Received: 19 July 2022 | Revised: 21 October 2022 | Accepted: 29 October 2022

DOI: 10.1002/cncr.34608

ORIGINAL ARTICLE

AVALON: The Italian cohort study on real-life efficacy of hypomethylating agents plus venetoclax in newly diagnosed or relapsed/refractory patients with acute myeloid leukemia

Elisabetta Todisco MD[1,2] | Cristina Papayannidis MD[3] | Nicola Fracchiolla MD[4] | Elisabetta Petracci PhD[5] | Chiara Zingaretti PhD[5] | Calogero Vetro MD[6] | Maria Paola Martelli MD, PhD[7] | Patrizia Zappasodi MD[8] | Nicola Di Renzo MD[9] | Susanna Gallo MD[10] | Ernesta Audisio MD[11] | Davide Griguolo MD[12] | Claudio Cerchione MD, PhD[13] | Carmine Selleri MD[14] | Daniele Mattei MD[15] | Massimo Bernardi MD[16] | Monica Fumagalli MD[17] | Giuliana Rizzuto MD[18] | Luca Facchini MD[19] | Claudia Maria Basilico MD[20] | Ilenia Manfra MD[21] | Erika Borlenghi MD[22] | Roberto Cairoli MD[23] | Prassede Salutari MD[24] | Michele Gottardi MD[25] | Alfredo Molteni MD[26] | Vincenza Martini MD[27] | Monia Lunghi MD[28] | Luana Fianchi MD[29] | Daniela Cilloni MD, PhD[30] | Francesco Lanza MD[31] | Elisabetta Abruzzese MD, PhD[32] | Nicola Cascavilla MD[33] | Flavia Rivellini MD[34] | Felicetto Ferrara MD[35] | Luca Maurillo MD[36] | Jacopo Nanni MD[3] | Alessandra Romano MD[6] | Valeria Cardinali MD[7] | Federica Gigli MD[1] | Elisa Roncoroni MD[8] | Vincenzo Federico MD[9] | Giovanni Marconi MD[13] | Roberta Volpi BSc[5] | Mariarita Sciumè MD[4] | Corrado Tarella MD[1] | Giuseppe Rossi MD[22] | Giovanni Martinelli MD, PhD[13] | for the AVALON Cooperative Group

[1]Divisione di Oncoematologia, IRCCS Istituto Europeo di Oncologia, Milano, Italy

[2]SC Ematologia, Ospedale Busto Arsizio, ASST Valle Olona, Varese, Italy

[3]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy

[4]UOC Oncoematologia, Fondazione IRCCS "Ca'Granda" Ospedale Maggiore Policlinico, Milano, Italy

[5]Unità di Biostatistica e Clinical Trials, IRCCS Istituto Romagnolo per lo Studio dei Tumori (ISRT) "Dino Amadori", Meldola, Italy

[6]Divisione di Ematologia, AOU Policlinico "G. Rodolico-San Marco", Catania, Italy

[7]Dipartimento di Medicina e Chirurgia, Università di Perugia, Ospedale "Santa Maria della Misericordia", Perugia, Italy

[8]Dipartimento di Oncoematologia, Fondazione IRCCS Policlinico "San Matteo", Pavia, Italy

[9]Unità di Ematologia e TCS, Ospedale "Vito Fazzi", Lecce, Italy

[10]SCDU di Ematologia e Terapie Cellulari, AO Ordine Mauriziano, Torino, Italy

[11]SC Ematologia 2, AOU Città della Salute e della Scienza, Torino, Italy

Elisabetta Todisco, Cristina Papayannidis, and Nicola Fracchiolla contributed equally to this work.

[12]SC Ematologia, ASU Giuliano Isontina, Trieste, Italy
[13]Dipartimento di Oncologia ed Ematologia Clinica e Sperimentale, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy
[14]UOC Ematologia, AOU "San Giovanni di Dio e Ruggi D'Aragona", Salerno, Italy
[15]SC di Ematologia, AO "Santa Croce e Carle", Cuneo, Italy
[16]UO Ematologia e Centro Trapianto di Midollo Osseo, IRCCS Ospedale "San Raffaele", Milano, Italy
[17]SC Ematologia, Ospedale "San Gerardo", ASST di Monza, Monza, Italy
[18]UOC Ematologia e Centro Trapianto di Midollo Osseo, ASST "Papa Giovanni XXIII", Bergamo, Italy
[19]UOC Ematologia, Azienda USL IRCCS di Reggio Emilia, Reggio Emilia, Italy
[20]UO Ematologia, ASST Settelaghi, Ospedale di Circlo Fondazione Macchi, Varese, Italy
[21]UO Ematologia, Azienda Ospedaliera "S. G. Moscati", Avellino, Italy
[22]UO Ematologia, ASST Spedali Civili di Brescia, Brescia, Italy
[23]SC Ematologia, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy
[24]UOC Ematologia Clinica, Ospedale Civile "Santo Spirito", Pescara, Italy
[25]Dipartimento di Oncologia, UOC Oncoematologia, Istituto Oncologico Veneto (IOV) IRCCS, Padova, Italy
[26]UO Ematologia, ASST di Cremona, Cremona, Italy
[27]UOC Ematologia, Ospedale "F. Spaziani", Frosinone, Italy
[28]SCDU Ematologia, AOU "Maggiore della Carità", Novara, Italy
[29]UOC Ematologia e TCSE, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Roma, Italy
[30]Dipartimento di Scienze Cliniche e Biologiche, Università di Torino, Torino, Italy
[31]UO Ematologia, Ospedale "Santa Maria delle Croci", AUSL Romagna, Ravenna, Italy
[32]Dipartimento di Ematologia, Ospedale "S. Eugenio", Università Tor Vergata, Roma, Italy
[33]UO Ematologia, Ospedale "Casa Sollievo della Sofferenza" IRCCS, San Giovanni Rotondo, Italy
[34]UOC Oncoematologia, Presidio Ospedaliero "A. Tortora", Pagani, Italy
[35]UOC Ematologia, AORN "A. Cardarelli", Napoli, Italy
[36]Dipartimento di Biomedicina e Prevenzione, Università Tor Vergata, Roma, Italy

Correspondence
Elisabetta Todisco, SC Ematologia, Ospedale Busto Arsizio, ASST Valle Olona, Via A. da Brescia 1, 21052 Busto Arsizio, VA, Italy.
Email: elisabetta.todisco@asst-valleolona.it

Giovanni Martinelli, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Via P. Maroncelli 40, 47014 Meldola, FC, Italy.
Email: giovanni.martinelli@irst.emr.it

Abstract

Background: Venetoclax in combination with hypomethylating agents (HMA) is revolutionizing the therapy of acute myeloid leukemia (AML). However, evidence on large sets of patients is lacking, especially in relapsed or refractory leukemia.

Methods: AVALON is a multicentric cohort study that was conducted in Italy on patients with AML who received venetoclax-based therapies from 2015 to 2020. The study was approved by the ethics committee of the participating institution and was conducted in accordance with the Declaration of Helsinki. The effectiveness and toxicity of venetoclax + HMA in 190 (43 newly diagnosed, 68 refractory, and 79 relapsed) patients with AML are reported here.

Results: In the newly diagnosed AML, the overall response rate and survival confirmed the brilliant results demonstrated in VIALE-A. In the relapsed or refractory AML, the combination demonstrated a surprisingly complete remission rate (44.1% in refractory and 39.7% in relapsed evaluable patients) and conferred to treated patients a good expectation of survival. Toxicities were overall manageable, and most incidents occurred in the first 60 days of therapy. Infections were confirmed as the most common nonhematologic adverse event.

Conclusions: Real-life data show that the combination of venetoclax and HMA offers an expectation of remission and long-term survival to elderly, newly diagnosed patients, and to relapsed or chemoresistant AML, increasing the chance of cure through a

different mechanism of action. The venetoclax + HMA combination is expected to constitute the base for triplet combinations and integration of target therapies. Our data contribute to ameliorate the understanding of venetoclax + HMA effectiveness and toxicities in real life.

KEYWORDS
acute myeloid leukemia, hypomethylating agents, real-life data, relapsed and refractory AML, venetoclax

INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous disease that still has a dismal prognosis, especially in patients who are unfit for intensive treatment or who relapse or are refractory (REL/REF) to standard therapy.[1] Inside the conundrum of novel agents, the combination of venetoclax (VEN), a B-cell lymphoma/leukemia inhibitor, with hypomethylating agents (HMA) azacytidine (AZA) or decitabine, represents a practice-changing innovation in AML.[2] Indeed, because of the synergistic activity and innovative mechanism of action,[3–6] combined VEN + HMA has become the standard of care for newly diagnosed (ND) patients with AML who are unfit for intensive chemotherapy[7–9] and is frequently administered "off-label" to REL/REF patients.[10–12] Furthermore, whether VEN + HMA should be even considered as the first line of therapy in certain molecular subsets of younger and fit ND patients with AML is currently a matter of debate.[13–15]

Phase 1/2 clinical trials of VEN combined with HMA or low-dose cytarabine in previously untreated patients provided promising results. significantly affecting disease management and leading to an early Food and Drug Administration approval.[9,16] Thereafter, a randomized phase 3 trial confirmed the clear benefits of the addition of VEN to HMA (AZA) in ND unfit patients.[7] Recently, several real-world retrospective studies have been published on the VEN + HMA combination in ND,[17,18] REL/REF,[19–21] and post-allogeneic stem cell transplant.[22] Specifically, a meta-analysis of a REL/REF study[11,23] confirmed an overall activity of VEN + HMA in a setting where no VEN + HMA prospective clinical trial had ever been conducted and where no standard therapy exists, except for FLT3-[24] and IDH1/2-[25,26] mutated patients. In REL/REF AML, VEN + HMA showed an overall response rate (ORR) between 21% and 45% and a median overall survival (OS) variable from 3 to 11 months.[11,23] The limited number of patients included in the retrospective studies and the intrinsic low homogeneity between the study populations make these data highly variable and poorly reliable.

In this study, we report data from a large set of elderly ND and REL/REF patients who received VEN + HMA in a real-life setting and were enrolled in the multicenter cohort study AVALON. Safety and efficacy data of patients treated with this regimen outside of clinical trials in 32 different Italian centers have been collected to provide further evidence regarding the management of this novel therapy in a real-world scenario.

METHODS

Study design

AVALON is an Italian cooperative multicenter observational cohort study promoted by IRCCS Istituto Romagnolo per lo studio dei Tumori (IRST) "Dino Amadori" (IRST) and IRCCS Istituto Europeo di Oncologia as representatives of Rete Ematologica Lombarda (hematological regional network). The study aims to investigate the effectiveness and safety profile of ND, and REL/REF patients with AML treated with VEN. A total of 222 patients were enrolled in 32 Italian hematological centers, 218 had sufficient clinical data for the analyses and 28 patients were treated with different VEN-based therapies; 190 patients were included in the analysis (Figure S1).

Patients

Patients treated from January 1, 2015, to April 1, 2020, were enrolled in the study. Key eligibility criteria were being older than age 18 years, having a confirmed diagnosis of AML according to World Health Organization criteria,[27] and having received VEN + HMA as a first-line or rescue therapy. Patients who had participated in any other clinical trial were excluded. Most of the patients (83.8%) who obtained VEN were reimbursed by 5% from the AIFA fund (law no. 326 of 2003) or purchased it at the hematological center. The patients enrolled were categorized as ND whenever they did not receive any line of therapy for AML before VEN + HMA (a short pretreatment of less than 2 months of single-agent HMA was allowed in case of VEN unavailability). REF was defined as resistance (i.e., not obtaining complete recovery [CR], complete remission with incomplete recovery [CRi], morphological leukemia-free state [MLFS]) to at least two intensive induction chemotherapy courses unless the patient was declared unfit for further intensive treatment, with no expected benefit from a second induction or in marked progressive disease after course one. Patients treated with nonintensive therapies were defined refractory whenever they did not obtain CR, CRi, MLFS, partial remission, or did not show any clinically relevant improvement after four courses or whenever they experienced a clinically relevant progression of the disease. REL were defined as the presence of bone marrow blasts >5% or evidence of circulating blasts confirmed in two

separate samplings after at least 7 days any time after obtaining CR, CRi, or MLFS. Within REL patients, we further defined "refractory relapse" (first, second, and third refractory relapse) patients who relapsed and thereafter failed a reinduction therapy before VEN + HMA treatment. A line of therapy is considered as one or more courses administered with the objective of achieving and maintaining CR (e.g., induction, reinduction, consolidation and transplant, *n* courses of VEN + AZA). Fitness in ND patients was defined per investigator judgment, mainly based on largely adopted criteria.[28,29]

Outcomes and assessments

Cytogenetic-molecular risk and treatment responses were defined according to the recommendations of the European LeukemiaNet 2017.[30] Particularly, CR, CRi, MLFS, partial remission, and treatment failure were defined based on peripheral blood counts and on the bone marrow blast percentage. Time points for the response assessment were not standardized and were defined based on the investigator's judgment. Measurable residual disease was collected in few patients and is not reported in this analysis. The outcomes for effectiveness were the composite complete remission (cCR, CR + CRi + MLFS), the ORR (cCR + partial remission), the duration of response (DOR) defined as the time in months from any response (including partial remission) to relapse or death from any cause; the OS was defined as the time in months from the first day of treatment to death from any cause, and the event-free survival (EFS) defined as the time in months from the first day of treatment to disease progression, confirmed relapse, or death from any cause, whichever occurred first.

All patients who received VEN + HMA were included in the safety analysis. Adverse events (AEs) were collected that occurred from the first dose until 30 days after the discontinuation of treatment. The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.[31] For the safety analysis, the outcomes were reported as the proportion of patients who experienced at least a grade equal or greater than three AEs and the proportion of patients who experienced at least a serious AE (SAE) of any grade. The last follow-up update was in June 2021.

Ethical statement

The AVALON study (CT.gov: NCT04070807) was approved by the Romagna Ethics Committee on April 10, 2019 (Prot. 3371/2019), and subsequently by the ethics committee of each participating institution. It was also conducted in accordance with the ethical standards in the 1964 Declaration of Helsinki. Written informed consent from patients was not required because of the retrospective nature of the study. No identifiable images were included in the manuscript; therefore, consent for publication was not applicable.

Statistical analysis

Data were summarized by the median, interquartile range, reporting the first (1Q) and third (3Q) quartiles, and minimum and maximum values for continuous variables and by means of absolute frequencies and percentages for categorical ones.

Comparisons among ND, REF, and REL patients were performed using the Pearson's χ^2 test of the Fisher exact test, as appropriate, for categorical variables and through the Wilcoxon signed-rank sum test or the Kruskal–Wallis test, as appropriate, for continuous ones.

Logistic regression was used for the association of patient characteristics and the probability of overall response; results were reported in terms of relative risks and corresponding 95% CIs. The DOR was computed using the Kaplan–Meier method.

The time-to-event outcomes were analyzed using the Kaplan–Meier method, the log-rank test for group comparisons, and the Cox proportional hazards model. The association between receiving a hematopoietic stem cell transplantation (HSCT) after the start of treatment, and survival was assessed by the inclusion of a time-dependent covariate for transplant in the Cox model. Results were reported as median and in terms of hazard ratios and corresponding 95% CIs. The median follow-up time was computed using the reverse Kaplan–Meier method.

All analyses were performed with STATA 15.0 (College Station, Texas, USA).

RESULTS

Patient characteristics

The clinical and biological characteristics of the 190 patients included in the analysis are summarized in Table 1. Forty-three patients had ND, 68 REF, and 79 REL AML. The median age at the start of VEN + HMA treatment of the whole population was 68 years, with REL/REF being younger than ND patients (median age, 64 vs 74, respectively). The majority of patients had "low proliferative" AML before treatment, with a median number of bone marrow blasts of 31.5% (1Q-3Q, 12-60) and white blood cells of 4200 per cubic milliliter (1Q-3Q, 1900–16,500); most of the patients had intermediate- or high-risk disease. In ND patients, de novo AML occurred in 39.5% of cases, whereas secondary AML (mainly myelodysplastic syndrome) in 55.8% of cases; conversely, in the REF and REL population, de novo AML were 61.8% and 72.1% and secondary AML 29.4% and 22.8%, respectively ($p = .004$). In the ND cohort, only 16.3% of the patients were fit for intensive chemotherapy at the time of VEN + HMA, whereas in the REF and REL cohorts up to 76.5% and 62%, respectively ($p < .001$), were fit. Among REL patients, 39/79 (49.4%) were in their first relapse, whereas the remaining were more advanced and/or in refractory relapses. Forty-one of 77 (53.2%) relapsed within 12 months from previous CR, and 36/77 (46.7%) had late relapse (previous treatment data were not available for two patients). The median number of previous lines was one for REF and

TABLE 1 Patient characteristics of ND, REF, and REL patients with AML treated with VEN + HMA

	Total (*n* = 190)		ND (*n* = 43)		REF (*n* = 68)		REL (*n* = 79)		
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*p*
Median age at the start of the combo [1Q–3Q], years	68 [56–73]		74 [67–78]		64.5 [52.5–70]		64 [54–72]		<.001
Age ≤60	64	(33.7)	4	(9.3)	27	(39.7)	33	(41.8)	
Age >60	126	(66.3)	39	(90.7)	41	(60.3)	46	(58.2)	
Sex									.412
Female	85	(44.7)	23	(53.59)	28	(41.2)	34	(43.0)	
Male	105	(55.3)	20	(46.5)	40	(58.8)	45	(57.0)	
AML type									.004
De novo AML	116	(61.1)	17	(39.5)	42	(61.8)	57	(72.1)	
Secondary AML	62	(32.6)	24	(55.8)	20	(29.4)	18	(22.8)	
MDS	47	(75.8)	22	(91.7)	15	(75.0)	10	(55.6)	
ET	2	(3.2)	0		0		2	(11.1)	
PV	2	(3.2)	0		0		2	(11.1)	
IMF	3	(4.8)	0		2	(10.0)	1	(5.6)	
CML	2	(3.2)	1	(4.2)	1		0		
CMML	6	(9.7)	1	(4.2)	2		3	(16.7)	
Therapy related	12	(6.3)	2	(4.7)	6	(8.8)	4	(5.1)	
Type of relapse									
First relapse							39	(49.4)	
First refractory relapse							14	(17.7)	
Second relapse							4	(5.1)	
Second refractory relapse							19	(24.1)	
Third relapse							3	(3.8)	
Patient fitness									<.001
Fit	108	(56.84)	7	(16.3)	52	(76.5)	49	(62.0)	
Unfit for intensive CT	78	(41.1)	35	(83.7)	15	(22.1)	28	(35.4)	
Frail	4	(2.1)	1	(2.3)	1	(1.5)	2	(2.5)	
2017 ELN risk stratification by genetics[a]									.048
Favorable	13	(7.9)	6	(17.1)	2	(3.2)	5	(7.6)	
Intermediate	91	(55.5)	19	(54.3)	31	(49.2)	41	(62.1)	
Adverse	60	(36.6)	10	(28.6)	30	(47.6)	20	(30.3)	
NPM1 status									.033
WT	97	(83.6)	18	(72.0)	43	(93.5)	36	(80.0)	
Mutated	19	(16.4)	7	(28.0)	3	(6.5)	9	(20.0)	
Not evaluable	1						1		
Not determined	73		18		22		33		
FLT3-ITD status									.435
WT	111	(86.72)	22	(88.0)	48	(90.7)	40	(81.6)	
Mutated	17	(13.28)	3	(12.0)	5	(9.3)	9	(18.4)	
Not evaluable	1				1				

(Continues)

TABLE 1 (Continued)

	Total (n = 190)		ND (n = 43)		REF (n = 68)		REL (n = 79)		
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*p*
Not determined	61		18		13		30		
FLT3-TKD status									.313
WT	64	(94.1)	11	(84.6)	29	(96.7)	24	(96.0)	
Mutated	4	(5.9)	2	(15.4)	1	(3.3)	1	(4.0)	
Not determined	122		30		38		54		
Pretreatment hematologic values									
Median WBC ($\times 10^9$/L) [1Q –3Q][b]	4.2 [1.9–16.5]		6.3 [2.8–26.7]		3.4 [1.4–8.0]		3.5 [1.4–17]		
Median Hgb (g/dL) [1Q– 3Q][b]	9 [8.2–10]		9.2 [8.5–11.4]		9.0 [8.2–9.9]		8.7 [8.2–9.8]		
Median PLT ($\times 10^9$/L) [1Q–3Q][b]	40 [18–100]		42.5 [13–84]		70 [26–22.5]		29.5 [15–55]		
Median bone marrow blasts (%) [1Q–3Q][c]	31.5 [12–60]		40 [20–69.5]		26 [10–62.5]		30 [7.5–55]		

Abbreviations: 1Q, first quartile; 3Q, third quartile; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CT, chemotherapy; ELN, European Leukemia Network; ET, essential thrombocythemia; Hgb, hemoglobin; IMF, idiopathic myelofibrosis; IQ, first quartile; MDS, myelodysplastic syndrome; ND, newly diagnosed; PLT, platelets; PV, polycythemia vera; REF, primary refractory patients; REL, relapsed; WBC, white blood cells; WT, wild type.

[a]Missing/not evaluable for 30 patients.

[b]WBC, Hgb, and PLT were missing for 76 patients.

[c]Missing for 22 patients.

two for REL patients, approximately 70% of the patients in each group received one intensive chemotherapy line, whereas 29.4% in the REF and 44.3% in the REL cohort failed a previous line with HMA agents with a median number of eight HMA cycles in the REF cohort and nine in REL patients (Table S1). Notably, 50/68 REF patients were considered refractory to intensive chemotherapy, 20/50 after a single course because of loss of fitness, progressive disease, persistent pancytopenia, or the physician's judgment. This population of early-REF patients had similar demographics and clinical characteristics as well as response and survival when compared with European Leukemia Network (ELN)-defined primary refractory (Table 2 and Figure S2). Twenty of 68 (29.4%) REL and 35/79 (44.3%) REF patients received a previous SCT (Table S1).

Treatment

A total of 128 of 190 patients (67.4%) received VEN + AZA and 62 patients (32.6%) received VEN + decitabine; VEN ramp-up was performed in 167/190 (87.9%) patients. At the time of treatment initiation, after ramp-up, 129/190 (67.89%) patients received a VEN target dose of 400 mg, 16/190 (8.42%) a dose of 200 mg, and 42/190 (22.11%) a dose of 100 mg per day. The main reason for dose reduction was antifungal prophylaxis. Seventy-eight percent of patients (36/46) receiving antifungal prophylaxis with strong CYP-3A inhibitors reduced venetoclax daily dosage. The median duration of the VEN + HMA was 4.6 (1Q–3Q, 2.4–11.3) months for ND, 2.8 (1Q–3Q, 1.5–6.9) for REF, and 2.8 (1Q–3Q, 1.2–6.3) for REL patients. The median time to first response assessment was approximately 2 months in each group.

Response and survival

The response was assessed for 166/190 patients and is summarized in Table 2; 24/190 patients did not receive a response assessment. Overall, the cCR rate was 39.0% and the ORR was 50.5%; we observed a cCR of 48.8%, 38.2%, and 34.2% and an ORR of 65.1%, 51.5%, 41.8% in ND, REF, and REL patients, respectively.

For patients with evaluable responses, the median time to the first response was 2.2 months and the median DOR was 7.6 months. Median time to best response was similar across the three groups, median DOR was 10.6, 8.3, and 7.6 months in ND, REF, and REL patients, respectively.

With a median follow-up time of 20.9 (95% CI, 17–25.9) months, median EFS was 5.8 (95% CI, 4.4–6.8) months, median OS was 8.1 (95% CI, 6.3–9.7) months. Median EFS and median OS were 5.8 and 12.7 months in ND, 6.2 and 9.1 months in REF, and 4.4 and 6.3 months in REL patients, respectively (Figure 1). A total of 146 patients (76.8%) were dead at the time of data cutoff (67.4% of ND, 70.6% of REF, and 87.3% of REL patients); the cause of death was relapse or disease progression in 90 (61.6%) patients, adverse events in 9 (6.2%) patients, and other causes not related to VEN + HMA in 40 (27.4%) patients (7/146 not available). The 30-day and 60-day mortality rates were 5.3% (10/146) and 14.5% (24/146), respectively, without any significant difference between ND, REL, and REF patients.

Within the population of patients who had a previous line of HMA (55 patients: 20 REF and 35 REL), ORR was 36.4% and cCR 32.7%.

Overall, in 43/190 (22.6%) patients, VEN + AZA was an effective bridge to alloSCT, including 5/46 ND patients (Table 2).

TABLE 2 Clinical response to VEN + HMA of ND, REF, and REL patients with AML

	Total		ND		REF		REL		
	(*n* = 190)		(*n* = 43)		(*n* = 68)		(*n* = 79)		*p*
Best response	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	.639
ORR	96	(50.5)	28	(65.1)	35	(51.5)	33	(41.8)	
cCR	74	(39.0)	21	(48.8)	26	(38.2)	27	(34.2)	
PR	22	(11.6)	7	(16.3)	9	(13.2)	6	(7.6)	
SD/PD[a]	70	(36.8)	11	(25.6)	24	(35.3)	35	(44.3)	
Not evaluable	24	(12.6)	4	(9.3)	9	(13.2)	11	(13.9)	
									.336
Median time to best response (months) [1Q–3Q]	2.2 [1.2–4.4]		2.8 [1.5–5.9]		1.9 [1.1–4.0]		2.3 [1.2–3.8]		
									.789
Median DOR (months) [95% CI]	7.6 [5.1–11.2]		10.6 [4.0–11.9]		6.8 [4.4–12.6]		8.3 [4.7–11.9]		

	Total (*n* = 190)		ND (*n* = 43)		REF (*n* = 68)		REL (*n* = 79)		
	n	(%)	*n*	(%)	N	(%)	*n*	(%)	
HSCT after start of combination therapy	43	(22.6)	5	(11.6)	22	(32.4)	16	(20.3)	.032

Abbreviations: 1Q, first quartile; 3Q, third quartile; cCR, composite complete remission; DOR, duration of response; HSCT, hematopoietic stem cell transplantation; ND, newly diagnosed; ORR, overall response rate; PR, partial remission; REF, primary refractory patients; REL, relapsed.

[a]Including patients who died within 3 months of starting VEN + HMA without a disease reevaluation.

Thirty of 43 patients (69.7%) received HSCT having less than 5% of bone marrow blast and 8/43 (18.6%) in PR. From a subgroup analysis, patients who were able to receive an alloSCT had a median OS of 16 (95% CI, 11.3–22.1) vs 6.3 (95% CI, 4.5–8.1) months of patients not receiving alloSCT. Including the information on alloSCT into a Cox model as a time-dependent covariate, we observed a favorable effect of the transplant on patient prognosis even though it was statistically not significant (hazard ratio, 0.76; 95% CI, 0.48–1.22; $p = .260$). Five of 55 (9%) patients with a previous line of HMA were bridged to HSCT.

Patients who received VEN + HMA for a relapse after previous HSCT had an ORR of 30%, a median EFS of 3.2 months (95% CI, 2–6.4), and a median OS of 4.3 months (95% CI, 2.6–8.5).

Univariate and multivariate analysis

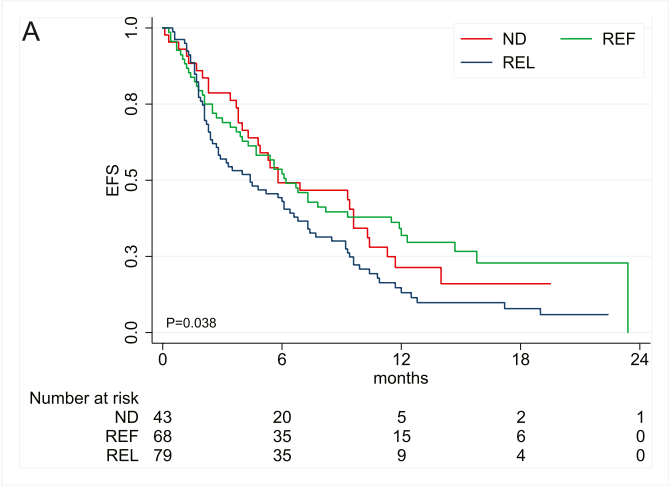
The impact on the ORR and survival of classical determinants of outcome are shown in (Figure 2 for OS and Table S3). In our set, only NPM1 mutation significantly affected the probability of response ($p = .039$), conferring an advantage in terms of EFS ($p = .017$) and OS ($p = .022$). To have a secondary AML or to be classified in the intermediate or high ELN 2017 risk class at diagnosis was associated with a shorter EFS and OS. In a few patients, VEN was started with a minor delay after HMA for practical reasons (delayed drug availability); this delay did not influence ORR, EFS, or OS. We built a multivariate regression model for OS and EFS, in which factors with a significant level of 10% at univariate analysis were considered (Table 3). The AML type, ELN risk, and REL status were confirmed to contribute to the definition of the optimal prognostic model.

Safety

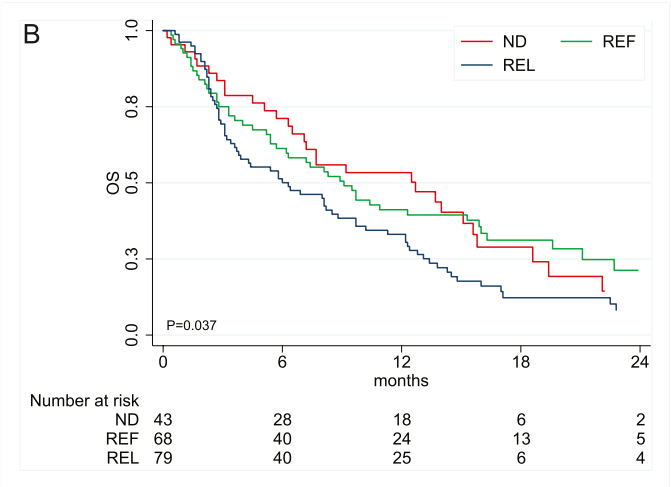
Overall, 154 patients had at least one AE of any grade: 30 patients (19.5%) in the ND cohort, 57 (37%), and 67 (43.5%) in the REF and REL groups, respectively.

AEs of grade ≥3 and SAEs are summarized in Table 4. The most frequently reported hematologic AEs in the three groups (ND, REF, and REL) included neutropenia (in 37.2%, 20.6% and 26.6%, respectively), thrombocytopenia (in 20.9%, 16.2%, and 24.1%, respectively), and febrile neutropenia (in 18.6%, 16.2%, and 21.5%, respectively); the most frequent nonhematological AEs were pneumonia (4.7%, 4.4%, and 10.1%, respectively) and sepsis (2.3%, 2.9%, and 8.9%, respectively).

Fifty patients (26.3%) experienced at least one SAE and, for most of the patients ($n = 37$, 19.5%), the SAE occurred within 60 days from the start of VEN + HMA. The most frequent SAEs were febrile neutropenia (in 16.3% of the ND patients, 13.2% of REF, and 10.1% of REL) and infections (in 7% of the ND patients, 11.7% of REF, and 17.8% of REL cohorts). Tumor lysis syndrome was reported in only one patient (1.3%) in the REL group and occurred during VEN ramp-up and required therapy interruption. Nine SAEs resulted in death, 51 required patient hospitalization or prolonged ongoing hospitalization, one resulted in a persistent or significant disability, and two in a life-threatening condition. SAEs that resulted in death were of



	Total (n=190)		ND (n=43)		REF (n=68)		REL (n=79)	
	n	(%)	n	(%)	n	(%)	n	(%)
Events	150	(79.0)	31	(72.1)	48	(70.6)	71	(89.9)
Median EFS (months) [95% CI]	5.8 [4.4 – 6.8]		5.8 [4.0 – 9.6]		6.2 [4.3 – 9.3]		4.4 [2.7 – 6.4]	



	Total (n=190)		ND (n=43)		REF (n=68)		REL (n=79)	
	n	(%)	n	(%)	n	(%)	n	(%)
Events	146	(76.8)	29	(67.4)	48	(70.6)	69	(87.3)
Median follow-up time (months) [95% CI]	20.9 [17.0 – 25.9]		17.3 [12.8 – 25.9]		20.7 [15.9 – 24.9]		26.1 [16.9 – NR]	
Median OS (months) [95% CI]	8.1 [6.3 – 9.7]		12.7 [6.5 – 15.6]		9.1 [5.7 – 15.3]		6.3 [3.6 – 8.8]	

FIGURE 1 (A) Event-free survival curves for patients with AML treated with VEN + HMA. (B) Overall survival curves for patients with AML treated with VEN + HMA. Abbreviations: EFS indicates event-free survival; HMA, hypomethylating agent; ND, newly diagnosed; NR, not reached; OS, overall survival; REF, primary refractory; REL, relapsed; VEN, venetoclax

infective origin, occurred after a median of 60 days (interquartile range, 44–167), and in six of nine cases in patients with active leukemia.

Concerning treatment modifications resulting from adverse events, the dose of VEN + HMA was changed in 47/190 patients (24.7%) and permanently discontinued in 22/190 (11.6%). The most common reason for dose modification was hematologic toxicity (49%) or infection (29%), as reported in Table S4. The rate of dose reduction and treatment discontinuation from an AE were similar between ND, REL, and REF patients (data not shown).

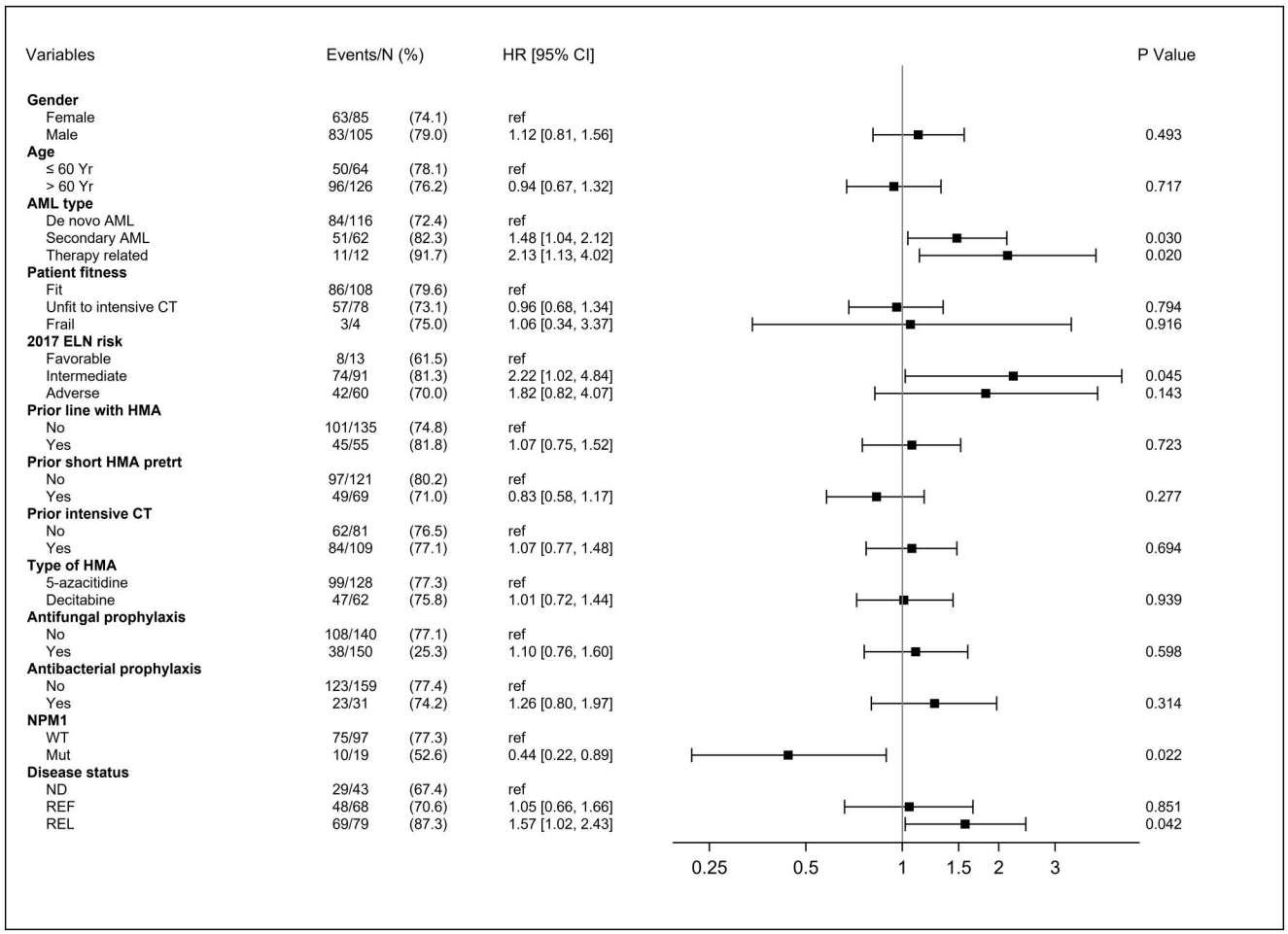


FIGURE 2 Forest plot of factors affecting overall survival in univariate analysis. Abbreviations: AML indicates acute myeloid leukemia; CT, chemotherapy; ELN, European Leukemia Network; HMA, hypomethylating agent; ND, newly diagnosed; NPM1, nucleophosmin 1; REF, refractory; REL, relapsed; WT, wild type

TABLE 3 Results from multivariate analysis of EFS and OS for patients with AML treated with VEN + HMA

	EFS		OS	
	HR [95% CI]	***p***	**HR [95% CI]**	***p***
Disease status				
ND	1 (ref)		1 (ref)	
REF	1.25 [0.75–2.07]	.386	1.44 [0.86–2.43]	.167
REL	1.69 [1.03–2.76]	.039	1.92 [1.14–3.22]	.014
AML type				
De novo AML	1 (ref)		1 (ref)	
Secondary AML	1.56 [1.04–2.32]	.029	1.65 [1.10–2.47]	.015
Therapy-related	1.94 [0.99–3.81]	.053	2.21 [1.12–4.35]	.022
2017 ELN risk stratification by genetics				
Favorable	1 (ref)		1 (ref)	
Intermediate	2.12 [0.96–4.68]	.062	1.96 [0.89–4.34]	.096
Adverse	1.72 [0.76–3.89]	.192	1.66 [0.73–3.76]	.226

Abbreviations: ELN, European Leukemia Network; ND, newly diagnosed; REF, refractory; REL, relapsed.

DISCUSSION

We reported the results of the largest real-life study investigating the effectiveness and toxicity profile of VEN + HMA. In ND patients, ORR and median OS were slightly lower than those reported in the experimental arm of the recently published prospective randomized study VIALE-A (cCR 53.8% AVALON vs 66.4% VIALE-A and median OS 12.7 months AVALON vs 14.7 months VIALE-A).[7] However, these results seem excellent considering the "real-life" nature and the inclusion of trial-ineligible patients. Furthermore, secondary AML (55.8%) were overrepresented in the ND AVALON study cohort; data for secondary AML are reported in Table S5 and Figure S3, may largely account for the unexpected and low median OS, and can reflect a "worst prognosis patients" selection bias for novel therapy.

In the REL/REF setting, most of the currently published experiences with VEN + HMA should be interpreted with caution because patient numbers are small (median, 32; range, 8–90) and data are heterogeneous.[23] Although it is a cohort study, AVALON has a large sample size (n = 147 REL/REF AML), thus providing an estimation of effects with high confidence. In REF patients, it was surprising to

TABLE 4 AEs and SAEs in patients with AML treated with VEN + HMA (counts refer to the number of patients who experienced AEs)

	Total (*n* = 190)		ND (*n* = 43)		REF (*n* = 68)		REL (*n* = 79)	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
	AEs (including SAE) of grade ≥3							
Hematologic AEs (not from AML)								
Anemia	16	8.4	3	7.0	6	8.8	7	8.9
Neutropenia	51	26.8	16	37.2	14	20.6	21	26.6
Thrombocytopenia	39	20.5	9	20.9	11	16.2	19	24.1
Nonhematologic AEs								
Cardiac toxicity	2	1.1	0		1	1.5	1	1.3
Fatigue	2	1.1	1	2.3	1	1.5	0	
Liver toxicity	2	1.1	1	2.3	0		1	1.3
Nausea	1	0.5	0		0		1	1.3
Diarrhea	1	0.5	0		0		1	1.3
Tumor lysis syndrome	1	0.5	0		0		1	1.3
Other	4	2.1	2	4.7	2	2.9	0	
Infections								
Febrile neutropenia	36	18.9	8	18.6	11	16.2	17	21.5
Pneumonia	13	6.8	2	4.7	3	4.4	8	10.1
Sepsis	10	5.3	1	2.3	2	2.9	7	8.9
Urinary tract infection	2	1.1	1	2.3	1	1.5	0	
Other infection	5	2.6	0		3	4.4	2	2.5
	SAEs of any grade							
Hematologic SAEs								
Neutropenia	1	0.5	0		0		1	1.3
Nonhematologic SAEs								
Cardiac toxicity	1	0.5	0		1	1.5	0	
Fatigue	1	0.5	0		1	1.5	0	
Tumor lysis syndrome	1	0.5	0		0		1	1.3
Other	2	1.1	0		0		2	2.5
Infections								
Febrile neutropenia	24	12.6	7	16.3	9	13.2	8	10.1
Pneumonia	12	6.3	2	4.7	3	4.4	7	8.9
Sepsis	9	4.7	1	2.3	2	2.9	6	7.6
Urinary tract infection	1	0.5	0		1	1.5	0	
Other infection	3	1.6	0		2	2.9	1	1.3

Abbreviations: AE, adverse event; HMA, hypomethylating agent; ND, newly diagnosed; REF, primary refractory; REL, relapsed; SAE, severe adverse event; VEN, venetoclax.

observe outcomes that are comparable with ND AML, which were similar for ELN-defined REF patients and for early REF established in the "real-life" setting. The heavily pretreated REL population still maintains good chances of CR and may achieve long-term survival. It is important to note that in REL/REF patients the median age is 10 years lower than ND patients, and they are not enriched for secondary AML; however, VEN + HMA seems to offer a poor prognosis population a strategy that is an alternative to intensive chemotherapy for the mechanism of action and that could bring to remission regardless to chemorefractoriness.[4,32]

The AVALON study represents the preliminary experience with VEN + HMA in a large nation, in a timeframe in which any administration of VEN for AML was considered "off-label." Patient assignment to the treatment and in-treatment procedures varied among institutions and reflected the local guidelines, representing the main limitation of this study. The antifungal prophylaxis was underused, especially before 2019, mainly because of the early concerns about interactions, whereas we empirically report that antifungal prophylaxis and pharmacokinetic-based VEN dose adjustment are widely applied in more recent times. For a subcohort of patients for which VEN was available with a minor delay (because of request approval timing), a short pretreatment with HMA alone was administered without diminishing ORR or survival; thus, it could be repurposed for very unfit patients in the future. Instead, patients who relapsed after or were refractory to a previous HMA line had a poor prognosis. From our data, the detrimental impact seems to be particularly noticeable for the REF subgroup ORR (data not shown). This is consistent with other experiences.[11,33]

The study has some limitations; for most of the patients, the response was evaluated after two or more courses, measurable residual disease was poorly tested, baseline molecular characterization was not comprehensive, and patient management, including supportive care, was performed paying less attention to response and myelotoxicity because it was comparable for most of the clinicians to order single-agent HMA therapy. With the recent wider adoption of the combination, the publications of VIALE-A,[7] recent guidelines,[34,35] and measurable residual disease data,[36] the management of patients receiving VEN + HMA has changed dramatically.

Indeed, we had the opportunity to observe the administration of the most promising AML combination therapy in a "real-life" setting. In patients who harbored NPM1 mutation, VEN confirmed groundbreaking effectiveness, reinforcing the idea that these patients should become strong candidates for VEN-based therapies.[6,19,34] We reported in univariate and multivariable analysis the prognostic impact of secondary disease and ELN 2017 risk at diagnosis. This adapted model should not be considered definitive. A better cytogenetic-molecular prognostic system dedicated to VEN + HMA is highly warranted because of the impact of the novel combination on AML therapy[2,35] and the difference in the mechanism of resistance from that of intensive chemotherapy.[37,38] Hematological and nonhematological toxicities were globally manageable, infrequent, and low in grade; presumably severe infection, in-hospital stay, and AEs are lower than what is expected from chemotherapy. However, during VEN + AZA treatment, SAEs and infections were prevalent in the first 60 days of treatment and early mortality was comparable with the mortality expected in patients treated with intensive chemotherapy, as demonstrated also by Matthews and colleagues[33]; these data reflect a toxicity profile that is overall favorable, and it becomes even better whenever a patient obtains remission, thus demonstrating that most of the AEs in this patient population are related or contributed by the leukemia itself. Hematological toxicities and infections were the prevalent causes for dose adjustment (Table S4). Furthermore, we observed three deaths in CT, thus underlining the importance of appropriate management of neutropenia and the need for prompt administration of appropriate antiinfective treatments for the entire duration of the therapy. Consistently, in AVALON and other large studies, VEN + HMA demonstrated long-term survival, and fine-tuning of the therapy and supportive measures are still ongoing.[18,34] Finally, our study included the largest cohort of REL/REF patients who received VEN + HMA as a bridge to alloSCT (n = 43), most of which in response, suggesting the value of VEN + HMA rescue followed by transplants in consolidation for REL/REF AML; survival of these patients was comparable with other reports.[33] Instead, with the limitations because of the low numbers in the subcohort, an inhomogeneous and high-risk population, as reported in other studies,[21] posttransplant salvage with VEN + HMA remain unsatisfactory with poor results in terms of ORR and survival, as with most of the other approaches. Results can be potentially ameliorated with the use of Donor Lymphocyte infusion.[39,40]

In conclusion, VEN + HMA was confirmed to be a promising combination, with an innovative mechanism of action that could be offered also to chemorefractory patients with a good expectation of CR. In the near future, the VEN + HMA combination will be widely applied and is expected to constitute the base for triplet combinations and integration of target or immunological therapies. In this highly dynamic context, our data ameliorate the understanding of VEN + HMA effectiveness and toxicities in real life.

AUTHOR CONTRIBUTIONS

The AVALON scientific committee members collaborated on the study design, analysis, and interpretation of the results. The first draft of the manuscript was written by the first author with input from all the authors. All authors critically reviewed and provided feedback on all subsequent versions of the manuscript. All authors read and approved the final version of the manuscript.

ACKNOWLEDGMENTS

AVALON Cooperative Group: Prof. Adriano Venditti, U.O.C. Ematologia, A.O.U. Fond. Policlinico Tor Vergata; Dr. Agostino Tafuri, U.O.C. Ematologia, A.O.U. Sant'Andrea, Roma; Dr. Alessandro Cignetti, Divisione Universitaria di Ematologia e Terapie Cellulari, A.O. Ordine Mauriziano, Torino; Dr. Annalisa Imovilli, Dip. Oncologico e Tecnologie avanzate, IRCCS Arcispedale S. Maria Nuova, Reggio Emilia; Dr. Bruna Messere, Dip. Oncopneumoematologico, A.O.R.N. "A. Cardarelli", Napoli; Dr. Carla Mazzone, Dep. Hematology S. Eugenio Ospital, Roma; Dr. Endri Mauro, Azienda U.L.S.S.9 Ospedale Regionale Cà Foncello, Treviso; Dr. Fabio Ciceri, U.O. Ematologia e TMO, Ospedale S. Raffaele, Milano; Dr. Federica Monaco, AUSL della Romagna, Ospedale S. Maria delle Croci, Ravenna; Dr. Federico Lussana, Department of Oncology and Hematology University of Milan, and Azienda SocioSanitaria Territoriale Papa Giovanni XXIII, Bergamo; Dr. Francesco Di Raimondo, A.O.U. Policlinico Vittorio Emanuele, Catania; Dr. Francesco Zaja, S. C. Ematologia, A.O.U. Giuliano Isontina, Trieste; Dr. Giorgio Priolo, SC Ematologia 2, Dip. di Ematologia e Oncologia, AOU Città della Salute e della Scienza, Torino; Dr.

Idalucia Ferrara, A.O.U. S. Giovanni di Dio e Ruggi d'Aragona, Università di Salerno, Salerno; Dr. Irene Urbino, SC Ematologia 2, Dipartmento di Ematologia e Oncologia, AOU Città della Salute e della Scienza, Torino; Dr. Irene Valli, IRCCS Istituto Romagnolo per lo studio dei Tumori "Dino Amadori" - IRST S.r.l., Meldola; Dr. Katia Codeluppi, Dip. Oncologico e Tecnologie avanzate, IRCCS Arcispedale S. Maria Nuova, Reggio Emilia; Dr. Liliana Calabrese, European Institute of Oncology, Milano; Dr. Maria Benedetta Giannini, IRCCS Istituto Romagnolo per lo studio dei Tumori "Dino Amadori" - IRST S.r.l., Meldola; Dr. Maria Chiara Abbenante, Dip. Onco-ematologia IRCCS Casa Sollievo della Sofferenza, S. Giovanni Rotondo (FG); Dr. Michelina Dargenio, Hematology and SCT Unit, "Vito Fazzi" Hospital, Lecce; Dr. Paolo De Fabritis, Dep. Hematology S. Eugenio Ospital, Roma; Dr. Pasquale De Roberto, U.O.C. Oncoematologia, Fond. IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milano; Dr. Raffaele Palmieri, U.O.C. Ematologia, A.O.U. Fond. Policlinico Tor Vergata; Dr. Rita Pepe, A.O.U. S. Giovanni di Dio e Ruggi d'Aragona, Università di Salerno, Salerno; Dr. Simona Menna, European Institute of Oncology, Milano; Dr. Sofia Sciabolacci, Department of Medicine – Section of Hematology and Clinical Immunology, Perugia University, "Santa Maria della Misericordia" Hospital, Perugia; Dr. Valentina Oliva, Dip. Oncoematologico, A.O.R.N. "A. Cardarelli", Napoli; Dr. Viviana Amato, Div. Oncoematologia, European Institute of Oncology, Milano. This work was partly supported by a contribution by Ricerca Corrente by the Italian Ministry of Health within the research line 2 "Innovative therapies, phase 1-III clinical trials and therapeutic strategy trials based on preclinical models, onco-immunological mechanisms and nanovectors." This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Open access funding provided by BIBLIOSAN.

CONFLICT OF INTEREST

Giovanni Marconi reports being a consultant/on a speaker bureau for Menarini/Stemline, Pfizer, Syros, and Astellas, and research support from Pfizer, AbbVie, and AstraZeneca. Calogero Vetro reports being on an advisory board for AbbVie. Giovanni Martinelli reports consultant/advisor/speaker bureau of Ariad/Incyte, Pfizer, Celgene/BMS, Amgen, Roche, AbbVie, GlaxoSmithKline, Astellas, Daiichi Sankyo, Takeda, and Janssen, and research support from Pfizer, AbbVie, AstraZeneca, Daiichi Sankyo, Takeda, and Ariad/Incyte. Cristina Papayannidis reports Honoraria from Abbvie, Amgen, Astellas, Blueprint, BMS, GSK, Incyte, Novartis, Pfizer. Corrado Tarella reports consultant/advisory role for Incyte and Astellas. The remaining authors made no disclosures.

DATA AVAILABILITY STATEMENT

Raw data are available for nonprofit use from the corresponding author on reasonable request.

ORCID

Nicola Di Renzo https://orcid.org/0000-0003-0604-6934
Erika Borlenghi https://orcid.org/0000-0002-4666-3817
Elisabetta Abruzzese https://orcid.org/0000-0001-5228-6491
Luca Maurillo https://orcid.org/0000-0001-7297-4988
Alessandra Romano https://orcid.org/0000-0002-6333-4433
Giovanni Martinelli https://orcid.org/0000-0002-1025-4210

REFERENCES

1. Estey E, Karp JE, Emadi A, Othus M, Gale RP. Recent drug approvals for newly diagnosed acute myeloid leukemia: gifts or a Trojan horse? *Leukemia*. 2020;34(3):671-681. doi:10.1038/s41375-019-0704-5
2. Pollyea DA, Amaya M, Strati P, Konopleva MY. Venetoclax for AML: changing the treatment paradigm. *Blood Adv*. 2019;3(24):4326-4335. doi:10.1182/bloodadvances.2019000937
3. DiNardo CD, Lachowiez CA, Takahashi K, et al. Venetoclax combined with FLAG-IDA induction and consolidation in newly diagnosed and relapsed or refractory acute myeloid leukemia. *J Clin Oncol*. 2021;39(25):2768-2778. doi:10.1200/jco.20.03736
4. Pollyea DA, Stevens BM, Jones CL, et al. Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. *Nat Med*. 2018;24(12):1859-1866. doi:10.1038/s41591-018-0233-1
5. Pollyea DA. Venetoclax in AML: where we are and where we are headed. *Clin Lymphoma Myeloma Leuk*. 2020;20(suppl 1):S25-S26. doi:10.1016/s2152-2650(20)30450-x
6. Wang YW, Tsai CH, Lin CC, et al. Cytogenetics and mutations could predict outcome in relapsed and refractory acute myeloid leukemia patients receiving BCL-2 inhibitor venetoclax. *Ann Hematol*. 2020;99(3):501-511. doi:10.1007/s00277-020-03911-z
7. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629. doi:10.1056/nejmoa2012971
8. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020;135(24):2137-2145. doi:10.1182/blood.2020004856
9. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood*. 2019;133(1):7-17. doi:10.1182/blood-2018-08-868752
10. Aldoss I, Yang D, Aribi A, et al. Efficacy of the combination of venetoclax and hypomethylating agents in relapsed/refractory acute myeloid leukemia. *Haematologica*. 2018;103(9):e404-e407. doi:10.3324/haematol.2018.188094
11. Bewersdorf JP, Giri S, Wang R, et al. 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. *Haematologica*. 2020;105(11):2659-2663. doi:10.3324/haematol.2019.242826
12. Al-kali A, Begna K, Elliott M, et al. Venetoclax and hypomethylating agents in acute myeloid leukemia: Mayo Clinic series on 86 patients. *Am J Hematol*. 2020;95(12):1511-1521. doi:10.1002/ajh.25978
13. Maiti A, DiNardo CD, Kadia TM, et al. 10-day decitabine and venetoclax (DEC10-VEN) vs intensive chemotherapy (IC) in acute myeloid leukemia (AML): a propensity score matched analysis stratified by risk of treatment-related mortality. *Hemaspere*. 2020 Supplement:Abstract S141.
14. Duchmann M, Micol JB, Duployez N, et al. Prognostic significance of concurrent gene mutations in intensively treated patients with IDH-mutated AML: an ALFA study. *Blood*. 2021;137:2827-2837. doi:10.1182/blood.2020010165
15. Aldoss I, Zhang J, Pillai R, et al. Venetoclax and hypomethylating agents in TP53-mutated acute myeloid leukaemia. *Br J Haematol*. 2019;187(2):e45-e48. doi:10.1111/bjh.16166
16. Wei AH, Strickland SA, Hou JZ, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute

myeloid leukemia: Results from a phase Ib/II study. *J Clin Oncol*. 2019;37(15):1277-1284. doi:10.1200/jco.18.01600
17. Winters AC, Gutman JA, Purev E, et al. Real-world experience of venetoclax with azacitidine for untreated patients with acute myeloid leukemia. *Blood Adv*. 2019;3(20):2911-2919. doi:10.1182/bloodadvances.2019000243
18. Papayannidis C, Nanni J, Cristiano G, et al. Impact of infectious comorbidity and overall time of hospitalization in total outpatient management of acute myeloid leukemia patients following venetoclax and hypomethylating agents. *Eur J Haematol*. 2022;108(6):449-459. doi:10.1111/ejh.13753
19. Lachowiez CA, Loghavi S, Kadia TM, et al. Outcomes of older patients with NPM1-mutated AML: current treatments and the promise of venetoclax-based regimens. *Blood Adv*. 2020;4(7):1311-1320. doi:10.1182/bloodadvances.2019001267
20. DiNardo CD, Rausch CR, Benton C, et al. Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies. *Am J Hematol*. 2018;93(3):401-407. doi:10.1002/ajh.25000
21. Ganzel C, Ram R, Gural A, et al. Venetoclax is safe and efficacious in relapsed/refractory AML. *Leuk Lymphoma*. 2020;61(9):2221-2225. doi:10.1080/10428194.2020.1761964
22. Byrne M, Danielson N, Sengsayadeth S, et al. The use of venetoclax-based salvage therapy for post-hematopoietic cell transplantation relapse of acute myeloid leukemia. *Am J Hematol*. 2020;95(9):1006-1014. doi:10.1002/ajh.25859
23. Báez-Gutiérrez N, Rodríguez-Ramallo H, Moreno MAP, Arboli ER, Abdel-kader Martín L. Venetoclax combination therapy with hypomethylating agents in young adults with relapsed/refractory acute myeloid leukaemia. *Ther Adv Hematol*. 2021;12:20406207211040335. doi:10.1177/20406207211040335
24. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381(18):1728-1740. doi:10.1056/nejmoa1902688
25. DiNardo CD, Schuh AC, Stein EM, et al. Enasidenib plus azacitidine versus azacitidine alone in patients with newly diagnosed, mutant-IDH2 acute myeloid leukaemia (AG221-AML-005): a single-arm, phase 1b and randomised, phase 2 trial. *Lancet Oncol*. 2021;22(11):1597-1608. doi:10.1016/s1470-2045(21)00494-0
26. DiNardo CD, Stein AS, Stein EM, et al. Mutant isocitrate dehydrogenase 1 inhibitor ivosidenib in combination with azacitidine for newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 2021;39:57-65. doi:10.1200/jco.20.01632
27. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405. doi:10.1182/blood-2016-03-643544
28. Palmieri R, Othus M, Halpern AB, et al. Accuracy of SIE/SIES/GITMO Consensus Criteria for Unfitness to Predict Early Mortality After Intensive Chemotherapy in Adults With AML or Other High-Grade Myeloid Neoplasm. *J Clin Oncol*. 2020;38(35):4163-4174. doi:10.1200/jco.20.01392
29. Ferrara F, Barosi G, Venditti A, et al. Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. *Leukemia*. 2013;27(5):997-999. doi:10.1038/leu.2012.303
30. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447. doi:10.1182/blood-2016-08-733196
31. National Institute of Healh (NIH). Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Published 2017. Accessed December 15, 2022. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
32. Lee J, Khan DH, Hurren R, et al. Venetoclax enhances T cell-mediated anti-leukemic activity by increasing ROS production. *Blood*. 2021;138:234-245. doi:10.1182/blood.2020009081
33. Matthews AH, Perl AE, Luger SM, et al. Real-world effectiveness of CPX-351 vs venetoclax and azacitidine in acute myeloid leukemia. *Blood Adv*. 2022;6(13):3997-4005. doi:10.1182/bloodadvances.2022007265
34. Jonas BA, Pollyea DA. How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia. *Leukemia*. 2019;33(12):2795-2804. doi:10.1038/s41375-019-0612-8
35. DiNardo CD, Wei AH. How I treat acute myeloid leukemia in the era of new drugs. *Blood*. 2020;135(2):85-96. doi:10.1182/blood.2019001239
36. Pratz KW, Jonas BA, Pullarkat V, et al. Measurable residual disease response and prognosis in treatment-naïve acute myeloid leukemia with venetoclax and azacitidine. *J Clin Oncol*. 2022;40(8):855-865. doi:10.1200/jco.21.01546
37. Stevens BM, Jones CL, Pollyea DA, et al. Fatty acid metabolism underlies venetoclax resistance in acute myeloid leukemia stem cells. *Nat Cancer*. 2020;1(12):1176-1187. doi:10.1038/s43018-020-00126-z
38. Thijssen R, Diepstraten ST, Moujalled DM, et al. Intact TP53 function is essential for sustaining durable responses to BH3-mimetic drugs in leukemias. *Blood*. 2021;137(20):2721-2735. doi:10.1182/blood.2020010167
39. Ciotti G, Marconi G, Martinelli G. Hypomethylating agent-based combination therapies to treat post-hematopoietic stem cell transplant relapse of acute myeloid leukemia. *Front Oncol*. 2022;11:810387. doi:10.3389/fonc.2021.810387
40. Zhao P, Ni M, Ma D, et al. Venetoclax plus azacitidine and donor lymphocyte infusion in treating acute myeloid leukemia patients who relapse after allogeneic hematopoietic stem cell transplantation. *Ann Hematol*. 2022;101(1):119-130. Epub 2021 Sep 27. doi:10.1007/s00277-021-04674-x

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Todisco E, Papayannidis C, Fracchiolla N, et al. AVALON: the Italian cohort study on real-life efficacy of hypomethylating agents plus venetoclax in newly diagnosed or relapsed/refractory patients with acute myeloid leukemia. *Cancer*. 2023;1-13. doi:10.1002/cncr.34608