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Venetoclax-based therapy for relapsed or refractory acute myeloid leukaemia following intensive induction chemotherapy

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Abstract

Background: The treatment of relapsed or refractory (R/R) acute myeloid leukaemia (AML) remains challenging and outcomes extremely poor. The introduction of venetoclax has transformed the treatment of AML and emerging data suggest that venetoclax-based therapy may enforce salvage treatment.

Materials and Methods: In this nationwide Danish retrospective study, we analysed treatment outcomes of venetoclax-based salvage treatment for R/R AML between 2019 and 2022. Only venetoclax-naive patients who had previously received treatment with intensive chemotherapy therapy were included.

Results: The cohort consisted of 43 R/R patients with a median age of 57 years. Nine (20.9%) were primary refractory and 34 (79.1%) patients had relapsed, including 21 after previous allogeneic stem cell transplantation. The overall response rate was 76.2% including 61.9% with composite complete remission (CRc: CR + CRi). Among CRc-responders with information on measurable residual disease (MRD), 8/13 (61.5%) obtained an MRD-negativity response. The overall survival was 9.3 months for all patients with an estimated 1-year overall survival of 34%. For CRc-responders the median overall survival was 13.3 months, and the median relapse-free survival was 12.8 months.

Conclusion: Venetoclax-based salvage treatment for R/R AML produced high response rates; however, for most patients the response was of limited duration. This study is limited by an observational design and prone to selection bias.

KEYWORDS
acute myeloid leukaemia, BCL-2, measurable residual disease, relapse/refractory, venetoclax

Novelty statement

What is the new aspect of your work?

Here we provide real-world outcomes of venetoclax-based salvage therapy for relapsed/refractory AML following intensive chemotherapy in Denmark.

What is the central finding of your work?

We observed an overall response rate of 76.2% including 61.9% composite complete remission (CRc), with a median overall survival for CRc-responders of 13.3 months and relapse-free survival of 12.8 months.

What is (or could be) the specific clinical relevance of your work?

Relapse/refractory AML remains a challenging clinical situation and here we provide additional information of high response rates that may improve outcomes in this population.

1 | INTRODUCTION

The survival for acute myeloid leukaemia (AML) patients has improved continuously over the last decades due to advances in allogeneic hematopoietic stem cell transplantation (AHSCT) regimens, improved supportive care and more intensive and effective combinations of cytoreductive therapy.[1–3] Still, the most common causes of death are refractory disease or relapse after initial remission.[3–5] Current standard treatment for adult fit patients includes a backbone of an anthracycline and cytarabine (often "DA 3 + 7") which produces complete remission (CR) rates in the range of 70%.[6] Per European LeukemiaNet (ELN) criteria, patients where first-line treatment fails to attain CR following two courses of induction chemotherapy (primary refractory disease, prAML) or patients relapsing after initial CR (rAML), are collectively referred to as relapsed/refractory (R/R) AML. This group of patients remains notoriously challenging to treat due to limited effective treatment options and consequently dismal outcomes. Most centres use salvage regimens with higher doses of cytarabine combined with a purine nucleoside analogue or etoposide to bridge patients to AHSCT. Despite salvage treatment, the prognosis for R/R AML remains poor with 5-year OS ~10% for patients treated with chemotherapy alone and ~20%–25% for patients referred to AHSCT.[7–11] The optimal salvage therapy of R/R AML remains an open issue since commonly used therapies have only been scantily compared with no apparent differences.[12]

In September 2022 venetoclax in combination with azacytidine (AZA) was approved for first-line treatment of elderly/unfit AML patients in Denmark, but off-label use of venetoclax has been increasingly used in R/R AML due to emerging data of its efficacy in this hard-to-treat patient population. In this retrospective nationwide cohort study, we report real-world data on the efficacy of off-label use of venetoclax-based salvage therapy for R/R AML patients in Denmark.

2 | MATERIALS AND METHODS

2.1 | Patients and setting

We conducted a nationwide retrospective cohort study including patients from all AML treating centres in Denmark. During the study period, the use of venetoclax in combination with low-dose Ara-C (LDAC), AZA or intensive chemotherapy for R/R AML was not approved, and, consequently, all treatment was off-label. The recommended dose of venetoclax combined with low-intensity and intensive backbone was 400 mg/daily (reduction to at least 25% and 50% when treatment was combined with a strong and moderate CYP3A4 inhibitor, respectively).

Eligible patients were adults (≥18 years) diagnosed with AML according to 2016 World Health Organization (WHO) criteria[13] treated with venetoclax-based regimens for R/R AML between November 25, 2019, and October 22, 2022. We included patients with biopsy-verified extramedullary relapse, measurable residual disease-relapse (MRD-relapse, defined as a 10-fold increase in transcript between any two positive samples measured in the same tissue within 28 days),[14] morphological relapse, or prAML according to the ELN criteria.[6] Treatment with venetoclax had to contain a minimum of one cycle including 7 days of venetoclax for low-intensity backbone and a minimum of 3 days when combined with intensive chemotherapy. We restricted our analysis to patients treated with intensive chemotherapy as first line treatment.

2.2 | Clinical information

All data were assessed using a case report form and were collected and managed in the browser-based data capture program Research Electronic Data Capture (REDCap) hosted by The North Denmark Region.[15] Information on AML-subtype (de novo, secondary and therapy-related) was classified according to World Health Organization,[13] cytogenetic risk category was grouped according to Medical Research Council (MRC),[16] and for prognostic classification the ELN 2017 risk stratification was used.[6]

First-line treatment was divided into DA 3 + 7-like (the standard treatment in Denmark is cytarabine administered for 10 days in combination with an anthracycline or anthracycline-related compound [i.e., mitoxantrone]), FLAG-Ida-like (fludarabine, cytarabine, granulocyte colony-stimulating factor in combination with idarubicin or mitoxantrone) and CPX-351 (liposomal formulation of daunorubicin and cytarabine) or other regimens including MEC (mitoxantrone, etoposide and intermediate to high dose cytarabine), MACE (amsacrine, cytarabine, etoposide) or TAD (thioguanine, cytarabine, and daunorubicin).

Targeted next-generation-sequencing (NGS) results and cytogenetics were obtained from pathology reports and done per

institutional practice as standard-of-care. At diagnosis, cytogenetics and NGS from the diagnostic bone marrow were included. At the time of R/R AML, information from relapsed patients included new cytogenetics and NGS when available, whereas for refractory disease information from diagnosis was used.

Information on MRD was retrieved from pathology reports. Patients were screened at diagnosis for applicable MRD markers by qPCR (in this cohort *NPM1*, *DEK-NUP214*, *MLLT3-KMT2A* or *WT1* overexpression). A subset of patients was monitored by digital droplet PCR (ddPCR) for somatic mutations in genes screened for by NGS as suggested in the updated ELN 2022 guideline.[17] Flow cytometry based MRD was not included due to lack of national standardized panels and reporting.

2.3 | Outcomes and statistical analysis

Patient characteristics were described from time of diagnosis and time of R/R AML before venetoclax treatment. Categorical variables were presented as counts and percentages and continuous variables as medians and interquartile ranges (IQR) or numeric ranges. In the instance of missing data, the proportion is given as patients with available information. Response rates were assessed using ELN 2017 response criteria and included composite complete remission (CRc, complete remission [CR] or complete remission with incomplete hematologic recovery [CRi]) and overall response rate (ORR, CRc + partial response [PR]).[6] Responses were only included for patients assessed by bone marrow morphology, or, in the instance of extramedullary relapse, examination by positron emission tomography–computed tomography (PET-CT) or lumbar puncture and given as the best response ever obtained by venetoclax-based treatment. An MRD-negative CRc was defined as undetectable levels of MRD by either qPCR or ddPCR except for *WT1* for which normalization of expression was appropriate. Response assessed by PET-CT was modified according to the ELN 2017 response criteria as follows: CR required total regression of all morphological tumour(s) and metabolic activity in addition to blast-free bone marrow, PR required a reduction in the tumour size of at least 50% from R/R baseline, and no response/progressive disease was defined as either unchanged or growth of tumour(s) from baseline.

Overall survival (OS) was defined as the time from first day of venetoclax treatment until death from any cause. Relapse-free survival was estimated for patients achieving CRc and defined as the time from first day of venetoclax treatment until relapse or death whichever came first. Patients were censored at the end of follow-up ranging from April 2022 to November 2022, depending on when the medical record was assessed. All tests were two-sided at a significance level of 5%. Statistical analyses were done using the statistical programming language "R" (version 4.2.2, Vienna, Austria, http://www.R-project.org). The study was conducted in accordance with national regulations on observational studies using medical records (record number: 2021-011009).

TABLE 1 Baseline characteristics at diagnosis.

Variable	All patients ($n = 43$)
Sex, male, *n* (%)	25 (58.1)
Age, median, years (IQR)	56 (44–62)
Antecedent myeloid neoplasm, *n* (%)	6 (14.0)
AML WHO classification, *n* (%)	
AML with recurrent genetic abnormalities	9 (20.9)
AML with myelodysplasia-related changes	10 (23.3)
AML not otherwise specified	22 (51.2)
Therapy-related AML	2 (4.7)
CNS-involvement, n (%)	4 (9.3)
Cytogenetic risk[a,b], *n* (%)	
Intermediate	28 (68.3)
Adverse	13 (31.7)
Cytogenetic aberrations[a], *n* (%)	
Normal karyotype	19 (46.3)
Monosomal karyotype	7 (17.1)
Complex karyotype	10 (24.4)
-17/-17p	1 (2.4)
KMT2A-rearrangement	2 (4.9)
European LeukemiaNet 2017 risk[a], *n* (%)	
Favourable	9 (22.0)
Intermediate	12 (29.3)
Adverse	20 (48.8)
Mutations[a], *n* (%)	
NPM1	9 (23.1)
IDH2	8 (20.5)
FLT3-ITD/TKD	10 (25.6)
RAS-pathway mutations[c]	10 (25.6)
TP53	1 (2.6)
MDS-related-mutations[d]	12 (30.8)

Abbreviations: AML, acute myeloid leukaemia; CNS, central nervous system; IQR, interquartile range (25th–75th percentiles); WHO, World Health Organization.
[a]For cytogenetics $n = 2$ (4.7%) have missing information, for targeted next-generation sequencing $n = 4$ (9.3%) have missing information;
[b]Risk according to the Medical Research Council.
[c]RAS-pathway mutations: *NRAS*, *KRAS*, *HRAS*, *PTPN11*.
[d]MDS-related-mutations: *ASXL1*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2*.

3 | RESULTS

3.1 | Study cohort

During the study period 66 patients were treated with venetoclax. A total of 12 patients received venetoclax upfront and were excluded from further analysis, 54 patients were salvaged with venetoclax-based regimens of which 43 (79.6%) received intensive induction therapy as first-line therapy and were included for analysis.

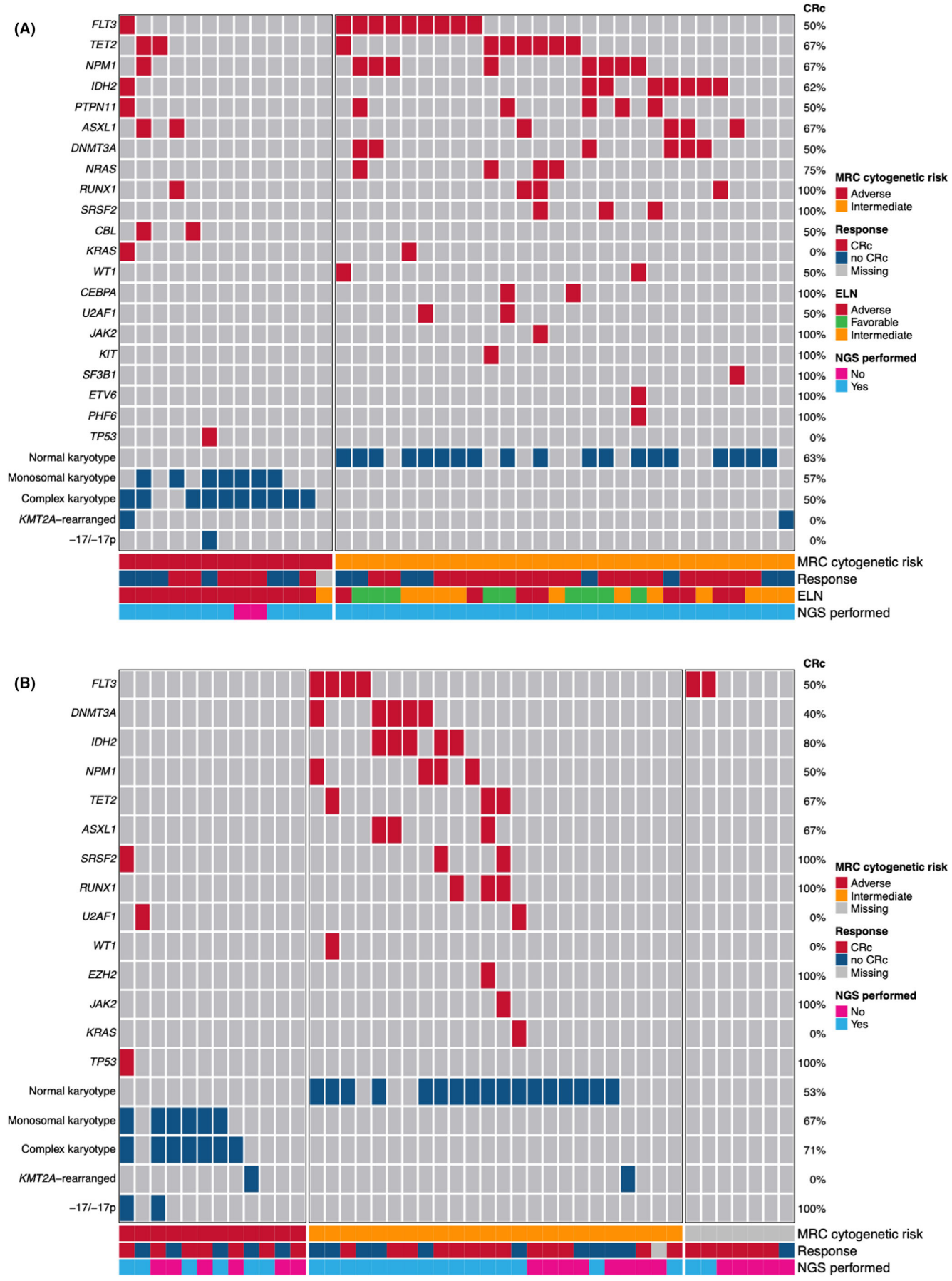

FIGURE 1 Legend on next page.

TABLE 2 Baseline characteristics at relapse or refractory disease.

Variable	All patients (n = 43)
Age, median, years (IQR)	57 (46–65)
Bone marrow blast, median %, (IQR)	15 (3–30)
CNS-involvement, *n* (%)	2 (4.7)
Primary refractory, *n* (%)	9 (20.9)
Relapse, *n* (%)	34 (79.1)
Relapse <12 months from diagnosis, *n* (%)	17 (50.0)
Prior lines before venetoclax, median (range)	2 (1–5)
≥2 prior lines, *n* (%)	28 (65.1)
Previous HMA exposure, *n* (%)	16 (37.2)
Previous AHSCT, *n* (%)	21 (48.8)
Venetoclax backbone therapy, *n* (%)	
Low dose cytarabine	3 (7.0)
Hypomethylating agent	33 (76.7)
Intensive chemotherapy	7 (16.3)
Venetoclax dose, median, *mg*, (range)	100 (50–400)
Concomitant CYP3A4 inhibitor, *n* (%)	39 (90.7)
Numbers of cycles, median, *n* (range)	3 (1–12)
Cytogenetic risk[a,b], *n* (%)	
Intermediate	24 (66.7)
Adverse	12 (33.3)
Cytogenetic aberrations[a], *n* (%)	
Normal karyotype	17 (47.2)
Monosomal karyotype	6 (16.7)
Complex karyotype	7 (19.4)
-17/-17p	2 (5.9)
KMT2A-rearrangement	2 (5.9)
Mutations[a], *n* (%)	
NPM1	4 (16.7)
IDH2	5 (20.8)
FLT3-ITD/TKD	6 (25.0)
RAS-pathway mutations[c]	1 (4.2)
TP53	1 (4.2)
MDS-related-mutations[d]	9 (37.5)

Abbreviations: AML, acute myeloid leukaemia; CNS, central nervous system; AHSCT, allogeneic haematopoietic stem cell transplantation; IQR, interquartile range (25th–75th percentiles).
[a]For cytogenetics *n* = 7 (16.3%) have missing information, for targeted next-generation sequencing *n* = 17 (39.5%) have missing information.
[b]Risk according to the Medical Research Council.
[c]RAS-pathway mutations: *NRAS*, *KRAS*, *HRAS*, *PTPN11*.
[d]MDS-related-mutations: *ASXL1*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2*.

3.2 | Characteristics at diagnosis and relapse/refractory disease

Patient characteristics at diagnosis are presented in Table 1. The median age at diagnosis was 56 (IQR: 44–62) years with a male-predominance (58.1%). Six patients (14.0%) had secondary AML and two patients (4.7%) had therapy-related AML. Karyotyping was available in 95.3%, and of these 53.7% had an abnormal karyotype. No patients had favourable cytogenetics, 68.3% and 31.7% had intermediate and adverse cytogenetic risk according to MRC cytogenetic risk classification, respectively. Results from NGS were available for 90.7% of patients. Among these, 22.5% had favourable risk, 27.5% intermediate risk and 50% had adverse risk per ELN 2017. Specific mutational results can be seen in Table 1 and Figure 1A.

For frontline treatment, most patients received DA 3 + 7-like chemotherapy (69.8%), whereas FLAG-Ida-like, CPX-351 and other regimens were given in 9.3%, 16.3%, and 4.7% of patients, respectively. A total of 34 patients (74.4%) received two courses of induction therapy, among these patients the proportion of DA 3 + 7-like chemotherapy and CPX-351 dropped to 55.9% and 11.8%, respectively, whereas FLAG-Ida-like and other increased to 26.5% and 5.9%, respectively. Induction treatment with DA 3 + 7-like chemotherapy was combined with the *FLT3*-inhibitor midostaurin in seven patients (16.3%) and gemtuzumab ozogamicin in 11 patients (25.6%).

Baseline characteristics at time of R/R are presented in Table 2. The median age was 57 (46–65) years. Nine patients (20.9%) had primary refractory disease and 34 patients (79.1%) had relapsed disease and the median time from diagnosis to relapse was 10.6 (IQR: 4.6–16.9) months and 50% of relapses occurred <12 months from diagnosis. Among relapsed patients, seven had MRD-relapse, 21 had morphological relapse, six had isolated extramedullary relapse (five myelosarcoma and one isolated central nervous system infiltration). The median number of previous lines of treatment, including first line, was 2 (range: 1–5). Here, 32 patients (65.1%) had received two or more prior lines, and 16 patients (37.2%) had previous hypomethylating agent (HMA) exposure. Additionally, 21 patients (48.8%) had post-AHSCT relapse. Of relapsed patients, 18/34 had available information from new NGS and 27/34 had new cytogenetics (Table 2 and Figure 1B).

3.2.1 | Venetoclax treatment

The backbone of venetoclax therapy was low intensity for 83.7% and intensive chemotherapy for 16.3%. Of the latter, five had FLAG-Ida-like and two had MEC-regimen as backbones and all patients received one cycle. Venetoclax was administered at a median dose of 100 mg/day, for a total of 7 days for two patients, 14 days for three

FIGURE 1 Oncoplot showing mutational and cytogenetic characteristics at (A) diagnosis and (B) relapse or refractory disease and composite complete remission (CRc) rates. Only patients with available information are included. At diagnosis information from karyotyping was available for 41 patients and targeted next-generation sequencing from 39 patients. At relapse or refractory disease karyotyping was available from 35 patients and targeted next-generation sequencing from 26.

TABLE 3 Clinical outcomes and responses among 42 evaluable for response R/R AML patients treated with venetoclax-based salvage.

Clinical outcome	$n = 42$
Response, *n* (%)	
ORR (CR + CRi + PR)	32 (76.2)
CRc (CR + CRi)	26 (61.9)
CR	19 (45.2)
CRi	7 (16.7)
PR	6 (14.3)
PD/no response	10 (23.8)
CRc_{MRD-} [a]	8/13 (61.5)
CRc by prior treatment lines, *n* (%)	
1	12/15 (80.0)
≥2	14/27 (51.9)
CRc by R/R-type, *n* (%)	
Relapse <12 months from diagnosis	8/16 (50.0)
Relapse ≥12 months from diagnosis	11/17 (64.7)
Morphological relapse	11/20 (55.0)
MRD-relapse	4/7 (57.1)
Extramedullary relapse	4/6 (66.7)
Primary refractory	7/9 (77.8)
CRc by previous AHSCT, *n* (%)	
Previous AHSCT	13/20 (65.0)
No previous AHSCT	13/22 (59.1)
CRc by backbone, *n* (%)	
LDAC/HMA	20/35 (57.1)
Intensive	6/7 (85.7)
Relapse among CRc	
1-year RFS, % (95% CI)	63.1 (45.4–85.7)
Median RFS, months (95% CI)	26.9 (9.2-NR)
Survival	
1-year OS, % (95% CI)	34.0 (21.5–53.7)
Median OS, months (95% CI)	9.3 (5.2–NR)

Abbreviations: AML, acute myeloid leukaemia; HMA, hypomethylating agent; AHSCT, allogeneic hematopoietic stem cell transplantation; LDAC, low dose cytarabine; MRD, measurable residual disease; NR, not reached.
[a]Among 13 patients achieving CRc with available information on MRD.

patients and 28 days for two patients, all with a concomitant strong CYP3A4 inhibitor (antifungal prophylaxis).

For low-intensity backbone, 8.3% received LDAC and 91.7% HMA, where all was AZA except one who received decitabine. LDAC was given at a median dose of 20 mg/m^2/day for a median of 10 days and AZA was given at a median dose of 75 mg/m^2/day for a median of 5 days. The median dose of venetoclax was 100 mg/day for a median of 28 days (IQR 14–28) and for a median of 4 (IQR 3–6) cycles. Most patients (88.9%) received a concomitant strong CYP3A4 inhibitor (antifungal prophylaxis). For all patients, 7/43 (16.3%) were successfully bridged to AHSCT.

3.3 | Response

A total of 42 patients were evaluable for response, and the ORR was 76.2%, including 61.9% with CRc and 14.3% with PR (Table 3). Molecular MRD monitoring was applicable in 27/42 patients and among patients achieving CRc 8/13 (61.5%) achieved MRD-negativity. The CRc-rates among patients receiving venetoclax-based therapy as first salvage treatment was 80.0% compared with 51.9% among patient having ≥2 prior lines of therapy. The CRc-rate for patients with post-AHSCT relapse was 65.0% compared with 59.1% for relapsed non-transplanted patients. When venetoclax was combined with intensive backbone, the CRc-rate was 85.7% compared with 57.1% when combined with low-intensity therapy. For relapsed patients the CRc-rate was 57.6% compared with 77.8% for patients with primary refractory disease. Notably, the CRc-rates were very similar between patients with morphological relapse, MRD-relapse, and extramedullary relapse at 55.0%, 57.1% and 66.7%, respectively. Responses according to mutational and cytogenetic alterations at diagnosis and relapse are displayed in oncoplots (Figure 1A,B).

3.4 | Survival

With a median follow-up of 12.5 (IQR: 10.9–18.0) months (by reverse Kaplan–Meier method) from venetoclax initiation, the estimated 1-year OS for all patients was 34% (95% CI: 21.5–53.7) and the median OS was 9.3 months (95% CI: 5.2 to not reached) (Figure 2A). For patients with CRc the median OS was 13.3 (95% CI: 10.9 to not reached) months. Among CRc-responders, the 1-year RFS was 48.7% (95% CI: 31.6–75.1) and the median RFS was 12.8 (95% CI: 7.3 to not reached) months (Figure 2B). Patients treated with venetoclax as first salvage treatment had a higher crude OS of 13.3 (95% CI: 9.3 to not reached) months compared with patients with two or more previous treatment lines at 7.9 (95% CI: 4.8–11.8) months ($p = .04$; Figure 2C). When stratifying patients according to response, the median OS for patients responding with CR with MRD-negativity was not reached (95% CI: 13.3 to not reached) compared with 11.6 (95% CI: 9.2 to not reached) months for patients achieving CR with positive MRD-marker and patients with CR without an MRD-marker or unavailable information, and 3.2 (2.4 to NR) months for patients with PR or no response ($p < .0001$) (Figure 2D). No crude differences according to treatment backbone was seen, where the median OS for patients with an intensive backbone was 9.3 (95% CI: 2.1 to not reached) months compared with 9.7 (95% CI: 5.2 to not reached) months for low-intensity backbone.

4 | DISCUSSION

This Danish nationwide real-world study addresses the clinical efficacy of venetoclax-based salvage therapy in 43 R/R AML patients. The oral selective Bcl-2 inhibitor venetoclax in combination with HMA represents the most significant improvement for treating elderly

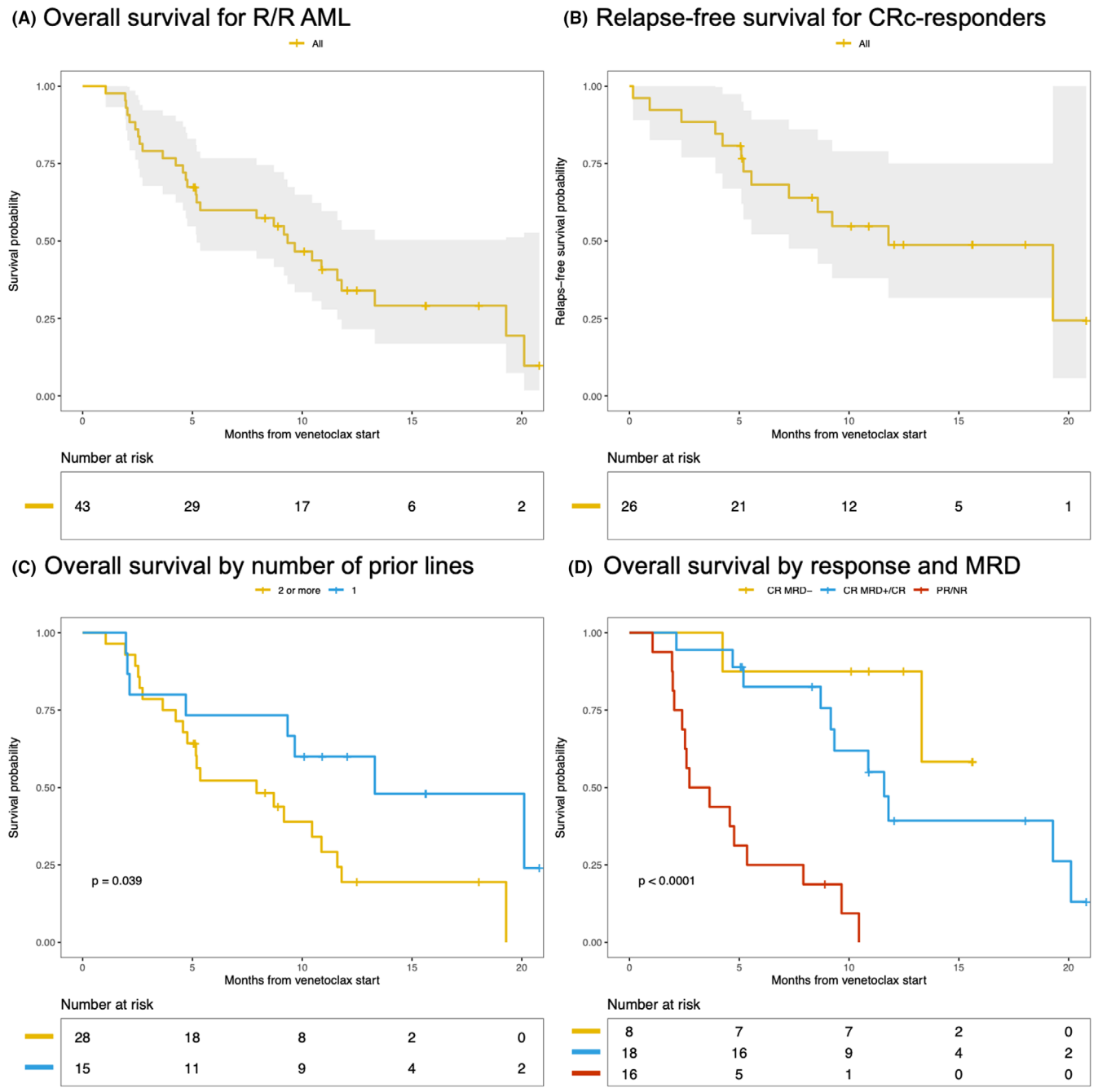

FIGURE 2 (A) Overall survival (95% CI) for all R/R patients treated with venetoclax-based salvage therapy, (B) Relapse-free survival (95% CI) for CRc-responders, (C) Overall survival for all patients stratified by number of prior lines before venetoclax-based salvage therapy, (D) Overall survival for all patients stratified by response (CRc with MRD-negativity, CRc without MRD-marker or MRD-quantification, partial response/no response).

and unfit patients with newly diagnosed AML with significant increase in OS and CR rates[18,19] and in the R/R AML setting, compelling evidence supports the addition of venetoclax to intensive salvage chemotherapy with reported CR/CRi rates of ~70%.[20,21] Reportedly, for prAML patients, median OS for those offered supportive care is only ~3.5 months and for those treated with intensive cytoreductive therapy, the median OS is ~7 months.[7,8,11,22–24] Even if AHSCT remains indispensable for long term OS, the relapse rates post-AHSCT remain very high.[11,22,24] This study included nine patients with prAML in whom treatment with venetoclax combined with low-intensity treatment or intensive chemotherapy as salvage therapy resulted in CRc in 7/9 (77.8%). Regardless of the small series of venetoclax treatment in prAML, ORRs for venetoclax-based therapy seem to consistently exceed chemotherapy-alone salvage regimens.[11,12,22] The formal role of venetoclax in the treatment of prAML remains to be established including dosing of venetoclax and selection of the most effective

chemotherapy combinations. Likewise, results for long-term survival following AHSCT are lacking.

Relapsed AML patients are equally challenging to treat, that being relapse before or post AHSCT. In this series of 34 relapsed patients, where 33 were evaluable for response, 12/19 (63.2%) achieved CRc when salvaged with venetoclax-based therapy following post-AHSCT relapse, and 7/14 (50%) without prior AHSCT achieved CRc. The majority of relapsed patients are not eligible for intensive salvage treatment. However, when reinduction can be offered, AHSCT or donor lymphocyte infusion represent the only option to increase long-term survival up to 25%[8] and treatment with HMA monotherapy for post-AHSCT relapse produce only very modest ORR of 19%.[25] For R/R AML patients who are not re-AHSCT candidates, some can be offered supportive care only, while others may be offered treatment with cytoreductive agents in an attempt to stabilizing the disease or even induce CR. The absence of controlled evidence in this setting is prominent and clinical management is dependent on multiple factors. Considering patients ineligible for intensive chemotherapy, an accumulating body of evidence indicates that quality of life can be improved for patients who achieve CR following therapy as opposed to those who do not obtain CR.[26–29] Thus, even if a curatively intended treatment strategy cannot be pursued, stabilization of disease or CR may provide better quality of life which may favour venetoclax-based treatment over less intensive regimens or supportive care only. Needless to say, these considerations need further elucidation.

Comparing our results with other studies on R/R AML, we find numerically higher response rates and better survival. The largest studies to date are the Italian AVALON multicentre study,[30] the Spanish PETHEMA registry study,[31] and two single-centre studies from Memorial Sloan Kettering Cancer Center[35] and City of Hope Medical Center.[32] Jointly, these studies report outcome of 374 patients with R/R AML with a median age ranging from 59 to 68 years treated primarily with venetoclax combined with low-intensity backbone. The reported ORRs range between 31% and 46%[30,31,33] and CRc-rates range from 18% to 46%[30–33] with a median OS ranging from 3.4 to 7.8 months.[30–33] Additionally, a Chinese multicentre study including 150 younger (median age 54) patients with R/R AML reported an ORR and CRc of 56.2% and 43.3%, respectively, and a median OS of 10 months.[34] The discrepancies between these studies and the present study may originate in selection bias as a clear limitation in our study, since venetoclax-based therapy for R/R AML was off-label treatment. Thus, patients may be highly selected according to characteristics, that is, cytogenetic risk, associated with response to therapy. For example, only 1/3 had adverse risk factors at R/R compared with 35%–66% in the aforementioned studies.[30–33] Additionally, our study population is younger since we selected patients with R/R after front-line intensive chemotherapy, which may also affect response rates and OS. The response to venetoclax-based therapy is known to be highly dependent upon the underlying disease genetics both in newly diagnosed and R/R AML. In the R/R setting, the presence of activated signalling mutations (i.e., *FLT3*-ITD or RAS-pathway mutations) or *TP53*-mutation/loss of chromosome 17/17p are associated with inferior response and outcome whereas mutations in *NPM1* and *IDH1/2* confer better outcomes.[33,34] Although our study is not powered to draw conclusions regarding the underlying genetics, we did not observe large discrepancies in responses between patients with *FLT3*-mutation or *TP53*-mutation/loss of chromosome 17/17p compared with *NPM1* or *IDH2*-mutated patients. To overcome the observed resistance for molecular subgroups, efforts are ongoing to test combinations of venetoclax and AZA with a third drug (triplets) including *FLT3*-inhibitors or anti-CD47 antibodies[35,36] or paring venetoclax with novel agents in duplets, that is, a MDM2-inhibitor.[37] Additionally, in the front-line setting, venetoclax combined with intensive chemotherapy for fit patients is also under clinical evaluation with promising results.[20,38] In our study, we did not find any large differences in OS for low-intensity backbone compared with intensive backbone, although we found numerically higher CRc-rates for intensive backbone.

In the current study, six patients (14%) had isolated extramedullary relapse (one isolated CNS) and were evaluated for response to venetoclax-based therapy. In this setting response rates were also encouraging at 66.7% (4/6) and durable with 3/6 having sustained remission. Albeit we acknowledge that the follow-up and response evaluation of patients with extramedullary relapse is controversial, and knowledge and recommendations are lacking. In Denmark, we have a tradition of using PET-CT which is generally considered the best modality for non-CNS extramedullary disease.[39,40]

Finally, MRD-measurements were available for a subset of patients, including 13 patients achieving CRc. Notably, we observed a high MRD-negativity conversion rate among CRc-responders resulting in a significantly higher crude OS compared with CRc with positive MRD or without available MRD-marker or measurement. This finding is not surprising; however, it highlights the prognostic potential of MRD monitoring in this treatment setting.

In conclusion, venetoclax-based salvage therapy produced encouraging response rates in R/R AML after failure of intensive chemotherapy; however, median OS was comparable to historic data on R/R AML treated with intensive chemotherapy-based salvage treatment. Additionally, we found significantly improved OS for patients achieving MRD-negativity which argues for MRD-monitoring for prognostication during therapy.

AUTHOR CONTRIBUTIONS

Daniel Tuyet Kristensen and Anne Stidsholt Roug designed the study. Daniel Tuyet Kristensen designed the REDCap database. Data was collected by Daniel Tuyet Kristensen, Andreas Due Ørskov, Claus Werenberg Marcher, Claudia Schöllkopf, Anne Louise Tølbøll Sørensen, and Anne Stidsholt Roug. Data were analysed by Daniel Tuyet Kristensen, Rasmus Froberg Brøndum, Anne Stidsholt Roug and Martin Bøgsted. Daniel Tuyet Kristensen and Anne Stidsholt Roug wrote the final draft of the manuscript with input from all authors. All authors contributed to interpretation of the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Daniel Tuyet Kristensen: Consulting fees: AbbVie, Atheneum, Astellas Pharma. Anne Louise Tølbøll Sørensen: Consultancy fees; Servier and AbbVie, travel grant; AbbVie. Claudia Schöllkopf: Consultancy fees; BMS, travel grant; AbbVie and Jazz Pharmaceuticals. Anne Stidsholt Roug: Consulting fees: AbbVie and Pfizer, travel grant; Jazz Pharmaceuticals. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data may be made available by contacting the corresponding author upon reasonable request.

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