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All oral therapy in elderly and unfit AML

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Author contributions

F.R. designed the study. T.W.H., J.K., A.B., and S.P. collected data. T.W.H. performed statistical analysis and drafted manuscript. All authors critically reviewed the manuscript and approved the final version.

Disclosures

M.K. serves on advisory board for AbbVie, Auxenion GmbH, Dark Blue Therapeutics, Legend, MEI Pharma, Menarini/Stemline Therapeutics, Novartis, Servier, Syndax, Vincer and has received consulting from: AbbVie, Adaptive, AmMax, AstraZeneca, Curis, Intellisphere, Janssen, Kyowa Kirin, Menarini/Stemline Therapeutics, Mitsubishi Tanabe Pharma, Sanofi Aventis, Servier, Vincerx and research funding: from AbbVie, Janssen, Klondike Biopharma

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Data sharing statement

Data is available upon reasonable request from the corresponding author.

ABSTRACT

Oral decitabine/cedazuridine plus venetoclax offers a fully oral regimen for older or unfit patients with acute myeloid leukemia (AML). We previously reported outcomes from a phase II study; here we present extended follow-up of the frontline cohort. In this single-center phase II study, adults with AML ineligible for intensive induction received oral decitabine/cedazuridine (35 mg/100 mg, days 1-5) plus venetoclax in 28-day cycles. This analysis included newly diagnosed (ND) AML. Endpoints included overall response rate (ORR), overall survival (OS), relapse-free survival (RFS), duration of response (DOR) and safety. Outcomes were compared between de novo and secondary AML. Between March 2021, and January 2026, 68 patients were treated, including 32 de novo and 36 secondary AML; median age was 79 years. The cohort was high risk, with >50% ECOG ≥2, less favorable genomics and 16% prior hypomethylating agents exposure. ORR was 75% in de novo AML and 58% in secondary AML. Among responders, MRD negativity was 58% and 56%. With median follow-up of 32 months, median OS was 12.7 months (95% CI, 9.1-20.3) vs 7.2 months (95% CI, 3.6-29.9) (P = 0.61). Median RFS was 9.2 months vs 11.7 months (P = 0.56). No statistically significant differences were observed in survival, relapse or non-relapse mortality. Oral decitabine/cedazuridine plus venetoclax is an effective oral treatment for older or unfit patients with ND AML. Response rates were higher in de novo AML, while survival outcomes were not statistically significant. These findings highlight the need for improved therapeutic strategies particularly in secondary AML.

INTRODUCTION

Acute myeloid leukemia (AML) is a biologically diverse hematological malignancy that accounts for 1% of all malignancies globally and remains a leading cause of leukemia-related mortality.[1, 2] In the United States, AML is the most common form of acute leukemia in adults, with incidence increasing steadily with age and a median age at diagnosis of approximately 68 years.[3] Outcomes are particularly poor in older adults, especially those aged ≥ 75 years, due to diminished physiological reserve, comorbidities, and a higher prevalence of adverse-risk disease biology.[4, 5] Older adults with AML more commonly exhibit high-risk cytogenetic and molecular features, including complex karyotypes, and *TP53* mutations.[6, 7] In addition, AML in this age group often arises from antecedent hematologic disorders such as myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML) or myeloproliferative neoplasms (MPN) or prior cytotoxic therapy, and these secondary and therapy-related AML subtypes confer a particularly poor prognosis, often characterized by primary resistance to standard treatments and inferior overall survival.[8-10]

Although intensive chemotherapy remains standard for younger, fit patients, it is often unsuitable for older or frail individuals. Hypomethylating agents (HMAs) such as azacitidine and decitabine have historically provided modest benefits as lower-intensity therapies.[11, 12] The introduction of venetoclax, a selective BCL-2 inhibitor, has significantly improved outcomes in this population.[13, 14] When combined with HMAs, venetoclax has demonstrated high remission rates and meaningful improvements in survival. The phase III VIALE-A trial established azacitidine plus venetoclax as a new standard of care, reporting a composite complete remission (CRc) rate of 66% and a median overall survival of 14.7 months.[15] Similar efficacy has been observed with decitabine-based combinations.[16]

Venetoclax-based low-intensity regimens are now central to treating older adults with AML and those ineligible for intensive induction. These approaches typically

combine venetoclax with HMAs, or low-intensity backbones and achieved outcomes comparable to those observed with intensive chemotherapy.[15-21] However, a key limitation of these approaches is the reliance on parenteral administration, requiring frequent visits to infusion centers or hospital-based settings which may impose a substantial burden on older patients and caregivers.

Oral decitabine/cedazuridine (ASTX727), a fixed-dose combination of decitabine and the cytidine deaminase inhibitor cedazuridine, provides pharmacokinetic exposure similar to intravenous decitabine and offers the potential for entirely oral treatment regimens.[22]

We previously reported results from a prospective, single-center phase II study evaluating oral decitabine/cedazuridine in combination with venetoclax in older or unfit patients with newly diagnosed (ND) or relapsed/refractory (RR) AML, demonstrating promising clinical activity and a favorable safety profile.[23] In this updated analysis, we focus on the frontline, ND AML cohort, presenting outcomes from a larger patient population with extended follow-up. We aim to more comprehensively characterize the durability of response, survival outcomes of this fully oral regimen.

METHODS

Study design and patient characteristics

We performed a long-term follow-up analysis of a previously reported single-center phase II trial at the University of Texas MD Anderson Cancer Center evaluating oral decitabine/cedazuridine combined with venetoclax in AML.[23] This analysis focuses on the frontline cohort with data cutoff January 18, 2026.

Eligible patients were ≥18 years with AML defined by WHO 2016 criteria.[24] Patients in the frontline cohort were considered ineligible for intensive induction based on age ≥75 years or significant comorbidities (e.g., cardiac or pulmonary or Eastern

Cooperative Oncology Group (ECOG) performance status 2-3). Patients with antecedent MDS, including those previously treated with HMAs, were eligible.

Key exclusions were acute promyelocytic leukemia, active central nervous system involvement, or uncontrolled infection. The study was approved by the institutional review board and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Treatment

Patients received oral decitabine/cedazuridine (35 mg/100 mg) on days 1-5 of each 28-day cycle with venetoclax (ramp-up to 400 mg). During cycle 1, venetoclax was given for 21-28 days based on early marrow assessment performed around day 21 of cycle 1. Per protocol, treatment interruption and dose modification were permitted for prolonged cytopenia or delayed hematologic recovery, including ANC <500/µL or platelet recovery <50 $x10^9$/L beyond approximately 42 days. GCSF support and antimicrobial prophylaxis, generally including levofloxacin, voriconazole, valacyclovir, or equivalents were administered according to institutional practice.

Patients were hospitalized during the first cycle and received tumor lysis syndrome prophylaxis and antimicrobial prophylaxis according to institutional guidelines. During remission and long-term follow-up, supportive care, CBC monitoring, growth factor support, treatment modifications, were individualized according to hematologic recovery, infectious complications, and investigator discretion. CBC monitoring frequency ranged from once to twice weekly during active cytopenia to every 2-4 weeks during stable therapy. Dose modifications and delays were permitted from cycle 2 onward to manage cytopenias.[23] Treatment continued until disease progression, unacceptable toxicity, or completion of up to 24 cycles. Cycle delays of up to 56 days were allowed to support hematologic recovery. Venetoclax dosing was adjusted concomitant CYP3A inhibitors.

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Study objectives and definitions

The primary endpoint was overall response rate (ORR), defined as patients achieving complete remission (CR), CR with incomplete hematologic recovery (CRi), partial remission (PR), or morphologic leukemia-free state (MLFS), according to International Working Group criteria[24], as previously described.[23]

Secondary endpoints included overall survival (OS), relapse-free survival (RFS), duration of response (DOR), measurable residual disease (MRD) negativity, transition to allogeneic stem cell transplantation, and safety. OS was measured from treatment initiation to death from any cause, RFS and DOR from response to relapse or death.

Cytogenetic and molecular analyses used karyotyping and targeted next-generation sequencing.[25] MRD was assessed by multiparameter flow cytometry (sensitivity 0.1%).[26]

Risk stratification was reassessed according to the European LeukemiaNet (ELN) 2024 classification[27, 28] to reflect updated risk categorization in patients receiving less-intensive therapy. Patients were also categorized using the molecular prognostic risk signature (mPRS), applied as previously described.[23, 27, 29]

Predefined subgroups analysis included de novo and secondary.

Statistical Analysis

Efficacy analyses used a modified intent-to-treat approach, including all patients receiving at least one treatment cycle. Response rates were summarized with 95% confidence intervals. Time-to-event outcomes (OS, RFS, DOR) were estimated using Kaplan-Meier methods and compared using log-rank test.

Competing-risk analyses were performed to estimate cumulative incidence of relapse (CIR) and non-relapse mortality (NRM), with comparisons using Gray's test. A 60-day landmark analysis was performed to account for potential bias from early mortality.

RESULTS

Patient Characteristics

Between March 16, 2021, and January 18, 2026, 68 patients with ND AML were treated with oral decitabine/cedazuridine plus venetoclax, including 32 with de novo AML and 36 with secondary AML (Table 1). Median age was 81 years (range, 78-84) in the de novo cohort and 78 years (range, 75-82) in the secondary cohort, with a higher proportion aged ≥80 years in the de novo group (66% vs 42%). ECOG performance status was similar between groups, with ECOG 2-3 observed in 50% of patients. ELN 2024 risk distribution was comparable between cohorts. Among all included patients, antecedent myelodysplastic syndrome was present in 25 patients (37%), including 11 (16%) with prior HMA exposure, and 2 (3%) with prior venetoclax exposure. Therapy-related AML was identified in 11 patients (16%). Cytogenetic profiles differed between groups: normal karyotype was more frequent in de novo AML (53% vs 17%), whereas complex karyotype was more common in secondary AML (33% vs 19%). *NPM1* mutations were enriched in de novo AML (22% vs 6%), while *TP53* mutations occurred at similar frequencies. The most frequent mutations overall were *TET2* (37%), *ASXL1* (31%), *RUNX1* (22%), *SRSF2* (21%), *TP53* (18%), and *NRAS* (12%). Cytoreduction with hydroxyurea was administered in 6 patients (9%), with a median dose of 1.6 g/day (range, 1-4) and duration of 5 days (range, 1-7).

Treatment Exposure and Response

The median number of treatment cycles was 4 (IQR, 2-7) in de novo AML and 3 (IQR,1-8) in secondary AML (Table 2). Venetoclax schedule modification during longitudinal therapy was common, most frequently involving shortening to 14- or 7-days schedules beginning in cycle 2 or later. Progressive treatment attenuation over time was frequently observed, with some patients subsequently requiring additional reduction to 5-day or 3-day venetoclax schedules. Oral decitabine/cedazuridine schedule reductions also occurred during prolonged therapy, most commonly in 3 days schedules. The median venetoclax duration was 26 days (IQR, 21-28) in cycle 1 and 14 days (IQR, 7-21) in cycle 2. The ORR was 75% (24/32; 57-89) in de novo AML and 58% (21/36; 41-75) in secondary AML. CR occurred in 56% and 31% of patients, respectively, while CRi was observed in 19% in each group. Among responders with available samples, MRD negativity by multiparameter flow cytometry was achieved in 58% (14/24; 37-78) of de novo AML and 56% (10/18; 31-79) of secondary AML. Responses occurred early, with a median of one cycle to first response. Patients who died before response assessment were considered non-responders. Among 11 patients with prior exposure to HMAs, the ORR was 36% (4/11), including 1 CR, 2 CRi, and 1 MLFS. No response was observed in both patients with prior venetoclax exposure. Response distribution and early mortality are shown in supplementary figure 1.

Survival Outcomes

At a median follow-up of 32 months (95%CI, 25.8-NR), the median OS in the overall cohort was 10.2 months (95% CI, 5.9-15.1). Among responders, the median RFS and DOR were both 9.9 months (95% CI, 8-15.4) (Figure 2). In subgroup analysis, median OS was 12.7 months (95% CI, 9.1-20.3; 24 events) in de novo AML and 7.2 months (95% CI, 3.6-29.9; 28 events) in secondary AML (Figure 3). The 1-year and 2-year OS rates were 50.5% and 16.5% in de novo AML, and 41.7% and 31.1% in secondary AML (P = 0.61). Among patients achieving CR or CRi, RFS was 9.2 months (95% CI 6.9-15.4; 18 events) in de novo AML and 11.7 months (95% CI 7.3-NR; 13 events) in secondary AML. One-year

RFS rates were 31.6% and 48.5%, respectively (*P* = 0.56) (Supplementary figure 2). DOR showed a similar pattern to RFS, with median DOR of 9.2 months in de novo AML and 11.7 months in secondary AML. One-year DOR rates were 34.7% and 51.7%, respectively (*P* = 0.56). At data cutoff, 8 patients remained on treatment. The most common reason for treatment discontinuation was disease progression occurring in 51 patients (75%), including relapses in 28 patients (41%) and refractory disease in 23 patients (34%). Two patients proceeded with allogeneic stem cell transplantation (SCT). Other reasons included comorbidities (4%), loss to follow-up (3%), prolonged cytopenia (1%), and hospice or treatment refusal (4%), including one patient who elected to switch to another medication. Individual patient treatment duration, best response, relapse, and survival status are summarized in supplementary figure 4.

Subgroup Analyses

According to ELN 2024 classification, median OS was 15.1 months (95% CI, 10.4-34.3) in the favorable-risk group, 9.1 months (95% CI, 4.7-NR) in the intermediate-risk group, and 2.0 months (95% CI, 1.7-NR) in the adverse-risk group (*P* < 0.001) (Figure 4B). Their one-year OS rates were 62.5%, 22.5%, and 16.7%, respectively (*P* < 0.001). The mPRS stratification demonstrated clear separation of outcomes, with median OS of 16.2, 9.4, and 2.0 months in the high-, intermediate-, and low-benefit groups, respectively (*P* <0.001) (Figure 4C). Corresponding one-year OS rates were 59.5%, 36.4%, and 16.7%. CR/CRi rates were 68%, 67%, and 33% across these groups. No significant difference in OS was observed between patients aged <80 years and ≥80 years (*P* = 0.236) (Figure 4A). RFS did not differ significantly across ELN 2024, mPRS, or age subgroups. Patients with de novo AML received a median of 4 treatment cycles (IQR, 2-7), whereas those with secondary AML received a median of 3 cycles (IQR, 1-8).

Safety and Adverse Events

At least one treatment-emergent adverse event (TEAE) of any grade occurred in 79% (54/68) of patients, and grade ≥3 events in 65% (44/68) (Table 3). The most common all-grade non-infectious adverse events were constipation (18%), fatigue (18%), nausea (18%), and oral mucositis (16%). The most frequent grade ≥3 events were thrombocytopenia (15%), febrile neutropenia (12%), and fatigue (7%). Infections occurred in 28% of patients, most commonly pneumonia (9%) and sepsis (6%). A total of four fatal grade 5 TEAEs were reported, comprising one case each of sepsis, gastrointestinal hemorrhage, cerebral hemorrhage, and respiratory failure. Notably, three of these events observed in patients who were in remission, specifically due to sepsis, gastrointestinal hemorrhage, and respiratory failure and were considered potentially treatment-related deaths. Early mortality was low in de novo AML (6% in both 4 and 8 weeks). In secondary AML, 4-week and 8-week mortality rates were 8% and 22%, respectively; most deaths occurred in non-responders and were attributable to progressive disease.

Competing risks

Among patients achieving CR/CRi, relapse occurred more frequently in de novo AML, whereas non-relapse mortality (NRM) was more common in secondary AML (Supplementary figure 3). The 2-year cumulative incidence of relapse was 73.3% in de novo AML and 40.9% in secondary AML, while NRM was 4.2% and 16.7%, respectively. The difference in relapsed incidence was not statistically significant (Gray's test $P = 0.086$). In a 60-day landmark analysis including patients alive and relapse-free at day 60, relapse remained numerically higher in de novo AML, with 2-year cumulative incidence of 70.8% versus 55.6% in secondary AML. Post-landmark NRM was low and similar between groups (4.5% vs 6.2%). These differences were not statistically significant (Gray's test $P = 0.282$).

Myelosuppression and Dose Adjustments

Among patients achieving platelet recovery >50×10⁹/L (62%), the median time to platelet recovery was 24 days (IQR 20-31). Neutrophil recovery >1×10⁹/L (46%) occurred at a median of 41 days (IQR 30-48). Median time to cycle 2 initiation was 36 days (IQR 27-46). Granulocyte colony-stimulating factor was used in 26% of patients during cycle 1 and in 39% overall. Venetoclax dose reductions were required in 59% of patients by cycle 2, and 19% required dose reduction of both agents. Among patients achieving CR/CRi, the median cycle length was 42 days (IQR, 36-49). Th median oral decitabine/ cedazurine dose duration per cycle was 4 days (IQR, 3-5), while the median venetoclax duration per cycle across longitudinal treatment cycles was 7 days (IQR, 4-14).

DISCUSSION

In this extended follow-up analysis, we evaluated the long-term outcomes of oral decitabine/cedazuridine plus venetoclax in older or unfit patients with newly diagnosed AML. With a median follow-up of 32 months, this regimen demonstrated clinical activity in a high-risk population, although relapses were common. Nevertheless, some patients maintained durable remissions at extended follow up, highlighting heterogeneity in treatment responses.

The efficacy observed in this study is broadly consistent with outcomes reported for other venetoclax-based lower-intensity regimens in older AML populations, including the VIALE-A trial. In our cohort, response rates particularly among patients with de novo AML, were comparable to those reported with HMA-venetoclax combinations.[15,30] Our findings support the use of oral decitabine/cedazuridine as an alternative HMA backbone. However, overall survival appeared shorter than that reported in VIALE-A, likely reflecting the biological risk profile of our study population including a substantial proportion of patients with secondary AML, antecedent hematologic disorders, adverse cytogenetics, or *TP53* mutations, which are associated with resistance to venetoclax-based therapy and inferior outcomes.[31, 32]

A key finding of this study is the continued importance of AML biology in determining outcomes despite treatment with venetoclax-based therapy. Patients with de novo AML demonstrated higher response rates, with a trend toward improved survival compared with secondary AML; however, this did not reach statistical significance. The crossing of Kaplan-Meier curves suggests temporal heterogeneity in outcomes, with consistently higher relapses in de novo AML and a greater contribution of early NRM in secondary AML, and these findings should be interpreted with caution given the small sample size. Prior studies have shown that AML arising from antecedent hematologic disorders or previous cytotoxic therapy is associated with poorer clinical outcomes.[33, 34]

Competing risk analyses among patients achieving CR/CRi showed that relapse was numerically more frequent in de novo AML, whereas NRM contributed more substantially to secondary AML, although differences were not statistically significant. A 60-day landmark analysis showed similar trends. These findings suggest potential differences in patterns of treatment failure between biologic subtypes, although they remain exploratory.

Molecular risk stratification further supported the biological heterogeneity of this cohort. The ELN 2024 classification retained prognostic value, with clear separation of outcomes across risk groups.[28] The molecular prognostic risk signature (mPRS) incorporating *TP53, FLT3-ITD,* and *RAS*-pathway mutations, also showed significant prognostic value for OS. In contrast, differences in RFS were not statistically significant, suggesting the prognostic impact of mPRS is not driven by differences in relapse risk. This may reflect biological determinants of sensitivity to venetoclax-based therapy, as mutations such as *TP53, FLT3-ITD*, and *RAS*-pathway alterations are associated with reduced *BCL-2* dependence and relative resistance to venetoclax.[31, 35, 36]

The absence of a clear overall survival difference by age, with a numerical trend favoring patients aged ≥ 80 years (figure 4A), was observed and should be interpreted with caution given the small sample size.

Compared with VIALE-A[15], fewer treatment cycles were administered in our cohort, reflecting the more advanced age of the patients, adverse-risk disease biology, high prevalence of secondary AML, cumulative toxicities requiring longitudinal treatment attenuation. These findings likely reflect the challenges of delivering prolonged based therapy in older AML patients with adverse-risk disease.

The safety profile observed in this extended follow-up analysis was consistent with that reported for venetoclax based regimens.[15,16,30] Although grade ≥3 febrile neutropenia occurred in only 12% of patients, lower than reported in many HMA-venetoclax studies, this may partly reflect early treatment delays and venetoclax schedule attenuation for cytopenia in our cohort. However, infectious complications were the most frequent adverse events in our cohort. Compared with VIALE-A data[15], the median neutrophil recovery in our cohort was broadly comparable, whereas platelet recovery appeared somewhat shorter. However, cross-study comparisons should be interpreted with caution given differences in patient populations, supportive care and treatment adjustment. Despite these toxicities, early mortality remained relatively low in the de novo AML cohort, supporting the feasibility of this regimen when paired with appropriate supportive care.

Outcomes in our cohort are broadly consistent with findings reported by Madarang et al. in octogenarian and nonagenarian AML patients treated with venetoclax-based lower-intensity regimens, supporting the feasibility of venetoclax/HMA therapy in very elderly patients.[37] Similarly, treatment schedule attenuation and individualized venetoclax duration reduction were frequently required during prolonged therapy to mitigate myelosuppression and delayed hematologic recovery.

A practical advantage of this regimen is its fully oral administration. Oral decitabine/cedazuridine achieves systemic decitabine exposure comparable to

intravenous decitabine through inhibition of cytidine deaminase, enabling oral delivery of a drug that previously required intravenous administration.[38] When combined with venetoclax, this approach provides a completely oral treatment regimen, potentially reducing treatment burden and improving access for older adults who may face challenges attending frequent infusion appointments.

This study has a few limitations. It was conducted at a single center and included a relatively small patient population, particularly within biology-defined subgroups. Additionally, the lack of a randomized comparator arm limits the ability to directly compare outcomes with other venetoclax-based regimens. Nonetheless, the extended follow-up and the focus on disease biology offer meaningful insights into patterns of response and treatment failure among patients receiving this regimen.

In conclusion, oral decitabine/cedazuridine in combination with venetoclax is an effective oral treatment option for older or unfit patients with newly diagnosed AML. In this extended follow-up analysis, disease biology remained a key determinant of outcomes with distinct outcome patterns observed between de novo and secondary AML. These findings highlight the continued unmet need for improved therapeutic strategies in patients with secondary AML. Future studies evaluating treatment-free remission strategies and optimized maintenance duration following deep remission achievement may further refine long-term management approaches for older AML patients receiving venetoclax based therapy. These studies are likely best designed with detailed MRD analysis, further optimizing the decision-making process.

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Table 1. Baseline patient characteristics

		De novo ND AML (n=32)	Secondary ND AML (n=36)
Age, years		81 (78-84)	78 (75-82)
Sex			
	Male	25 (78%)	20 (56%)
	Female	7 (22%)	16 (44%)
Ethnicity			
	White	29 (91%)	31 (86%)
	Black	1 (3%)	4 (11%)
	Asian	1 (3%)	1 (3%)
	Others or did not answer	1 (3%)	0
Eastern Cooperative Oncology Group performance status			
	0	1 (3%)	2 (6%)
	1	13 (41%)	18 (50%)
	2	17 (53%)	16 (44%)
	3	1 (3%)	0
White blood cell count x 10^9/L		2.7 (1.5-7.1)	2.9 (2-6.9)
Hemoglobin, g/dL		8.9 (8-9.4)	8.3 (7.8-9.1)
Creatinine, mg/dL		1.08 (0.9-1.2)	1.03 (0.76-1.19)
Total bilirubin, mg/dL		0.6 (0.5-1)	0.4 (0.3-0.9)
Bone marrow blasts, %		32 (23-64)	23 (20-37.5)
Cytogenetics			
	Normal	17 (53%)	6 (17%)
	Other intermediate	3 (9%)	14 (39%)
	11q23-rearranged	1 (3%)	1 (3%)
	Inv (3)/t(3,3)	1 (3%)	2 (6%)
	-5/5q-	5 (16%)	8 (22%)
	-7/7q-	5 (16%)	8 (22%)
	-17/17p-	3 (9%)	1 (2%)
	Complex	6 (19%)	12 (33%)
Mutations			
	NPM1	7 (22%)	2 (6%)
	FLT3-ITD	3 (9%)	1 (3%)
	IDH1/IDH2	3 (9%)	0
	TP53	5 (16%)	7 (19%)
European LeukemiaNet 2024 risk			
	Favorable	19 (59%)	22 (61%)
	Intermediate	8 (25%)	7 (19%)
	Adverse	5 (16%)	7 (19%)

Previous untreated myelodysplastic syndrome or myeloproliferative neoplasm		10 (28%)
Previous treated myelodysplastic syndrome or myeloproliferative neoplasm		15 (42%)
Therapy-related acute myeloid leukemia		11 (31%)

Data shown as n (%) or median (IQR), ND AML, newly diagnosed acute myeloid leukemia

Table 2. Responses in intention-to-treat analysis

	De novo ND AML (n=32)	Secondary ND AML (n=36)
ORR†	24 (75%; 57-89)	21 (58%; 41-75)
CRc	24 (75%; 57-89)	18 (50%; 33-67)
CR	18 (56%; 38-74)	11(31%; 16-48)
CRi	6 (19%; 7-36)	7 (19%; 8-36)
MLFS	0	3 (8%; 2-23)
PR	0	0
4-week mortality	2 (6%; 1-21)	3 (8%; 2-23)
8-week mortality	2 (6%; 1-21)	8 (22%; 10-39)
MRD negativity (all patients)	14 (44%; 27-61)	10 (28%; 14-45)
MRD negativity (CR/CRi)	14 (58%;37-78)	10 (56%; 31-79)
Cycles to first response	1 (1-1)	1 (1-1)
Cycles to best response	1 (1-1)	1 (1-1)
Total cycles given	4 (2-7)	3 (1-8)

Data are n (%; 95% CI) or median (IQR). †Overall response rate (ORR) is the sum of complete remission (CR), complete remission with incomplete blood count recovery (CRi), partial remission (PR), and morphologic leukemia-free state (MLFS). CRc denotes composite complete remission (CR + CRi).

Table 3. Treatment emergent adverse events

Events	Any grade n (%)	Grade ≥3 n (%)
Hematologic		
Neutrophil count decreased	7 (10%)	7 (10%)
Platelet count decreased	10 (15%)	10 (15%)
Febrile neutropenia	8 (12%)	8 (12%)
Non-hematologic (including infectious)		
Constipation	12 (18%)	1 (1%)
Nausea	12 (18%)	0
Fatigue	12 (18%)	5 (7%)
Mucositis (oral)	11 (16%)	2 (3%)
Diarrhea	9 (13%)	2 (3%)
Fall	7 (10%)	4 (6%)
Vomiting	6 (9%)	1 (1%)
Alaine aminotransferase increased	6 (9%)	2 (3%)
Dizziness	6 (9%)	0
Pneumonia	6 (9%)	6 (9%)
Headache	5 (7%)	0
Sepsis	4 (6%)	4 (6%)
Confusion	4 (6%)	1 (1%)
Atrial fibrillation	4 (6%)	4 (6%)
Insomnia	4 (6%)	0
COVID-19	3 (4%)	3 (4%)
Abdominal distension	3 (4%)	0
Failure to thrive	3 (4%)	3 (4%)
Deep vein thrombosis (DVT)	3 (4%)	3 (4%)
Anorexia	2 (3%)	1 (1%)
Respiratory failure	1 (1%)	1 (1%)
Gastrointestinal hemorrhage	1 (1%)	1 (1%)
Arthralgia	1 (1%)	1 (1%)
Leukocytosis	1 (1%)	1 (1%)
Altered mental status	1 (1%)	1 (1%)
Skin bleeding	1 (1%)	1 (1%)
Angioedema	1 (1%)	1 (1%)
Anterior uveitis	1 (1%)	1 (1%)
Bone pain	1 (1%)	1 (1%)
Colonic obstruction	1 (1%)	1 (1%)
Bacteremia	1 (1%)	1 (1%)
Ischemic stroke	1 (1%)	1 (1%)
Pericardial effusion	1 (1%)	1 (1%)
Renal insufficiency	1 (1%)	1 (1%)
Bacteremia	1 (1%)	1 (1%)
Urinary tract infection	1 (1%)	1 (1%)
Clostridium difficile colitis	1 (1%)	1 (1%)
Diverticulitis	1 (1%)	1 (1%)
Epididymitis	1 (1%)	1 (1%)
Sinusitis	1 (1%)	1 (1%)

Data is presented as number of patients (%), n=68, patients may have experienced more than one adverse event; therefore, counts may exceed the total number of patients. A total of 54 patients experienced at least one treatment-emergent adverse event, including 44 with grade ≥3 events. Fatal (grade 5 events) are not included in the table and are described separately in the text.

Figure Legends

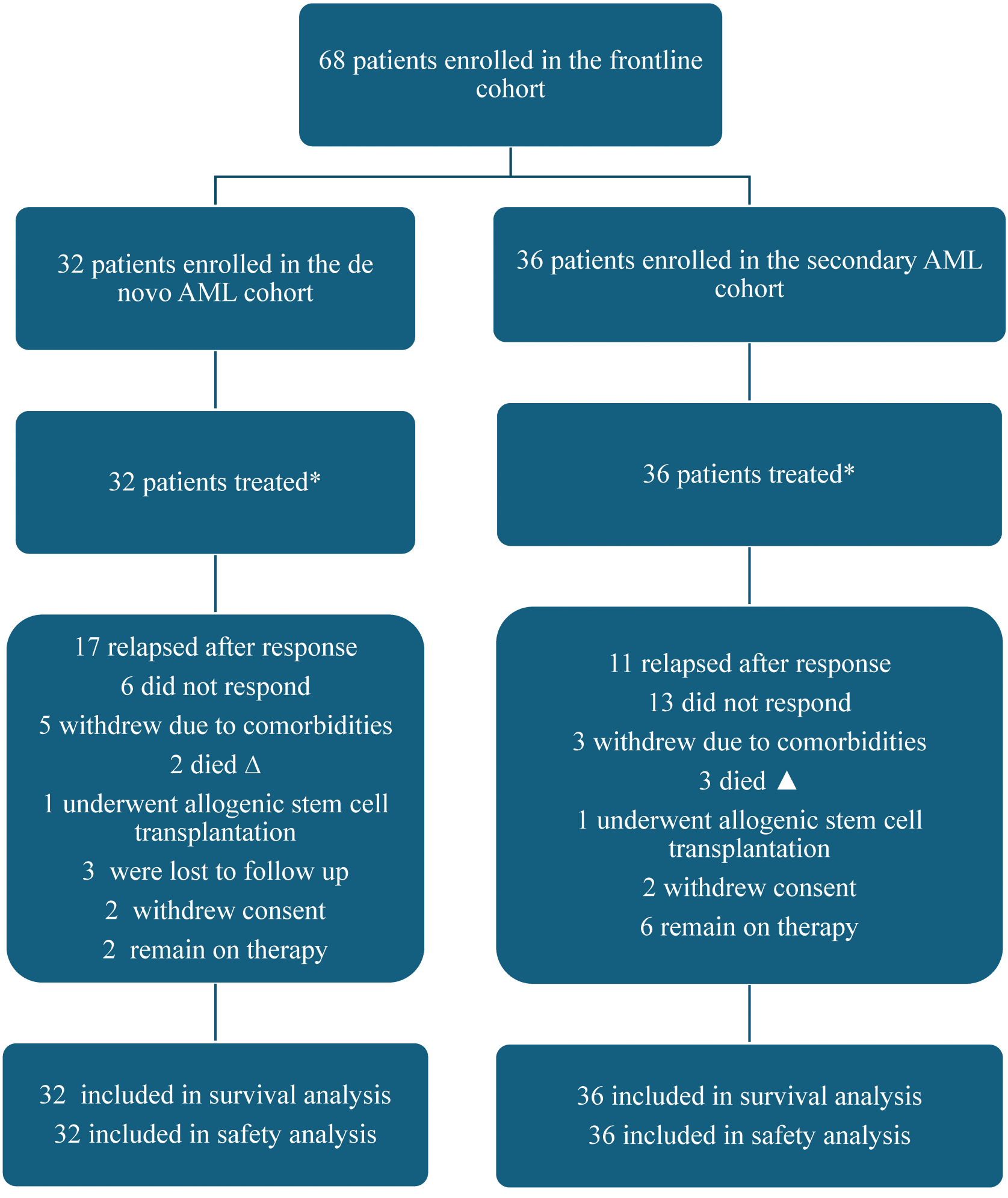
Figure 1. Trial profile

Eligible patients were treated with decitabine (35 mg) and cedazuridine (100 mg) on days 1-5 plus venetoclax 100 mg on day 1, 200 mg on day 2, then 400 mg on days 3-21 or 28. Venetoclax was stopped at day 21 if bone marrow showed blast clearance. ∆ Two patients died before response assessment; one opted for hospice care, and one died from underlying end stage chronic kidney disease (hospice care), ▲ Two patients died before response assessment; one died from pneumonia and respiratory failure, one died from ischemic cerebrovascular accident with pneumonia, and one died from pneumonia. Patients who died before bone marrow response assessment were considered non-responders in the intention-to-treat analysis. *Outcomes during follow-up are not mutually exclusive; individual patients may be represented in more than one category.*

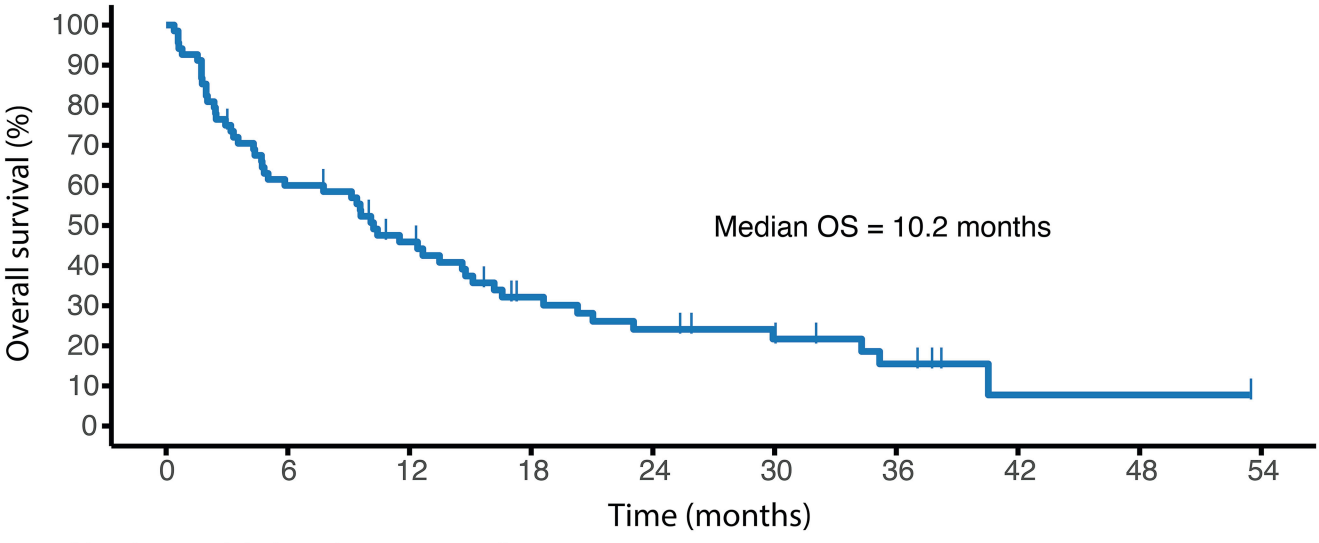
Figure 2. Overall survival (OS), relapse-free survival (RFS), and duration of response (DOR) in the overall frontline cohort (A) OS (B) RFS among patients achieving CR or CRi. (C) DOR among patients achieving CR or CRi.

Figure 3. OS, RFS, DOR in frontline cohort subgroup analysis comparing de novo AML (DN-AML) and secondary AML (sAML) (A) OS (B) RFS among patients achieving CR or CRi. (C) DOR among patients achieving CR or CRi. mo: months

Figure 4. Overall survival in the overall frontline cohort (A) Stratified by age categories (80 years vs ≥80 years). (B) Stratified by ELN 2024 risk. (C) Stratified by the molecular prognostic risk signature (mPRS). ELN = European LeukemiaNet; mPRS-H = higher benefit, mPRS-I = intermediate benefit, mPRS-L = lower benefit. mo: months


68 patients enrolled in the frontline cohort
32 patients enrolled in the de novo AML cohort
36 patients enrolled in the secondary AML cohort
32 patients treated*
36 patients treated*
17 relapsed after response
6 did not respond
5 withdrew due to comorbidities
2 died Δ
1 underwent allogenic stem cell transplantation
3 were lost to follow up
2 withdrew consent
2 remain on therapy
11 relapsed after response
13 did not respond
3 withdrew due to comorbidities
3 died ▲
1 underwent allogenic stem cell transplantation
2 withdrew consent
6 remain on therapy
32 included in survival analysis
32 included in safety analysis
36 included in survival analysis
36 included in safety analysis

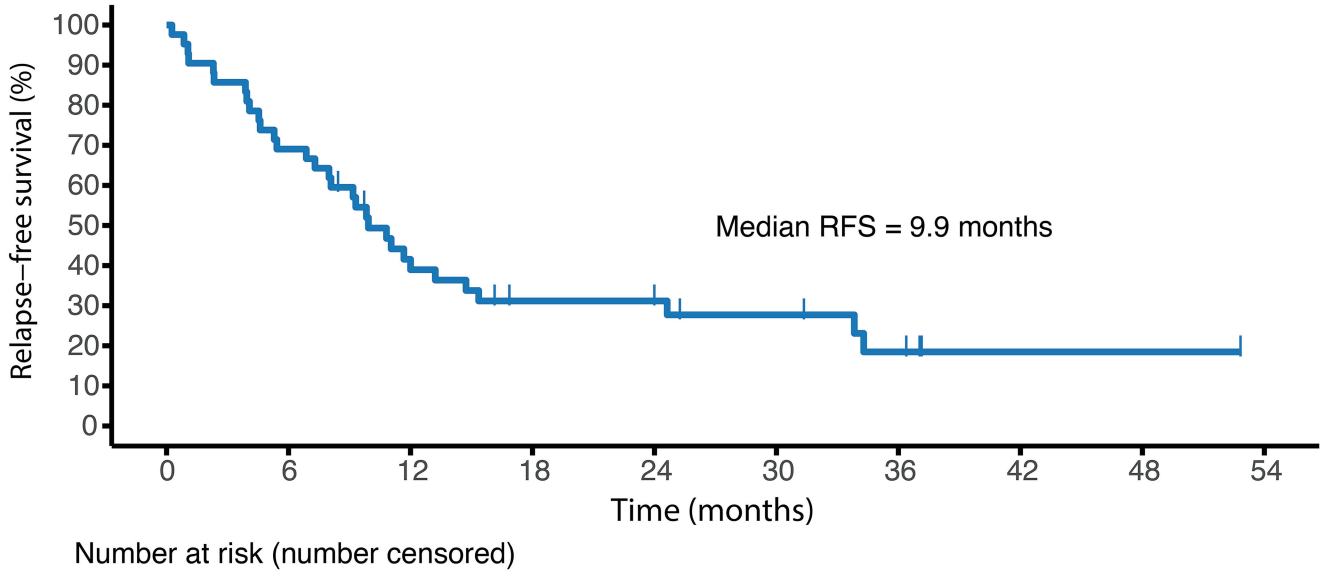
A



Number at risk (number censored)

68 (0)	40 (1)	28 (4)	16 (8)	12 (8)	8 (11)	5 (12)	1 (15)	1 (15)	0 (16)

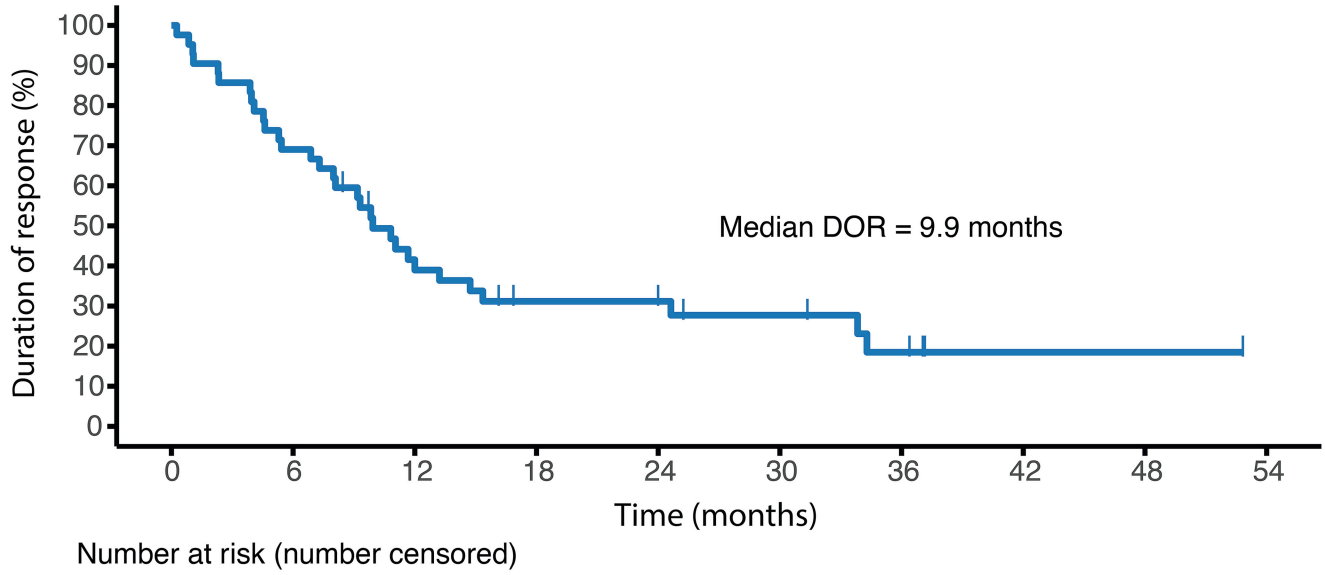
B



Number at risk (number censored)

42 (0)	29 (0)	15 (2)	10 (4)	9 (5)	7 (6)	4 (7)	1 (10)	1 (10)	0 (11)

C



Number at risk (number censored)

42 (0)	29 (0)	15 (2)	10 (4)	9 (5)	7 (6)	4 (7)	1 (10)	1 (10)	0 (11)

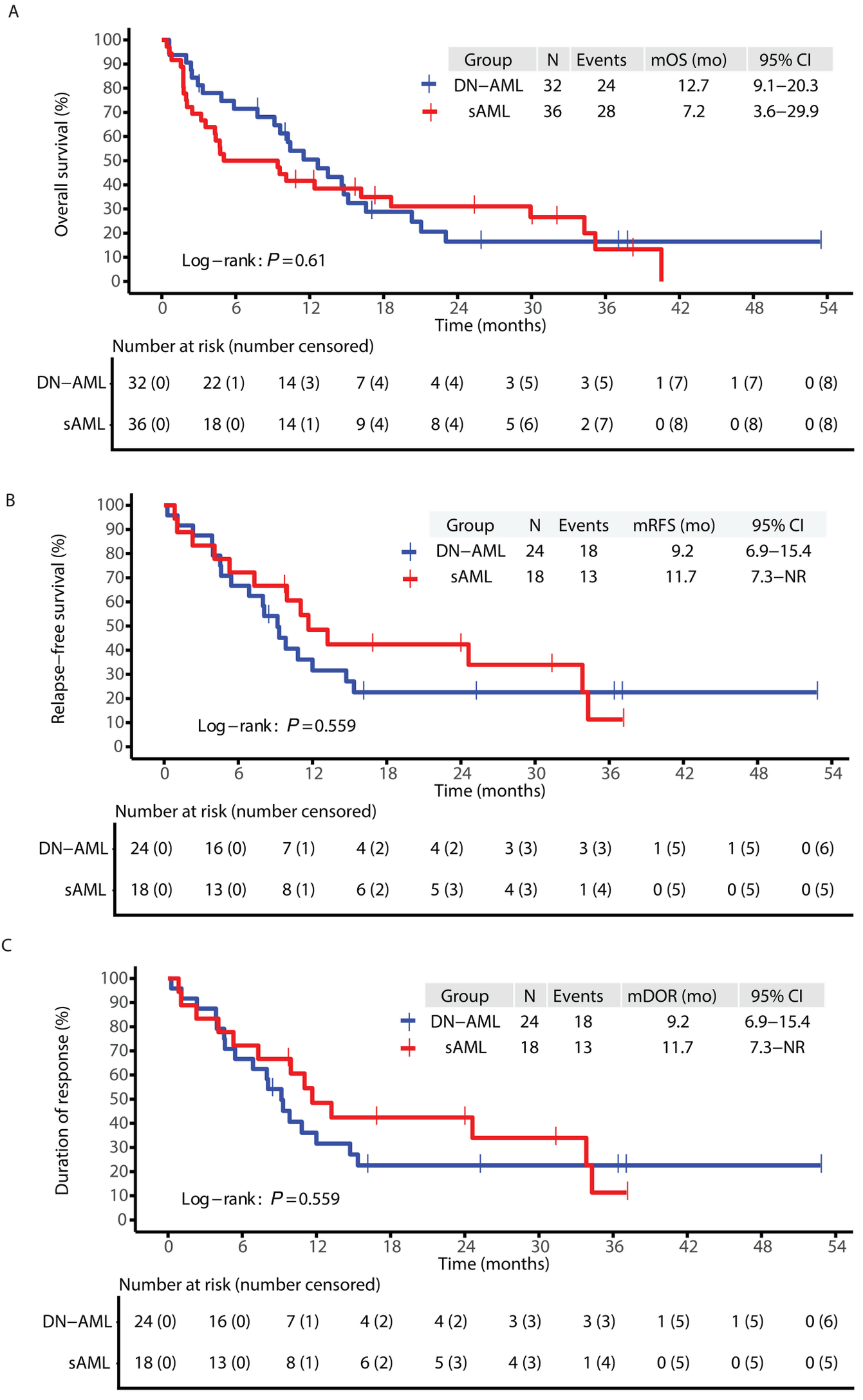
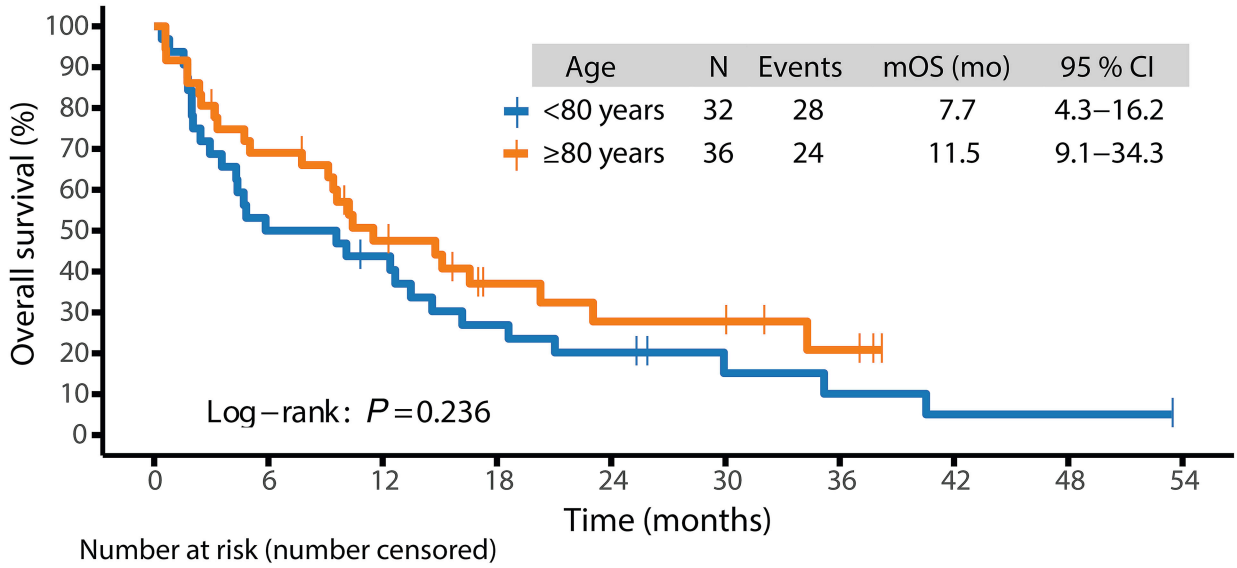

A
Overall survival (%)
Group N Events mOS (mo) 95% CI
DN–AML 32 24 12.7 9.1–20.3
sAML 36 28 7.2 3.6–29.9
Log–rank: P = 0.61
Time (months)
Number at risk (number censored)
DN–AML 32 (0) 22 (1) 14 (3) 7 (4) 4 (4) 3 (5) 3 (5) 1 (7) 1 (7) 0 (8)
sAML 36 (0) 18 (0) 14 (1) 9 (4) 8 (4) 5 (6) 2 (7) 0 (8) 0 (8) 0 (8)
B
Relapse–free survival (%)
Group N Events mRFS (mo) 95% CI
DN–AML 24 18 9.2 6.9–15.4
sAML 18 13 11.7 7.3–NR
Log–rank: P = 0.559
Time (months)
Number at risk (number censored)
DN–AML 24 (0) 16 (0) 7 (1) 4 (2) 4 (2) 3 (3) 3 (3) 1 (5) 1 (5) 0 (6)
sAML 18 (0) 13 (0) 8 (1) 6 (2) 5 (3) 4 (3) 1 (4) 0 (5) 0 (5) 0 (5)
C
Duration of response (%)
Group N Events mDOR (mo) 95% CI
DN–AML 24 18 9.2 6.9–15.4
sAML 18 13 11.7 7.3–NR
Log–rank: P = 0.559
Time (months)
Number at risk (number censored)
DN–AML 24 (0) 16 (0) 7 (1) 4 (2) 4 (2) 3 (3) 3 (3) 1 (5) 1 (5) 0 (6)
sAML 18 (0) 13 (0) 8 (1) 6 (2) 5 (3) 4 (3) 1 (4) 0 (5) 0 (5) 0 (5)

Figure 3

A

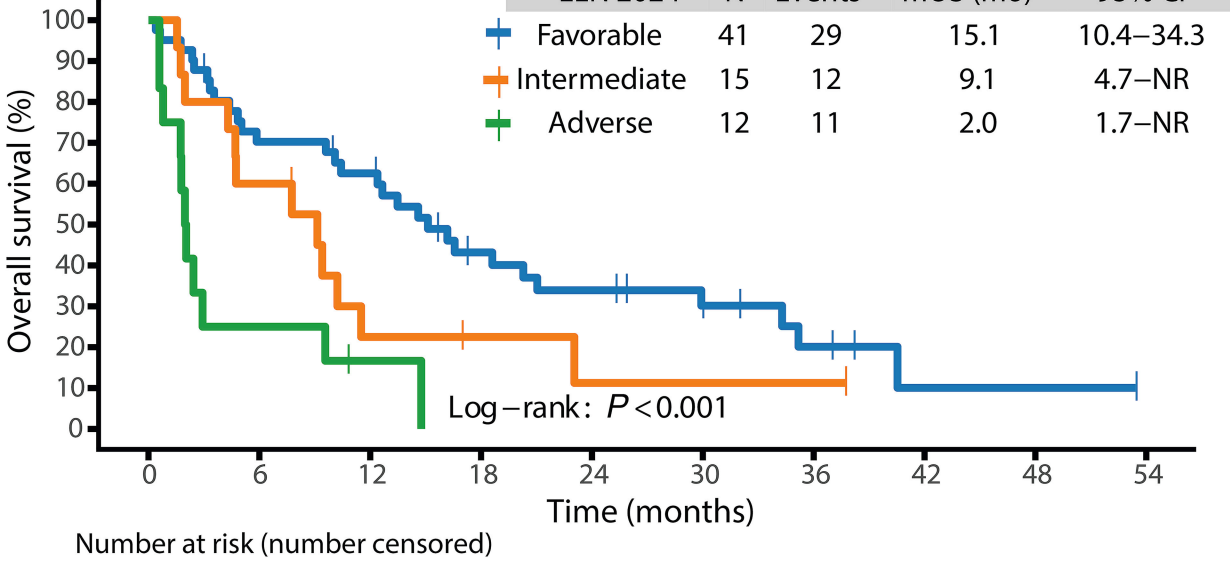


Age	N	Events	mOS (mo)	95 % CI
<80 years	32	28	7.7	4.3–16.2
≥80 years	36	24	11.5	9.1–34.3

Number at risk (number censored)

<80 years	32 (0)	16 (0)	13 (1)	8 (1)	6 (1)	3 (3)	2 (3)	1 (3)	1 (3)	0 (4)
≥80 years	36 (0)	24 (1)	15 (3)	8 (7)	6 (7)	5 (8)	3 (9)	0 (12)	0 (12)	0 (12)

B

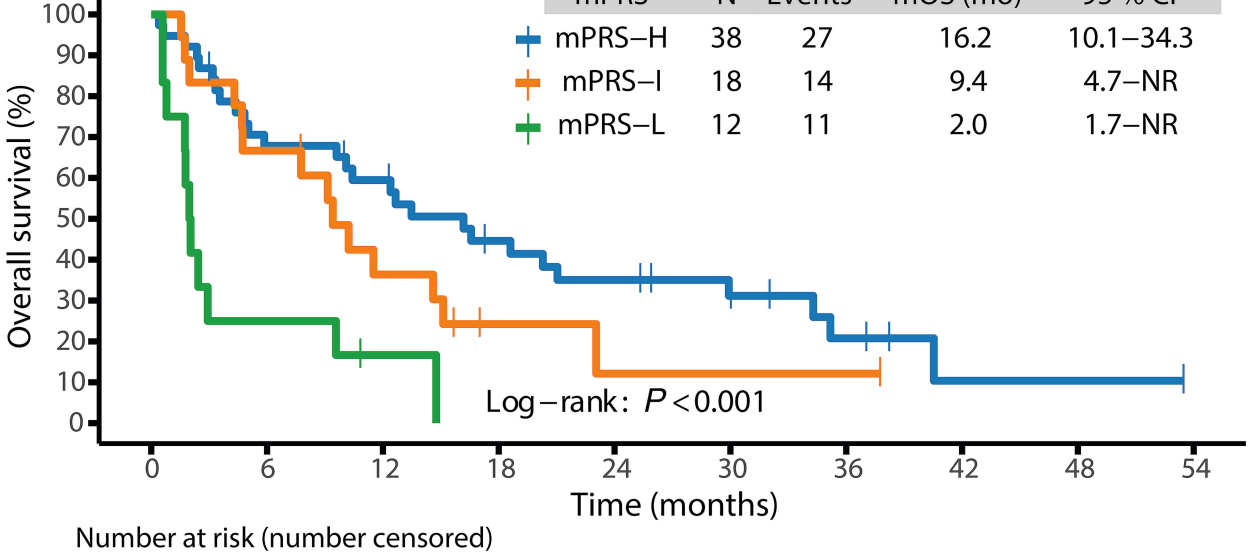


ELN 2024	N	Events	mOS (mo)	95% CI
Favorable	41	29	15.1	10.4–34.3
Intermediate	15	12	9.1	4.7–NR
Adverse	12	11	2.0	1.7–NR

Number at risk (number censored)

Favorable	41 (0)	28 (1)	24 (2)	14 (5)	11 (5)	7 (8)	4 (9)	1 (11)	1 (11)	0 (12)
Intermediate	15 (0)	9 (0)	3 (1)	2 (2)	1 (2)	1 (2)	1 (2)	0 (3)	0 (3)	0 (3)
Adverse	12 (0)	3 (0)	1 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)

C



mPRS	N	Events	mOS (mo)	95 % CI
mPRS−H	38	27	16.2	10.1–34.3
mPRS−I	18	14	9.4	4.7–NR
mPRS−L	12	11	2.0	1.7–NR

Number at risk (number censored)

mPRS−H	38 (0)	25 (1)	21 (2)	14 (4)	11 (4)	7 (7)	4 (8)	1 (10)	1 (10)	0 (11)
mPRS−I	18 (0)	12 (0)	6 (1)	2 (3)	1 (3)	1 (3)	1 (3)	0 (4)	0 (4)	0 (4)
mPRS−L	12 (0)	3 (0)	1 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)

Supplementary Appendix

Figure legends

Supplementary Figure 1. Response and early mortality in frontline cohort.

Supplementary Figure 2. Relapse-free survival in the overall frontline cohort (A) Stratified by age categories (80 years vs ≥80 years). (B) Stratified by ELN 2024 risk. (C) Stratified by the molecular prognostic risk signature. ELN = European LeukemiaNet; mPRS-H = high benefit, mPRS-I = intermediate benefit, mPRS-L = low benefit. mo: months

Supplementary Figure 3. Cumulative incidence of relapse and death in remission among CR/CRi patients (A) overall, (B) 60-day landmark analysis.

Supplementary Figure 4. Swimmer plot of treatment duration and clinical outcomes.

Supplementary Figure 1. Response and early mortality in frontline cohort.

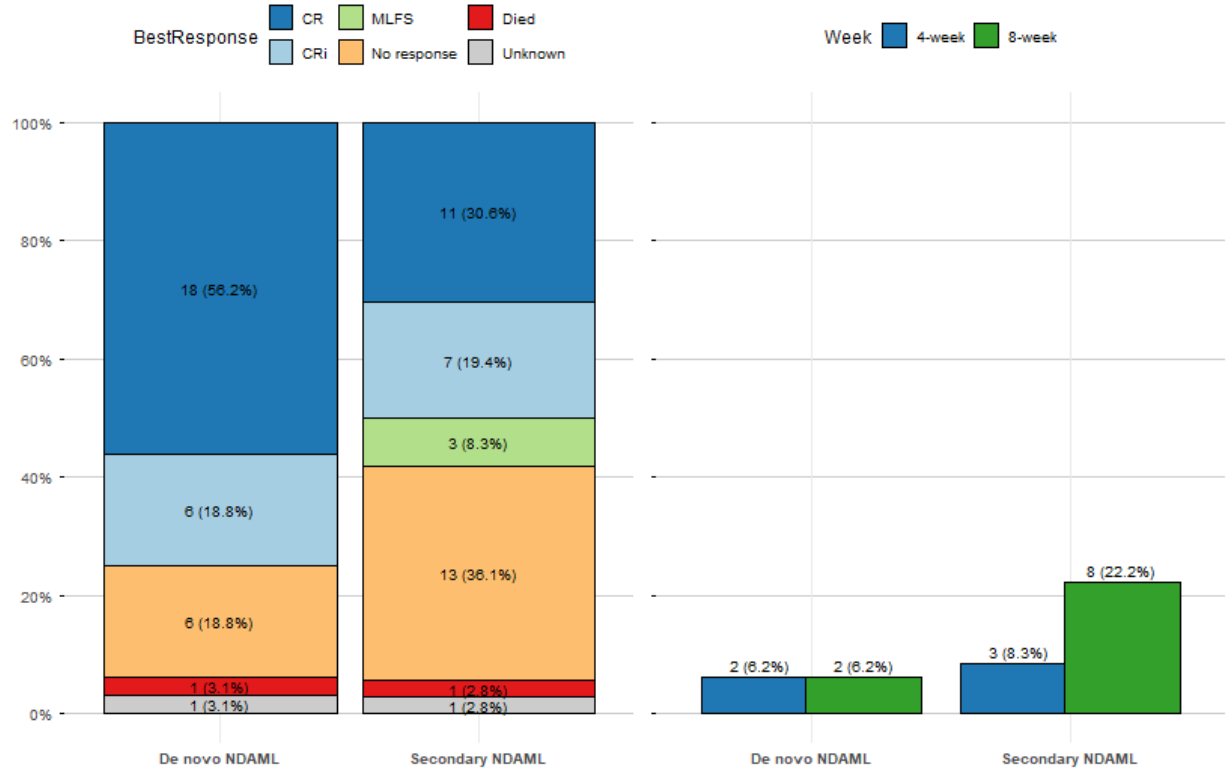
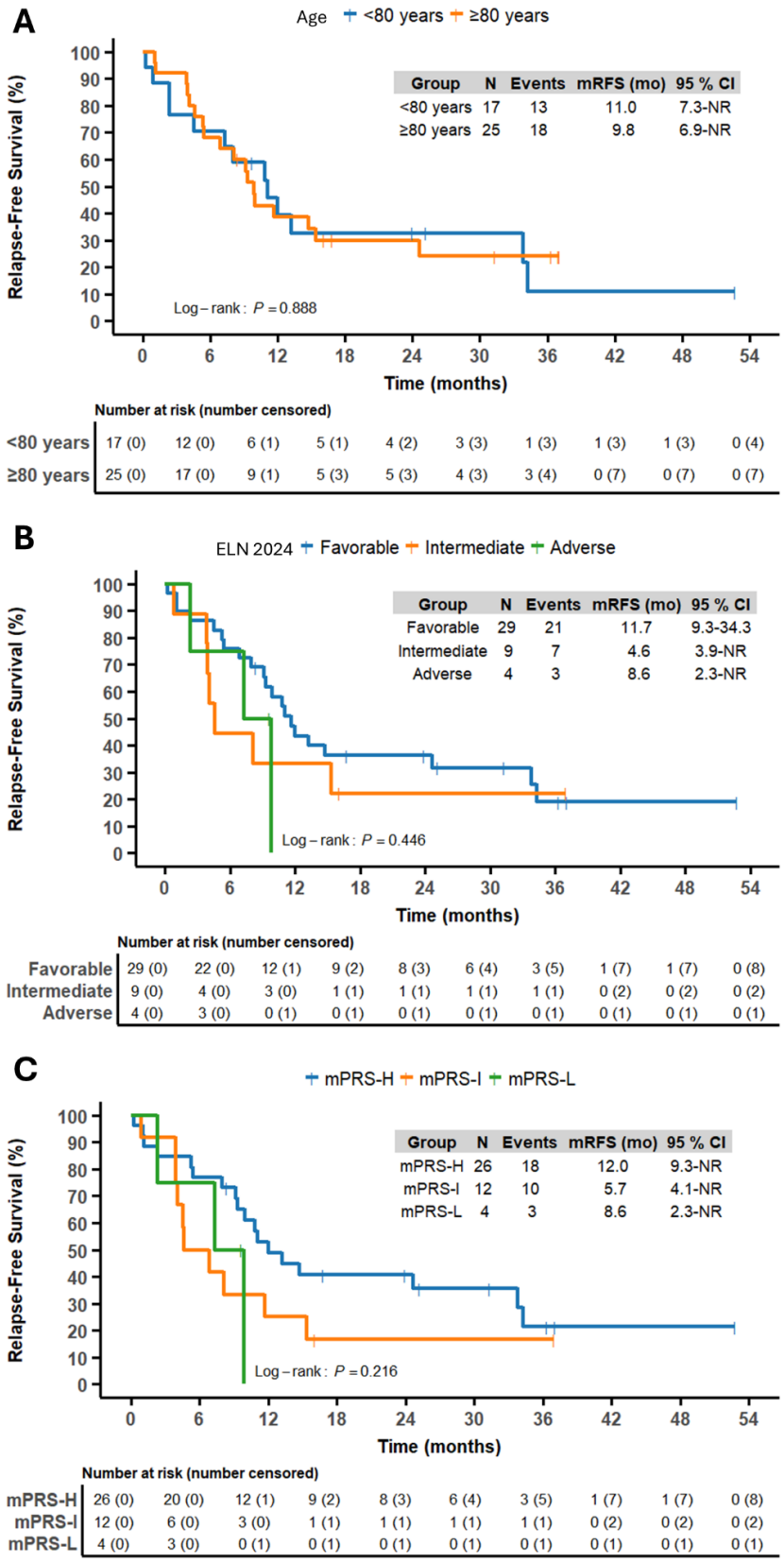


Figure.1A Figure.1B

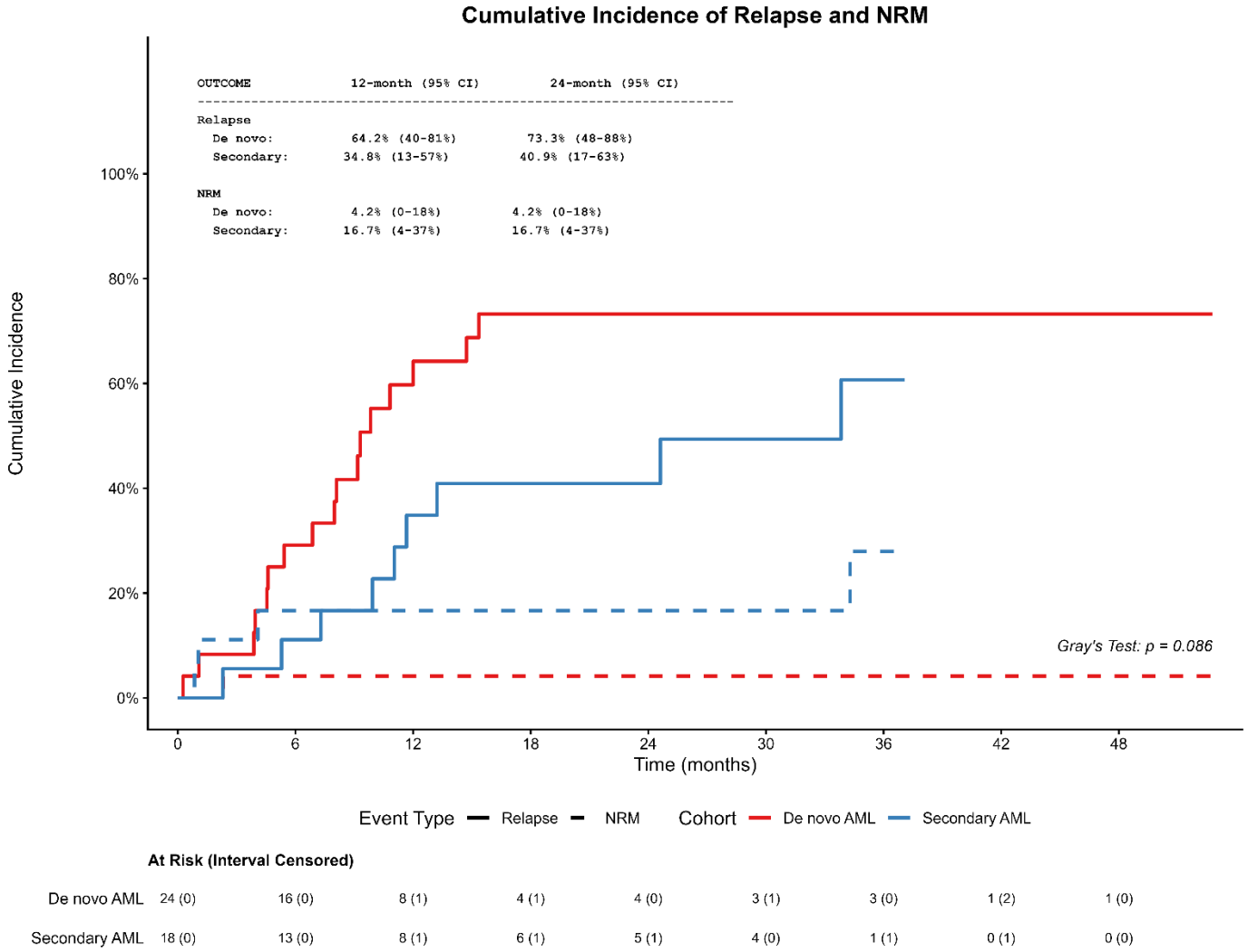
(A) Stacked bar plot showing best treatment response. Responses include complete remission (CR), CR with incomplete count recovery (CRi), morphologic leukemia-free state (MLFS), partial remission (PR), no response, and death. The numbers within each bar represent the count and percentage of patients. De novo NDAML and Secondary NDAML are shown separately.
(B) Early mortality at 4 and 8 weeks after treatment initiation, stratified by AML type. Bars indicate the percentage of patients who died, with the numbers in the bars representing absolute counts and percentages.

Supplementary Figure 2. Relapse-free survival in the overall frontline cohort (A) Stratified by age categories (80 years vs ≥80 years). (B) Stratified by ELN 2024 risk. (C) Stratified by the molecular prognostic risk signature. ELN = European LeukemiaNet; mPRS-H = high benefit, mPRS-I = intermediate benefit, mPRS-L = low benefit. mo: months

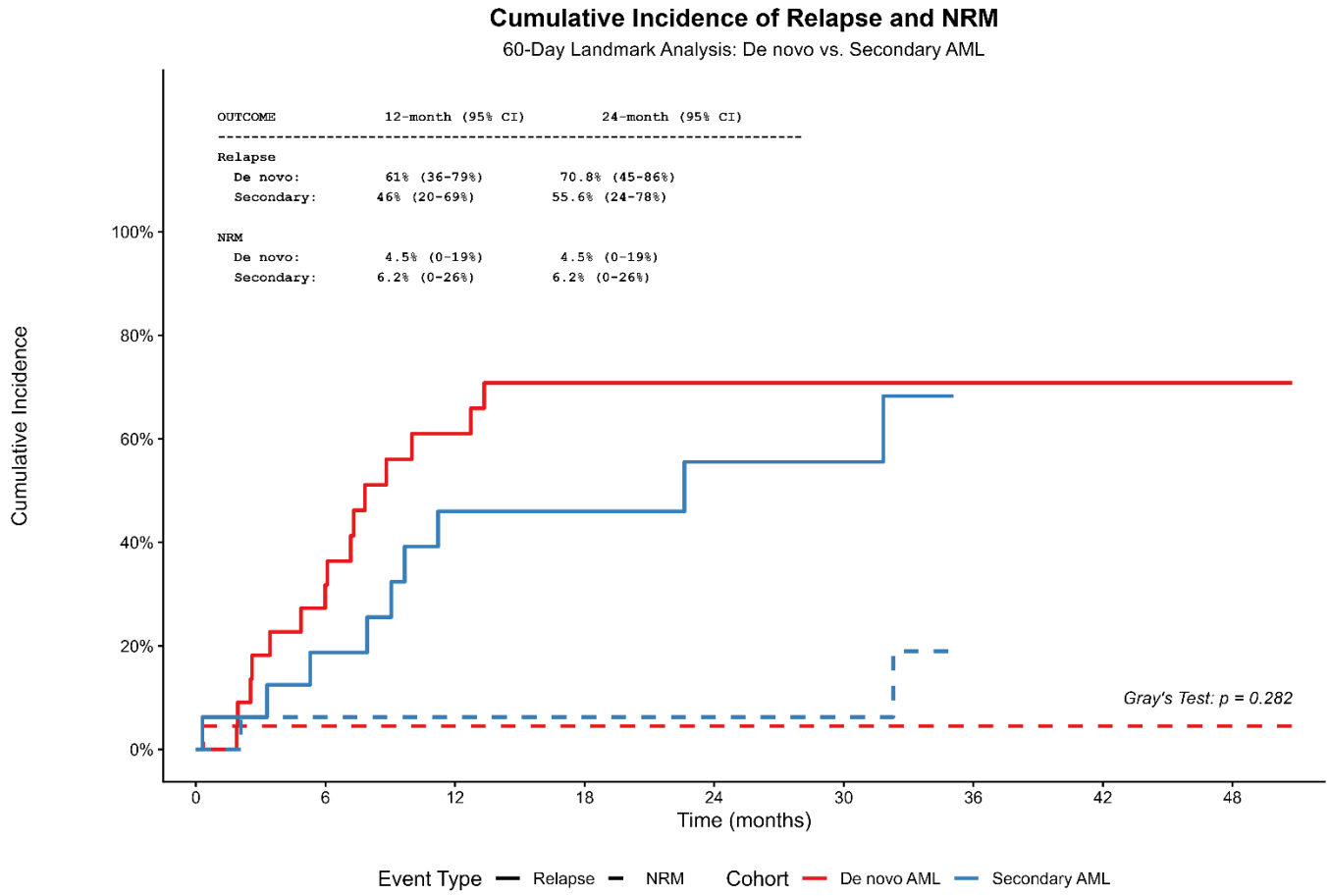


Supplementary Figure 3. Cumulative incidence of relapse and death in remission among CR/CRi patients (A) overall, (B) 60-day landmark analysis. The *p*-value represents Gray's test for the comparison of cumulative incidence of relapse between the two cohorts.

A



B



At Risk (Interval Censored)

De novo AML	22 (0)	14 (0)	7 (1)	4 (1)	3 (1)	3 (0)	1 (2)	1 (0)	1 (0)
Secondary AML	16 (0)	12 (0)	7 (1)	6 (1)	4 (1)	3 (1)	0 (1)	0 (0)	0 (0)

Supplementary Figure 4. Swimmer plot of treatment duration and clinical outcomes. Each bar represents an individual patient treated with oral decitabine/cedazuridine plus venetoclax for newly diagnosed acute myeloid leukemia in two different cohorts (De novo and secondary NDAML). Symbols indicate best response and key clinical events, relapse and death.