ARTICLE - Acute Myeloid Leukemia

Fludarabine, cytarabine, and idarubicin with or without venetoclax in patients with relapsed/refractory acute myeloid leukemia

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Supplementary Materials

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Supplementary methods

Treatment administration

All patients had received venetoclax for salvage chemotherapy in combination with fludarabine (30 mg/m^2/day continuous intravenous infusion over 30 minutes days 1–5), cytarabine (1,500 mg/m^2/day continuous intravenous infusion over 3 hours days 1–5) and idarubicin (10 mg/m^2/day continuous intravenous infusion over 30 minutes days 1–3) (FLAVIDA).[1] Venetoclax was administered without dose ramp-up at a dose of 100 mg instead of 400 mg once daily per orally (days 1–7) due to mandatory co-medication with a CYP3A4 inhibitor for fungal prophylaxis, primarily posaconazole. A seven-day course of venetoclax was administered based on previously reported higher rates of sepsis and early death when a 14 or 21-day schedule of venetoclax had been used.[2-3] Cytarabine was administered 4 hours after the start of fludarabine administration. In patients older than >60 years (n=10) a lower dose of fludarabine (20 mg/m^2/day continuous intravenous infusion days 1–5), cytarabine (500 mg/m^2/day continuous intravenous infusion day 1–5), and idarubicin (8 mg/m^2/day continuous intravenous infusion days 1–3) was used, while pegfilgrastim (6 mg subcutaneously on day 7) and uric acid-reducing agents for tumor lysis prophylaxis were recommended. Additionally, all patients received supportive care measures including transfusions, hydration and antiemetic agents.

FLA-IDA cohort

The control patients were selected from the in-house database of Hannover Medical School and were treated with FLA-IDA between 2000 and 2018 for relapsed or refractory AML. FLA-IDA treated patients were selected based on data availability (response and outcome data available). Of 93 patients treated with FLA-IDA between 2000 and 2018 for relapsed or refractory AML, 81 patients were found to have available response and outcome data. Patients

received either a four-day course (fludarabine (30 mg/m^2/day continuous intravenous infusion over 30 minutes days 1–4), cytarabine (1,000 mg/m^2/day continuous intravenous infusion over 4 hours days 1–4), and idarubicin (8 mg/m^2/day continuous intravenous infusion over 30 minutes days 1 and 3) or a five-day course (fludarabine 30 mg/m^2/day continuous intravenous infusion over 30 minutes days 1–5, cytarabine 2,000 mg/m^2/day continuous intravenous infusion over 4 hours days 1–5, and idarubicin 10 mg/m^2/day continuous intravenous infusion over 30 minutes days 1–3) of the FLA-IDA salvage chemotherapy.

Safety and efficacy assessment

Patients' charts were searched for physician-assessed adverse events (AEs) that emerged during treatment beginning from the first day of salvage chemotherapy to day 35 after the start of chemotherapy and are reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. However, since this is a retrospective registry-based analysis, AEs and SAEs were not documented in a prospective randomized trial and thus are prone to underreporting.

Time to neutrophil and platelet recovery was calculated for patients who recovered before the next cycle of treatment, usually alloHCT or DLI. Patients who did not recover the counts above the set cutoffs were excluded from this analysis. Time to count recovery was calculated from the first day of FLA(V)IDA treatment to the first day neutrophils or platelets exceeded the predetermined cutoff.

Patients with delayed recovery of neutrophils and platelets were considered in CR, if neutrophils and platelets recovered before the next course of treatment and blasts were below 5% in bone marrow and absent in peripheral blood. Blasts in bone marrow ≥ 5%, persisting blasts in peripheral blood, or extramedullary disease at the end of induction 1 was defined as refractory disease (RD).

Molecular Analysis

Mutations associated with myeloid leukemias were detected using a custom TruSight or Nextera myeloid sequencing panel, which included 46 and 48 genes, respectively. (Illumina, San Diego, CA). Samples were sequenced on a MiSeq sequencer and sequencing data was analyzed as described previously.[4] Measurable residual disease (MRD) was assessed on bone marrow specimens using either mutation specific real-time quantitative polymerase chain reaction (RQ-PCR) with a sensitivity of 10^{-5} for *NPM1*, capillary electrophoresis for *FLT3-ITD* with a sensitivity of 10^{-3}, or NGS-based MRD detection with a median sensitivity of 10^{-4} for any other MRD marker as reported previously.[5-8] In patients without detectable mutations by NGS, multi-parameter flow cytometry using leukemia-associated immunophenotypes (LAIP) was performed before start of FLAVIDA chemotherapy and for detection of measurable residual disease after the first cycle. MFC-MRD positivity was defined as ≥ 0.1% of CD45-expressing cells with the target immunophenotype.[9]

Statistical Considerations

Median follow-up was estimated using the reverse Kaplan-Meier method. A Cox proportional-hazards regression model was used for generation of time-to-event data. The Kaplan-Meier method and log-rank test were used to visualize and estimate the distribution of OS, EFS, RFS, and recovery of peripheral blood counts, respectively. Landmark OS was compared between patients who achieved MRD negative response and those who achieved MRD positive response in both groups. Landmark analysis was performed from time of complete remission. Comparison between patients included in this study and historical controls were conducted using the Wilcoxon-Mann-Whitney-Test for continuous variables and Fisher's exact test or $\chi 2$ test for categorical variables.

Supplementary results

Treatment response and survival in subgroups

Response and outcome parameter in relapsed patients compared to refractory patients

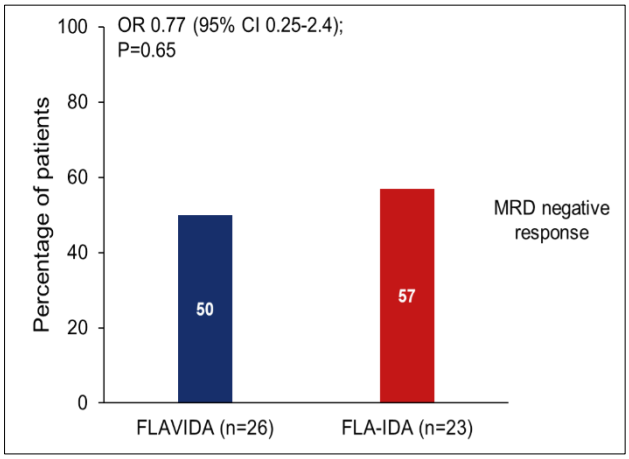
In the FLAVIDA cohort ORR was similar between refractory and relapsed patients (ORR refractory patients n=13/18 (72%) vs. relapsed patients n=16/19 (84%), *P*=0.38). OS and EFS were not significantly different between refractory and relapsed patients (Supplementary Figures S2A and S2B). In the FLA-IDA cohort ORR was also similarly distributed between refractory and relapsed patients (ORR refractory patients n=17/34 (50%) vs. relapsed patients n=21/47 (47%); *P*=0.6) with similar OS and EFS outcomes between these groups (Supplementary Figures S3A and S3B).

Usage of alloHCT was not significantly different in refractory FLAVIDA and refractory FLA-IDA patients (FLAVIDA alloHCT n=17/18 (94%), FLA-IDA alloHCT n=26/34 (77%); *P*=0.1). Further, usage of alloHCT was similar in relapsed FLAVIDA and FLA-IDA patients (FLAVIDA alloHCT n=10/19 (53%), FLA-IDA alloHCT n=23/47 (49%); *P*=0.9).

Impact of patients treated before 2007

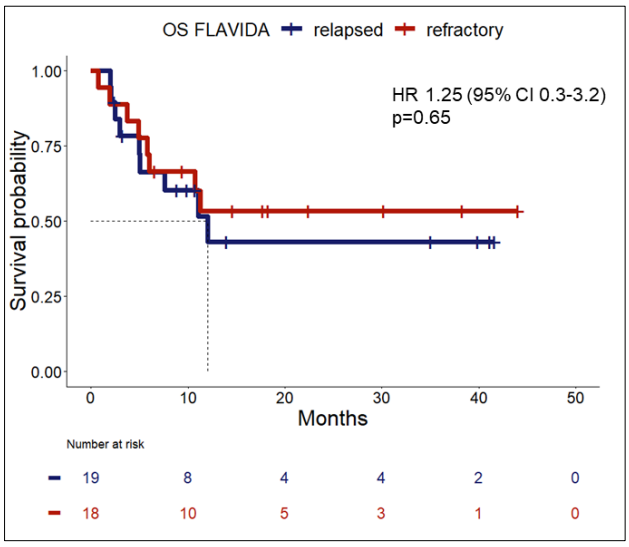
Ten out of 81 patients were treated with FLA-IDA before 2007. Excluding these ten patients from our comparator arm, however, did not change the response rate nor the survival outcomes compared to FLAVIDA treated patients. Overall survival rates at 1 and 2 years were 52% and 48% in the FLAVIDA cohort and 61% and 52% for patients treated with FLA-IDA after 2007 (n=71) (Supplementary Figure S4A). Median EFS was 11.3 months for FLAVIDA treated patients and 6.9 months for FLA-IDA treated patients (*P*=0.16) (Supplementary Figure S4B). The ORR remained significantly higher in the FLAVIDA cohort compared to the FLA-IDA control cohort when patients treated before 2007 were excluded (FLAVIDA 78% vs. FLA-IDA 47%; *P*=0.001).

Supplementary Figures



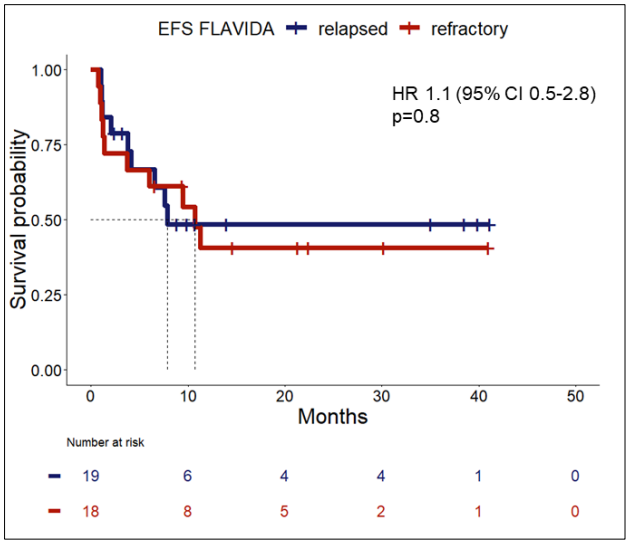
Supplementary Figure S1. Frequency of MRD negative response in patients who achieved an overall response and for whom MRD could be assessed (n=26 in the FLAVIDA and n=23 in the FLA-IDA cohorts).

Abbreviations: CI, confidence interval; OR, odds ratio; P, p value.



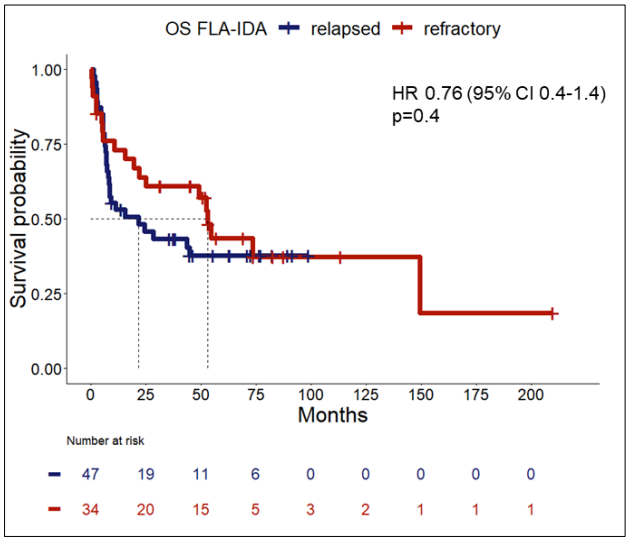
Supplementary Figure S2A. Kaplan Meier curves of overall survival in relapsed (n=19) and refractory (n=18) FLAVIDA patients.

Abbreviations: CI, confidence interval; HR, hazard ratio; P, p value.



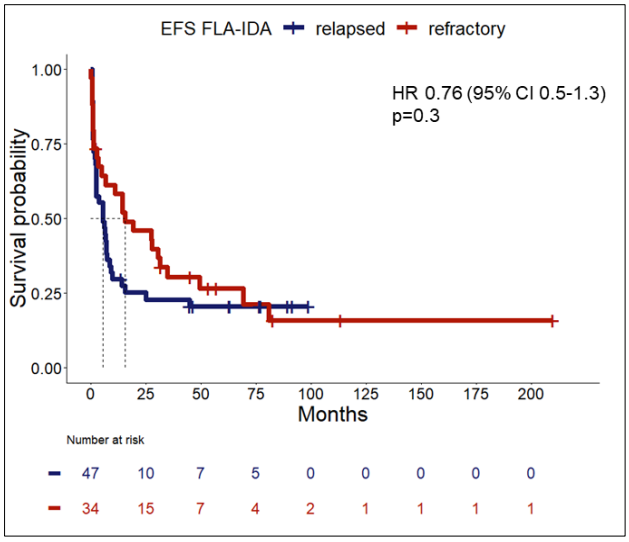
Supplementary Figure S2B. Kaplan Meier curves of event-free survival in relapsed (n=19) and refractory (n=18) FLAVIDA patients.

Abbreviations: CI, confidence interval; HR, hazard ratio; P, p value.



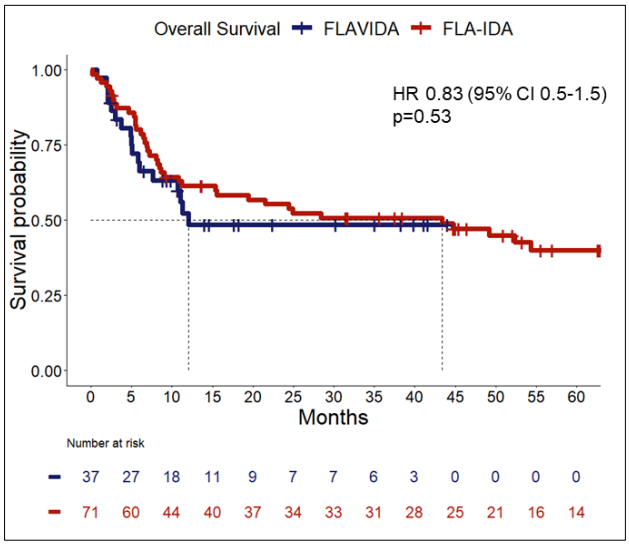
Supplementary Figure S3A. Kaplan Meier curves of overall survival in relapsed (n=47) and refractory (n=34) FLA-IDA control patients.

Abbreviations: CI, confidence interval; HR, hazard ratio; P, p value.



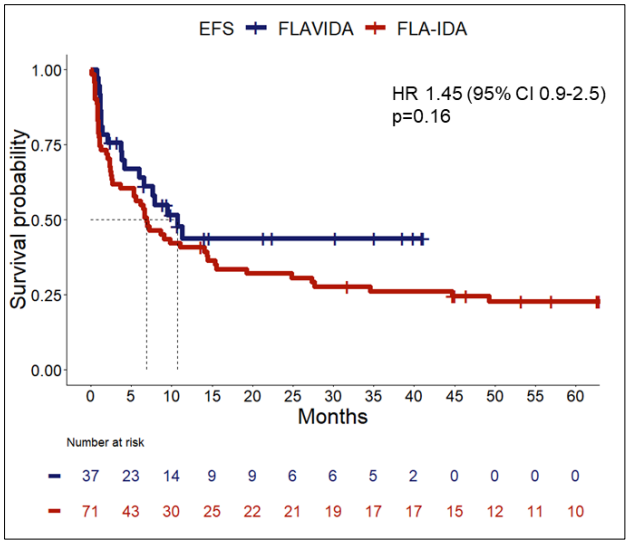
Supplementary Figure S3B. Kaplan Meier curves of event-free survival in relapsed (n=47) and refractory (n=34) FLA-IDA control patients.

Abbreviations: CI, confidence interval; HR, hazard ratio; P, p value.



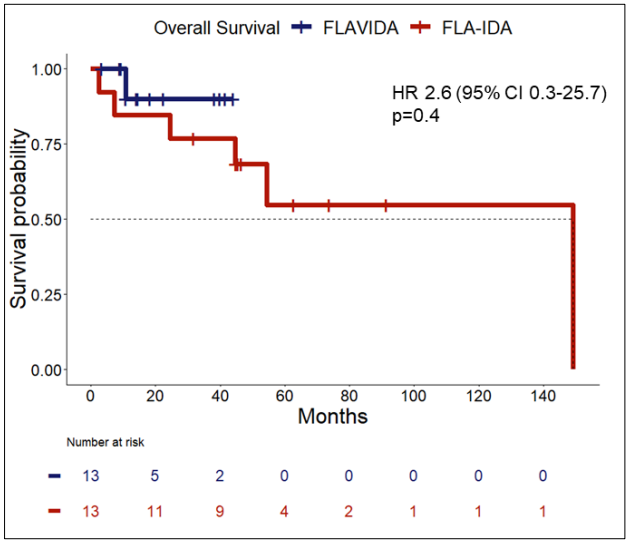
Supplementary Figure S4A: Kaplan Meier curves of overall survival in the FLAVIDA cohort (n=37) and the FLA-IDA control cohort (n=71) excluding patients treated before 2007.

Abbreviations: CI, confidence interval; HR, hazard ratio; P, p value.



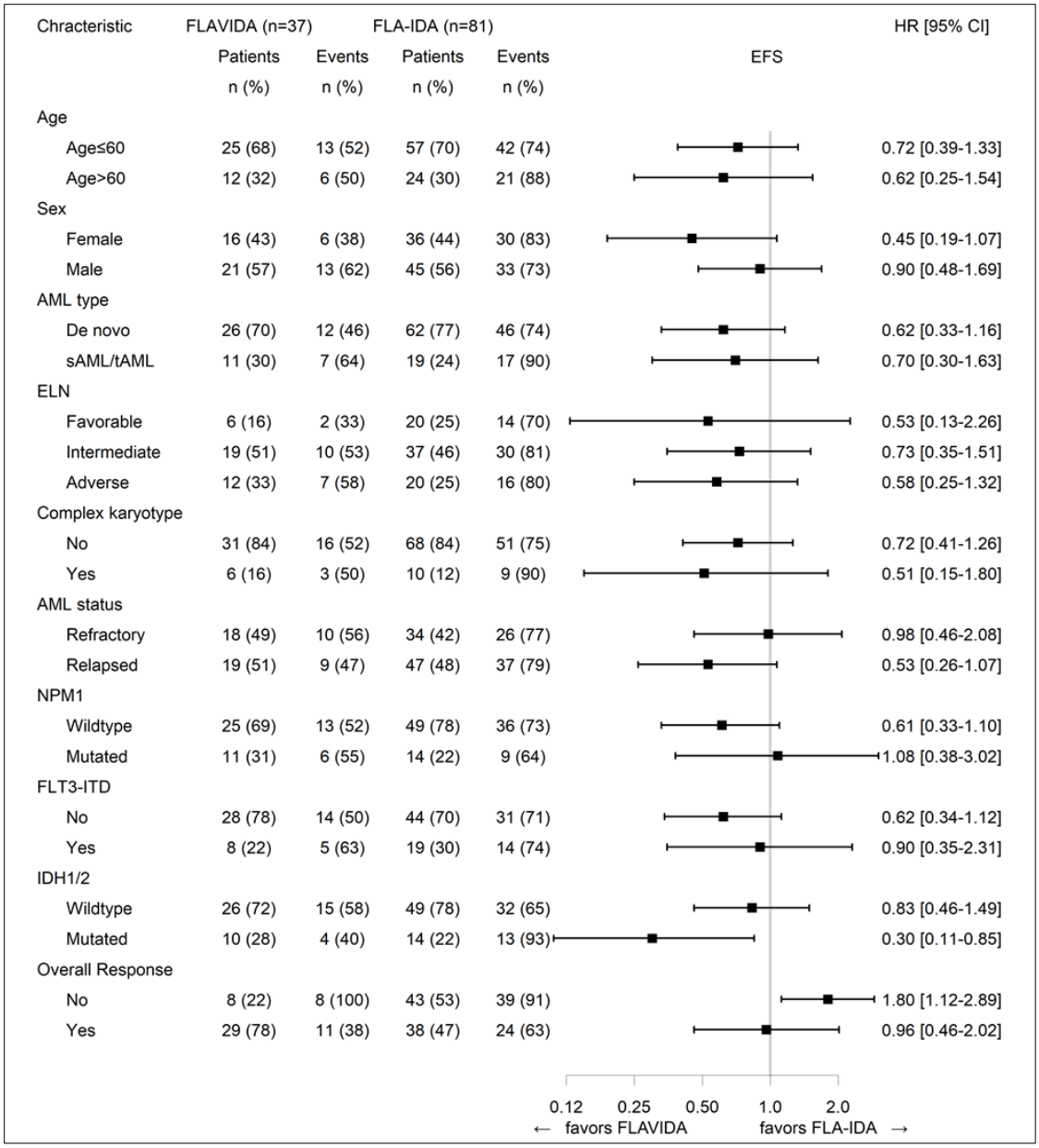
Supplementary Figure S4B: Kaplan Meier curves of event-free survival in the FLAVIDA cohort (n=37) and the FLA-IDA control cohort (n=71) excluding patients treated before 2007.

Abbreviations: CI, confidence interval; HR, hazard ratio; P, p value.



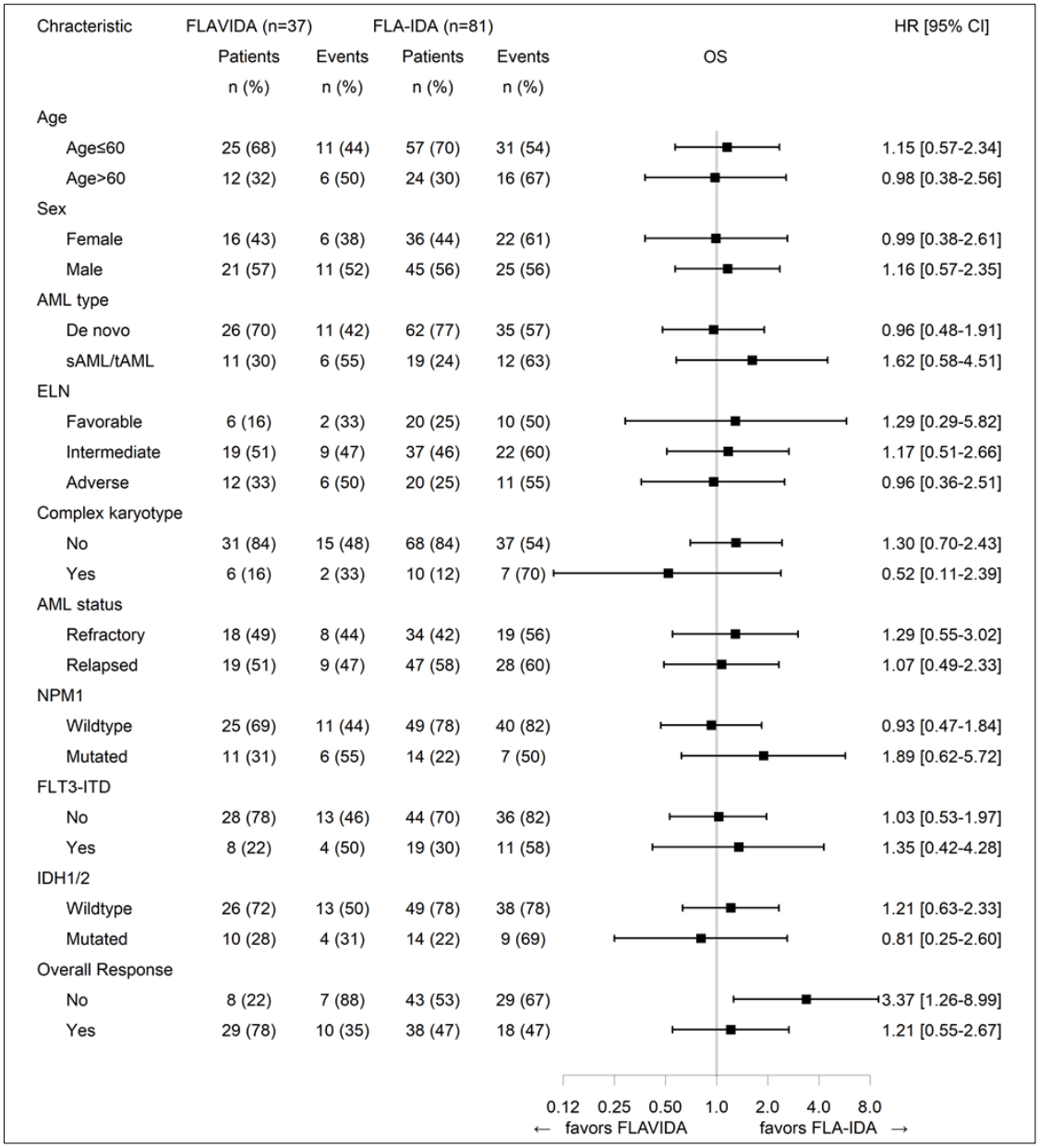
Supplementary Figure S5. Kaplan Meier curves of overall survival in MRD negative FLAVIDA (n=13) and MRD negative FLA-IDA patients (n=13).

Abbreviations: CI, confidence interval; HR, hazard ratio; P, p value.



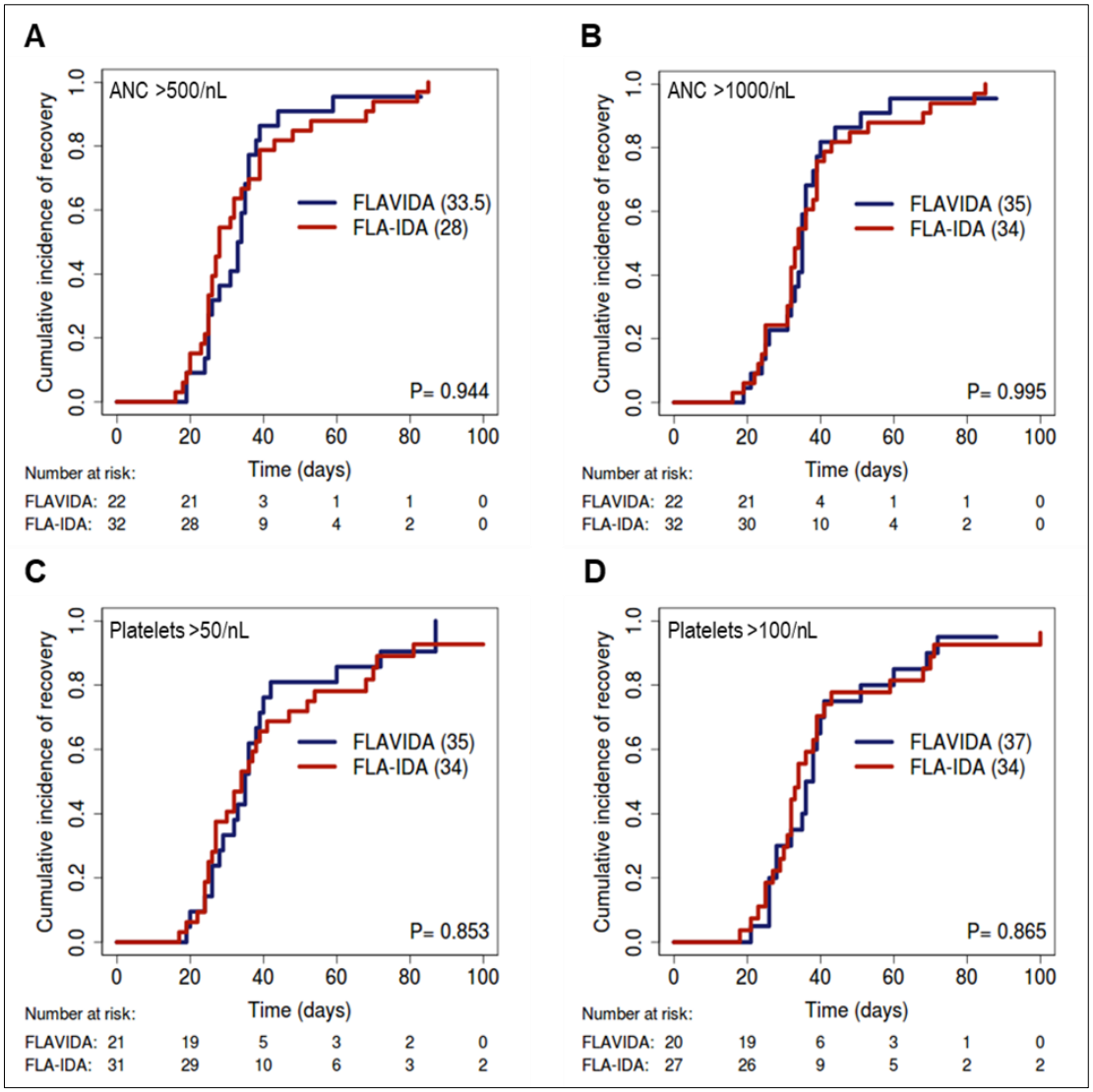
Supplementary Figure S6. Prognostic effect of FLAVIDA and FLA-IDA on event-free survival in clinical and genetic subgroups.

Abbreviations: CI, confidence interval; EFS, event-free survival; ELN, EuropeanLeukemiaNet; HR, hazard ratio; sAML, secondary AML; tAML, therapy-related AML.



Supplementary Figure S7. Prognostic effect of FLAVIDA and FLA-IDA on overall survival in clinical and genetic subgroups.

Abbreviations: CI, confidence interval; ELN, EuropeanLeukemiaNet; HR, hazard ratio; OS, overall survival; sAML, secondary AML; tAML, therapy-related AML.



Supplementary Figure S8. Blood count recovery of patients in responding FLAVIDA and FLA-IDA treated patients.

(A) Absolute neutrophil count (ANC) recovery >500/nL in FLAVIDA and FLA-IDA treated patients.

(B) Absolute neutrophil count (ANC) recovery >1,000/nL in FLAVIDA and FLA-IDA treated patients.

(C) Platelet recovery (PLT) >50/nL in FLAVIDA and FLA-IDA treated patients.

(D) Platelet recovery (PLT) >100/nL in FLAVIDA and FLA-IDA treated patients.

Supplementary Tables

Supplementary Table S1. Consolidation treatment and bridge to transplant for patients in FLAVIDA and FLA-IDA cohorts.

	FLAVIDA (n=37)	**FLA-IDA (n=81)**	***P***
Type of consolidation, n (%)			0.88
Transitioned to consolidation chemotherapy	3 (8)	9 (11)	
Transitioned to alloHCT/DLI	30 (81)	64 (79)	0.9
After FLA(V)IDA	28 (76)	57 (70)	
After additional salvage	2 (5)	7 (9)	
• First alloHCT	25	34	
• DLI	3	15	
• Second alloHCT	2	5	
No additional treatment	4 (11)	8 (10)	
Time to alloHCT/DLI, months (range)			0.27
alloHCT	2.1 (0.6–8.4)	2.5 (0.9–33.3)	
DLI	2.4 (1.2–8.7)	1.2 (1.4–50.6)	

Abbreviations: AlloHCT, allogeneic hematopoietic cell transplantation; DLI, donor lymphocyte infusion; n, number; P, p value.

Supplementary Table S2. Survival outcomes in FLAVIDA and FLA-IDA treated patients.

	FLAVIDA (n=37)	**FLA-IDA (n=81)**	**HR (95% CI)**	***P***
Follow up				
Median, months (95% CI)	22.4 (16.3–28.5)	62.9 (44.5–81.4)		
Overall survival				
Median, months (95% CI)	12 (7.6–NE)	43.4 (15.5–NE)	1.25 (0.7–2.24)	0.4
1-year OS	52%	61%		
2-year OS	48%	52%		
Event-free survival				
Median, months (95% CI)	11.3 (6.57–NE)	6.87 (4.87–14.4)	0.7 (0.4–1.15)	0.1
1-year EFS	44%	42%		
2-year EFS	44%	32%		

Abbreviations: CI, confidence interval; HR, hazard ratio; n, number; NE, not estimated; P, p value.

Supplementary Table S3. Patient demographics and baseline characteristics of non-responding FLAVIDA and FLA-IDA treated patients.

Baseline characteristics	**FLAVIDA (n=8)**	**FLA-IDA (n=43)**	***P***
Age Median (years, range)	 58 (31–70)	 51 (22–72)	0.27
Sex, n (%) Male Female	 5 (62.5) 3 (37.5)	 22 (51) 21 (49)	0.56
Type of AML, n (%) De novo Secondary Therapy-related	 3 (37.5) 4 (50) 1 (12.5)	 30 (70) 11 (25) 2 (5)	0.21
ELN risk group 2017, n (%) Favorable Intermediate Adverse Missing	 1 (12.5) 5 (62.5) 2 (25) 0 (0)	 9 (21) 18 (42) 12 (28) 4 (9)	0.65
Complex karyotype, n (%) Yes No Missing	 2 (25) 6 (75) 0 (0)	 7 (16) 33 (77) 3 (7)	0.65
Extramedullary disease, n (%) Yes No	 0 (0) 8 (100)	 6 (14) 37 (86)	0.74
Treatment lines before FLA(V)IDA Median (range) Salvage 1, n (%) Salvage 2, n (%) Salvage 3 or greater, n (%)	 2 (1–5) 2 (25) 5 (62.5) 1 (12.5)	 1 (1–4) 30 (69.8) 8 (18.6) 5 (11.6)	0.02
Disease status, n (%) Refractory AML Relapsed AML	 5 (62.5) 3 (37.5)	 17 (40) 26 (60)	0.23
WBC count at start of FLA(V)IDA ($x10^9$/L) Median (range) Missing, n (%)	 3·65 (0.7–77) 0 (0)	 3.8 (0.2–117.3) 6 (14)	0.5
Hemoglobin at start FLA(V)IDA (g/dL) Median (range) Missing, n (%)	 7.85 (7.4–10.6) 0 (0)	 9.1 (6.6–14.1) 6 (14)	0.8
Platelet count at start of FLA(V)IDA ($x10^9$/L) Median (range) Missing, n (%)	 48 (8–196) 0 (0)	 48.5 (5–731) 6 (12)	0.83
Blasts in BM at start of FLA(V)IDA (%) Median (range) Missing, n (%)	 60 (25–98) 1 (12.5)	 49.5 (5–95) 21 (49)	0.26
Blasts in PB at start of FLA(V)IDA (%) Median (range) Missing, n (%)	 17·1 (0–96) 0 (0)	 16 (0–79) 15 (35)	0.62
Molecular mutations, n (%) *DNMT3A* *NPM1*	 2 (25) 2 (25)	 10 (23) 5 (12)	 0.92 0.31

SRSF2	3 (37.5)	2 (5)	0.004
FLT3-ITD	1 (12.5)	8 (19)	0.68
TET2	3 (37.5)	10 (23)	0.4
IDH1	1 (12.5)	2 (5)	0.39
IDH2	0 (0)	7 (16)	0.23
RUNX1	2 (25)	5 (12)	0.31
NF1	2 (25)	4 (9)	0.21
K/NRAS	1 (12.5)	3 (7)	0.59
RAD21	0 (0)	1 (2)	0.66
BCOR	1 (12.5)	7 (16)	0.79
TP53	2 (25)	5 (12)	0.01
AlloHCT before FLA(V)IDA, n (%)			0.89
Yes	3 (32.5)	15 (35)	
No	5 (62.5)	28 (65)	
AlloHCT/DLI after FLA(V)IDA, n (%)			0.05
Yes	4 (50)	35 (81)	
No	4 (50)	8 (19)	
FLAMSA Conditioning, n (%)			0.35
Yes	1 (25)	12 (50)	
No	3 (75)	12 (50)	
Use of G-CSF after FLA(V)IDA, n (%)			0.74
Yes	6 (75)	30 (70)	
No	2 (25)	10 (23)	
Missing	0 (0)	3 (7)	
Overall survival status at last follow-up, n (%)			0.25
Alive	1 (12.5)	14 (33)	
Dead	7 (87.5)	29 (67)	

Abbreviations: AlloHCT, allogeneic hematopoietic cell transplantation; BM, bone marrow; ELN, EuropeanLeukemiaNet; FLAMSA, fludarabine, cytarabine, amsacrine[10]; G-CSF, granulocyte colony stimulating factor; n, number; P, p-value; PB, peripheral blood; WBC, white blood cell count.

Supplementary Table S4. Patient demographics and baseline characteristics of responding FLAVIDA or FLA-IDA treated patients.

Baseline characteristics	**FLAVIDA (n=29)**	**FLA-IDA (n=38)**	***P***
Age			
Median (years, range)	49 (19–68)	52 (24–69)	0.9
Sex, n (%)			0.66
Male	16 (55.2)	23 (60.5)	
Female	13 (44.8)	15 (39.5)	
Type of AML, n (%)			0.26
De novo	23 (79.3)	32 (84.2)	
Secondary	6 (20.7)	4 (10.5)	
Therapy-related	0 (0)	2 (5.3)	
ELN risk group 2017, n (%)			0.25
Favorable	4 (13.8)	11 (37.9)	
Intermediate	15 (51.7)	19 (50)	
Adverse	10 (34.5)	7 (18.4)	
Missing	0 (0)	1 (2.6)	
Complex karyotype, n (%)			0.43
Yes	4 (13.8)	3 (7.9)	
No	25 (86.2)	35 (92.1)	
Extramedullary disease, n (%)			0.88
Yes	2 (6.9)	3 (7.9)	
No	27 (93.1)	35 (92.1)	
Treatment lines before FLA(V)IDA			0.98
Median (range)	1 (1–3)	1 (1–3)	
Salvage 1, n (%)	24 (82.8)	27 (71.1)	
Salvage 2, n (%)	4 (13.8)	8 (21.1)	
Salvage 3 or greater, n (%)	1 (3.4)	3 (7.8)	
Disease status n (%)			1.0
Refractory AML	13 (44.8)	17 (45)	
Relapsed AML	16 (55.2)	21 (55)	
WBC count at start of FLA(V)IDA ($x10^9$/L)			<0.001
Median (range)	2.1 (0.2–58.9)	2.85 (0.1–82.8)	
Missing, n (%)	1 (3.4)	8 (21.1)	
Hemoglobin at start FLA(V)IDA (g/dL)			<0.001
Median (range)	9.15 (6.5–14.5)	9.8 (7.9–14.9)	
Missing, n (%)	1 (3.4)	8 (21.1)	
Platelet count at start of FLA(V)IDA ($x10^9$/L)			0.32
Median (range)	44 (5–418)	66 (8–245)	
Missing, n (%)	1 (3.4)	8 (21.1)	
Blasts in BM at start of FLA(V)IDA (%)			0.47
Median (range)	50 (10–100)	46.5 (5–95)	
Missing, n·(%)	4 (13.8)	22 (57.9)	
Blasts in PB at start of FLA(V)IDA (%)			0.1
Median (range)	2.7 (0–96)	7 (0–90)	
Missing, n·(%)	2 (6.9)	20 (52.6)	
Molecular mutations, n (%)			
DNMT3A	11 (37.9)	11 (28.9)	0.44
NPM1	9 (31)	9 (23.7)	0.5
SRSF2	6 (20.7)	1 (2.6)	0.02

FLT3-ITD	7 (24)	11 (28.9)	0.66
TET2	4 (13.8)	4 (10.5)	0.68
IDH1	1 (3)	3 (8)	0.45
IDH2	8 (27.6)	2 (5.3)	0.01
RUNX1	4 (13.8)	0 (0)	0.02
NF1	3 (10.3)	1 (2.6)	0.19
K/NRAS	3 (10.3)	5 (13.2)	0.73
RAD21	3 (10.3)	1 (2.6)	0.19
BCOR	3 (10.3)	2 (5.3)	0.43
TP53	0 (0)	0 (0)	-
AlloHCT before FLA(V)IDA, n (%)			0.7
Yes	5 (32.5)	8 (21.1)	
No	24 (62.5)	30 (78.9)	
AlloHCT/DLI after FLA(V)IDA, n (%)			0.07
Yes	27 (93.1)	29 (76.3)	
No	2 (6.9)	9 (23.7)	
FLAMSA Conditioning, n (%)			0.46
Yes	6 (26.1)	9 (36)	
No	17 (73.9)	16 (64)	
Use of G-CSF after FLA(V)IDA, n (%)			0.24
Yes	19 (65.5)	26 (68.4)	
No	10 (34.5)	10 (26.3)	
Missing	0 (0)	2 (5.3)	
Overall survival status, n (%)			0.29
Alive	19 (65.5)	20 (52.6)	
Dead	10 (34.5)	18 (47.4)	

Abbreviations: AlloHCT, allogeneic hematopoietic cell transplantation; BM, bone marrow; ELN, EuropeanLeukemiaNet; FLAMSA, fludarabine, cytarabine, amsacrine[10]; G-CSF, granulocyte colony stimulating factor; n, number; P, p-value; PB, peripheral blood; WBC, white blood cell count.

Supplementary Table S5. Treatment-emergent adverse events of FLAVIDA patients.

Treatment-emergent adverse events	**Any grade, n (%)**	**Grade 3/4, n (%)**
Anemia	37 (100)	37 (100)
Thrombocytopenia	37 (100)	37 (100)
Febrile neutropenia	36 (97)	36 (97)
Bacteremia	10 (27)	10 (27)
Sepsis	4 (11)	4 (11)
Fungal pneumonia	4 (11)	4 (11)
Viral infection	4 (11)	0 (0)
Elevated liver enzymes	4 (11)	4 (11)
Creatinine increased	4 (11)	1 (3)
Nausea, Vomiting	3 (8)	0 (0)
Bleeding (vaginal, gastrointestinal, pulmonary)	3 (8)	0 (0)
Infusion reaction	2 (5)	0 (0)
Pneumonia	1 (3)	1 (3)
Respiratory insufficiency	1 (3)	1 (3)
SSTI (skin and soft tissue)	1 (3)	0 (0)
Urinary tract infection	1 (3)	0 (0)
Cardiac disorder	1 (3)	0 (0)

Supplementary Table S6. Hematological recovery in FLAVIDA or FLA-IDA treated patients.

	FLAVIDA	**FLA-IDA**	***P***
Time to ANC recovery >500/nL in responding patients (n)	29	38	0.94
Median, days (95% CI)	33 (30–36)	28 (23–33)	
Missing/not recovered, n (%)	1 (3.4)	2 (5.2)	
Time to ANC recovery >1,000/nL in responding patients (n)	29	38	1.0
Median, days (95% CI)	35 (34–36)	34 (30–38)	
Missing/not recovered, n (%)	1 (3.4)	2 (5.2)	
Time to PLT recovery >50/nL in responding patients (n)	29	38	0.85
Median, days (95% CI)	35 (32–38)	34 (27–41)	
Missing/not recovered, n (%)	2 (6.9)	6 (15.8)	
Time to PLT recovery >100/nL in responding patients (n)	29	38	0.87
Median, days (95% CI)	36 (33–39)	34 (31–37)	
Missing/not recovered, n (%)	2 (6.9)	8 (21.1)	

Abbreviations: ANC, absolute neutrophil count; CI, confidence interval; n, number; P, p-value; PLT, platelet.

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