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Targeting Molecular Measurable Residual Disease and Low-Blast Relapse in AML With Venetoclax and Low-Dose Cytarabine: A Prospective Phase II Study (VALDAC)

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ABSTRACT

PURPOSE A prospective phase II study examined the safety and efficacy of venetoclax combined with low-dose cytarabine (LDAC) in AML at first measurable residual disease (MRD) or oligoblastic relapse.

METHODS Patients with either MRD (≥1 $\log_{10}$ rise) or oligoblastic relapse (blasts 5%-15%) received venetoclax 600 mg once daily D1-28 plus LDAC once daily D1-10 in 28-day cycles. The primary objective was MRD response in the MRD relapse cohort or complete remission (CR/CRh/CRi) in the oligoblastic relapse cohort.

RESULTS Forty-eight adults with either MRD (n = 26) or oligoblastic (n = 22) relapse were enrolled. Median age was 67 years (range, 18-80) and 94% had received previous intensive chemotherapy. Patients received a median of four cycles of therapy; 17% completed ≥12 cycles. Patients with oligoblastic relapse had more grade ≥3 anemia (32% *v* 4%; $P = .02$) and infections (36% *v* 8%; $P = .03$), whereas grade 4 neutropenia (32 *v* 23%) or thrombocytopenia (27 *v* 15%) were comparable with the MRD relapse cohort. Markers of molecular MRD relapse included mutant *NPM1* (77%), *CBFB::MYH11* (4%), *RUNX1::RUNX1T1* (4%), or *KMT2A::MLLT3* (4%). Three patients with a $\log_{10}$ rise in *IDH1/2* (12%) were included. By cycle 2 in the MRD relapse cohort, a $\log_{10}$ reduction in MRD was observed in 69%; 46% achieved MRD negative remission. In the oligoblastic relapse cohort, 73% achieved CR/CRh/CRi. Overall, 21 (44%) underwent hematopoietic cell transplantation. Median overall survival (OS) was not reached in either cohort. Estimated 2-year OS rate was 67% (95% CI, 50 to 89) in the MRD and 53% (95% CI, 34 to 84) in the oligoblastic relapse cohorts.

CONCLUSION For AML in first remission and either MRD or oligoblastic relapse, venetoclax plus LDAC is well tolerated and highly effective.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Relapsed AML within the first 2 years after achieving remission presents a major barrier to cure.[1] AML evolves as a multiclonal hierarchy, with outgrowth of chemoresistant ancestral and subclonal populations a dominant cause of treatment failure.[2,3] Treatment of relapsed AML is made challenging by reduced efficacy of treatment and a high complication rate related to disease-associated cytopenia.

Measurable residual disease (MRD) encompasses quantifiable disease below the resolution of morphologic assessment.[4] The European LeukemiaNet (ELN) defines MRD relapse as a ≥1-$\log_{10}$ interval increase in molecular MRD confirmed by repeat testing.[4] MRD relapse with rising *NPM1*^{MUT}, *RUNX1::RUNX1T1*, *CBFB::MYH11*, or *KMT2A* rearrangements confer a near-universal risk of clinical relapse.[5-8] Although several studies report promising results for therapeutic intervention at MRD relapse, most studies have been retrospective.[9] The prospective RELAZA2 study explored MRD-directed therapy (using azacitidine) in 53 patients with MRD persistence or relapse after allograft. MRD response (≥1 $\log_{10}$ reduction) was observed in 58% patients (36% MRD-negative).[10]

CONTEXT

Key Objective

To conduct the first prospective clinical study, to our knowledge, exploring potential for enhanced feasibility and efficacy of preemptive intervention with venetoclax and low-dose cytarabine to target molecular measurable residual disease (MRD) or early morphologic relapse (5%-15% bone marrow blasts) in patients with AML.

Knowledge Generated

Response to treatment was rapid (median one cycle), with MRD response (≥1 $\log_{10}$ reduction) in 69% (46% MRD negative) in the MRD relapse cohort. Hematologic response (CR/CRh/CRi) was 73% in the oligoblastic relapse cohort. Successful transition to hematopoietic cell transplantation was achieved in 44% of patients and median overall survival not reached in either cohort.

Relevance *(C.F. Craddock)*

Prospective MRD monitoring provides an important opportunity to treat molecular relapse early in selected patients with a defined molecular marker who have previously received intensive chemotherapy. The observation that early intervention with a venetoclax-based regimen was well tolerated and associated with high response rates requires confirmation in larger patient cohorts but demonstrates the clinical benefits of molecular MRD monitoring in AML.*

*Relevance section written by *JCO* Associate Editor Charles F. Craddock, MD.

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At diagnosis, first-line therapy with venetoclax and azacitidine was associated with complete remission (CR/CRi) in 66% (67% for *NPM1*^{MUT} AML).[11] For venetoclax plus low-dose cytarabine (LDAC), CR/CRi was achieved in 48% (78% for *NPM1*^{MUT} AML).[12] Utilization of these regimens at molecular relapse resulted in MRD response in 86% with *NPM1* mutation.[13] Similar findings were observed in another retrospective series.[14] To our knowledge, we now report the first prospectively conducted phase II study examining outcomes with venetoclax plus LDAC in 48 patients with AML and either MRD or oligoblastic relapse (ACTRN12619000746134). The high rates of MRD response observed, along with encouraging long-term survival, highlight this preemptive salvage approach as a novel and effective treatment strategy for patients with early AML relapse.

METHODS

Patients

Eligible patients had AML in first morphologic remission, Eastern Cooperative Oncology Group performance status 0-2, and either MRD or oligoblastic relapse (5%-15% bone marrow blasts) after no more than one previous line of intensive chemotherapy. Hematopoietic cell transplantation (HCT) in remission was considered a component of first-line therapy. MRD relapse was defined as a ≥1 $\log_{10}$ interval rise in molecular MRD (from nadir or limit of detection), confirmed on repeat testing from the same tissue. Previous exposure to venetoclax/BCL2 inhibitors was excluded. Full eligibility criteria are provided in the Protocol (online only). The study was approved by Alfred Health (No. 196/19).

Study Design

This phase II study was conducted at five centers and enrolled patients between December 2019 and April 2022, with a data cutoff on March 31, 2023. Patients were stratified to an MRD or oligoblastic relapse cohort. The primary objective was MRD or hematologic (CR/CRh/CRi) response within two cycles in the MRD or the oligoblastic relapse cohort, respectively. A predictive probability design was used (Data Supplement).[15] Secondary objectives included overall survival (OS), HCT realization, safety, and hospital resource utilization. Post hoc analyses included MRD or hematologic response beyond two cycles of therapy, and event-free survival including MRD relapse (EFS_{MRD}).[16]

Study Treatment

Patients received venetoclax (600 mg oral once daily days 1-28) in combination with LDAC (20 mg/m^2 subcutaneous once daily days 1-10). For the MRD relapse cohort, venetoclax dose ramp-up was not required. In the oligoblastic relapse cohort, tumor lysis prophylaxis was included and venetoclax dose-ramped from 100 to 600 mg over 4 days. Hospitalization was at the discretion of the treating clinician. Supportive care transfusions, granulocyte colony-stimulating factor, and antimicrobial prophylaxis (venetoclax reduced to 50 mg if concurrent posaconazole) were according to institutional practice.

Assessments

For MRD evaluation, *NPM1*^{MUT} and gene rearrangements (per 100 *ABL1*) were analyzed by using RT-qPCR; *IDH1*/2^{MUT} was

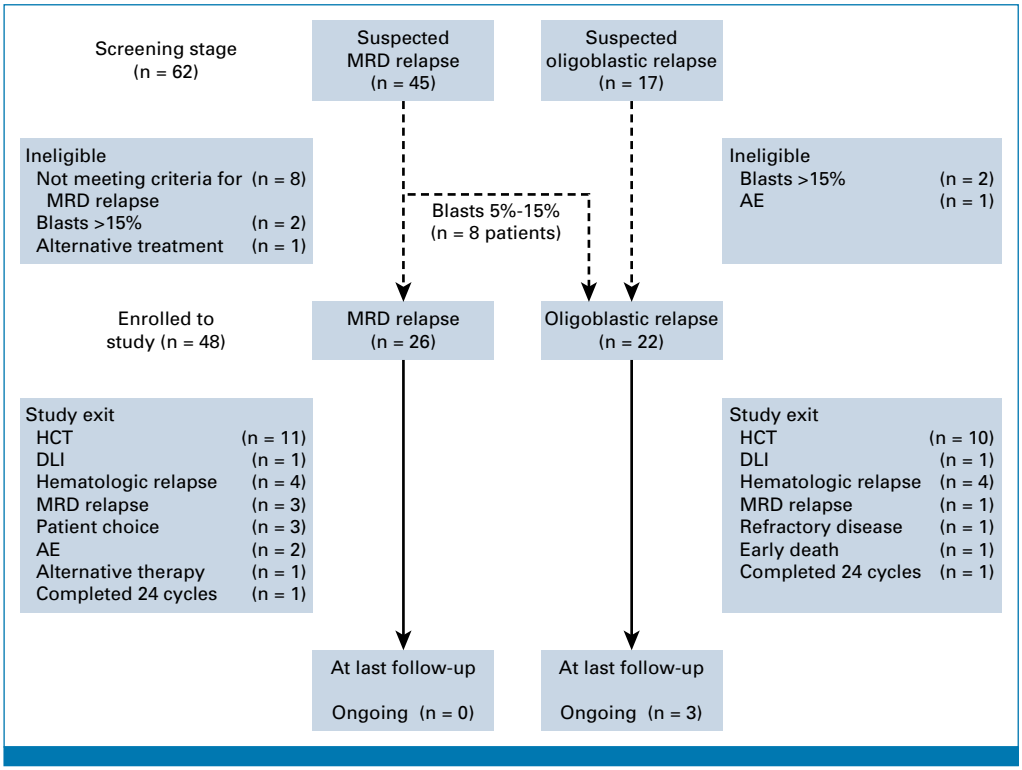

FIG 1. Flow diagram for the prospective phase II VALDAC study. AE, adverse event; DLI, donor lymphocyte infusion; HCT, hematopoietic cell transplantation; MRD, measurable residual disease.

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monitored by droplet digital polymerase chain reaction (PCR; Bio-Rad, Hercules, CA). Response was assessed after cycles 1, 2, 5, 8, 12, 16, 20, and 24 using the ELN 2022 criteria.[4,16] Adverse events (AEs) were graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03.

Targeted next-generation sequencing (NGS) involved a molecular index–based, error-corrected sequencing panel with a sensitivity of 0.5% as previously described[17] or a hybridization capture–based panel with a sensitivity of 1% (Supplemental Methods). *FLT3*-ITD was measured by either conventional capillary electrophoresis (sensitivity 1%), or amplicon-based deep NGS (sensitivity 0.001%), as previously described.[18]

Historical Cohorts

Two historical cohorts with *NPM1*^{MUT} AML were included for retrospective comparison of outcomes after intensive salvage therapy: MRD or oligoblastic *NPM1*^{MUT} relapse from the UK NCRI AML17 (2009-2014) and AML19 (2015-2021) studies[19,20] and first morphologic *NPM1*^{MUT} relapse (≥5% marrow blasts) from Melbourne, Australia (2010-2023).

Statistical Analyses

Patients receiving at least one dose of study drug were included in safety, efficacy, and survival analyses. 95% credible intervals (CrI) for response were based on minimally informative Dirichlet prior distribution (a_o = 0.2, b_o = 0.8; Data Supplement, Table S1). Mann-Whitney *U* and Fisher's exact tests were used to compare numerical and categorical variables, respectively. Kaplan-Meier or Simon-Makuch survival was calculated from day 1 of therapy. EFS_{MRD} was calculated from day 1 to MRD relapse, hematologic relapse, or death from any cause, whichever occurred first; patients not responding or dying before response assessment were considered an event on day 1; patients alive but nonevaluable for response were censored at day 1; patients achieving a response were censored on the date of last follow-up. HCT was considered as a time-dependent covariate in Cox regression analysis. R software (version 4.2.3) packages used included survival, ggsurvfit, and ggplot2.

RESULTS

Screening and Baseline Characteristics

A total of 62 patients provided consent and underwent screening for either MRD or oligoblastic relapse (Fig 1). Fourteen were excluded (eight did not meet MRD relapse criteria, four had >15% marrow blasts, one had comorbidities, and one sought alternative therapy). Forty-eight patients were enrolled to either the MRD (n = 26) or oligoblastic (n = 22) relapse cohorts. Median time from MRD relapse to start of study therapy was 1.6 months (range,

TABLE 1. Baseline Patient and Disease Characteristics of 48 Patients in the Study Cohort

Variable	Total (N = 48)	MRD Relapse (n = 26)	Oligoblastic (n = 22)
Age, years, median (range)	67 (18-80)	62 (18-76)	70 (50-80)
Over 70 years, No. (%)	21 (44)	9 (41)	12 (55)
Male, %/female, %	65/35	54/46	77/23
ECOG performance status, No. (%)			
0	32 (67)	19 (73)	13 (59)
1	16 (33)	7 (27)	9 (41)
Diagnostic cytogenetics, No. (%)			
Favorable risk	2 (4)	2 (8)	—
Intermediate risk	43 (91)	24 (92)	19 (90)
Adverse risk	2 (4)	—	2 (10)
Diagnostic molecular profile, No. (%)			
NPM1	30 (63)[a]	20 (77)[b]	9 (41)
IDH1 or *IDH2*	20 (42)	13 (50)	7 (32)
FLT3-ITD	20 (42)[c]	15 (58)[b]	6 (27)
CBFB::MYH11	1 (2)	1 (4)	—
RUNX1::RUNX1T1	1 (2)	1 (4)	—
KMT2A::MLLT3	1 (2)	1 (4)	—
Diagnostic ELN 2017 risk, No. (%)			
Favorable	29 (62)	20 (77)[b]	9 (43)
Intermediate	13 (28)	6 (23)	7 (33)
Adverse	5 (11)	—	5 (24)[b]
Previous intensive therapy, No. (%)	45 (94)	25 (96)	20 (91)
No. of cycles, median (IQR)	3 (2-4)	4 (3-5)[b]	3 (2-4)
HCT	2 (4)	1 (4)	1 (5)
Duration of CR1, months, No. (%)			
<6	12 (25)	8 (31)	4 (18)
6-12	18 (38)	10 (38)	8 (36)
>12	18 (38)	8 (31)	10 (45)
Time from CR1 to date of study therapy, months, median (95% CI)	12.6 (11.0-16.9)	11.4 (8.7-16.8)	16.6 (11.7-24.6)

NOTE. Missing data: diagnostic cytogenetics and ELN 2017 risk (n = 1 in oligoblastic cohort due to failed karyotype).
Abbreviations: CR1, first morphologic remission; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; HCT, hematopoietic cell transplantation; IQR, interquartile range; MRD, measurable residual disease; RT-qPCR, reverse transcription-quantitative polymerase chain reaction.
[a]One patient (MRD cohort) with *NPM1* mutation at diagnosis entered the study with *IDH2* molecular relapse but undetectable $NPM1^{MUT}$ by RT-qPCR.
[b]Significantly higher values ($P < .05$) between the MRD relapse and oligoblastic cohorts.
[c]One patient newly acquired a *FLT3*-ITD mutation at study entry with oligoblastic relapse.

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0.5-3.8 months). The disposition of 361 patients who underwent MRD monitoring (before study enrollment) during the recruitment period is shown in the Data Supplement (Fig S1).

Baseline characteristics of the study cohort are summarized in Table 1. Median age was 67 years (range, 18-80). At AML diagnosis, most had intermediate cytogenetic risk (91%). Mutations most frequently involved *NPM1* (63%), *IDH1/2* (42%), or *FLT3*-ITD (42%). Most (94%) had received previous intensive chemotherapy (median, 3 cycles, range, 2-4) and 2 (4%) had undergone HCT in first morphologic remission (CR1). The median times from CR1 to MRD or morphologic relapse were 9.0 and 11.6 months (Fig 2A), respectively, and the median times to commencement of study therapy were 11.4 and 16.6 months, respectively (Table 1). Disease markers used for response tracking in the MRD relapse cohort were mutated *NPM1* (77%), *IDH1/2* (12%), *CBFB::MYH11* (4%), *RUNX1::RUNX1T1* (4%), and *KMT2A::MLLT3* (4%). Baseline molecular characteristics are illustrated in the Data Supplement (Fig S2).

As expected, baseline bone marrow blasts were higher for patients with oligoblastic (median blasts, 11%; range, 5%-14%), compared with MRD relapse (median blasts, 2%; range, 0%-4%; Fig 2B). Baseline peripheral blood counts were mostly normal for patients in the MRD relapse cohort

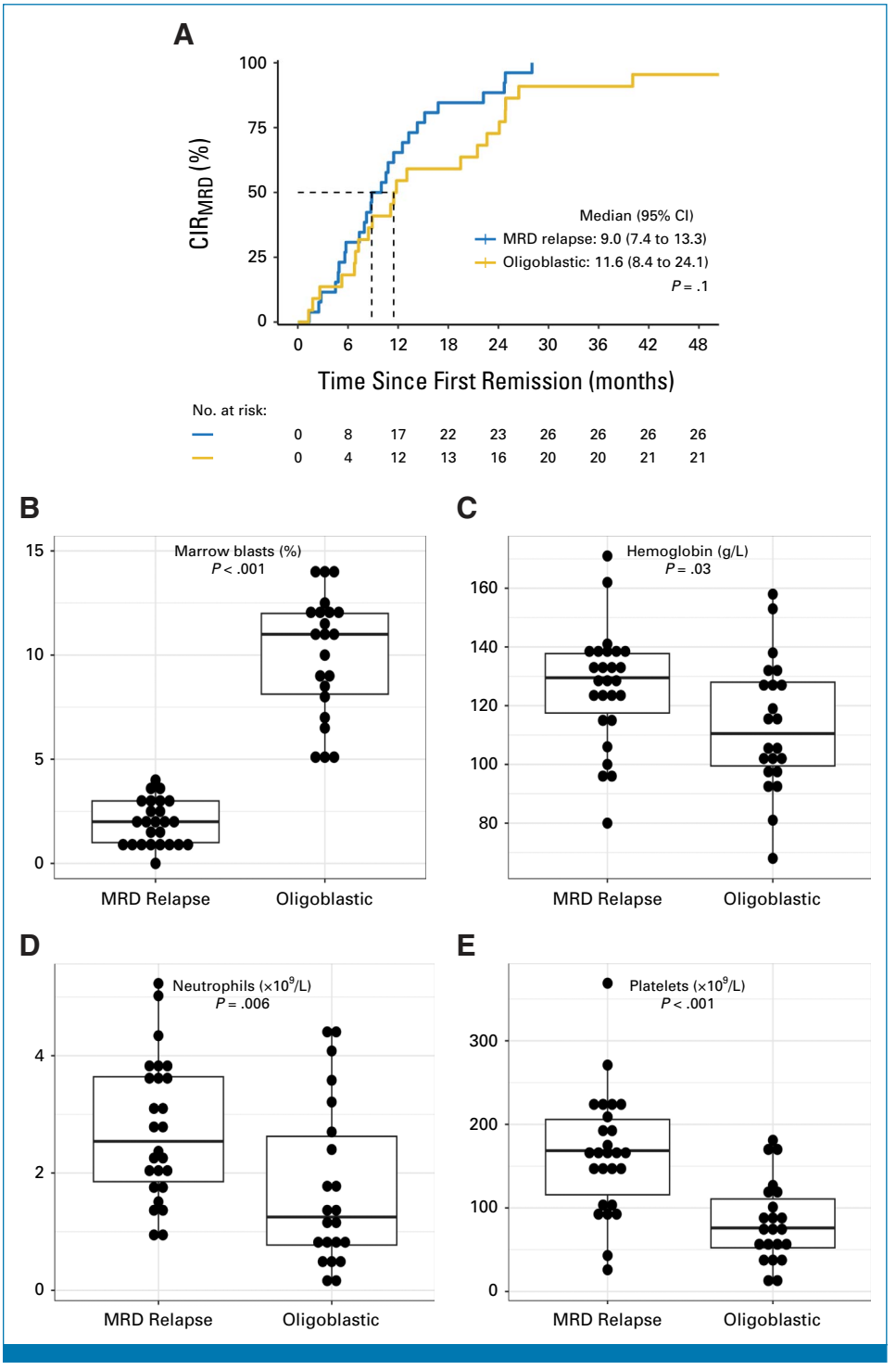

FIG 2. (A) Cumulative incidence of relapse from date of first morphologic remission to date of MRD or oligoblastic relapse. Two subjects from the oligoblastic cohort relapsed after 3.3 and 11 years and are not included in the graph. (B-E) Hematologic parameters at study screening according to MRD or oligoblastic relapse: (B) bone marrow blasts, (C) hemoglobin, (D) neutrophils, and (E) platelets. MRD, measurable residual disease.

(Figs 2C-2E). No patient had grade 4 neutropenia (<0.5 × 10^9/L) or thrombocytopenia (<25 × 10^9/L) in the MRD relapse cohort at study screening, compared with 14% with grade 4 neutropenia and 9% with grade 4 thrombocytopenia in the oligoblastic relapse cohort.

Safety

Patients received a similar number of venetoclax plus LDAC cycles in the MRD (median 4) and oligoblastic relapse (median 3.5) cohorts. At least 12 cycles of therapy

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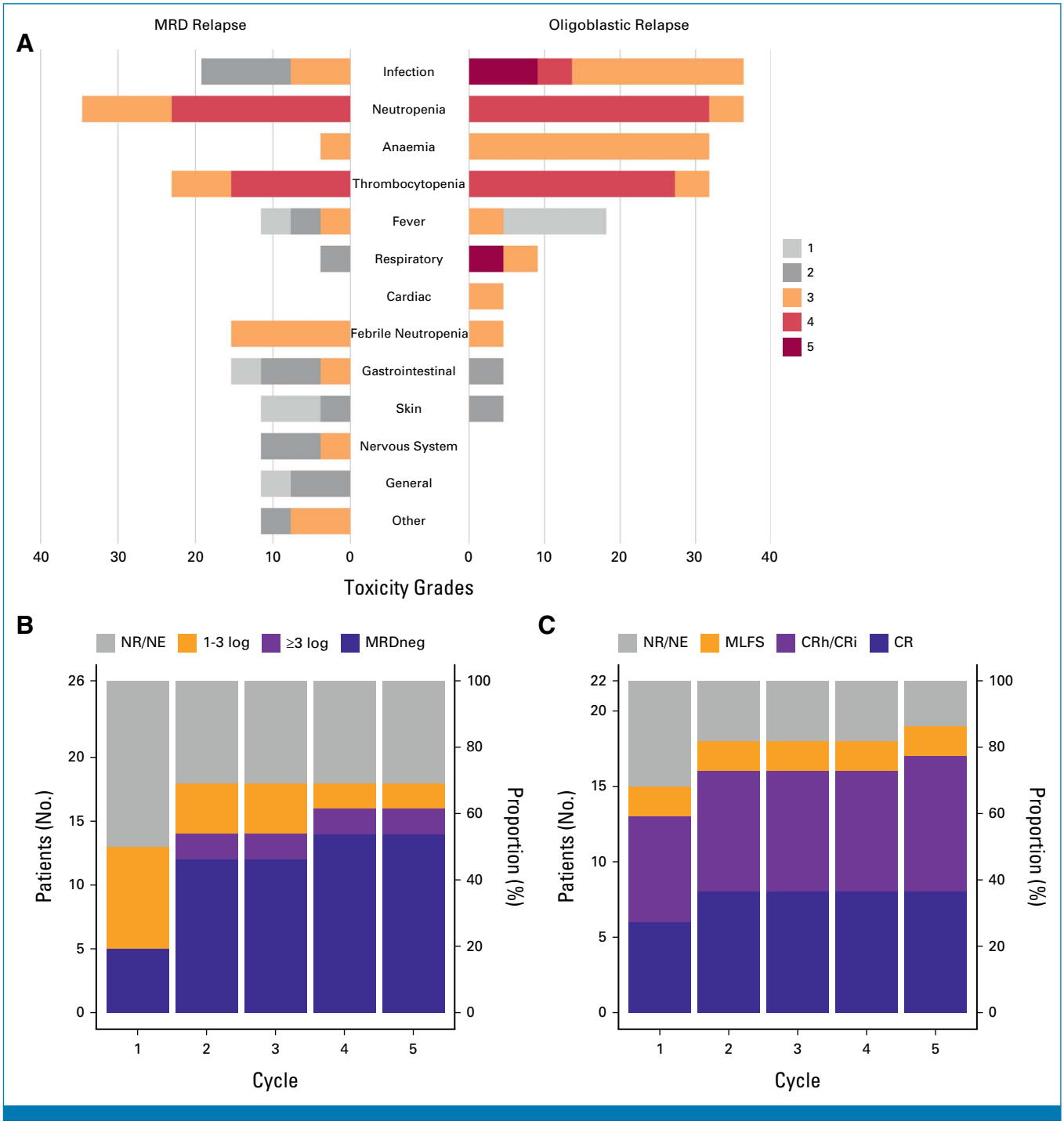

FIG 3. (A) Treatment-emergent adverse events regardless of causality in the MRD relapse (left) and oligoblastic (right) cohorts. (B) MRD response in the MRD relapse cohort, including NR or NE, 1-3 $\log_{10}$ reduction, ≥3 $\log_{10}$ reduction, and CR/CRh/CRi_{MRD-} (MRDneg), censored at best response. (C) Hematologic response in the oligoblastic cohort, including NR or NE, MLFS, CRh/CRi, or CR censored at best response. Two subjects were NE: one early exit because of an adverse event (MRD relapse cohort) and one early death (oligoblastic cohort). CR, complete remission; CRh/CRi, CR/with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NE, nonevaluable; NR, no response.

were completed by 17% patients across both cohorts (Data Supplement, Fig S3). The median duration of venetoclax administered was 28 days for 13 of the first 14 cycles of therapy, indicative of excellent tolerance to therapy. Treatment-emergent AEs are summarized in Figure 3A. Patients in the oligoblastic relapse cohort had more grade ≥3 anemia (32% *v* 4%; $P = .02$) and infections during treatment (36% *v* 8%; $P = .03$), whereas grade 4 neutropenia (32 *v* 23%), thrombocytopenia (27 *v* 15%), and febrile neutropenia (15% *v* 5%) were comparable with

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the MRD relapse cohort. Three patients in the oligoblastic relapse cohort died during treatment of lung infection, liver abscess, or pneumonitis. No laboratory or clinical tumor lysis syndrome was recorded. During therapy, 36 episodes of unplanned hospital admissions occurred in 9/26 (35%) and 13/22 (59%) patients in the MRD and oligoblastic relapse cohorts, respectively, and median durations of hospitalization were six and 7.5 days per episode (range, 2-13), respectively. The majority of all hospital admissions occurred within the first two cycles of therapy, predominantly related to infection (41%), febrile neutropenia (18%), or non-neutropenic fever (9%; Data Supplement, Table S2). The frequency of hospitalizations was similar between the MRD and oligoblastic relapse cohorts. Twenty-one (44%) patients ceased therapy and proceeded to HCT, 11/26 (42%) and 10/22 (45%) patients in the MRD and oligoblastic relapse cohorts, respectively. At last follow-up, three patients remained on study therapy.

Response

In the MRD relapse cohort, 69% (95% CrI, 49 to 83) achieved MRD response by two cycles of therapy; 46% had undetectable MRD, 8% had ≥3-$\log_{10}$ reduction, and 15% had 1-3-$\log_{10}$ reduction, whereas 27% had no MRD response and one patient was nonevaluable (Fig 3B). Median time to first MRD response was one cycle (range, 1-2). Deepening of response was observed in two patients beyond second cycle, resulting in 54% (95% CrI, 34 to 70) patients achieving MRD-negative remission.

In the oligoblastic relapse cohort, 73% (95% CrI, 50 to 86) achieved CR/CRh/CRi by cycle 2, with an additional 9% achieving morphologic leukemia-free state; 14% had no response and one patient died early (Fig 3C). One additional patient achieved CRh/CRi beyond cycle 2, resulting in an overall CR/CRh/CRi rate of 77% (95% CrI, 56 to 90). Median time to hematologic response was one cycle (range, 1-5). Among eight patients with *NPM1*^{MUT} in the oligoblastic cohort, CR/CRh/CRi was recorded in 100% cases, with undetectable MRD in 75% patients.

Survival

With a median follow-up of 25 months, median OS in the MRD relapse cohort has not yet been reached (Fig 4A); estimated 2-year OS rate was 67% (95% CI, 50 to 89). Sixty-day landmark analysis was performed to determine if survival outcome was associated with depth of MRD response. Patients achieving undetectable MRD had an estimated 2-year OS rate of 92% (median not reached), compared with 75% (median 25 months) among patients with an MRD response (≥1 $\log_{10}$ reduction), which was still detectable, and 25% (median 11 months) among those with no MRD response (Fig 4C). Two-year EFS_{MRD} in the MRD relapse cohort was 58%, which included MRD relapse, morphologic relapse, or death as events (Fig 4E).

In the oligoblastic relapse cohort, with a median follow-up of 22 months, median OS was not reached (estimated 2-year OS, 53% [95% CI, 34 to 84]; Fig 4B). Among patients achieving CR/CRh/CRi, median OS (60-day landmark) was also not reached (2-year OS, 62%), compared with 14 months (2-year OS, 33%) for those not achieving CR/CRh/CRi in the oligoblastic cohort (Fig 4D). Median EFS_{MRD} in the oligoblastic cohort (including MRD relapse) was 14 months (Fig 4F).

Transplantation

Seventeen patients were considered HCT-ineligible by treating physicians because of age, comorbidities, or no suitable donor. Among 31 HCT-eligible patients, 22 (71%) proceeded to transplantation: 12/18 (67%) and 10/13 (77%) in the MRD relapse and oligoblastic cohorts, respectively, after a median of 3.8 and 5.0 months from commencement of study therapy ($P = .9$). Median OS after HCT was not reached in either the MRD relapse or oligoblastic cohorts: 2-year OS rates were 83% (95% CI, 63 to 100) and 62% (95% CI, 35 to 100), respectively (Figs 4G and 4H). In the MRD relapse cohort, seven proceeded to HCT with MRD negativity and all remain disease-free and alive at last follow-up (range 3-27 months), compared with the 2-year OS rate of 60% if transplanted with persistent MRD (Data Supplement, Fig S4A). In the oligoblastic cohort, insufficient patient numbers preclude a meaningful analysis of pre-HCT response status and post-HCT outcome (Data Supplement, Fig S4B). Nonrelapse mortality occurred in three patients (SARS-CoV-2 infection, sepsis, or cytomegalovirus pneumonitis). Although HCT did not improve OS, compared with patients not proceeding to transplant (Data Supplement, Figs S5A and S5B), the cumulative incidence of relapse appeared lower but was offset by higher nonrelapse deaths in the HCT cohort (Data Supplement, Figs S5C and S5D).

Outcomes in the *NPM1*^{MUT} Subgroup

Patients with *NPM1*^{MUT} comprised 63% of the study population (Table 1). *NPM1*^{MUT} MRD levels were lower at screening in the MRD relapse cohort compared with the oligoblastic cohort (Data Supplement, Fig S6). In the MRD relapse cohort, complete molecular clearance of *NPM1*^{MUT} was achieved in 55% (Fig 5A). In the oligoblastic cohort, 100% with *NPM1*^{MUT} achieved CR/CRh/CRi, with 6/8 patients (75%) also clearing *NPM1*^{MUT}; one patient had a rare *NPM1*^{MUT} transcript not amenable to molecular MRD monitoring (Fig 5B). Among 29 patients with *NPM1*^{MUT} across both cohorts, median OS was not reached (2-year OS, 63%; Fig 5C). Thirteen patients with *NPM1*^{MUT} AML were bridged to HCT, comprising 8 (31%) and 5 (23%) in the MRD and oligoblastic relapse cohorts, respectively. Median OS after HCT for patients with *NPM1*^{MUT} was not reached (2-year OS, 73%; Fig 5D).

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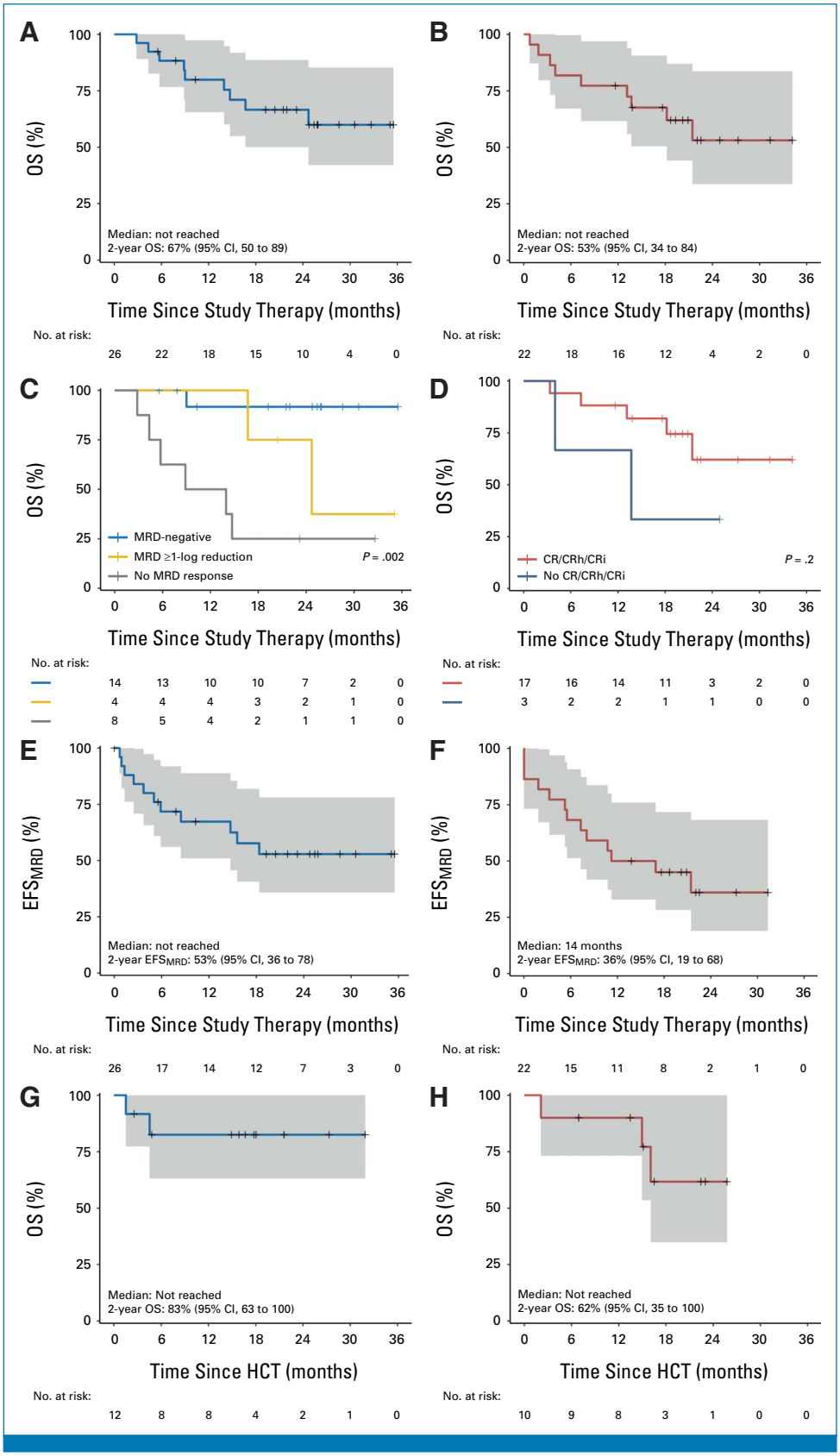

FIG 4. Kaplan-Meier survival in the (A, C, E, G) MRD relapse and (B, D, F, H) oligoblastic cohorts. (A and B) OS in the MRD relapse and oligoblastic cohorts, (C and D) 60-day landmark analysis stratified according to (C) MRD or (D) hematologic response. (E and F) Event-free survival including MRD relapse, hematologic relapse, or deaths as events (EFS_{MRD}) in each cohort. (G and H) (continued on following page)

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FIG 4. (Continued). OS post-HCT in each cohort. CR, complete remission; CRh/CRi, CR/with incomplete hematologic recovery; EFS_{MRD}, event-free survival including MRD relapse; HCT, hematopoietic cell transplantation; MRD, measurable residual disease; OS, overall survival.

Intensive chemotherapy for *NPM1*^{MUT} MRD or Morphologic Relapse: Historical Outcomes

We next compared outcomes among two historical cohorts with *NPM1*^{MUT} AML salvaged with intensive chemotherapy. The first included 52 patients with *NPM1*^{MUT} and MRD (n = 46) or oligoblastic relapse (n = 6) salvaged in the NCRI AML17 and AML19 studies (Data Supplement, Table S3).[19,20] The median age was 52 years and the median time from CR1 to salvage chemotherapy 9.5 months (95% CI, 7.7 to 12). Treatment included FLAG-idarubicin (77%), CPX-351 (17%), or high-dose cytarabine-based therapies (6%); HCT was realized in 79%. MRD response was observed in 38 patients (73%), with negative MRD in 46%. Median OS after salvage was not reached (median follow-up 36 months) and the 2-year OS rate was 61% (95% CI, 49 to 76; Fig 5E).

The second cohort included 42 patients with *NPM1*^{MUT} in first morphologic relapse. The median age was 61 years and the median time from CR1 to salvage chemotherapy 7.2 months (95% CI, 5.5 to 10.8; Data Supplement, Table S4). The median bone marrow blast count at relapse was 45% (blasts >15% in 79%). CR/CRh/CRi was achieved in 73% and HCT realized in 48%. With a median follow-up 32 months, the median OS was 11.1 months (2-year OS, 29%; Fig 5F).

Response in Other Molecular Subgroups

In addition to patients with *NPM1*^{MUT}, the current study cohort also included patients with *IDH1/2*^{MUT} (n = 3), *CBFB::MYH11* (n = 1), *RUNX1::RUNX1T1* (n = 1), or *KMT2A::MLLT3* (n = 1; Data Supplement, Table S5). At screening, three patients with *IDH1/2*^{MUT} had a ≥1 $\log_{10}$ increase in variant allele frequency (VAF) from <0.01% to 1.4%, 0.27% to 37.3%, or 0.33% to 11.2% before study treatment. A molecular MRD response was observed in 2/3 patients (Data Supplement, Figs S7A-S7C). Patients with *KMT2A::MLLT3* or *CBFB::MYH11* also demonstrated MRD responses, with negative MRD observed in both cases. One patient with *RUNX1::RUNX1T1* did not respond (Data Supplement, Figs S7D-S7F).

Using a NGS-based MRD assay, *FLT3*-ITD was detected in 9/38 (24%) patients at screening: eight had concurrent *NPM1*^{MUT} and one had *RUNX1::RUNX1T1*. Six patients presented with MRD relapse (*FLT3*-ITD VAF, 0.002%-0.06%) and three had oligoblastic relapse (VAF, 2.7%-6.0%; Data Supplement, Fig S2). Despite initial treatment response, all three patients treated with *FLT3*-ITD–associated oligoblastic relapse had early disease progression. For patients with *FLT3*-ITD MRD <1% at study baseline, survival outcomes appeared comparable with patients who were *FLT3*-ITD–negative (Data Supplement, Figs S8A and S8B). *NPM1*^{MUT} MRD clearance was achieved in 5/7, with a ≥3-$\log_{10}$ MRD reduction in another patient. Dynamic changes in *FLT3*-ITD MRD mirrored *NPM1*^{MUT} in patients carrying both variants (Data Supplement, Figs S8C and S8D).

Mutation Landscape at Relapse After Venetoclax-LDAC for MRD or Oligoblastic Relapse

A total of 16 patients relapsed morphologically after venetoclax-LDAC therapy by the cutoff date, nine in the MRD cohort and seven in the oligoblastic relapse cohort, with median relapse-free survival of 6.2 and 7.3 months, respectively. Targeted NGS analysis was performed in 10 patients with available material at relapse. Variants enriched at relapse involved kinase-activating pathways, such as *FLT3*-ITD (n = 2, 20%), *KRAS* (n = 1), or *CSF3R* (n = 1). Other variants acquired at relapse in the absence of a concomitantly activated kinase included *ASXL1* (n = 2), *TP53*, *DNMT3A*, or *ZRSR2* (n = 1 each; Fig 6A). OS after relapse was poor, with a median survival of only 3.3 months (Fig 6B).

DISCUSSION

Outcomes for morphologically relapsed AML remain poor despite intensive chemotherapy. Alternative approaches, such as venetoclax-azacitidine, appear promising, but follow-up is currently limited.[21] In this study, we prospectively identified patients with early (MRD or low-blast) relapse after first remission for preemptive treatment with venetoclax + LDAC. Our hypothesis was that earlier treatment with lower baseline disease levels would result in longer disease remissions. Proof of concept for this approach has been established for blinatumomab in MRD-positive B-acute lymphoblastic leukemia and arsenic trioxide in acute promyelocytic leukemia.[22,23]

In this study, venetoclax-LDAC yielded an MRD response in 69% (including 54% with undetectable MRD) and a 2-year OS rate of 67%. Survival appeared higher for patients with MRD clearance, indicating the relevance of improved response depth for optimized outcomes. MRD monitoring may occasionally fail to detect relapse if the kinetics of progression are rapid; thus, our study included patients with oligoblastic relapse, defined as 5%-15% blasts. A 77% hematologic response rate was observed for patients with oligoblastic relapse, with a 2-year OS rate of 53%. MRD or

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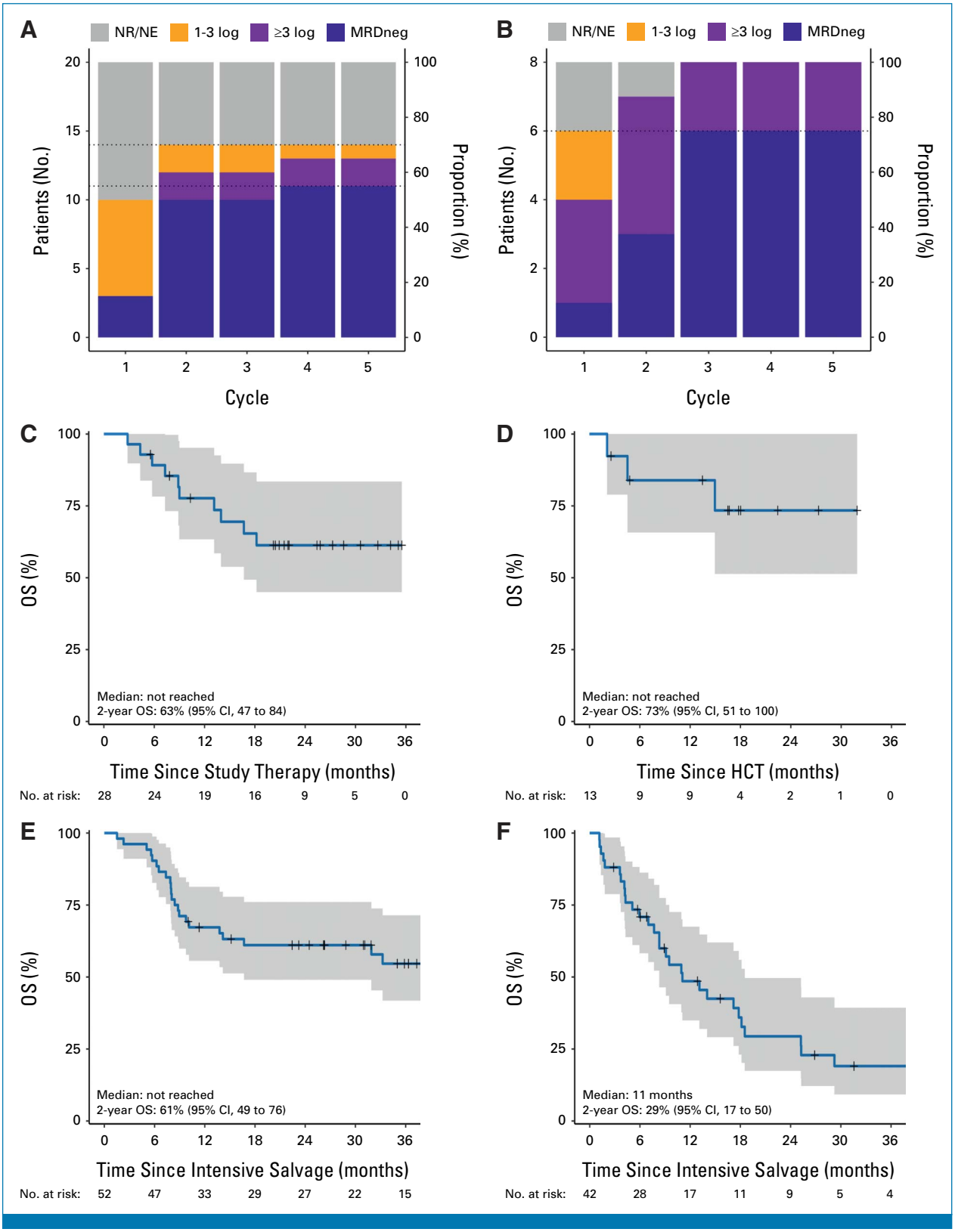

FIG 5. Response and OS among the *NPM1*^{MUT} molecular subgroup. (A and B) Cumulative best *NPM1*^{MUT} MRD response in the (A) MRD relapse cohort and (B) oligoblastic relapse cohort, including NR or NE, 1-3 $\log_{10}$ reduction, ≥3 $\log_{10}$ reduction, and CR/CRh/CRi_{MRD}− (MRDneg). One subject in the MRD relapse cohort was NE: early exit because of an adverse event. One subject was excluded from the oligoblastic cohort: rare *NPM1*^{MUT} transcript not amenable to molecular MRD monitoring. (C and D) OS in the *NPM1*^{MUT} subgroup (C) among combined MRD relapse and oligoblastic cohorts, and (D) among patients with HCT. (E and F) OS after intensive salvage chemotherapy in the (E) UK NCRI AML17 and AML19 cohorts with *NPM1*^{MUT} and MRD and oligoblastic relapse, and (continued on following page)

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FIG 5. (Continued). (F) retrospective cohort with morphologic relapsed *NPM1*^{MUT} AML treated with intensive chemotherapy. HCT, hematopoietic cell transplantation; MRD, measurable residual disease; NE, nonevaluable; NR, no response; OS, overall survival.

hematologic response was rapid and most therapy was outpatient-based. Almost half transitioned to HCT. Post-HCT outcomes after venetoclax-LDAC were encouraging.

Two thirds of the study population had *NPM1*^{MUT} as this was the commonest molecular MRD marker. In the MRD relapse cohort, 55% with *NPM1*^{MUT} and treated with venetoclax-LDAC became MRD-negative and had a 2-year OS rate of 89%. Among patients with *NPM1*^{MUT} and oligoblastic disease, the 2-year OS rate was 63%. By contrast, historical outcomes for *NPM1*^{MUT} AML and first morphologic relapse treated with intensive chemotherapy indicated a 2-year OS rate of 29%, comparable with another retrospective study reporting a 1-year OS rate of 37%.[24] Venetoclax-azacitidine in morphologically relapsed/refractory *NPM1*^{MUT} AML (n = 13) is associated with a 46% response rate and a median OS of approximately 9 months.[25]

A major advantage of treatment at MRD or oligoblastic relapse is the presence of minimal cytopenia. In the MRD relapse cohort, no patient had grade 4 neutropenia or thrombocytopenia at screening. The frequency of febrile neutropenia or grade 3+ infections during therapy was 19%, and most patients completed the intended 28-day venetoclax cycle without dose reductions. In contrast to salvage intensive chemotherapy, venetoclax-LDAC offers the clear advantage of outpatient-based administration with fewer serious complications, despite comparable efficacy. The lead time provided by MRD monitoring may facilitate timelier HCT planning and intervention.

Several theoretical possibilities support earlier intervention using an MRD-directed strategy. Clonal and nonclonal diversity of malignant and premalignant populations may be influenced by selective pressures imposed by the microenvironment, including marrow stroma, immune cells, and inflammatory cytokines, resulting in enhanced leukemic fitness and therapy resistance. As disease burden progresses, leukemic clones with highest fitness most likely have enhanced capacity to outcompete wild-type cells for increasingly limited marrow resources.[26]

The main limitation of this study is that it does not answer whether earlier intervention at MRD or oligoblastic relapse

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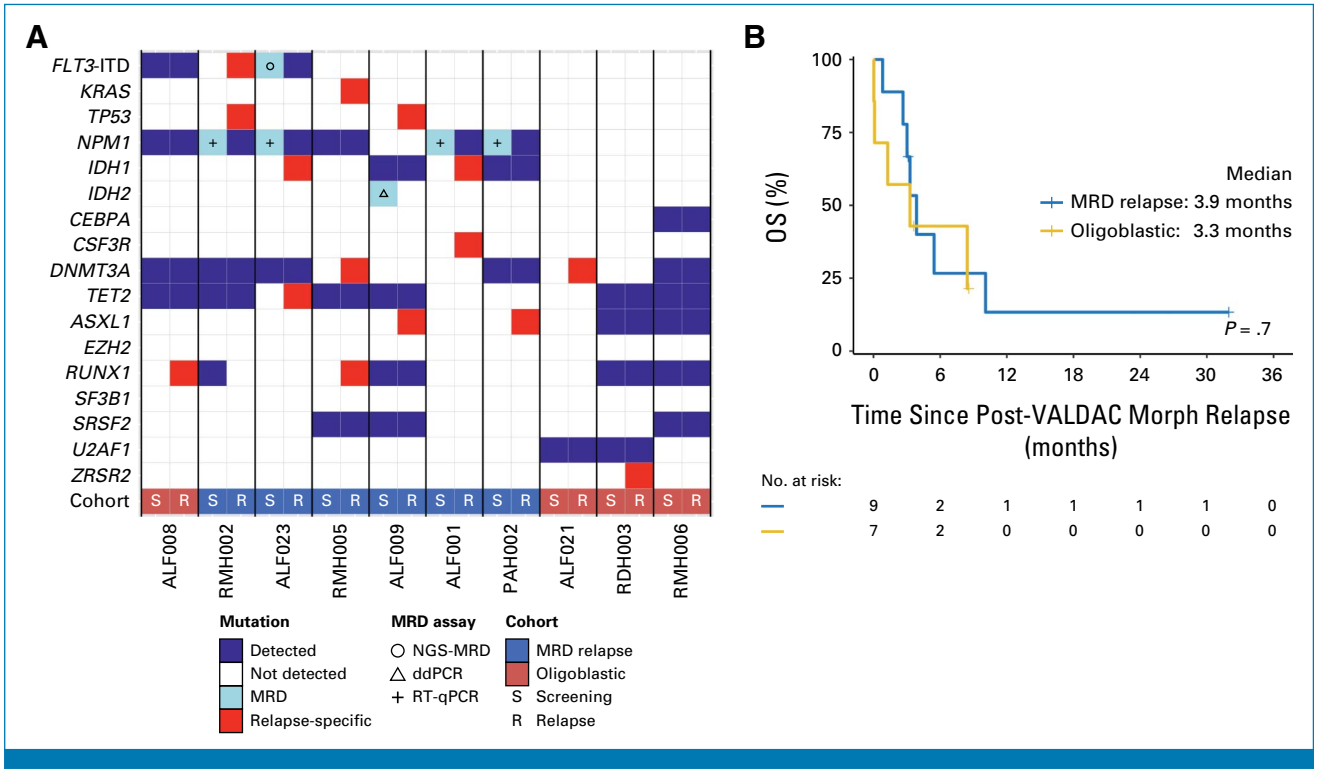

FIG 6. (A) Molecular landscape at S and R among 10 patients with available samples. Of note, four patients relapsed post-HCT in this study but samples were not available. (B) OS among patients with morphologic relapse after venetoclax-LDAC therapy. ddPCR, droplet digital polymerase chain reaction; HCT, hematopoietic cell transplantation; LDAC, low-dose cytarabine; MRD, measurable residual disease; NGS, next-generation sequencing; OS, overall survival; R, relapse; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; S, screening.

improves survival. In addition, although previous studies revealed inferior outcomes for patients with detectable MRD pre-HCT,[27-30] our study does not address whether MRD eradication will lead to improved post-HCT outcomes. The lack of flow MRD monitoring and small patient numbers limit generalizability of our findings beyond the *NPM1*^{MUT} subgroup. Approximately 40% of patients age 60 years and younger do not have an informative molecular target for MRD monitoring.[31] Although flow and NGS-based MRD have established prognostic utility after intensive chemotherapy,[32-35] validation of the utility of serial flow and/or NGS-based monitoring to trigger MRD-directed therapy is limited. Salvageability of patients with previous venetoclax exposure was also not addressed and will require future investigation, including among patients re-treated with venetoclax for MRD relapse after a period of treatment-free remission.[36,37] An ongoing clinical trial will prospectively incorporate flow and molecular MRD monitoring for MRD relapse–directed therapy using targeted agents against rising *FLT3*-ITD, *IDH1/2*^{MUT}, and *KMT2A* rearrangements (INTERCEPT; ACTRN12621000439842).

In conclusion, to our knowledge, this is the first prospective study of venetoclax-LDAC at first MRD or oligoblastic relapse, confirming feasibility, safety, and promising efficacy, especially for *NPM1*^{MUT} AML. Future studies are needed to determine the utility of pre-HCT MRD eradication compared with directly proceeding to HCT and the ability of MRD-directed intervention to alter the natural history of disease, compared with treatment at morphologic relapse.

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DATA SHARING STATEMENT

Deidentified data and the trial protocol are available to qualified researchers who submit an in-scope proposal. The data will be available from the authors of the publication to ensure that data are used in accordance with the informed consent. Data are provided for the sole use of the approved request (tertiary dissemination will not be permitted). To gain access, data requesters will need to sign a data sharing agreement.

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Targeting Molecular Measurable Residual Disease and Low-Blast Relapse in AML With Venetoclax and Low-Dose Cytarabine: A Prospective Phase II Study (VALDAC)

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