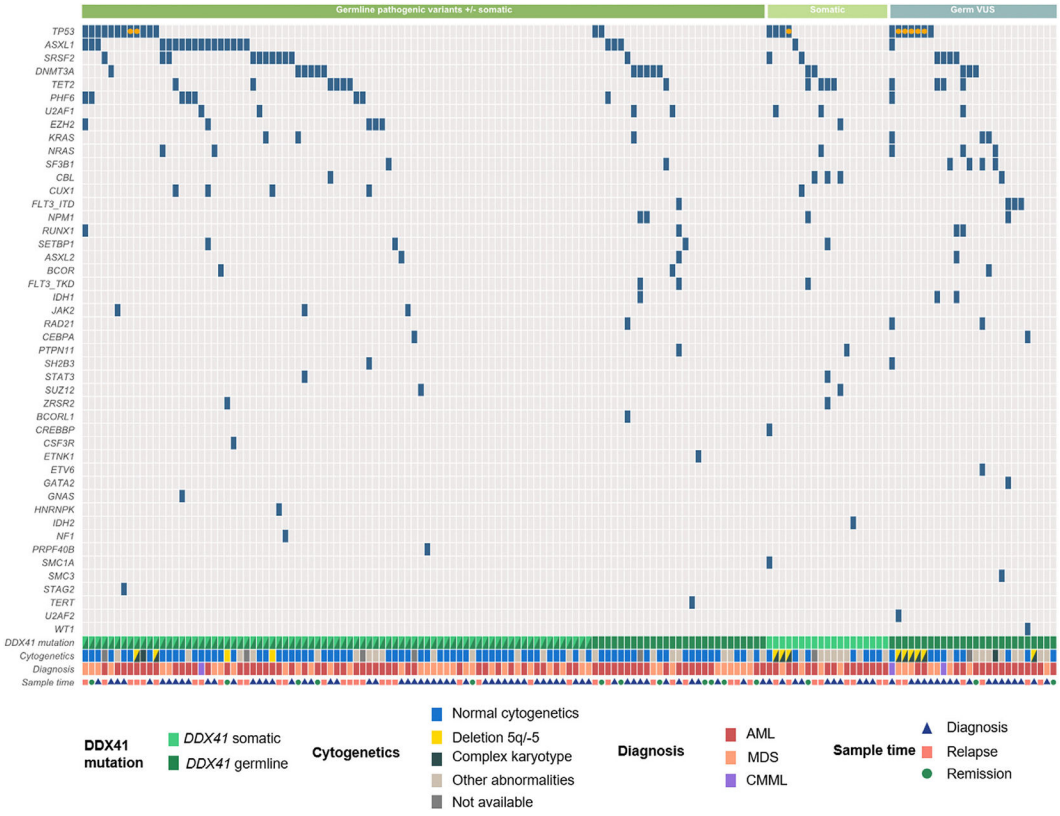

FIGURE 2.

Mutational profile of all patients in the study, together with the type of *DDX41* mutation, cytogenetic abnormalities, diagnosis and sample time. Patients with biallelic *TP53* alterations (2 or more mutations, VAF >40% or *TP53* mutation plus chromosome 17/17p deletion) are represented with a gold dot.

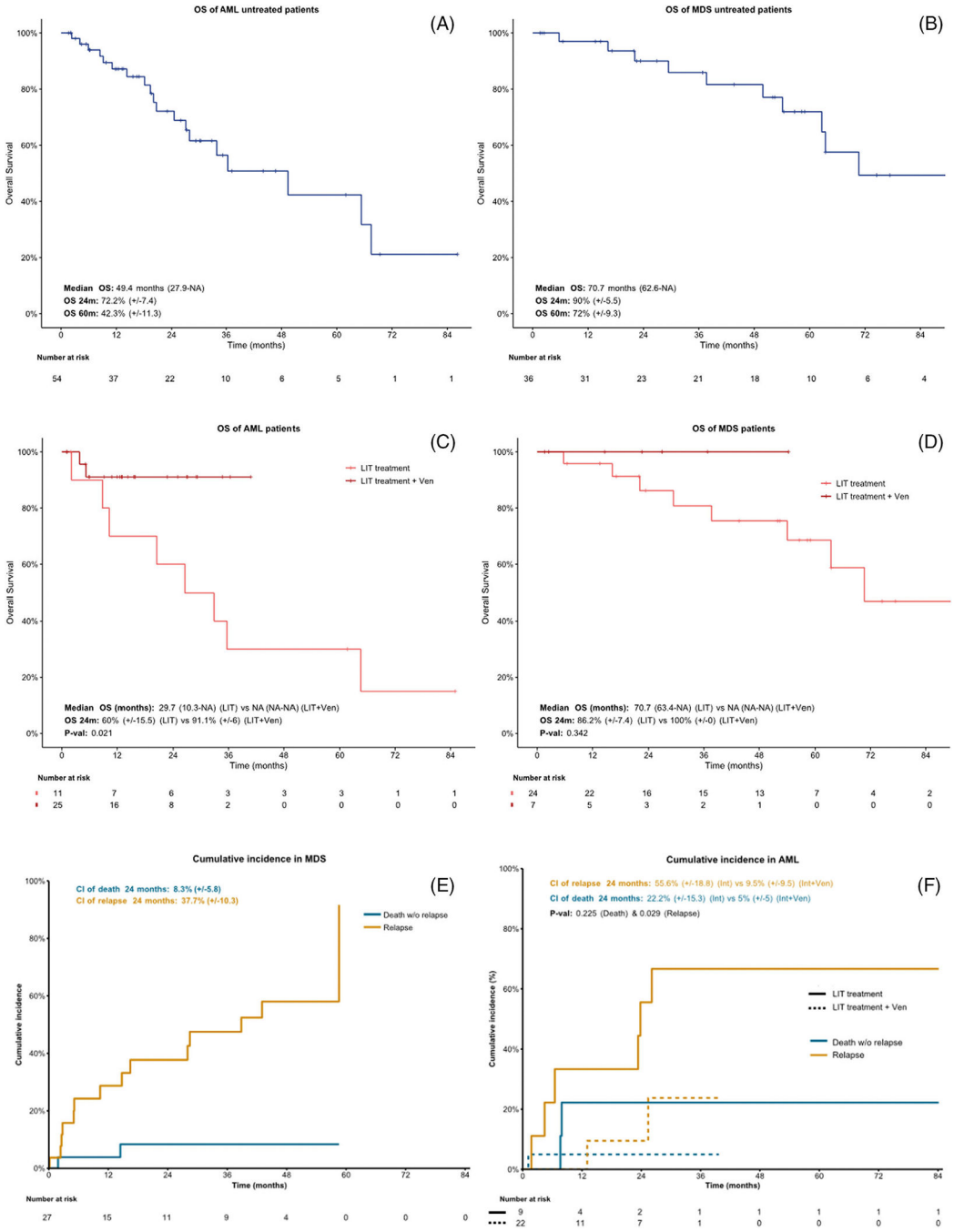

FIGURE 3.

(A) OS of patients with treatment-naïve AML. (B) OS of patients with treatment-naïve MDS. (C) OS of patients with treatment-naïve AML treated with low intensity treatment (LIT) stratified by venetoclax use. (C) OS of patients with treatment-naïve MDS treated with LIT stratified by venetoclax use. (E) CI of death and relapse in patients with treatment-naïve AML treated with LIT stratified by venetoclax use. (F) CI of death and relapse in patients with treatment-naïve MDS treated with LIT.

TABLE 1

Basel ine characteristics.

	All patients (*n* = 151)	AML (*n* = 96)	MDS (*n* = 52)	CMML (*n* = 3)
Age, years, median (range)	69 (21–90)	69 (21–90)	68 (49–88)	73 (63–74)
Sex, male, *n* (%)	114 (75.5)	72 (75)	40 (76.9)	2 (66.7)
Ethnicity, *n* (%)				
White	128 (84.8)	80 (83.3)	47 (90.4)	1 (33.3)
Black	5 (3.3)	2 (2.1)	2 (3.8)	1 (33.3)
Hispanic	12 (7.9)	9 (9.4)	2 (3.8)	1 (33.3)
Asian	6(4)	5(5.2)	1 (1.9)	0(0)
Hemoglobin, median (range) [g/L]	9.7(5.8–14.5)	9.3 (5.8–14.5)	11.2 (6.8–14.4)	13.9(9.9–14.5)
WBC count, median (range) [$\times 10^9$ cells/L]	2.1(0.2–118.7)	1.9 (0.2–118.7)	2.1 (0.7–7.3)	3.7 (2.5–5.4)
Neutrophil count, median (range) [$\times 10^9$ cells/L]	0.7 (0–4.7)	0.5 (0–4.3)	0.9 (0–4.7)	1.2 (1–3.5)
Platelet count, median (range) [$\times 10^9$ cells/L]	64(8–591)	48 (8–591)	92 (12–282)	87 (74–193)
Bone marrow blasts, median (range) [%]	21 (1–91)	28 (8–91)[a]	10(1–18)	4(2–10)
Cytogenetics				
Normal	89 (58.6)	53 (55.2)	32 (61.5)	3 (100)
Del 5q/−5	13 (8.6)	9 (9.4)	4 (7.7)	0 (0)
Chr 7 abnormality	12 (7.9)	9 (9.4)	3 (5.8)	0 (0)
Trisomy 8	5 (3.3)	2 (2.1)	3 (5.8)	0 (0)
t(8;21)	2 (1.3)	2 (2.1)	0(0)	0 (0)
Complex	13 (8.6)	9 (9.4)	4 (7.7)	0 (0)
ELN 2017/ELN 2022	-		-	-
Favorable		7 (7.3)/6 (6.2)		
Intermediate		47 (48.9)/30 (31.3)		
Adverse		40 (41.7)/58 (60.4)		
Not classifiable		2 (2.1)/2 (2.1)		
IPSS-R		-		
Very low			1 (1.9)	
Low	-		10 (19.2)	-
Intermediate			19 (36.5)	

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	All patients (*n* = 151)	AML (*n* = 96)	MDS (*n* = 52)	CMML (*n* = 3)
High			12 (23.1)	
Very High			7(13.5)	
Not classifiable			3 (5.8)	
Therapy-related, *n* (%)	24 (15.9)	13 (13.6)	10 (19.2)	1 (33.3)
Previous non-myeloid neoplasm, *n* (%)	43 (28.5)	24 (25)	18 (34.6)	1 (33.3)
Family history of cancer, *n* (%)	92 (60.3)	57 (59.4)	32 (61.5)	2 (66.6)
Prior myeloid-directed therapy				
Treatment naive	112 (74.2)	67 (69.8)	43 (82.7)	2 (66.7)
Previously treated	39 (25.8)	29 (30.2)	9 (17.3)	1 (33.3)

[a]Patients with AML with BM blasts <20% were all R/R AML with >5% blasts.

TABLE 2

Responses to treatment.

Diagnosis	Disease status	Treatment	Response
AML	Previously untreated	Intensive treatment (*n* = 11, 20.4%)	CR: 9 (81.8%)
		Intensive treatment + Venetoclax (*n* = 7, 13%)	CR: 7 (100%)
		Low intensity treatment (*n* = 11, 20.4%)	CR: 8 (63.6%) CRi: 2 (18.2%)
		Low intensity treatment + venetoclax (*n* = 25, 46.2%)	CR 21 (84%) CRi: 1 (4%)
	Relapse/Refractory	Intensive treatment (*n* = 2, 10.5%)	CR: 1 (50%) CRi: 1 (50%)
		Intensive treatment + Venetoclax (*n* = 1, 10.5%)	CR: 1 (100%)
		Low intensity treatment (*n* = 7, 36.8%)	CR: 2 (28.6%) CRi: 1 (14.3%) PR: 1 (14.3%) MLFS: 1(14.3%)
		Low intensity treatment + venetoclax (*n* = 4, 21.2%)	CR: 1 (25%) CRi: 1 (25%)
		Other (*n* = 5, 26.3%)	CR: 1 (20%) CRi: 1 (20%)
MDS	Previously untreated	Low intensity treatment (*n* = 24, 75%)	CR: 15 (62.5%) mCR: 5 (20.9%)
		Low intensity treatment + venetoclax (*n* = 7, 21.9%)	CR: 6 (85.7%)
		Other (*n* = 1, 3.1%)	CR: 1 (100%)
	Relapse/Refractory	Intensive treatment (*n* = 1, 16.7%)	mCR: 1 (100%)
		Low intensity treatment (*n* = 1, 16.7%)	CR: 1 (100%)
		Low intensity treatment + venetoclax (*n* = 2, 33.3%)	CR: 1 (50%) mCR: 1 (50%)
		Other (*n* = 2, 33.3%)	CR: 2 (100%)