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CORRESPONDENCE

Prospective multicenter study on infectious complications and clinical outcome of 230 unfit acute myeloid leukemia patients receiving first-line therapy with hypomethylating agents alone or in combination with Venetoclax

To the Editor:

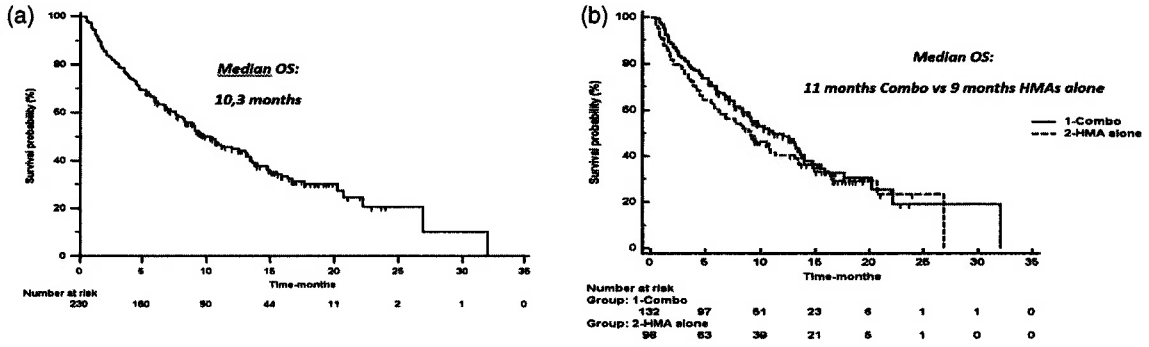
Hypomethylating agents (HMAs) are an important therapeutic option for older patients with acute myeloid leukemia (AML) and have become the backbone for combination regimens s1–s5. However, there are very limited real-life prospective studies investigating the infectious complications in AML treated with HMAs ± Venetoclax (VEN) outside of clinical trials.[1–5]

In this prospective study, designed and conducted by the SEIFEM group (Sorveglianza Epidemiologica Infezioni nelle Emopatie), we evaluated the infectious complications in a cohort of patients unfit for intensive chemotherapy, treated in first-line with HMAs alone or in combination with VEN, immediately after the introduction of this combination in clinical practice in Italy (between 2019 and 2020). Methods are reported in the Appendix S1.

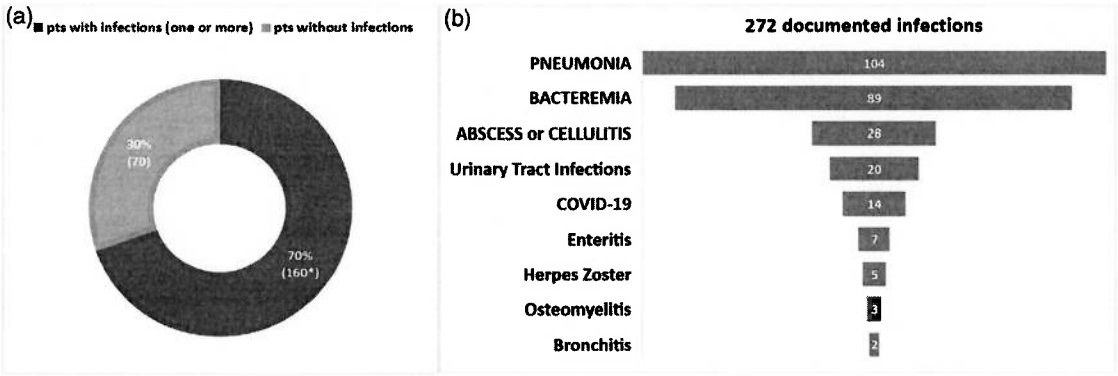
We enrolled 230 consecutive patients with a median age of 75 years (range 25–94); 157 patients (68%) had ≥2 relevant comorbidities. Patients' and AML characteristics are reported in Table S1. Of the 230 cases, 132 (57%) received first-line therapy with a combination of HMAs+VEN, while 98 (43%) were treated with HMA monotherapy. A total of 1552 HMAs cycles were administered (888/1552 with HMAs+VEN) with a mean number of cycles/patients of 6.7 ± 5.5. Notably, 82.5% (1281/1552) of cycles were administered in an outpatient setting. Table S2A shows the characteristics and duration of therapy. The best responses achieved with HMAs treatment were CR in 44% of cases with an ORR of 61% (72% for HMAs+VEN and 46% for HMAs alone, $p = .0007$)-Table S2B. After a median follow-up of 10 months (range 1–24) from the start of HMAs therapy, 144 (63%) patients had died and 86 (37%) were alive. The 1-year OS probability of the entire patient population was 46% with a median OS of 10.3 months (11 months in the HMAs+VEN cohort and 9 months in the HMAs alone cohort; p = ns)-Figure 1A. The primary causes of death were AML progression (42%), infection (26%-37/144), infection+AML (24%-35/144), and other causes (8%-12/144). The Infectious Related Mortality (IRM) was 26%, and 19/144 (13%) patients died of infectious complication while in AML response (16 in HMAs+VEN group and only 3 in the HMAs group; $p = .005$)-Table S2C.

Microbiologically or radiologically documented infectious complications (at least one) occurred in 160/230 (70%) of patients (Figure 1B). A total of 272 episodes of infection were reported in 160 patients (1.7 episodes per patient). The most common infections were pneumonia (104 episodes-42%), followed by bacteremia (89 episodes-33%), abscess or cellulitis (28 episodes-10%), and urinary tract infections (20 episodes-7%). In addition, 14 cases of COVID-19 were reported (5% of documented infections). Febrile neutropenia (one or more episodes) occurred in 38% of patients. Patients treated with HMAs+VEN had more documented infectious complications than those treated with HMAs alone (99/132–75% vs. 61/98–62%, $p = .04$) but, according to the type of hypomethylating agent used (AZA or DEC), no differences were found in the two groups (HMAs +VEN or HMAs alone). Indeed, in the HMAs+VEN group, at least 1 infection was documented in 79% of DEC + VEN-treated patients and in 72% of AZA + VEN-treated patients ($p = .41$). In the HMA single agent group, at least 1 infection was documented in 68% of DEC-treated patients and in 59% of AZA-treated patients ($p = .51$). Table S3A summarizes the characteristics of pneumonia and bacteremia, which were the most common infections. As reported, 42% of patients had at least one episode of pneumonia (a total of 104 episodes of pneumonia in 97 patients), mainly occurring within the first 3 treatment cycles (65%). The etiology of the pneumonia was bacterial in 46% of cases (47/104) or fungal in 25% of cases (26/104). At diagnosis of pneumonia, the median neutrophil count was 250/μl (range 0–19 500/μl). Notably, 86% of patients with pneumonia required hospitalization, and the related death rate (as a primary cause) was 16% (15/97 patients). The characteristics of bacteremias are reported in Table S3B. Overall, 29% of the entire patient population had at least one episode of bacteremia (with a total of 89 bacteremias in 67 patients), occurring mainly within the first three cycles of therapy. The most frequently isolated bacteria were *Escherichia coli* and *Staphylococcus spp*. At the onset of bacteremic fever, the median neutrophil count was 190/μl (range 0–20 000/μl); 94% of patients with bacteremia were hospitalized, and the related death rate was 33% (29/89 patients). Regarding antimicrobial prophylaxis in the entire patient cohort, 115/230 (50%) patients received at least anti-bacterial prophylaxis (mainly with levofloxacin-102/115) and 126/230 (55%) received at least anti-fungal mold-active prophylaxis (mainly with posaconazole-105/126). Only 90/230 patients (39%) received both prophylaxis (anti-bacterial+anti-mold). Interestingly, only 28% (13/47)

(A) **Overall Survival. [a] All 230 cases. [b] OS in patients treated with HMAs alone versus HMAs+VEN.**



(B) **[a] N° of patients with one or more infectious episodes (clinically or radiologically documented). [b] 272 documented infections.**



*61/98 (62%) in HMA alone group and 99/132 (75%) in HMA+VEN group.

(C) **Factors affecting OS in univariate and multivariate analysis.**

UNIVARIATE analysis-HMAs single agent (98 cases)				MULTIVARIATE analysis HMAs			
Covariate	**HR**	**95% CI**	***P***	**SE**	**Exp(b)**	**95% CI**	***P***
Age ≥ 75 years	**0,62**	**0,40-1,05**	**0,074**	0,2766	0,893	0,52 to 1,53	0,6823
Comorbidities ≥ 3	**0,59**	**0,63-0,98**	**0,03**	0,3018	0,6182	0,34 to 1,11	0,1111
High Risk cytogenetic molecular	**0,6**	**0,35-1,02**	**0,038**	0,3017	1,0777	0,59 to 1,94	0,8042
WBC ≥ 30000/μL	0,88	0,48-1,6	0,677				
Secondary AML	0,8	0,49-1,30	0,36				
Response to therapy (CR/PR)	**6,69**	**4,01-11,1**	**<0,0001**	**0,3255**	**8,7528**	**4,63 to 16,51**	**<0,0001**
Pneumonia	1,05	0,64-1,72	0,83				
Bacteremia	0,69	0,38-1,24	0,17				

UNIVARIATE analysis-HMAs+VEN (132 cases)				MULTIVARIATE analysis HMAs+VEN			
Covariate	**HR**	**95% CI**	***P***	**SE**	**Exp(b)**	**95% CI**	***P***
Age ≥ 75 years	0,8	0,51-1,27	0,34				
Comorbidities ≥ 3	0,81	0,49-1,32	0,37				
High Risk cytogenetic molecular	**0,66**	**0,42-1,05**	**0,06**	0,2431	1,1003	0,68 to 1,76	0,6943
WBC ≥ 30000/μL	1,37	0,77-2,33	0,33				
Secondary AML	0,79	0,50-1,24	0,29				
Response to therapy (CR/PR)	**5,6**	**2,91-10,8**	**<0,0001**	**0,264**	**5,9212**	**3,53 to 9,90**	**<0,0001**
Pneumonia	**0,51**	**0,32-0,81**	**0,0026**	**0,2377**	**0,6488**	**0,40 to 1,03**	**0,0488**
Bacteremia	**0,54**	**0,33-0,88**	**0,0053**	0,237	0,7421	0,46 to 1,17	0,2081

FIGURE 1 (A) Overall survival: (a) All 230 cases. (b) OS in patients treated with HMAs alone versus HMAs+VEN. (B) (a) *Number* of patients with one more infectious episodes (clinically or radiologically documented). (b) 272 documented infections. (C) Factors affecting OS in univariate and multivariate analysis.

of patients with bacterial pneumonia had received anti-bacterial prophylaxis, compared to 63% (84/133) of patients who did not develop any pneumonia (133/230) during treatment ($p = .0002$). In addition, only 31% (8/26) of patients with fungal pneumonia had received mold-active prophylaxis compared to 61% (81/133) of those who did not develop any fungal pneumonia ($p = .008$). A total of 28/67 patients (31.5%) with bacteremia had received anti-bacterial prophylaxis, compared to 90/163 patients (55%) without bacteremia ($p = .08$). Table S4 shows the factors affecting OS for all 230 cases. In multivariate analysis, the only factor affecting OS in the entire patient population and in the HMAs alone subgroup, was the achievement of AML response during therapy ($p < .0001$, 95% CI 4.26–8.95 and $p < .0001$, 95% CI 4.63–16.51, respectively). However, in the HMAs +VEN group, the OS was influenced not only by the achievement of AML response but also by the development of pneumonia ($p < .0001$, 95% CI 3.53–9.9, and $p = .046$, 95% CI 0.4-1.03, respectively) (Figure 1C). The following baseline factors were tested, in univariate and multivariate models, as possible factors affecting infection onset (predictive or protective factors) during HMAs±VEN therapy: antimicrobial prophylaxis (anti-bacterial+anti-mold), age ≥ 75 years, leukopenia at onset (WBC < 2000/μl), leukocytosis at onset (WBC > 30 000/μl), marrow blasts percentage (>or <50%), molecular cytogenetic risk (high risk vs. other) and secondary AML. Univariate and multivariate analysis showed secondary AML as a predictive factor for infection ($p = .05$ in univariate analysis and $p = .02$ in multivariate analysis), while combined antimicrobial prophylaxis (anti-bacterial+anti-mold agent) was a protective factor against pneumonia development ($p = .0003$ in univariate analysis and $p = .0001$ in multivariate analysis).

Although relevant to patients' outcomes, the issue of infectious complications in AML treated with HMAs±VEN, has not been prospectively investigated, and only retrospective studies are available. s6–s10 Some information on infectious complications is obtained from pivotal studies, which, however, did not include infections in either primary or secondary trial endpoints and, therefore, reported incomplete data. 2,s5 Recently, a few large retrospective observational studies on infectious complications in patients treated with HMAs+VEN, primarily focusing on invasive fungal infections (IFIs), have been published. However, these studies are not easily comparable due to differences in patients' characteristics and endpoints (some reporting only the incidence of fungal or bacterial infections). Furthermore, available information on prophylaxis (anti-bacterial, antifungal, or antiviral) and infection features (type of complication, timing of event, type of isolates, related mortality) is often incomplete. In addition, all these retrospective studies include patients who were treated with HMAs + VEN not only at diagnosis but also in a relapsed/refractory AML setting, thus making the treated population very heterogeneous.[3–5] The results of these studies are reported in the Supplementary Material.

The analysis of our study population (100% receiving a first-line therapy) reveals that infectious complications are very common (at least one infectious complication in 70% of patients), as reported in the VIALE-A trial (documented infections in 84% of patients), accounting for the primary cause of death in 26% of cases and being a contributing cause (associated with AML) in another 24%. Furthermore, in our study, infectious complications were found to affect the patients' outcome and survival, especially in the HMAs + VEN treated group. Indeed, in multivariate analysis, one of the factors that significantly and adversely affected OS in patients treated with the combo therapy, was the presence of pneumonia. Regrettably, a high rate of deaths in the CR phase was reported in the HMAs+VEN cohort (16/78–21%), 94% of whom were due to pneumonia or other infectious complications. Consequently, even if this prospective study confirms, in a real-life setting, a higher overall response rate (ORR) of HMAs + VEN therapy compared to monotherapy (ORR 72% vs. 46%), this finding did not translate into a significant OS benefit (median OS of 11 months in the HMA + VEN group versus 9 months in the HMAs monotherapy group; p = ns). However, it must be underlined that the patients included in this prospective observational study were the first cohort of patients treated with the HMAs + VEN combination in Italy. Therefore, the observed unsatisfactory results in terms of OS also probably reflect an early learning phase in the management of this treatment, in which the high risk of serious infectious complications was probably not properly assessed, being prophylaxis of complications is very heterogeneous and, perhaps, not always appropriate. In fact, we found that only 28% (13/47) of patients with a bacterial pneumonia had received anti-bacterial prophylaxis, only 31% (8/26) of patients with fungal pneumonia had received mold-active prophylaxis and only 31.5% (28/67) of patients with bacteremia had received anti-bacterial prophylaxis. Notably, the multivariate analysis demonstrated a significant preventive role against pneumonia for antimicrobial prophylaxis, while secondary AML represents a predictive factor for infection (this is in line with the results of Lee et al.).[5]

In conclusion, the results of this multicentric, prospective study confirm a higher ORR rate in patients treated with HMAs+VEN compared to HMAs alone ($p = .0001$). However, we found a high rate of infectious complications with a higher infection-related deaths in responder patients who were treated with the HMAs+VEN combination ($p = .005$). Multivariate analysis showed a significant preventive role against pneumonia of antimicrobial prophylaxis (anti-bacterial +mold-active prophylaxis). From a practical point of view, this study shows that infectious mortality adversely impacts the OS of this frail AML population and highlights the relevance of anti-infective prophylaxis during HMAs+VEN therapy in AML.[2,6]

DATA AVAILABILITY STATEMENT

All relevant data are within the paper. The full database are available from the Division of Hematology, University of Modena (IT) (contact: acandoni@unimore.it) for researchers who meet the criteria for access to confidential data.

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SUPPORTING INFORMATION

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

Filename	Description
ajh26846-sup-0001-AppendixS1.docx Word 2007 document , 17.6 KB	**Appendix S1.** Supplementary Material.-Patients and Methods. -Results of the retrospective observational studies.
ajh26846-sup-0002-AppendixS2.docx Word 2007 document , 15.2 KB	**Appendix S2.** Supplementary References
ajh26846-sup-0003-Tables.docx Word 2007 document , 29.2 KB	**Table S1.** Baseline characteristics of the 230 included patients. **Table S2.** HMAs therapy and outcome. 2A: Characteristics of HMAs therapy. 2B: Response to therapy. 2C: Clinical outcome. **Table S3.** Analysis of the two principal infectious complications. 3A. Pneumonia. 3B. Bacteremia.

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Supplementary Material-PATIENTS and METHODS.

a.STUDY DESIGN AND DEFINITIONS

This is a prospective, observational, multicenter study including consecutive patients diagnosed with AML who started a first-line therapy with HMAs±VEN at participating centers during the study period. Recruitment for this prospective study began in January 2019 and was completed on December 31st, 2020. The study was scheduled to complete follow-up of patients on December 31st, 2021. The patients included in this study were the first to receive the HMAs+VEN combination in Italy, and therefore represent a learning phase of this treatment in clinical practice. They received the standard schedule of HMAs (azacytidine 75 mg/m^2 sc days 1-7; decitabine 20 mg/m^2 iv days 1-5) and the choice of HMA was at the physician's discretion. The dosage of VEN ranged from 100 to 400 mg/day based on concomitant azoles administration.

The study was approved by the Ethics Committee of Friuli Venezia Giulia Region-IT (CE-Id-study:2908) and was conducted in accordance with the Declaration of Helsinki.

The Inclusion criteria were adult AML patients treated with HMAs±VEN as first-line therapy during the study enrollment period (2019-2020). Exclusion criteria were a) acute promyelocytic leukemia; b) relapsed or refractory (R/R) AML; c) patients included in a concomitant clinical trial.

Study Aims: To investigate the infectious complications and clinical outcome in AML patients treated with HMAs±VEN outside clinical trial. In detail:

1. To prospectively evaluate the incidence and characteristics of clinically or microbiologically documented infectious complications (bacterial, fungal, viral) in patients with AML treated with HMAs±VEN.
2. To assess the impact of these infectious complications on overall survival (OS)
3. To identify the treatment phases with higher risk of infectious complications
4. To assess the need for hospitalization due to infectious complications and their attributable mortality (IRM).

Data on patients, treatment, AML and infections were collected from the time of starting HMAs±VEN until discontinuation of therapy (for any reason), patient death, or the end of the established follow-up period. All data were collected anonymously in a specific electronic database (Microsoft Excel 2016; Microsoft Corporation, Redmond, WA, USA).

Responses to the HMAs based therapy (Complete Remission-CR, Partial Remission-PR, etc) were defined according to the International Working Group criteria.**s11** Overall response rate (ORR) was defined as CR rate + PR rate. AML risk was stratified according to the 2017 ELN risk stratification.**s12** At diagnosis, the Karnofsky index was assessed in all cases. The following comorbidities were assessed individually: diabetes, heart diseases, acute or chronic active liver or renal diseases, active or recent (diagnosis within 24 months) neoplasia, COPD, recent surgery (within 6 months), cognitive or/and degenerative disorders, other neurological diseases, cerebral ischemia.

b.STATISTICAL ANALYSIS

Patients' characteristics were analyzed and reported using descriptive statistics. Absolute values, percentages, mean and median (standard deviation (SD) or interquartile range (IQR)) were calculated. Categorical variables were compared using the Chi-squared test or Fisher's exact test,

while continuous variables were compared using a Student t-test. Univariable and multivariate logistic regression models were applied to study the association between infections (pneumonia and bacteremia) and the following variables: antimicrobial prophylaxis (antibacterial + antimold), age $\geq$ 75 years, comorbidities $\geq$ 3, leukopenia at onset (WBC< 2000/µL), leukocytosis at onset (WBC > 30000/µL), marrow blast percentage (> or < 50%), high molecular cytogenetic risk, and secondary AML. The multivariate analyses included all variables significant at p-value < 0.10 in the univariable analysis, considering potential collinearities.

Overall survival (OS) was defined as the time from AML diagnosis to either death or last follow-up of the patients and it was calculated according to Kaplan–Meier method, and log-rank test was used to compare groups. A p-value < 0.05 was considered statistically significant. The factors affecting OS were also assessed by multivariate Cox proportional hazard regression. Statistical Analyses were performed using MedCalc software (version 19.2.1).

Supplementary Material-DISCUSSION.

-The study by Aldoss et al. evaluated the incidence of IFIs in 119 patients (54% with R/R AML) treated with HMAs+VEN documenting a proven, probable, or possible IFI in 12.6% of cases (aspergillosis in 47% and zygomycosis in 33%). Data on bacterial infections and on antibacterial prophylaxis are not reported in this study. Regarding antifungal prophylaxis, it was not administered to 21% of patients, while azoles (unspecified) and micafungin were received by 41% and 38% of the entire population, respectively. According to the available data the authors concluded that the risk of IFIs is higher among nonresponders compared to responders to HMAs+VEN therapy (22% vs 6%, P = .0132), and in R/R AML than in newly diagnosed setting (19% vs 5%, P = .0498), thus suggesting the need to reevaluate antifungal prophylaxis to minimize the risk of IFIs during therapy.**3**

-The study by On et al. evaluated the incidence of IFIs in 235 patients (45,5% with R/R AML) treated with HMAs+VEN (either DEC or AZA). The study reported a proven, probable, or possible IFI in 18% of cases; the documented infections were aspergillosis, candidiasis and zygomycosis, but in 21 cases the fungal agent was not specified; 67% of patients had received a very heterogeneous antifungal prophylaxis (29% with posaconazole, 19% with voriconazole, 12% with isavuconazole and 5% with echinocandins), although it was not declared whether antibacterial prophylaxis was given. This study also reported one or more bacterial infections (including bacteremia, pneumonia and urinary tract infectious) in 33.6% (79/235) of treated patients.**4**

-In the retrospective monocentric study by Lee et al. the incidence of IFIs and bacteremia has been evaluated in 122 patients (68% with R/R AML) treated with HMAs+VEN. All patients received fluconazole prophylaxis without antibacterial agents. The authors found that secondary and therapy related AML was an independent risk factor for IFIs and patients with fungal infection showed significant poor outcome. However, bacteremia did not affect patients' outcome. Based on these findings, they suggest a mold-active prophylaxis, especially in high-risk cases (e.g., secondary or therapy related AML).**5**

-In the registrative study (VIALE-A) of AZA+VEN combination, infections were very common and were documented in 84% of patients treated with AZA+VEN (64% of patients with grade ≥ 3 infections) and in 67% of patients treated with AZA alone (51% of patients with grade ≥ 3 infections), with pneumonia in 20% and 27% of patients, respectively. The etiologic agents and characteristics of infectious complications are not detailed in this trial and data on antimicrobial prophylaxis are not provided. However, based on the high number of infections and the relevant incidence of

hematological toxicity, the authors recommend the use of antimicrobial prophylaxis in patients treated with the combination therapy.**2,6**

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Supplementary TABLE 1. Baseline characteristics of the 230 included patients.

	Total cases 230 (100%)	HMA single agent* 98/230 (43%)	HMA** + Venetoclax 132/230 (57%)	P
Median age (range)	75 (25-94)	76 (32-94)	73 (25-84)	
Age class				
- < 65 years	24/230 (10%)	8/98 (8%)	16/132 (12%)	0.388
- 65 - 75 years	106/230 (46%)	37/98 (38%)	69/132 (52%)	0.033
- ≥ 76 years	100/230 (44%)	53/98 (54%)	47/132 (36%)	0.007
Comorbidities N°				
- 0 - 1	73/230 (32%)	28/98 (29%)	45/132 (34%)	0.193
- 2 - 3	127/230 (55%)	53/98 (54%)	74/132 (56%)	0.790
- ≥ 4	30/230 (13%)	17/98 (17%)	13/132 (10%)	0.114
Secondary AML	114/230 (50%)	55/98 (56%)	59/132 (45%)	0.109
Cytogenetic-molecular HR	92/230 (40%)	34/98 (35%)	58/132 (44%)	0.175
WBC > 30000/μL	46/230 (20%)	22/98 (22%)	24/132 (18%)	0.505

HMA: hypomethylating agent; HR: high risk; WBC: white blood cells

*Azacitidine-AZA 64 cases and Decitabine-DEC 34 cases. ** AZA 74 cases and DEC 58 cases.

Supplementary. TABLE 2. HMAs therapy and outcome. 2A: Characteristics of HMAs therapy. 2B: Response to therapy. 2C: Clinical outcome.

2A. HMAs Therapy	Total cases	HMA single agent	HMA + VEN	P value
Total patients	230 (100%)	98/230 (43%)	132/230 (57%)	
HMAs				
- AZA	138/230	64/98	74/132	ns
- DEC	92/230	34/98	58/132	ns
Total cycles of therapy	1552	664 (43%)	888 (57%)	
- Inpatient	271 (17.5%)	97 (15%)	174 (20%)	ns
- Outpatient	1281 (82.5%)	567 (85%)	714 (80%)	ns
N° of cycles/pts (mean ± Sd)	6.7 ± 5.5	6,7 ± 5,5	6,8 ± 5,3	ns
Patients that stopped at the 5th cycle or earlier	80/230 (35%)	39/98 (39.8%)	41/132 (31.1%)	ns
Patients beyond 12th cycle	46/230 (20%)	23/98 (23.5%)	23/132 (17.4%)	ns
2B. Response to therapy	**Total cases**	**HMA single agent**	**HMA + VEN**	**P value**
ORR (CR + PR)	140/230 (61%)	45/98 (46%)	95/132 (72%)	0.0007
- Complete remission (CR)	101/230 (44%)	25/98 (25.5%)	76/132 (58%)	0.0001
- Partial remission (PR)	39/230 (17%)	20/98 (20.4%)	19/132 (14%)	ns
Stable disease (SD)	32/230 (14%)	23/98 (23.5%)	9/132 (6.8%)	0.0004
Non-response (NR)	37/230 (16%)	19/98 (19.4%)	18/132 (13.6%)	0.0071
Not evaluable	21/230 (9%)	11/98 (11.2%)	10/132 (7.6%)	ns
Allo-SCT	17/230 (7.4%)	7/98 (7%)	10/132 (7.6%)	ns
2C. Clinical outcome	**Total deaths**	**HMA single agent**	**HMA + VEN**	**P value**
N° of dead patients	144/230 (63%)	66/98 (67%)	78/132 (59%)	ns
Causes of death				
- AML progression	60/144 (42%)	28/66 (42%)	32/78 (41%)	ns
- Infection only	37/144 (26%)	13/66 (20%)	24/78 (31%)	ns
- AML + infection	35/144 (24%)	17/66 (26%)	18/78 (23%)	ns
- Other causes	12/144 (8%)	8/66 (12%)	4/78 (5%)	ns
Death with AML in CR or PR	19/144 (13%)	3/66 (5%)	16/78 (21%)	0.005

HMA: hypomethylating agent; AZA: azacitidine; DEC: decitabine; Sd: standard deviation; ORR: overall response rate; CR: complete remission; PR: partial remission; SD: stable disease; NR: no response; Allo-SCT: Allogeneic stem cell transplantation; AML: acute myeloid leukemia; ns: not significant.

Supplementary TABLE 3. Analysis of the two principal infectious complications.

3A. Pneumonia. 3B. Bacteremia.

3A. Pneumonia	Total cases	HMA single agent	HMA + Venetoclax	P value
N° of pts with pneumonia	97/230 (42%)	35/98 (36%)	62/132 (47%)	ns
N° of pneumonia episodes - In the first 3 cycles - Beyond 4th cycle	104 68/104 (65%) 36/104 (35%)	37 20/37 (54%) 17/37 (46%)	67 48/67 (72%) 19/67 (28%)	ns
Etiology of pneumonia episodes: - Bacterial - Viral - Fungal - NOS	 47/104 (46%) 15/104 (14%) 26**/104 (25%) 16/104 (15%)	 14/37 (37%) 7/37 (19%) 8/37 (22%) 8/37 (22%)	 33/67 (49%) 8/67 (12%) 18/67 (27%) 8/67 (12%)	
Prophylaxis in pts with pneumonia: - None - Only anti-bacterial°° - Only anti-mold° - Both°°/°	 40/97 (41%) 10/97 (10%) 22/97 (23%) 25/97 (26%)	 14/35 (40%) 3/35 (9%) 5/35 (14%) 13/35 (37%)	 26/62 (42%) 7/62 (12%) 17/62 (27%) 12/62 (19%)	ns
Hospitalization	89/104 (86%)	31/37 (84%)	58/67 (87%)	
Death directly related to pneumonia (as primary cause)	15/97 (16%)	5/35 (14%)	10/62 (16%)	
3B. Bacteremia	**Total cases**	**HMA single agent**	**HMA + Venetoclax**	**P value**
N° of pts with bacteremia	67/230 (29%)	24/98 (24.5%)	43/132 (32.6%)	ns
N° of bacteremia episodes - In the first 3 cycles - Beyond 4th cycle	89 67/89 (75%) 22/89 (25%)	26 24/26 (92.3%) 2/26 (7.7%)	63 43/63 (68.3%) 20/63 (31.7%)	0.01
N° of isolates: - *E. coli* - Staphylococci - *K. pneumoniae* KPC - *Pseudomonas* - *Acinetobacter* - Enterococci - Streptococci - *S. maltophilia* - *Enterobacter* - *Clostridium*	95 29/95 28/95 8/95 12/95 4/95 7/95 3/95 2/95 1/95 1/95	28 10/28 8/28 4/28 3/28 2/28 1/28 // // // //	67 19/67 20/67 4/67 9/67 2/67 6/67 3/67 2/67 1/67 1/67	
Prophylaxis in pts with bacteremia: - None - Only anti-bacterial°° - Only anti-mold° - Both°°/°	 26/67 (39%) 7/67 (10,5%) 13/67 (19,5%) 21/67 (31%)	 12/24 (50%) 4/24 (17%) 2/24 (8%) 6/24 (25%)	 14/43 (33%) 3/43 (7%) 11/43 (26%) 15/43 (34%)	ns
Hospitalization	84/89 (94%)	23/26 (88.5%)	61/63 (96.8%)	
Death directly related to bacteremia (as a primary cause)	29/89 (33%)	9/26 (34.6%)	20/63 (31.7%)	ns

HMA: hypomethylating agent; NOS: not otherwise specified; **10 Possible, 10 Probable, 6 Proven (4 *Aspergillus spp*, 2 *Candida not albicans*); °° Levofloxacine or Ciprofloxacine 80%, Amoxicilline±clavulanate or Trimethoprim sulfamethoxazole 20%; °Posaconazole 75%, Itraconazole or Voriconazole 25%.