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Venetoclax plus hypomethylating agents as a bridge to transplant or donor lymphocyte infusion in relapsed/refractory acute myeloid leukemia

by Kathelijn Verdeyen, Tom Reuvekamp, Walter J.F.M. van der Velden, Bas J. Wouters, Peter A. von dem Borne, Anna van Rhenen, Birgit I. Lissenberg-Witte, Daniëlle van Lammeren, Geerte L. van Sluis, Eva de Jongh, Roel B. Fiets, Maarten F. Corsten, Arie C. van der Spek, Anke M. Gerrits, Esther R. van Bladel, Lidwine W. Tick, Okke de Weerdt, Bregje van Zaane, Marjan J. Cruijsen, Eduardus F.M. Posthuma, Catharina H.M.J. van Elssen, Saskia K. Klein, Arjan A. van de Loosdrecht and David C. de Leeuw

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Author Contributions

Patient data was provided by WJFMvdV, BJW, PAvdB, AvR, DvL, GLvS, EdJ, RBF, MFC, ACvdS, AMG, ERvB, LWT, OdW, BvZ, MJC, EFMP, CHMJvE, SKK, AAvdL, DCdL; Statistical analysis was performed by KV and TR and checked by BILW; AAvdL and DCdL designed and supervised the study; the manuscript was written by TR and revised by KV, WJFMvdV, BJW, BILW, CHMJvE, SKK, AAvdL and DCdL and the results were reviewed and the manuscript was approved by all the authors.

Data availability statement

Data and code are available upon reasonable request to the corresponding author, David C. de Leeuw (d.deleeuw@amsterdamumc.nl).

Disclosure of Conflicts of interest

RBF has received travel funding from AbbVie. AAvdL has received honoraria from Amgen, Novartis, Celgene/BMS, and Takeda and has received research funding from Alexion. DCdL participates in the sponsored speaker's bureau of Servier, Roche and AbbVie; was part of the scientific advisory board of Takeda, Servier and Immedica Pharma. The remaining authors declare no competing interests.

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To the editor,

Patients with relapsed or refractory acute myeloid leukemia (R/R AML) have a poor prognosis with a 5-year survival of around 10%.(1,2) Potential curative treatment options include reinduction therapy followed by an allogeneic hematopoietic stem cell transplantation or disease control followed by immediate transplantation.(3) Non-intensive treatment with hypomethylating agents (HMA) combined with BCL2 inhibitor venetoclax is an alternative for patients without targetable mutations (*FLT3*, *IDH1/2*, *KMT2a*-rearranged AML) or those unfit for intensive reinduction therapy.(4) This combination improved remission rates and survival compared to HMA monotherapy in patients with newly diagnosed AML ineligible for intensive chemotherapy(5). Although widely used, there is limited evidence and venetoclax has not been approved for R/R AML. Various retrospective studies have suggested an improvement in remission rate by adding venetoclax to HMA in the R/R setting.

We aimed to determine if venetoclax-HMA can be effective as a bridge to transplant or donor lymphocyte infusion for patients with R/R AML. We screened all 180 patients who received venetoclax-HMA between January 2019 and September 2023 through named-patient basis access in the Netherlands **(Figure 1A)** or were treated with venetoclax-HMA off label (n=10). We included patients with R/R AML following prior intensive or non-intensive therapy, considered ineligible for further intensive chemotherapy. Patients receiving alternative venetoclax-based regimens were excluded. Venetoclax-HMA was initiated either with the intent to consolidate with transplant or donor lymphocyte infusion (DLI), or without consolidation. This treatment intent dichotomization was determined prior to therapy initiation at the discretion of the treating physician. The study was approved by the Medical Ethics Review Committee of Amsterdam UMC (number: 2023.0011) and subsequently by

other participating hospitals. By their decision, written informed consent was not required. Patients who were alive at the time of study initiation were informed and given the opportunity to opt out of participation. This study was conducted according to the declaration of Helsinki.

Study endpoints were maximal response achieved with venetoclax-HMA, overall survival (day of start of venetoclax-HMA until death), relapse-free survival (day of start of venetoclax-HMA until relapse after venetoclax-HMA or death) and bridging proportions. A cycle of venetoclax-HMA was defined as decitabine (20 mg/m^2, 5 or 10 days) or azacitidine (75 mg/m^2, 5 or 7 days) irrespective of days of venetoclax given. Responses were retrieved after each line of therapy or after consolidation when available and were determined according to ELN2022 recommendations(4).

Tumor cytogenetics and molecular mutations were assessed at diagnosis and at relapse according to local protocols. When cytogenetic and molecular analysis was not performed at relapse, aberrations present at diagnosis were used in the analysis. Statistical analysis was performed in R version 4.3.2 and RStudio version 2024.4.0.735, p-values below 0.05 were considered significant and p-values below 0.1 were considered a trend.

We included 146 patients (**Figure 1A**) with a median age of 64 (IQR: 52-70; **Table 1**). Of these patients, 39% received prior allogeneic transplant, 40% received prior treatment with HMA, and 14% received both. Patients were treated with venetoclax with either azacitidine (71%) or decitabine (29%) with a median number of 2 cycles (IQR: 1-3).

Mutational and cytogenetic analysis showed that *DNMT3A* mutations were most common, next to mutations in *NPM1*, *FLT3*-ITD, *ASXL1*, and *RUNX1* **(Figure**

1B). When stratifying for relapsed or refractory status, we found that mutations in *ASXL1*, *IDH2,* and *RUNX1* were more common in refractory patients, whereas *FLT3*-ITD, *NPM1,* and *RAS* mutations were more common in relapsed patients, however, due to small sample size, differences were not significant **(Table S1)**.

We analyzed our cohort by comparing two groups of patients based on the intended goal of venetoclax-HMA treatment: 1) patients who received venetoclax-HMA as a bridging strategy towards consolidation and 2) patients who received venetoclax-HMA as a non-curative treatment without intent to consolidate. This distinction was made prospectively by the treating physician prior initiation of therapy. The differentiation is clinically important, as the effectiveness of bridging therapy is only applicable to the subgroup in which consolidation was the intended therapeutic objective. In total, 63 patients were intended for treatment with a first transplantation, 12 for second transplantation, 36 for DLI and 35 without intent to consolidate. Patients receiving treatment intending to bridge to transplant had significantly longer survival compared to those without intent to consolidate **(Figure 1C;** survival entire cohort: **Figure S1)**. Patients in whom venetoclax-HMA was initiated without intent to bridge to consolidation had a median OS of only 3.2 months, questioning the value of venetoclax in this context.

The overall response rate (ORR, defined as complete remission (CR), CR with partial hematological recovery (CRh), CR with incomplete blood counts (CRi), and morphological leukemia-free state (MLFS)) was 53%. Composite CR (CRc) rate (CR+CRi+CRh) was 38%. Thirty-six percent of the patients had no or a partial response **(Figure 1D; Table 1)**. In patients treated with the intent to consolidate, CRc and MLFS were reached in 43% and 18% of cases, respectively **(Table 1)**. Patients who achieved a response (CRc and MLFS) had more prolonged survival than

patients who did not **(Figure 1E)**, as patients without response were less frequently transplanted. In patients without intent to consolidate after venetoclax-HMA treatment, CRc rates were lower; only 17% of patients with response evaluation (23/35) achieved CRc (n=4); 4% achieved MLFS, and 78% had no response, were non-evaluable or had progressive disease. In 34% (12/35) of patients, response assessment could not be performed, likely because of early death (median OS: 1.5 months). The lower ORR in this group could be explained by more patients being pretreated with HMA, associated with a lower response **(Figure 1E)**.

In a meta-analysis reporting on 224 patients from seven studies that received venetoclax-based regimens in the R/R setting, an ORR of 31% and a CR rate of 18% was found(6). The studies included primarily small and heterogeneous patient populations.(6) In the large AVALON cohort from Italy (n=147), not included in the meta-analysis, an ORR of 36% for patients treated with venetoclax-HMA(7) was shown. The higher ORR of 53% in our cohort is likely attributable to a more uniform and fitter population. As in other studies, treatment intent is underreported, possibly leading to inclusion of more patients with non-curative intent with shorter overall survival and lower CR rates.

Options for reinduction other than venetoclax-HMA include intensive chemotherapy, such as high-dose cytarabine, FLAG-IDA, or MEC. These regimens do not clearly differ in response, with CR rates around 70%.(8) In R/R patients receiving targeted therapy with gilteritinib (*FLT3* mutated), ivosidenib (*IDH1* mutated), enasidenib (*IDH2* mutated) and, revumenib (*KMT2a*-rearranged), a respective ORR of 54%(9), 39%(10), 39%(11) and 63%(12) was found. The ORR of venetoclax-HMA is in the same range as other less-intensive regimens, but true comparison between studies is difficult.

Factors associated with response were explored using logistic regression models, and no factors reached statistical significance. There was a trend towards a higher response in patients with *IDH2* mutated AML **(Figure 1F)**. Other mutations that have been associated with favorable response include *NPM1* and *IDH1*. In contrast, mutations in *TP53*, *FLT3*-ITD, *KRAS,* and *NRAS* are associated with poor response(4,13).

In patients who were treated with curative intent, 53% were bridged to transplant or DLI **(Table 1)**. Bridging was particularly successful in 62% of patients whose goal was first allogeneic transplantation; compared to 42% of patients intended for second transplant or DLI **(Figure 2A;** p=0.05**)**. Patients who achieved a response to venetoclax-HMA had a higher chance of successful bridging, with 79% of patients able to reach consolidation. In comparison, the AVALON study reported that 70% of patients received an allogeneic transplant in CRc or MLFS.(7) In the VEN-DEC GITMO trial, in which newly diagnosed older patients (median age: 68.5) received venetoclax-decitabine intending to transplant. CR was reached in 69% and transplant in 57%.(14) Venetoclax-HMA has high bridging rates for R/R patients achieving a response, even when compared to newly diagnosed patients.

To compare survival of patients who were consolidated and those who were not, we performed a landmark analysis at 3.5 months, since at 3.5 months all patients were consolidated **(Figure 2B)**. Survival at the landmark point was 68%. Consolidated patients had significantly longer survival compared to patients who were not (1-year survival: 67% vs 30%). The patients who were consolidated and went for first allogeneic transplantation had more prolonged survival than patients who underwent a second transplant or DLI (1-year survival: 60% vs 35%) **(Figure 2C)**. In patients who received venetoclax-HMA as a bridge to first allogeneic

transplant, those who were refractory to induction chemotherapy and subsequently received venetoclax-HMA did exceptionally well compared to patients who relapsed after induction therapy **(Figure 2D, Figure S2)**.

To determine factors associated with relapse-free survival after reaching response on venetoclax-HMA, we used univariable Cox regression and found that *RAS*, *NPM1,* and *CEBPA* (single, double, or BZIP) mutations were associated with poor outcomes **(Figure 2E)**. The reduced relapse-free survival observed in *NPM1*-mutated patients in our cohort could be explained by the fact that 52% (12/23) of these patients have co-mutated *FLT3*-ITD. In a German R/R cohort, *FLT3*-ITD among *NF1*, *PTPN11*, and *TP53* mutations were associated with poor outcomes.(15)

In conclusion, venetoclax-HMA is an effective bridging treatment for R/R AML patients, facilitating successful transition to consolidation. Half of the patients were successfully bridged, with high success rates observed in those undergoing a first allogeneic transplant.

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Tables

Table 1. Information on treatment and response to treatment

Characteristic	Overall, N = 146[1]	Intended for first alloSCT, N = 63[1]	Intended for second alloSCT or DLI, N = 48[1]	Without consolidation intent, N = 35[1]	p-value[2]
Age	64 (52-70)	61 (47-69)	62 (52-66)	71 (65-74)	<0.001
Sex: male	80 (55%)	38 (60%)	19 (40%)	23 (66%)	0.031
HMA pretreatment					<0.001
HMA	58 (40%)	14 (22%)	17 (35%)	27 (77%)	
No HMA	88 (60%)	49 (78%)	31 (65%)	8 (23%)	
Relapsed/Refractory					<0.001
Refractory	44 (30%)	29 (46%)	3 (6.3%)	12 (34%)	
Relapse	102 (70%)	34 (54%)	45 (94%)	23 (66%)	
Pretreatment with allogeneic transplant	57 (39%)	0 (0%)	48 (100%)	9 (26%)	<0.001
Type HMA					0.031
azacitidine	103 (71%)	38 (60%)	40 (83%)	25 (71%)	
decitabine	43 (29%)	25 (40%)	8 (17%)	10 (29%)	
Maximal response to venetoclax-HMA					
CR	12 (9.7%)	7 (12%)	4 (9.3%)	1 (4.3%)	
CRh	11 (8.9%)	1 (1.7%)	9 (21%)	1 (4.3%)	
CRi	24 (19%)	18 (31%)	4 (9.3%)	2 (8.7%)	
MLFS	19 (15%)	16 (28%)	2 (4.7%)	1 (4.3%)	
No response	41 (33%)	10 (17%)	18 (42%)	13 (57%)	
Nonevaluable for response	13 (10%)	3 (5.2%)	6 (14%)	4 (17%)	
PR	4 (3.2%)	3 (5.2%)	0 (0%)	1 (4.3%)	
Unknown	22	5	5	12	
Number of cycles (median, IQR)	2 (1-3)	2 (1-2)	2 (2-3)	2 (1-4)	0.2
Number of cycles after CR/CRi/CRh/MLFS of venetoclax-HMA					
1	28 (42%)	25 (60%)	2 (11%)	1 (20%)	
2	30 (45%)	16 (38%)	12 (63%)	2 (40%)	
3	3 (4.5%)	0 (0%)	3 (16%)	0 (0%)	
4	2 (3.0%)	0 (0%)	2 (11%)	0 (0%)	
6	2 (3.0%)	1 (2.4%)	0 (0%)	1 (20%)	
10	1 (1.5%)	0 (0%)	0 (0%)	1 (20%)	
Reached consolidation	59 (53%)[3]	39 (62%)	20 (42%)		0.05

[1]Median (IQR); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

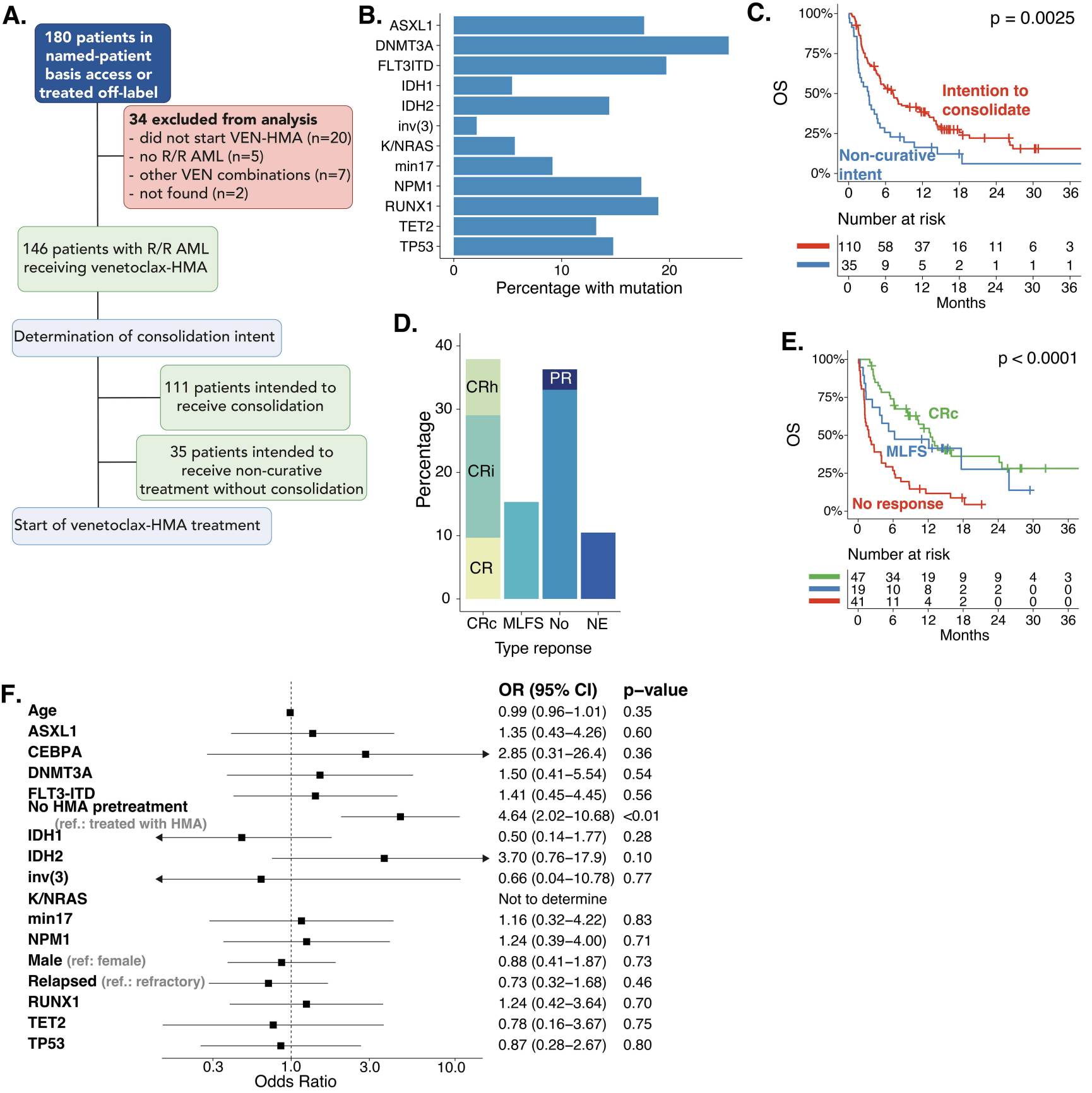
[3]Denominator: patients with the intent to consolidate

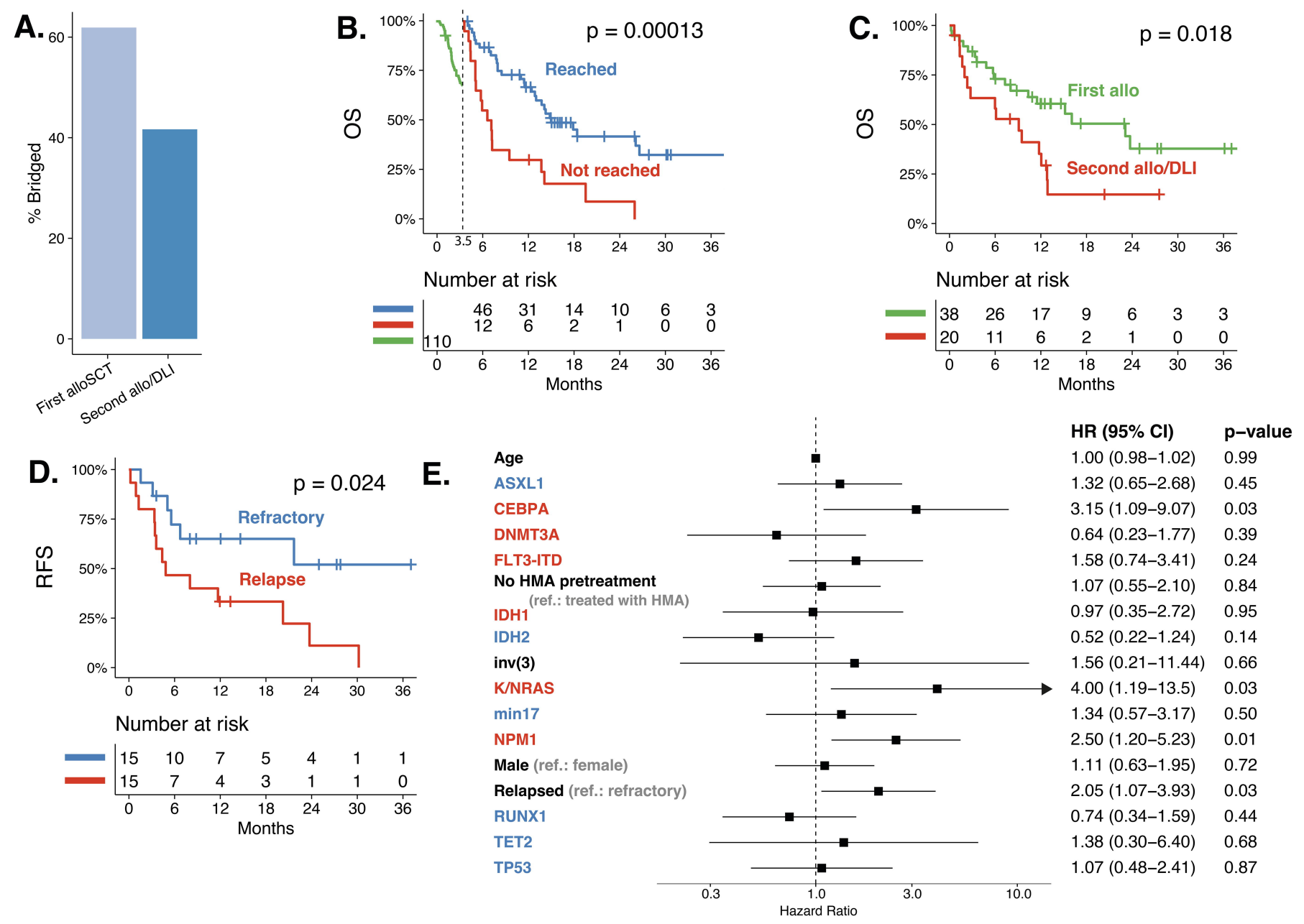
alloSCT = allogeneic stem cell transplantation; CR = complete remission; CRh = complete remission with partial hematological recovery; CRi = complete remission with incomplete blood counts; MLFS = morphological leukemia-free state; PR = partial response; HMA = hypomethylating agents

Figure legends

Figure 1. Patient overview, mutational status and results of response assessment. **A.** Overview of patient selection. **B.** Prevalence of mutations. **C.** Overall survival of patients with the intention to consolidate after remission with venetoclax and hypomethylating agent and patients without the intention to consolidate. **D.** Maximal response after venetoclax and hypomethylating agent treatment. **E.** Overall survival based on remission status. **F.** Univariable logistic regression with response to venetoclax (response defined as composite complete remission or morphologic leukemia-free state) as outcome.

Figure 2. Percentage of patients bridged to transplant, overall survival of bridged patients and factors associated with relapse-free survival after response **A.** Percentages of bridging to transplant for patients intended to consolidate. **B.** Overall survival by landmark analysis of patients reaching transplantation within 3.5 months or not reaching transplant within 3.5 months. This landmark was chosen as all transplanted patients received the transplant before that time. Green line represents the intention to consolidate cohort before 3.5 months. **C.** In patients that were consolidated, the overall survival for patients treated with first allogeneic stem cell transplantation or patients undergoing second transplant or donor lymphocyte infusion. **D.** Overall survival of patients undergoing first transplant stratified by their disease status after initial induction therapy. Numbers in this panel do not align with the green group in panel C because of patients that did not reach 3.5 months of survival. **E.** Univariable Cox regression models for relapse-free survival after reaching composite complete remission or morphologic leukemia-free state with venetoclax-HMA treatment. Red colored mutations are associated with the relapse cohort and the blue colored mutations are associated with the refractory group.


A.
180 patients in named-patient basis access or treated off-label
34 excluded from analysis
- did not start VEN-HMA (n=20)
- no R/R AML (n=5)
- other VEN combinations (n=7)
- not found (n=2)
146 patients with R/R AML receiving venetoclax-HMA
Determination of consolidation intent
111 patients intended to receive consolidation
35 patients intended to receive non-curative treatment without consolidation
Start of venetoclax-HMA treatment
B.
ASXL1
DNMT3A
FLT3ITD
IDH1
IDH2
inv(3)
K/NRAS
min17
NPM1
RUNX1
TET2
TP53
0
10
20
Percentage with mutation
C.
p = 0.0025
OS
100%
75%
50%
25%
0%
Intention to consolidate
Non-curative intent
0 6 12 18 24 30 36
Number at risk
110 58 37 16 11 6 3
35 9 5 2 1 1 1
0 6 12 18 24 30 36
Months
D.
Percentage
40
30
20
10
0
CRh
CRi
CR
PR
CRc MLFS No NE
Type reponse
E.
p < 0.0001
OS
100%
75%
50%
25%
0%
CRc
MLFS
No response
0 6 12 18 24 30 36
Number at risk
47 34 19 9 9 4 3
19 10 8 2 2 0 0
41 11 4 2 0 0 0
0 6 12 18 24 30 36
Months
F.
OR (95% CI)
p–value
Age 0.99 (0.96–1.01) 0.35
ASXL1 1.35 (0.43–4.26) 0.60
CEBPA 2.85 (0.31–26.4) 0.36
DNMT3A 1.50 (0.41–5.54) 0.54
FLT3-ITD 1.41 (0.45–4.45) 0.56
No HMA pretreatment (ref.: treated with HMA) 4.64 (2.02–10.68) <0.01
IDH1 0.50 (0.14–1.77) 0.28
IDH2 3.70 (0.76–17.9) 0.10
inv(3) 0.66 (0.04–10.78) 0.77
K/NRAS Not to determine
min17 1.16 (0.32–4.22) 0.83
NPM1 1.24 (0.39–4.00) 0.71
Male (ref: female) 0.88 (0.41–1.87) 0.73
Relapsed (ref.: refractory) 0.73 (0.32–1.68) 0.46
RUNX1 1.24 (0.42–3.64) 0.70
TET2 0.78 (0.16–3.67) 0.75
TP53 0.87 (0.28–2.67) 0.80
0.3
1.0
3.0
10.0
Odds Ratio


A.
% Bridged
60
40
20
0
First alloSCT
Second allo/DLI
B.
p = 0.00013
Reached
Not reached
OS
100%
75%
50%
25%
0%
3.5
0 6 12 18 24 30 36
Number at risk
46 31 14 10 6 3
12 6 2 1 0 0
110
0 6 12 18 24 30 36
Months
C.
p = 0.018
First allo
Second allo/DLI
OS
100%
75%
50%
25%
0%
0 6 12 18 24 30 36
Number at risk
38 26 17 9 6 3 3
20 11 6 2 1 0 0
0 6 12 18 24 30 36
Months
D.
p = 0.024
Refractory
Relapse
RFS
100%
75%
50%
25%
0%
0 6 12 18 24 30 36
Number at risk
15 10 7 5 4 1 1
15 7 4 3 1 1 0
0 6 12 18 24 30 36
Months
E.
HR (95% CI)
p−value
Age 1.00 (0.98–1.02) 0.99
ASXL1 1.32 (0.65–2.68) 0.45
CEBPA 3.15 (1.09–9.07) 0.03
DNMT3A 0.64 (0.23–1.77) 0.39
FLT3-ITD 1.58 (0.74–3.41) 0.24
No HMA pretreatment 1.07 (0.55–2.10) 0.84
(ref.: treated with HMA)
IDH1 0.97 (0.35–2.72) 0.95
IDH2 0.52 (0.22–1.24) 0.14
inv(3) 1.56 (0.21–11.44) 0.66
K/NRAS 4.00 (1.19–13.5) 0.03
min17 1.34 (0.57–3.17) 0.50
NPM1 2.50 (1.20–5.23) 0.01
Male (ref.: female) 1.11 (0.63–1.95) 0.72
Relapsed (ref.: refractory) 2.05 (1.07–3.93) 0.03
RUNX1 0.74 (0.34–1.59) 0.44
TET2 1.38 (0.30–6.40) 0.68
TP53 1.07 (0.48–2.41) 0.87
0.3
1.0
3.0
10.0
Hazard Ratio

Supplementary information to Venetoclax-HMA as a bridge to transplant or DLI in relapsed or refractory acute myeloid leukemia

Verdeyen and Reuvekamp et al.

Supplemental Figures

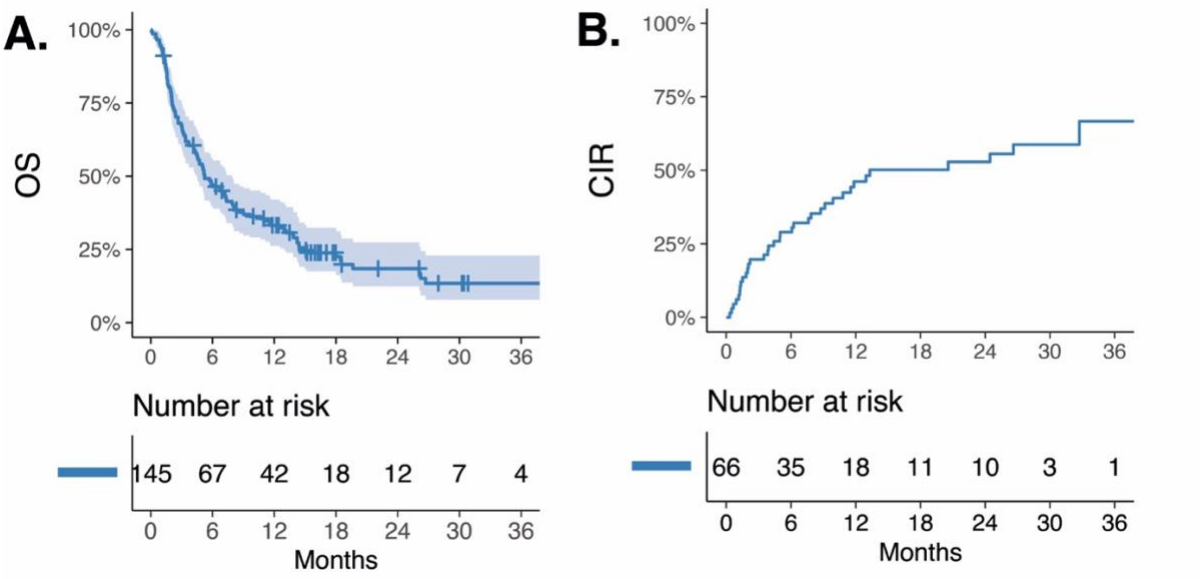


Figure S1. Overall survival and cumulative incidence of relapse in the whole cohort.

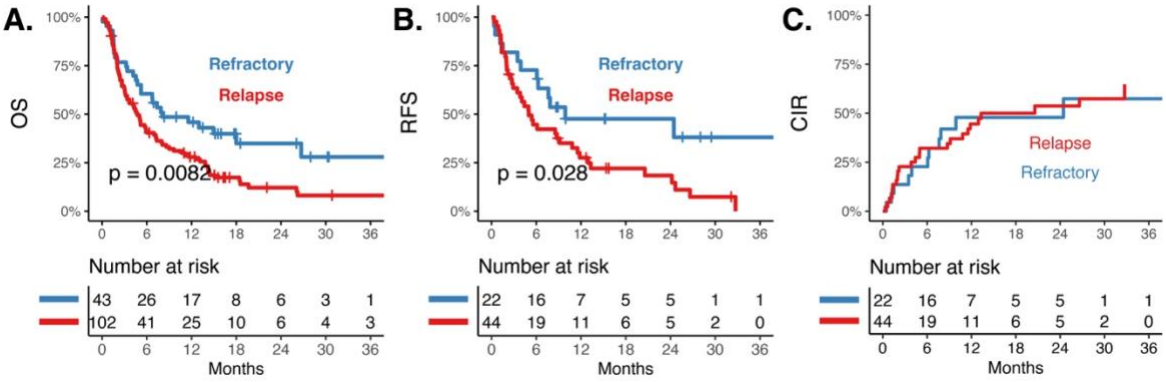


Figure S2. Survival of relapsed and refractory patients from start of venetoclax-HMA. A) overall survival. B) relapse-free survival. C) cumulative incidence of relapse

Supplemental Tables

Table S1. Mutations stratified by refractory and relapsed patients.

Characteristic	**Refractory**, N = 44[1]	**Relapse**, N = 102[1]	p-value[2]
Age	63 (51-70)	64 (52-69)	>0.9
Sex: male	27 (61%)	53 (52%)	0.3
NPM1			0.10
Negative	38 (93%)	80 (82%)	
Positive	3 (7.3%)	18 (18%)	
DNMT3A			0.8
Negative	11 (73%)	28 (65%)	
Positive	4 (27%)	15 (35%)	
TET2			0.7
Negative	13 (81%)	37 (86%)	
Positive	3 (19%)	6 (14%)	
FLT3-TID			0.2
Negative	37 (90%)	79 (81%)	
Positive	4 (9.8%)	19 (19%)	
TP53			0.5
Negative	32 (82%)	76 (86%)	
Positive	7 (18%)	12 (14%)	
IDH1			0.8
Negative	36 (92%)	80 (89%)	
Positive	3 (7.7%)	10 (11%)	
IDH2			0.088
Negative	32 (80%)	82 (91%)	
Positive	8 (20%)	8 (8.9%)	
RUNX1			0.11
Negative	30 (73%)	74 (85%)	
Positive	11 (27%)	13 (15%)	
ASXL1			0.11
Negative	29 (74%)	80 (86%)	
Positive	10 (26%)	13 (14%)	
Monosomy 17			0.4
Negative	37 (86%)	92 (92%)	
Positive	6 (14%)	8 (8.0%)	
Inversion 3			>0.9
Negative	41 (98%)	97 (97%)	
Positive	1 (2.4%)	3 (3.0%)	
KRAS/NRAS			0.6
Negative	16 (100%)	40 (91%)	
Positive	0 (0%)	4 (9.1%)	

Characteristic	**Refractory**, N = 44[1]	**Relapse**, N = 102[1]	**p-value**[2]
CEBPA			0.7
Negative	39 (98%)	92 (94%)	
Positive	1 (2.5%)	6 (6.1%)	

[1]Median (IQR); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test