Appendix 2. Supplementary Clinical Studies

Author / Year	Study Design & Patient Characteristics	Treatment Details	Efficacy Results	Limitations
Ye et al. 2025[28]	Multicentre retrospective cohort study (n =350) R/R AML with 154 patients (median age 50 years, 57.1% male) treated with venetoclax plus azacitidine (VA) as salvage therapy.	The VA regimen consisted of venetoclax (100 mg on day 1, 200 mg on day 2, and 400 mg on days 3–28) and azacitidine 75 mg/m² on days 1–7. Venetoclax doses were reduced by at least 50% in patients receiving moderate or strong CYP3A4 inhibitors, and FLT3 inhibitors were administered to patients with FLT3 mutations.	In the VA group (n = 154), the CRc rate was 39.6% after one cycle and 46.1% after two cycles of salvage therapy. The 3-year overall survival (OS) and event-free survival (EFS) from the start of VA therapy were 36.6% and 13.5%, respectively. Among the 44/154 (28.6%) patients who proceeded to allo-HSCT, 70.5% were in CRc and 64.5% were MRD-negative at transplantation. The 3-year post-transplant OS and EFS were 59.1% and 38.6%, respectively, with a 3-year cumulative incidence of relapse of 43.2% and transplant-related mortality of 18.2%.	Retrospective, non-randomised design, heterogeneous patient characteristics and prior therapies, limited follow-up in some subgroups, and the possibility of underreported adverse events, which may affect the interpretation of VA's efficacy and safety.
Garciaz et al. 2024[31]	Retrospective multicentre study of 84 adult AML patients (62 newly diagnosed, 22 R/R). Median age of R/R patients	The study did not specify the dosing or schedule; R/R AML patients received at	In 22 R/R AML patients, a median of 4 venetoclax plus azacitidine cycles (range 1–17) led to responses in all	Small, retrospective cohort; heterogeneous treatment approaches (variable number of venetoclax plus azacitidine

	was 73. Median prior treatment lines were 1 (range 1–3).	least one cycle of venetoclax plus azacitidine and achieved a response (CR, CRi, or MLFS) before discontinuing therapy.	patients: 54.5% achieved CR, 27.3% CRi, and 18.2% MLFS. Among the 10 evaluable patients, all achieved MRD negativity. With a median follow-up of 26 months, median OS was 19 months and median TFS 10 months; 5 patients were retreated at relapse, and 2 achieved a second CR/CRi lasting 4–6 months.	cycles and discontinuation of venetoclax alone versus venetoclax plus azacitidine); limited follow-up on post-HSCT outcomes; MRD assessments not standardized; and absence of a control group.
Garciaz et al. 2022[40]	Single centre retrospective study included 39 R/R AML patients treated with azacitidine plus venetoclax. Median age was 69 years. Most had adverse cytogenetics and prior therapies and were deemed to be ineligible for intensive chemotherapy (rationale not provided).	Standard-dose azacitidine (75 mg/m² daily for 7 days) combined with venetoclax, ramped over 3 days to 400 mg daily. For patients on strong CYP3A inhibitors, venetoclax was reduced to 100 mg. The first cycle lasted 14–28 days depending on age/comorbidities, with subsequent cycles adjusted for toxicity and marrow response.	In the R/R cohort (n = 39), the ORR was 37%, with a median OS of 5.9 months and EFS of 2.3 months. Early mortality within the first 56 days occurred in six patients. Among responders, median LFS was 10.3 months, and responses were generally durable. Four patients underwent HSCT, with three relapsing between 3–8 months post-transplant.	Small single-centre cohort; heterogeneous prior treatments and mutations, and short follow-up, which restrict the ability to generalise results or fully assess long-term response durability.
Graveno et al 2022[41]	Single centre retrospective study included 77 patients with R/R AML 60 of whom received VA. Median age for all patients	The combination of venetoclax and any treatment adjustments were made at treating	For the whole cohort after a median follow up of 9.9 months, 28% of patients were alive with median OS of 13.1	Single centre cohort; short follow-up.

	was 64 (IQR 54-69). The majority (72%) were ELN adverse risk.	physician discretion. Dosing schedule was not specified.	months. The ORR was 68% and composite CR rate 53%. Median time to response was 1 month and median PFS 12 months. 17 patients were bridged to HSCT and 6 to DLI. For the VA cohort (n = 60) median OS was 14.4 months.	
Weng et al 2022[42]	A multicentre retrospective study included 150 R/R AML patients, 135 of whom received VA. The median age of all patients was 53.5 years (range 40-62). 24% of patients had previously received HSCT.	Standard-dose azacitidine (75 mg/m² daily for 7 days) combined with venetoclax, ramped over 3 days to 400 mg daily over a 28-day cycle, adjusted as clinically required.	Results are reported for the whole cohort. With median follow up of 11.2 months (95% CI 7.2-14.8 months) 1- and 2- year OS was 46.9% (95%CI, 37.8%–58.1%) and 38.9% (95% CI, 28.7%–52.9%) respectively. Median OS was 10.0 months (range 7.4-NR). ORR was 56.2% and CR was achieved for 22% of all patients,	Results are not reported separately for the VA regimen limiting generalisability. Short follow up time.
Piccini et al 2021[43]	Single centre retrospective study included 47 R/R AML patients, 29 treated with VA. The remaining 18 received venetoclax in combination with decitabine or low dose cytarabine. Median age of all study patients was 56 years (range 33-74). 23% of patients had relapsed following previous HSCT.	Standard-dose azacitidine (75 mg/m² daily for 7 days) combined with venetoclax, ramped over 3 days to 400 mg daily over a 28-day cycle. Venetoclax was reduced to 21 days in the first cycle and 21 or 14 days in subsequent cycles due to evidence	Results are reported for the whole cohort, the median number of venetoclax based cycles was 2 (range 1-24). Composite complete response rate was 55% (26/47) and 13 of 26 responders obtained CRi/CRp status. DFS for all patients with CR (n = 26) was 10.6 months. EFS for the whole cohort (n = 47) was 4.5	Small, single centre retrospective study. Results not reported for VA regimen separately limiting generalisability.

		of treatment-related myelosuppression.	months. 13 patients went on to receive HSCT. Overall survival was 10.7 months. Median follow up was 10.7 months (range 0.8-30).	
Stahl et al. 2021[44]	Single centre retrospective study included 35 R/R AML patients treated with azacitidine plus venetoclax. Median age was 65 years. Median prior treatment lines was 1 (range 0-4), most (57%) had adverse ELN risk, 17% had previously received HSCT.	Standard-dose azacitidine (75 mg/m² daily for 7 days) combined with venetoclax, ramped over 3 days to 400 mg daily. Venetoclax dose was reduced to 100 mg daily if azole antifungal prophylaxis was required.	Results are reported separately for the VA cohort. The median number of cycles of VA was 2 (range 1-15). 26% of patients achieved CR and 11% achieved Cri. The ORR was 49% with a median OS of 25 months (5.8-NR). OS censored for HSCT was 8.1 months (range 5.7-NR). The relapse rate after response to venetoclax therapy was 41% with a median duration of response of 10.2 months.	Single centre, retrospective design.
Todisco et al. 2022[45]	A multicentre observational cohort study with 190 patients included in the final analysis. 67.4% of patients received VA and 32.6% received venetoclax with decitabine. Patients with newly diagnosed AML were included in the study as well as R/R, results are reported separately. The study included 68 refractory and 79 relapsed patient (total 147). Median age of R/R	Venetoclax dose ranged from 100 to 400 mg daily, dependent upon use of azole antifungals. Azacitidine dose not specified.	Median follow up was 20.9 months (95% CI, 17–25.9). Median duration of treatment was 2.8 months (IQR 1.5-6.9 months) for refractory patients and 2.8 months (IQR 1.2-6.3) for relapsed patients. In relapsed and in refractory patients CRc was reported in 38.2% and 34.2%; ORR was 51.5% and 41.8%; and median DOR was 6.8 months (range 4.4-12.6) and 8.3	Results are not reported separately for patients treated with VA.

	patients was 64 years. Of the R/R patients: 69% were considered fit; 29% unfit for intensive chemotherapy and 2% frail. 37% of R/R had previously received HSCT.		months (range 4.7-11.9) respectively. Median EFS was 6.2 and 4.4 months; OS was 9.1 and 6.3 months in relapsed and in refractory patients respectively. VA was a bridge to HSCT in 38 (26%) of R/R patients.	
Tenold et al. 2021[30]	Retrospective single-centre analysis of 25 patients with R/R AML: 14 received venetoclax plus azacitidine, and 11 received venetoclax plus decitabine. The median age was 57 years (range 25–86), and all patients had received at least one prior therapy (median 2, range 1–6).	azacitidine 75 mg/m^2 intravenously or subcutaneously daily on days 1–7 and venetoclax orally on days 1–28 of cycle 1. Venetoclax doses were ramped up with adjustments for CYP3A4 inhibitors under inpatient monitoring to ensure safety.	Results are reported for the entire cohort; the authors did not provide a separate breakdown of response or survival outcomes by treatment arm. The ORR was 52%, with a CR + CRi of 32%. Median OS for the cohort was 5.5 months (95% CI: 2.9–21.6), with one-year estimated survival of 38%. Among patients achieving CR, median OS was 21.6 months (95% CI: 15.2–not reached). Median duration of response was 14.7 months, with a median relapse-free survival of 17.0 months (95% CI: 3.0–not reached). Of the 13 responders, five patients eventually relapsed and died.	Small, single-centre, retrospective design, heterogeneous patient population, incomplete genomic profiling, and lack of a control group. Efficacy was reported only for the full cohort, preventing comparisons between azacitidine and decitabine subgroups, which limits generalizability and precludes conclusions about relative efficacy.
Ganzel et al. 2020[29]	Retrospective multicentre analysis included 40 patients with R/R AML from 11 Israeli medical centres. The median	The median daily dose was venetoclax 400 mg (range 100–800 mg), and patients	The study does not provide a separate CR/CRi rate or survival specifically for the venetoclax in combination	Small heterogeneous cohort; retrospective design; Venetoclax dosing was inconsistent, with a median daily dose of 400 mg

	age was 67 years (range 21–82). Patients received venetoclax mostly in combination with HMA (n = 25) or low-dose cytarabine (n = 9), while a few received monotherapy or other combinations. Patients had received a median of 2 prior lines of treatment (range 1–4), not including prior allogeneic hematopoietic cell transplantation, and 42.5% had previously undergone allogeneic HSCT.	received a median of 2.75 cycles (range 0.5–14). Dosing adjustments for concomitant CYP3A4 inhibitor treatment were individualised by the treating physicians, as no standardised guidelines were applied.	with HMA so all outcome measures reported entire cohort, not just HMA-treated patients. Among the 29 patients who survived more than 2 months, 52% achieved CR or Cri. Neutrophil recovery was observed in 76% of these patients and strongly correlated with improved OS (median 18 vs. 3 months, $p < 0.001$). The median OS was 5.5 months for all patients and 6.5 months for those surviving beyond 2 months.	(range 100–800 mg), and 17.5% of patients receiving lower doses. Dose adjustments for CYP3A4 inhibitors were not standardised.
CR: Complete remission; CRc: Composite complete remission; Cri: Complete remission with incomplete haematologic recovery; DFS: Disease-free survival; EFS: Event-free survival; HMA: Hypomethylating agent; HSCT / allo-HSCT: Haematopoietic stem cell transplant / allogeneic HSCT; LFS: Leukaemia-free survival; LDAC: Low-dose cytarabine: MLFS: Morphologic leukaemia-free state; MRD: Measurable residual disease; OS: Overall survival; R/R-AML: Relapsed or refractory acute myeloid leukaemia: TFS: Treatment-free survival; VA: Venetoclax with azacitidine				