Venetoclax as monotherapy and in combination with hypomethylating agents or low dose cytarabine in relapsed and treatment refractory acute myeloid leukemia: a systematic review and meta-analysis

Recent clinical data have shown a synergistic effect of venetoclax in combination with the hypomethylating agents (HMA) azacitidine and decitabine (complete remission [CR]/CR with incomplete cell count recovery [CRi]: 73%, median overall survival [OS] of 17.5 months) as well as low-dose cytarabine (LDAC; CR/CRi: 54%; median OS of 10.1 months) in the frontline setting in older patients with acute myeloid leukemia (AML) and those ineligible for intensive chemotherapy leading to approval of both combinations in the US.[1,2] However, data on relapsed/refractory (R/R)-AML are scarce and heterogenous. Outcomes of patients with R/R-AML are dismal with a median OS of 3-7 months and there is no approved standard of care.[3] Multiple clinical trials combining either venetoclax alone, venetoclax + HMA or venetoclax + LDAC as the backbone of therapy with other novel agents in R/R-AML are ongoing. As many of these trials are not randomized, it is vital to understand the response rate to venetoclax alone and venetoclax + HMA/LDAC in R/R-AML to use it as a benchmark for comparison.

Therefore, we performed a systematic literature review and meta-analysis to objectively assess overall response rates (ORR), and rates of CR/CRi for R/R-AML patients treated with venetoclax or venetoclax + HMA/LDAC.

MEDLINE *via* PubMed, Ovid EMBASE, the COCHRANE registry of clinical trials (CENTRAL), Scopus and the Web of Science electronic databases were

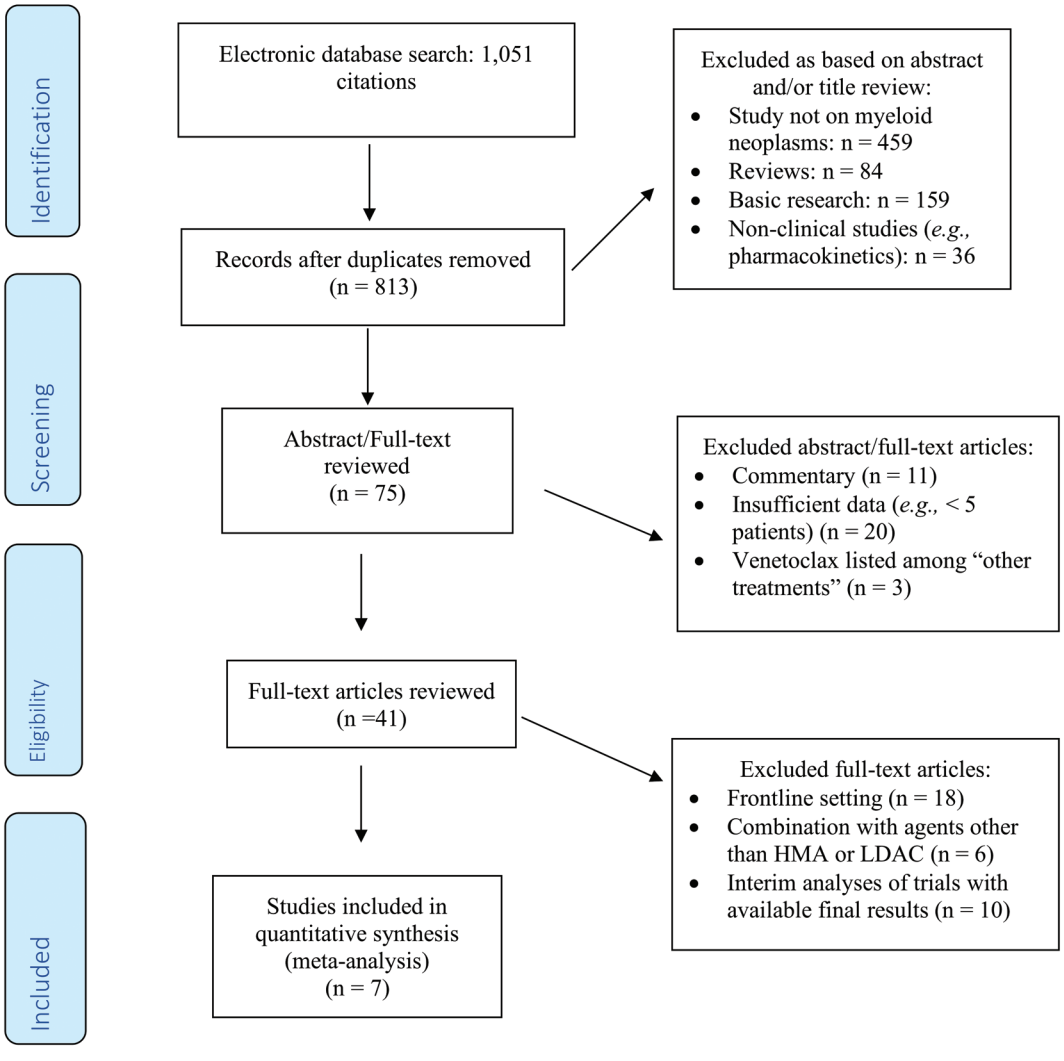

Figure 1. Flow chart showing study selection as per the MOOSE guidelines. Figure 1 illustrates the search strategy and stepwise process of the study selection used in this meta-analysis. MEDLINE *via* Ovid, Ovid EMBASE, Scopus, the COHRANE registry of clinical trials (CENTRAL), and the Web of Science electronic databases were searched with no language restriction from inception through August 2019, using the following combination of free-text terms linked by Boolean operators: "acute myeloid leukemia" OR "AML" OR "myelodysplastic syndrome" OR "MDS" AND "venetoclax". Two authors (MS and JPB) independently screened the titles and abstracts of all retrieved studies for eligibility and removed any duplicate records. In a second step, full texts of the potentially eligible studies were reviewed for the final eligibility. Reviews, basic science articles and articles with an insufficient patient number (<5 patients) were excluded. Furthermore, we excluded studies that i) lacked information on either overall response rate (ORR) or complete resposnse (CR) rate, ii) review articles, editorials, and correspondence letters that did not report independent data, iii) case series and studies reporting outcomes on fewer than five patients, iiii) studies that did were not conducted in acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) patients.

searched without language restriction from inception through August 2019, using the following combination of free-text terms linked by Boolean operators: "acute myeloid leukemia" OR "AML" OR "myelodysplastic syndrome" OR "MDS" AND "venetoclax". We performed a gray literature search through i) a manual search of bibliographies of all identified studies and ii) conference proceedings and abstracts of relevant annual meetings.

The study selection process is illustrated in Figure 1. The primary outcome was a combined rate of CR/CRi. Secondary outcome was ORR defined as CR + CRi + partial response (PR) + morphologic leukemia-free state (MLFS). Responses were reported by the individual publications using either the 2017 European Leukemia Network (ELN) AML response criteria[4,5] or International Working Group (IWG) criteria for AML.[6-9] Three studies

Table 1. Baseline characteristics of all relapsed/refractory acute myeloid leukemia patients treated with venetoclax among the included studies.

Author (Ref.)	Year	Treatment and treatment schedule	Number patients	Secondary AML (%)	Number prior HMA treatment (%)	ELN risk classification	Outcomes	Adverse effects
Konopoleva *et al.*[7]	2016	Venetoclax 800 mg/day (dose ramp up from 20 mg/day to target within 6 days; escalation to 1,200 mg/day permitted)	32	17 (54%)	24 (75%)	Not reported	ORR: 19% CR/CRi: 6%/13% Median OS: 4.7 months	All patients with any AE, 26 patients with grade 3/4
Huemer *et al.*[9]	2019	Venetoclax 800 mg/day (dose ramp up from 20 mg/day to target within 6 days)	7	7 (100%)	7 (100%)	Not reported	ORR: 29% CR/CRi: 29%/0% Median OS: 1.8 months (12.1 months in responders *vs.* 0.8 months in non-responders)	Not reported
Aldoss *et al.*[11]	2019	Venetoclax + AZA (9 patients) or DEC (81 patients); no dosing specified	90	22 (24%)	46 (51%)	Favorable: 8% Intermediate: 26% Adverse: 66%	ORR: 46% (AZA+VEN: 33%; DEC + VEN: 47%) CR/CRi: 26%/20% Median OS: 7.8 months (16.6 months in responders *vs.* 5.1 months in non-responders)	Not reported
DiNardo *et al.*[6]	2017	Venetoclax + AZA (8 patients), DEC (23 patients), LDAC (8 patients), or other (4 patients)	43	13 (31%)	33 (77%)	Favorable: 5% Intermediate: 49% Adverse: 47%	ORR: 21% (LDAC+VEN: 13%; AZA+VEN: 38%; DEC + VEN: 22%) CR/CRi: 5%/7% Median OS: 3.0 months (4.8 months in responders)	All patients with grade 3/4 AE 72% (infectious)
Ram *et al.*[10]	2019	Venetoclax 100-400 mg/day + AZA 37.5-75 mg/m^2 for 5-7 consecutive days or DEC 20 mg/m2 for 5 consecutive days	23	15 (66%)	23 (100%)	Favorable: 9% Intermediate: 48% Adverse: 43%	ORR: 43% CR/CRi: 21.5%/21.5% Median OS: 5.6 months (10.8 months in responders *vs.* 2.8 months in non-responders)	All patients with AE; no further information provided
Goldberg *et al.*[5]	2017	Venetoclax 400-800 mg (5-day ramp-up period during cycle 1) + AZA or DEC (8 patients) or LDAC (16 patients)	24	14 (58%)	16 (76%)	Favorable: 10% Intermediate: 28% Adverse: 62%	ORR: 29% (LDAC+ VEN: 23%; AZA+VEN: 50%; DEC + VEN: 0%) CR/CRi: 24% Median OS: not reported Not reported	
Shahswar *et al.*[12]	2017	Venetoclax 50-600 mg/day + AZA (5 patients) or DEC (1 patients) or LDAC (2 patients)	8	5 (63%)	7 (88%)	Not reported	ORR: 75% CR/CRi: 12.5%/37.5% Median OS: 6.6 months	Not reported

AE: adverse events; AML: acute myeloid leukemia AZA: azacitidine; CR: complete remission; CRi: complete remission with incomplete count recovery; DEC: decitabine; ELN: European Leukemia Network; HMA: hypomethylating agent; LDAC: low-dose cytarabine; ORR: overall response rate; OS: overall survival.

did not report which response criteria had been used.[10-12]

Quality assessments for individual studies using a modified Downs and Black checklist are provided in the *Online Supplementary Table S1*.[13]

Random-effects models were used to pool ORR, CR/CRi and CR rates. All effect sizes underwent logarithmic transformation prior to pooling using an inverse variance weighting approach. Heterogeneity of studies was determined using Cochran Q and I^2 indices and significant heterogeneity ($I^2 > 60\%$) was further explored with sensitivity analyses. Subgroup analyses were planned for venetoclax or venetoclax + HMA/LDAC. All analyses were performed with Comprehensive Meta-Analysis (CMA version 2.2, Biostat).

We identified 813 publications after removal of duplicates. Based on the title and the abstract review studies were excluded if they did not report results from AML or myelodysplastic syndromes (MDS) patients (n=459 studies), were reviews (n=84), basic research articles (n=159), or non-clinical studies (n=36). Of the remaining 75 articles, 34 were excluded because they were commentaries (n=11), had insufficient reporting of data (n=20) or listed venetoclax among "other treatments" (n=3). Articles reporting results of venetoclax in the frontline setting, in combination with agents other than HMA or LDAC, or publications of interim data were also excluded. Of the seven studies included, five were retrospective studies,[5,6,8,11,12] one prospective cohort study,[10] and one phase I/II clinical trial.[7] Patients were treated with venetoclax monotherapy in two studies[7,8] and with venetoclax in combination with either HMA or LDAC in five studies (Table 1).[5,6,10-12]

There was a total of 224 patients of whom 219 patients had R/R-AML, three MDS patients, and two blastic plasmacytoid dendritic cell neoplasm (BPDCN) patients. The average median age was 68.9 years (range: 59-76). A total of 156 patients (69.6%) had previously received HMA and 48 patients (21.4%) had a prior allogeneic stem cell transplant. The average median duration of follow-up was 7.3 months (range: 1.8-15.8).

Among patients with a reported cytogenetic profile, 13 (7.3%) patients had a favorable, 61 patients (34.5%) had an intermediate and 102 patients (57.6%) had an unfavorable cytogenetic risk profile. Five studies (n=211 patients) reported data on molecular testing which showed rates of *IDH1/2, FLT3, NPM1*, and *TP53* mutations of up to 38%, 28%, 13%, and 23%, respectively (*Online Supplementary Table S2*).[6-8,10,11]

All seven studies reported the ORR (Figure 2A), composite CR/CRi rate (Figure 2B) and CR rate (Figure 2C). For all studies combined, the ORR was 31.1% (95% confidence interval [CI]: 21.8-42.2). The ORR was 20.7%

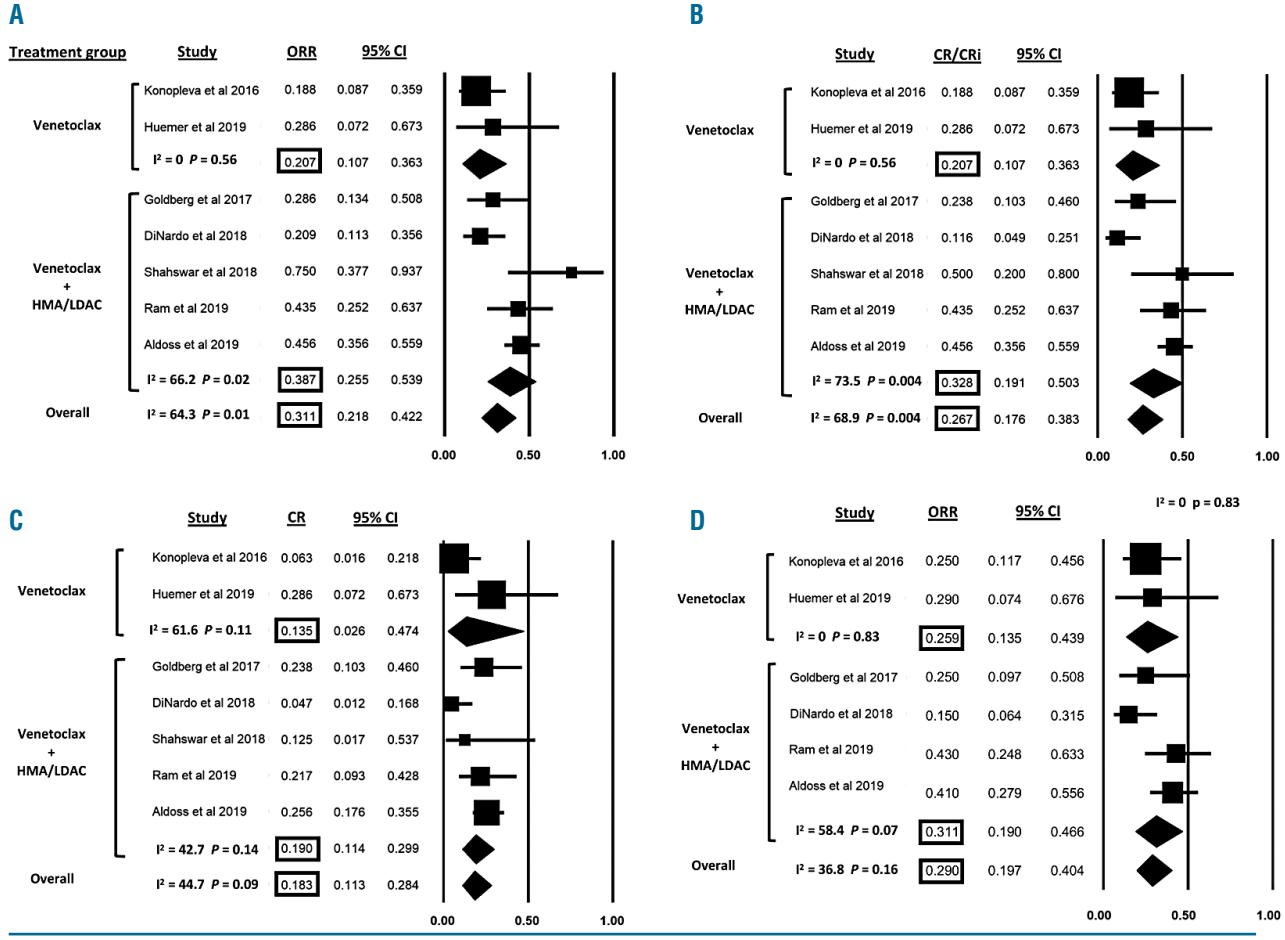

Figure 2. Response to venetoclax in relapsed/refractory acute myeloid leukemia (R/R-AML). Forest plots of odds ratios (squares, proportional to study weights used in meta-analysis, 95% confidence intervals) of response for venetoclax alone and in combination hypomethylating agents (HMA) or low-dose cytarabine (LDAC) with the summary measures (center line of diamond) and associated confidence intervals (lateral tips of diamond). Odds ratios for overall response rate (ORR), combined complete response (CR) and complete response with incomplete count recovery (CRi) rate and CR alone are shown in panel A, B and C respectively. Odds ratio for the ORR for patients, who received prior HMA therapy, is shown in panel D.

(95% CI: 10.7–36.3) for venetoclax monotherapy and 38.7% (95% CI: 25.5–53.9) for venetoclax + HMA/LDAC. There was significant heterogeneity among studies examining venetoclax + HMA/LDAC (Q=11.8; I^2=66.2%; *P*=0.02).

The CR/CRi rate was 26.7% (95% CI: 17.6–38.3), 20.7% (95% CI: 10.7–36.3) and 32.8% (95% CI: 19.1-50.3) for all studies combined, venetoclax monotherapy and venetoclax + HMA/LDAC, respectively. There was significant heterogeneity among studies examining venetoclax + HMA/LDAC (Q=15.1; I^2=73.5%; *P*=0.004).

The CR rate was 18.3% (95% CI: 11.3–28.4), 13.5% (95% CI: 2.6–47.4) and 19% (95% CI: 11.4–29.9) for all studies combined, venetoclax monotherapy and venetoclax + HMA/LDAC, respectively. There was significant heterogeneity for studies examining venetoclax alone (Q=2.6, I^2=61.6%, *P*=0.11).

Median OS reported in individual studies of all patients treated with venetoclax monotherapy and venetoclax + HMA/LDAC ranged between 1.8 to 7.8 months and 3.0 to 6.6 months, respectively. Among responding patients, the median OS in individual studies of all patients treated with venetoclax monotherapy and venetoclax + HMA/LDAC was 12.1 to 16.6 months and 4.8 to 12.1 months, respectively.[6-8,10-12]

In all studies combined, the ORR for patients with prior HMA exposure was 29% (95% CI: 19.7–40.4) (Figure 2D) and 25.9% (95% CI: 13.5–43.9) and 31.1% (95% CI: 19-46.6) for venetoclax monotherapy and venetoclax + HMA/LDAC, respectively. Data on the comparative efficacy of venetoclax + HMA *versus* venetoclax + LDAC were not available.

Separate analyses of response rates to various treatment combinations were available for only 3 of the 5 studies reporting venetoclax + HMA or LDAC.[5,6,11] The ORR ranged from 13-23%, 33-50%, and 0-47% for venetoclax in combination with LDAC, azacitidine, and decitabine, respectively.[5,6,11]

We have previously reported ORR and CR rates for HMA monotherapy in R/R-AML of 30% and 11%, respectively.[14] An ORR of 23% (18% CR) has been reported for LDAC monotherapy in R/R-AML.[15] In our meta-analysis, patients treated with venetoclax + HMA/LDAC demonstrated an ORR of 38.7% and a CR rate of 19% suggesting a greater efficacy of the combination treatment compared to HMA or LDAC monotherapy. Our results also suggest that prior exposure to HMA did not preclude a response to subsequent therapy with venetoclax-based therapies. Acknowledging the limitations of cross-study comparisons, our findings need to be verified in clinical trials directly comparing these treatment strategies.

Sensitivity analyses for ORR, CR/CRi and CR rate showed that exclusion of any one study did not change the overall effect size. The study by DiNardo *et al*. had the largest influence on the heterogeneity of the ORR, CR/CRi and CR rate.[6] Removal of this study increased the ORR by 5.4% (from 38.7% to 44.1%) in the subgroup analysis of studies examining venetoclax + HMA/LDAC and led to a loss of heterogeneity (Q=4.7, I^2= 36.6%, *P*=0.19).

Data on the mutational profile of patients were reported in five studies and the presence of *TET2-*, *IDH1/2-*, *ASXL1-*, and *RUNX1*-mutations were reported to be associated with higher response rates to treatment with venetoclax-based regimens.[6-8,10,11] However, reporting of predictive biomarkers was inconsistent among the studies.

Our study has several limitations. The significant heterogeneity between studies in terms of the number of patients included in each arm and the reporting of results precluded a comparison of the response rates for the various venetoclax combination strategies in a formal meta-analysis. While response rates seemed higher for the combination of HMA with venetoclax compared to LDAC with venetoclax, our study does not support any formal conclusion and highlights the lack of evidence. Second, there were insufficient data to assess adverse events in our meta-analysis. Third, we were unable to determine whether specific mutations could serve as biomarkers to predict response to venetoclax. Additionally, we could not differentiate between primary refractory, early and late relapses as well as first or advanced relapses and the impact of prior stem cell transplantation receipt or HMA treatment duration. Finally, we were unable to assess the effect of venetoclax-based treatment on OS.

In conclusion, this systematic review and meta-analysis of venetoclax treatment in R/R-AML included seven studies with a total of 224 patients and demonstrated an ORR of 38.7% and 20.7% for patients treated with venetoclax + HMA/LDAC and venetoclax monotherapy, respectively. Prior treatment with HMA did not preclude a response to subsequent venetoclax treatment. Additional studies testing venetoclax combination therapies in R/R-AML are ongoing and urgently needed.

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