



**HAL**  
open science

## **Predicting the toxicity-efficacy ratio of venetoclax in real-world patients**

Loïc Osanno, Lucy Brocque, Laurent Bourguignon, Carla Delpech, Laure Farnault, Julien Colle, Pauline Roche, Jacques Chiaroni, Caroline Izard, Régis Costello, et al.

### **► To cite this version:**

Loïc Osanno, Lucy Brocque, Laurent Bourguignon, Carla Delpech, Laure Farnault, et al.. Predicting the toxicity-efficacy ratio of venetoclax in real-world patients. *Annals of Hematology*, 2025, 104 (12), pp.6327-6337. <10.1007/s00277-025-06531-7>. <hal-05418276>

**HAL Id: hal-05418276**

**<https://hal.science/hal-05418276v1>**

Submitted on 5 May 2026

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC-ND 4.0 - Attribution - Non-commercial use - No Derivative Works - International License



# Predicting the toxicity-efficacy ratio of venetoclax in real-world patients

Loïc Osanno<sup>1,2</sup> · Lucy Brocque<sup>1</sup> · Laurent Bourguignon<sup>3,4</sup> · Carla Delpech<sup>1</sup> · Laure Farnault<sup>5</sup> · Julien Colle<sup>5</sup> · Pauline Roche<sup>5</sup> · Jacques Chiaroni<sup>6,8</sup> · Caroline Izard<sup>6,8</sup> · Régis Costello<sup>5</sup> · Mathilde Dacos<sup>1,2</sup> · Caroline Solas<sup>9</sup> · Chems Djezzar<sup>11</sup> · Joseph Ciccolini<sup>2,7</sup> · Thomas Cluzeau<sup>12</sup> · Geoffroy Venton<sup>5,10</sup> · Raphaëlle Fanciullino<sup>1,2</sup>

Received: 9 December 2024 / Accepted: 21 July 2025 / Published online: 11 December 2025  
© The Author(s) 2025

## Abstract

This study investigates the pharmacokinetic variability and exposure-response relationships of Venetoclax (VEN) in adult patients with acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy. The study was conducted in a real-world clinical setting and included 48 patients who were treated with VEN in combination with azacytidine. We found significant inter-individual variability of 68% and intra-individual variability of 39% in plasma VEN concentrations. In addition, higher VEN concentrations were associated with better hematological responses. Median overall survival for the entire cohort was 17.8 months, with 1- and 2-year survival rates of 51% and 36.4%, respectively. A comparison of the 14-day VEN and 28-day VEN protocols showed that patients benefited from longer treatment durations, which resulted in more courses being administered. Plasma concentrations in the 14-day VEN protocol were higher than in the 28-day VEN protocol (2330+1675 ng/mL vs. 1503+966 ng/mL, respectively) without an increase in toxicities. The optimal protocol would be 400 mg/14d if we consider survival as a function of the 1818ng/mL cutoff. These results highlight the importance of considering therapeutic drug monitoring (TDM) as a strategy to optimize treatment outcomes by balancing efficacy and safety.

**Keywords** Pharmacokinetic variability · Venetoclax · Acute myeloid leukemia · Therapeutic drug monitoring · Hematological toxicity

Geoffroy Venton and Raphaëlle Fanciullino contributed equally to this work.

✉ Laurent Bourguignon  
laurent.bourguignon@chu-lyon.fr

Raphaëlle Fanciullino  
raphaelle.fanciullino@ap-hm.fr

<sup>1</sup> Pharmacie hôpital la Conception, APHM, Marseille, France

<sup>2</sup> COMPO UMR Inserm 1068, CNRS UMR 7258, Aix Marseille Université, Marseille, France

<sup>3</sup> Service de Pharmacie, Hospices Civils de Lyon, Groupement Hospitalier Nord, Lyon, France

<sup>4</sup> Laboratoire de Biométrie et Biologie Évolutive, Univ Lyon, Université Claude Bernard Lyon 1, UMR CNRS 5558, Villeurbanne, France

<sup>5</sup> Service d'Hématologie et Thérapie Cellulaire, Centre Hospitalo-Universitaire de la Conception. Assistance Publique des Hôpitaux de Marseille, Marseille, France

<sup>6</sup> Etablissement Français du Sang PACA Corse, Marseille, France

<sup>7</sup> Laboratoire PRISM, Aix Marseille université, Marseille, France

<sup>8</sup> Aix Marseille Université CNRS EFS ADES UMR7268, Marseille, France

<sup>9</sup> Laboratoire de Pharmacocinétique et Toxicologie, APHM, Hôpital La Timone, Unité des Virus Émergents (UVE: Aix-Marseille Univ-IRD 190-Inserm 1207), Marseille, France

<sup>10</sup> Integrative molecular biology in hematopoiesis and leukemia, Equipe Labellisée Ligue Contre le Cancer, CRCM, Inserm UMR1068, CNRS UMR7258, Institut Paoli-Calmettes, Aix Marseille Univ, Marseille, France

<sup>11</sup> Hospitalisation à Domicile, APHM, Hôpital de la Conception, Marseille, France

<sup>12</sup> Département d'hématologie, Université Cote, D'azur, CHU de Nice, Nice, France

## Introduction

Acute myeloid leukemia (AML) is the most common type of acute leukemia [1]. Survival rates are particularly poor in older patients aged 65–70 years. In addition, elderly people with frequent comorbidities account for 50% of AML patients [2, 3]. For years, the canonical treatment for AML in the elderly has been azacytidine (AZA). Recently, the combination of Venetoclax (VEN) with azacytidine (i.e., VENZA) has been the new backbone for the treatment of AML in elderly or frail patients who are ineligible for chemotherapy. The phase III VIALE-A trial demonstrated a clinical benefit of the combination of VEN and AZA over single agent AZA in terms of overall survival (66.7% vs. 28.3%) [4]. VEN is administered after an induction phase from 100 to 400 mg over 3 days in cycle 1, followed by 400 mg once daily in combination with azacytidine as recommended in the VIALE-A study [4] for the first 7 days of each 28-day cycle until progression or unacceptable toxicity [4]. This combination results in significant haematological toxicity and high infection rates ranging from 32 to 42%, leading to empirical adjustments in the dosing and scheduling of VEN [4]. While the standard treatment is based on a continuous course of 400 mg daily, many adjustments are made to the protocol in real-world settings, particularly with regard to the duration of exposure to VEN, which ranges from a minimum of 7 days to a maximum of 28 days [5]. For example, it is now recommended to reduce VEN exposure to 21 days every 28 days in responders with grade IV cytopenia lasting > 7 days [6, 7]. This reduction applies to more than half of patients. Dose adjustments are frequent in the VENZA protocol. Indeed, in the Vacchini et al. study, venetoclax dose adjustments were required in 60% of patients [5]. Due to haematological toxicity, venetoclax dose adjustments were required in 61% of patients who achieved CR or Cri [8]. Shorter duration of venetoclax administration to 14 days has same efficacy and better safety profile in treatment of acute myeloid leukemia [9]. All of this is done empirically by adjusting how much to dose.

As with all oral targeted therapies, food intake, gene polymorphisms affecting liver enzymes or ABC-family transporters, and changes in CYP P450 metabolism such as drug-drug interactions are important sources of both inter and intra-individual pharmacokinetic variability. Compared with other oral targeted therapies [10], there are few data on therapeutic drug monitoring (TDM) with VEN, with most studies focusing on the influence of ethnicity on PK [11, 12]. In particular, exposure-response relationships have not been fully investigated. The primary objective of this real-world study was to evaluate the pharmacokinetic variability

of VEN in adult AML patients. Secondary objectives were to investigate a possible relationship between plasma exposure and toxicities and efficacy.

## Materials and methods

### Study design and patients

This was a retrospective, non-interventional, observational study. The study was approved by our Review Board (Cellule d'Evaluation, at the Direction de la Recherche Clinique & de l'Innovation (DRCI, APHM) and were conducted in accordance with the European recommendations regarding the Clinical Trials Regulation (EU) 536/2014 and the General Data Protection Regulation (GDPR, EU) 2016/679. This study has been granted French MR-004 legal status for non-interventional studies. Due to its non-interventional nature, the review board waived the requirement for patient informed consent. This study was registered as MR-004 RH7VH5 [13]. All adult patients with AML [14] ineligible for intensive chemotherapy and receiving VEN at the University Hospital of Marseille, Marseille, France between August 2022 and June 2024 were included. Most patients received VEN 400 mg orally once daily on days 1–14 or 1–28 and azacytidine 75 mg/m<sup>2</sup> subcutaneously once daily on days 1–7 once every 28-day cycle. We collected pseudo-anonymized data on VEN dosing, pharmacist analysis and TDM values of co-medications, biological and clinical data from our institute database.

### Outcomes and assessments

Disease response i.e. OS (Overall Survival), response, cytogenetic risk categorization, was recorded using the ELN 2022 criteria [15]. CR was defined as absolute neutrophils count > 1G/L, platelets > 100G/L, red cell transfusion independence, and BM with < 5% blasts. CRi was defined as all criteria for CR, except for neutropenia ≤ 1G/L or thrombocytopenia ≤ 100G/L. Bone marrow assessments were performed at screening and at the end of cycle 1. OS was defined as the time from random assignment to the date of death from any cause.

### Safety analyses

Adverse events (AEs) were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) at the end of cycle 1 [16]. AEs occurring from the first cycle onwards were recorded.

## Venetoclax Pharmacokinetic analysis

Blood samples were collected on Day 8 of the first course, or Day 6 for subsequent courses, to ensure that the drug had reached steady state. Blood samples were shipped at 4 °C to the analytical laboratory for centrifugation and freezing within 5 h to avoid degradation. The trough blood concentration of

**Table 1** Baseline demographic and clinical characteristics of the patients

Characteristics	Patients	
	N	Percentage
Patient's numbers	48	100%
Sex		
Female	20	42%
Male	28	58%
Age (years)*	77 (40–86)	
Acute Leukemia Myeloid		
Primary	24	50%
Secondary	24	50%
MRC	12	50%
Chemotherapy	12	50%
European Leukemia Network		
Favorable	2	4%
Intermediate	9	19%
Adverse	37	77%
Karyotype		
Normal	24	50%
Monosomic	9	19%
Complex	15	31%
Mutations		
FLT3	10	21%
IDH1	2	4%
IDH2	7	14%
NRAS	3	6%
KRAS	1	2%
NPM1	8	17%
TP53	13	27%
Treatment lines		
First line	33	69%
Second line or more	15	31%
Baseline blood cells		
Hemoglobin*	85.5 (62–124)	
Platelets*	53 (6–356)	
Neutrophil*	0.6 (0–10.2)	
White blood cell*	2.8 (0.6–42.1)	
Bone marrow blasts (%)		
≤30%	17	38%
]30%; 50%]	10	22%
>50%	18	40%
Median*	42 (8–98)	
Baseline cytopenia grade ≥3		
Anemia	12	25%
Thrombopenia	23	48%
Neutropenia	28	58%

\*Median (Minimum-Maximum)

VEN (C<sub>trough</sub>) was determined by liquid chromatography-mass spectrometry (LC/MS), validated according to EMA and ISO 15,189 guidelines, with both accuracy and precision below 15% [17]. If the sampling time missed the trough concentration, concentrations were then extrapolated to T24h using the formula of Van Eerden et al. [18].

## Statistical analysis

Demographics were analyzed using descriptive statistics. Pairwise comparison was used to show C<sub>trough</sub> as a function of dose administered and the C<sub>min</sub> distribution in the first dose. Inter- and intra-individual variabilities were calculated using the coefficient of variation of each patient's first residual concentration. The best cut-off was determined using a Maximally Selected Rank Statistics method [19, 20]. OS was estimated using the Kaplan-Meier method. Statistical analyses were performed using R<sup>®</sup> software (version 4.3.1). A value of  $p \leq 0.05$  was considered statistically significant.

## Results

### Patient's baseline characteristics

A total of 48 patients received VEN treatment, including 28 men and 20 women (Table 1). The median age at VEN initiation was 77 years, ages range from 40 to 86 years. The majority of patients had de novo AML ( $n=25$ ). Risk stratification according to the current ELN criteria 2022 classified patients into favorable (2 patients), intermediate (9 patients) and unfavorable risk groups (37 patients) (Table 1). Regarding molecular alterations, TP53 mutations affected 27%, FLT3 mutations 21%, IDH1/2 18% and NPM1 17% of the patients.

### Treatment

Patients were treated with the combination of VEN and azacytidine, except for some patients for whom azacytidine was replaced by cytarabine ( $n=3$ ). The median duration of VEN administration during this period was 7 cycles [1–42]. At the beginning of treatment, 11 patients started at 400 mg for 28 days (Table 2). Another 26 patients started at 400 mg as well, but due to frail condition, the duration of treatment was reduced to 7 days in 4 patients, 14 days in 16 patients and 21 days in 6 patients. Posaconazole was used as antifungal prophylaxis in 7 patients; these patients benefited from dose adjustment as recommended by the RCP and received a dose of 100 mg of VEN [21]. Of the remaining 4 patients, 2 started at 200 mg and 2 at 100 mg without antifungal

**Table 2** Population protocols description

VEN Protocol	Patients	
	N	Percentage
Initial dosage (mg)		
100	2	4%
100*	7	15%
200	2	4%
400	37	77%
Initial duration (j)		
7	5	10%
14	21	44%
21	10	21%
28	12	25%
Standard Protocol		
400 mg for 28 days	11	23%
Start protocol modification		
Dosage	4	8%
Duration	5	10%
Dosage and duration	1	2%
Cycle VEN duration		
[1–3]	23	48%
[4–9]	15	31%
>9	10	21%

\* Combined with posaconazole

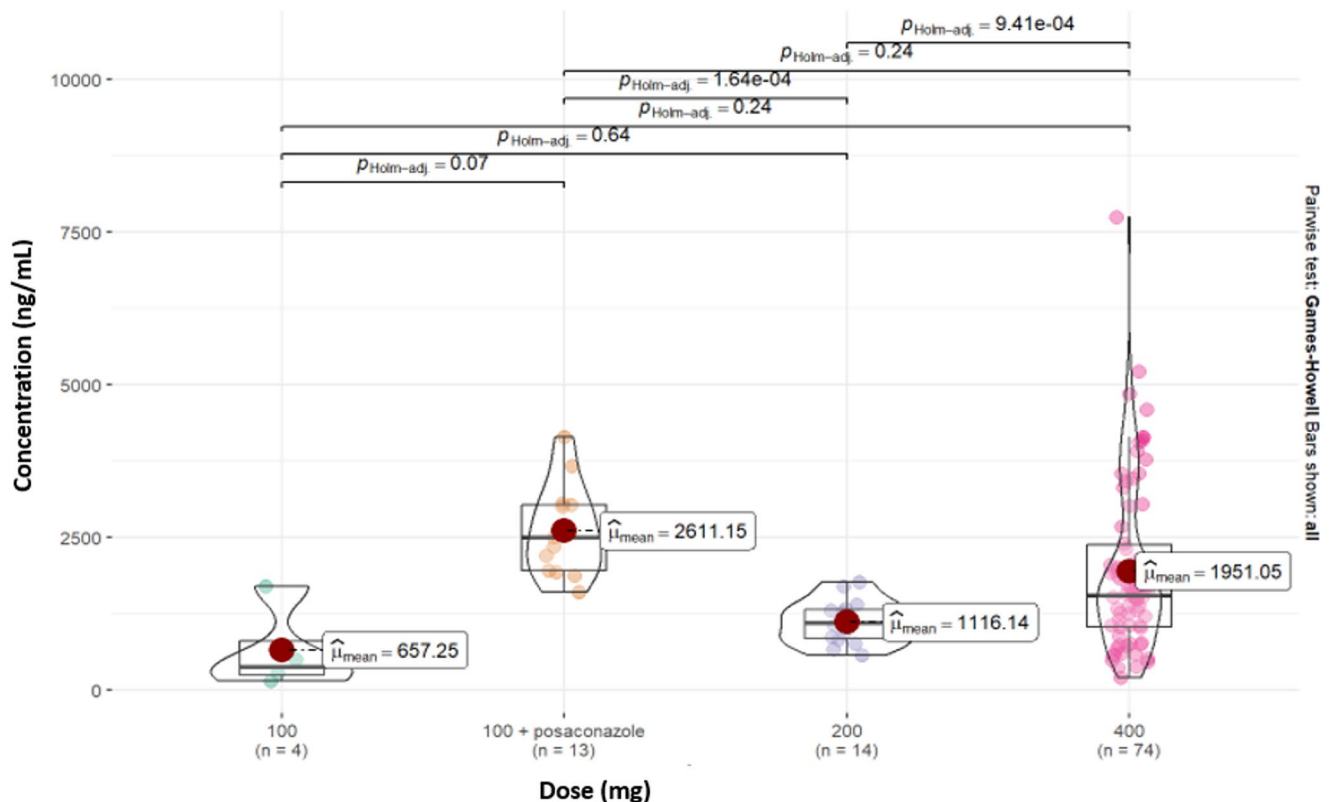
prophylaxis, based on clinician choice. The median interval between first and second treatment was 33.5 days.

### Pharmacokinetics of VEN in AML Patients.

A total of 105 blood samples were analyzed for VEN concentration (mean 2.2 samples per patient). The Ctrough in patients treated with the standard dose of 400 mg VEN was  $1951 \pm 1394$  ng/ml (CV=71%). The difference in VEN concentration between VEN 400 mg and VEN 100 mg plus posaconazole was not statistically significant ( $p=0.24$ ; Pairwise test) (Fig. 1).

The dose-related Ctrough was then examined as a function of the administered dose (Appendix Fig. 1). There were no significant differences between the mean concentrations of 6.57, 5.58 and 4.88  $\mu\text{g/L}$  for the 100, 200 and 400 mg dose related Ctrough, respectively. There was a statistically significant difference between VEN 100 mg plus posaconazole and VEN 400 mg ( $p=0.06$ ).

The inter-individual pharmacokinetic variability of Ctrough at first treatment was 68%, and in 12 patients with at least 3 assays, the observed intra-individual variability was 39% (Appendix Tables 1 and 2). The inter-individual variability was lower when VEN was co-administered with posaconazole (24%) (Fig. 2).

**Fig. 1** Comparison of Ctrough as a Function of the Administered Dose

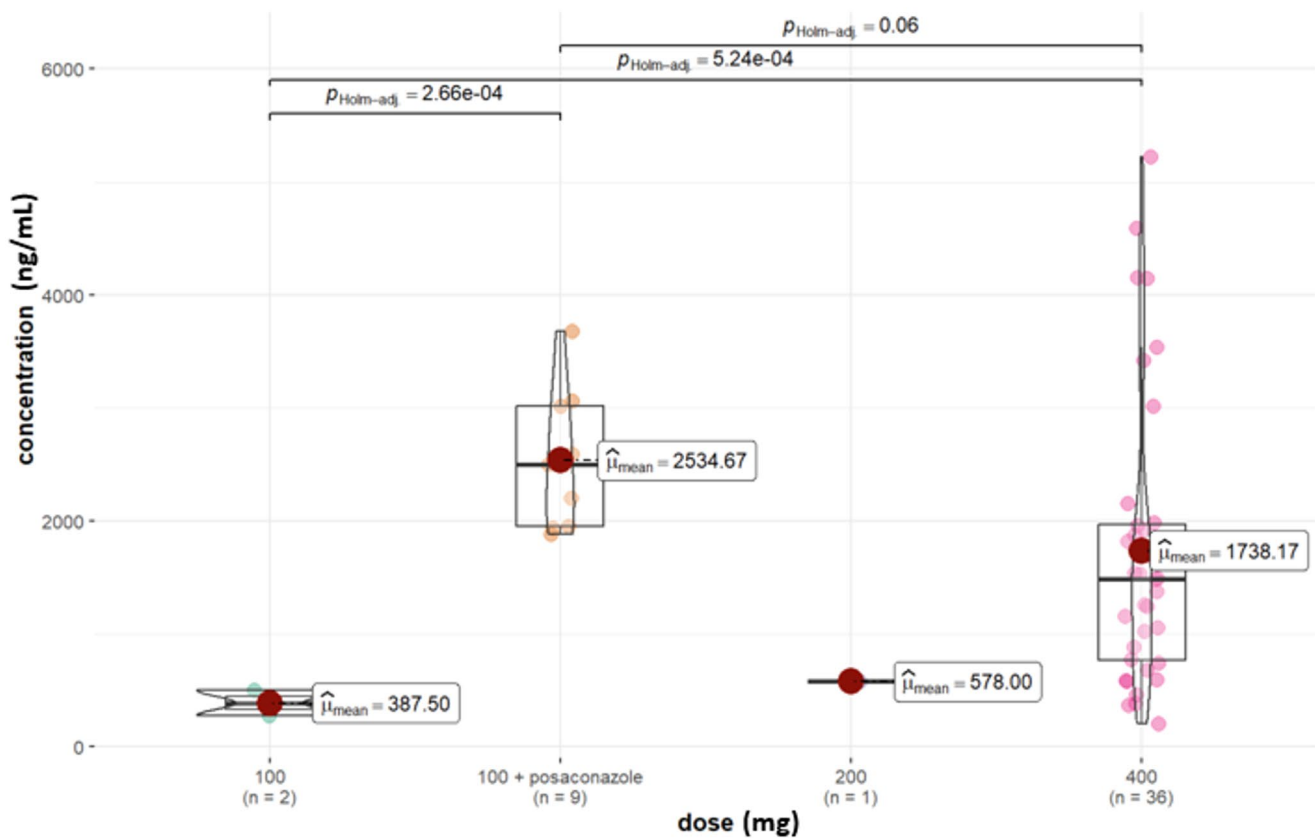


Fig. 2 Violin plot showing Cmin distribution in the first dose

## Adverse events

Myelosuppression was the most common AEs. All patients received at least one transfusion, with an average of 6 red cell transfusions and 3 platelet transfusions. In the first cycle, for protocol 28 days ( $n=11$ ), grade 3 and 4 hematologic side effects, including neutropenia, thrombocytopenia and anemia were 69%, 23% and 27% respectively (Appendix Table 3). In term of toxicities, we observed no difference between protocols 14 and 28 days. The rate of febrile aplasia did not differ between the 2 groups ( $p=0.7$ ; Fisher's exact test). Finally, there were no differences in delayed cures between the protocols ( $p=0.5$ ; Fisher's exact test).

On the other hand, when based on concentration values, the low concentration group (concentration below  $<1818$  ng/mL) had fewer delayed cures ( $0.9 \pm 1.4$ ) than the high concentration group with concentration above  $>1818$  ng/mL ( $4.2 \pm 5.2$ ) ( $p=0.092$ ; Welch two-sample t-test).

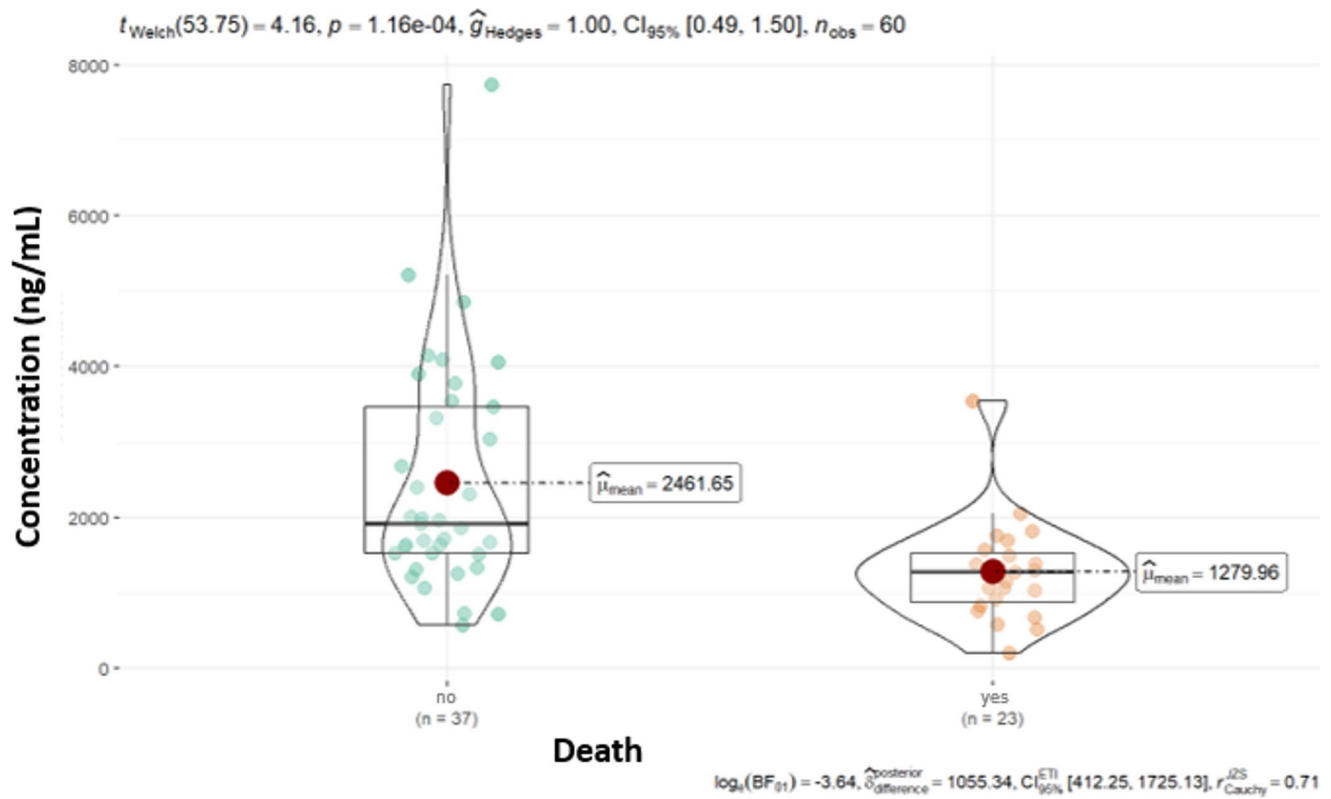
## Exposure-Response relationships

In the group of patients treated with VEN 400 mg, we identified 2 different protocols in terms of treatment duration. Twenty-six patients were evaluable for all cycles. Seventeen

patients were treated with the 14-day VEN protocol and 9 with the 28-day VEN protocol at a dose of 400 mg once daily. The 14-day group received an average of 8 cycles, while the 28-day group received an average of 4.5 cycles. A total of 50 blood samples were analysed. When comparing the concentrations and observing a variability according to the protocol used, the mean Ctrough was  $1503 \pm 966$  ng/ml in the 28-day VEN protocol ( $CV=64\%$ ) and  $2330$  ng/ml  $\pm 1675$  ( $CV=72\%$ ) in the 14-day VEN protocol. The difference in concentration between the two groups was statistically significant ( $p=0.032$ ; Welch two-sample t-test). Patients on the 14-day VEN protocol had fewer bone marrow blasts ( $9 \pm 10\%$ ) than patients on the 28-day protocol ( $19 \pm 9\%$ ) ( $p=0.03$ ; Welch two-sample t-test). Maximally Selected Rank Statistics method show a survival benefit for patients with a threshold concentration of  $1818$  ng/mL in cycle 1 ( $p=0.36$ ) (Appendix Fig. 2).

We focused on patients with more than 3 samples ( $n=12$ ) for a total of 60 samples (Fig. 3). We found that a high mean concentration ( $\mu=2462$  ng/mL) was associated with fewer deaths than a low mean concentration ( $\mu=1280$  ng/mL) ( $p=1.16e-04$ ; Welch two-sample t-test). We found extended OS in patients with higher concentrations.

CR, CRi and PD were 52%, 10% and 38% respectively. With a median follow-up of 7.3 months (1.0–40.7) as the



**Fig. 3** Disease related to concentration

majority of patients died due to relapse, progression, or infection leading to treatment discontinuation. In the overall population, 1- and 2-year OS were 51% and 36.4%, respectively. The median OS for the entire cohort was 17.8 months ( $n=45$ ; 3 lost to follow-up) (Fig. 4).

Survival curves for the 14- and 28-day VEN protocols show that, the median survival for the 14-day protocol was not reached, whereas it is reached with the 28-day protocol (5.4 months,  $p=0.0072$ ) (Fig. 5).

Survival curves by protocol and 1818 ng/mL cutoff show that, the median survival for the 14-day protocol was not reached, whereas it is reached with the 28-day protocol ( $p=0.033$ ) (Fig. 6).

Figure 7 shows the risk as a function of protocol. The 14-day protocol results in an HR of approximately 0.20 compared to 28 days. The result is significant for the 14-day protocol ( $p=0.009$ ). The risk is multiplied by 0.20, which corresponds to an 80% reduction in risk when using the 14-day protocol.

## Discussion

For elderly patients with AML who are ineligible for intensive chemotherapy, treatment with VEN plus azacytidine is now recommended as the new standard of care.

Observations of the use, management and safety of VEN in real-world patients have shown that the dose and duration of use differ from those in clinical trials. Compared to the recommendations of DiNardo et al., only 11 patients were started with the standard protocol, i.e. at a dose of 400 mg for 28 days. Taking this into account, as well as the frailty of the patients, the clinicians at our institute determine the standard protocol a priori.

This explains why both duration and dose have been modified to anticipate toxicities and preserve quality of life as much as possible. However, there were few data on the effectiveness of these changes in dose and duration in the population. We observed significant variability in exposure levels, both between patients (about 70%) and within patients (about 40%). This calls for the implementation of Therapeutic Drug Monitoring to optimize VEN, particularly because of exposure-response relationships on efficacy and toxicity endpoints. A few studies in the literature have focused on the pharmacokinetics of VEN [11, 12, 22]. Given the pharmacokinetic characteristics of VEN and the significant limitations of studying exposure by AUC, we chose to focus here on residual concentrations which are much more likely to be implemented in real-world setting because they do not require PK parameters identification to derive AUC from individual clearance. Our data show that our patients are more exposed, with a mean C<sub>trough</sub> of  $1951 \pm 1394$  ng/

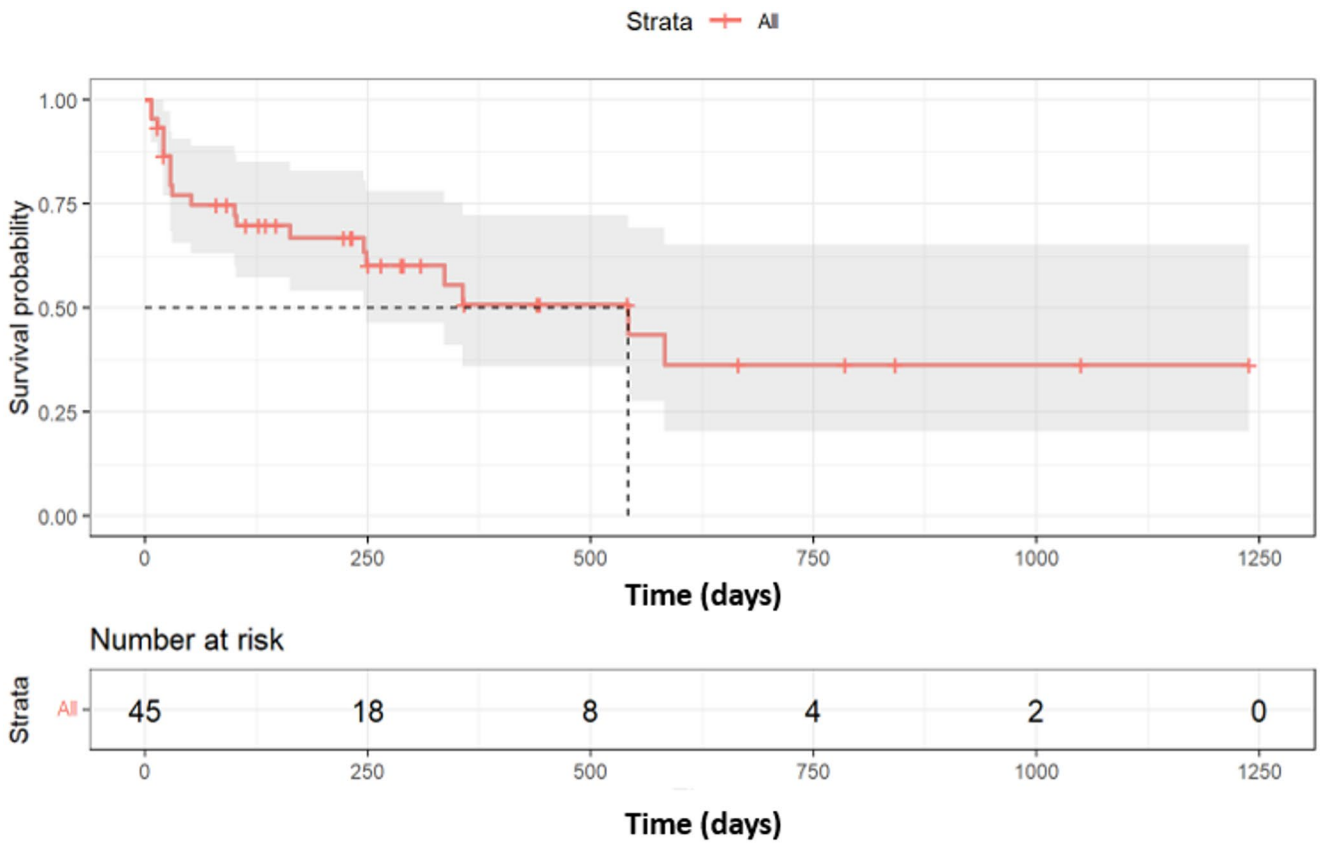


Fig. 4 Overall survival

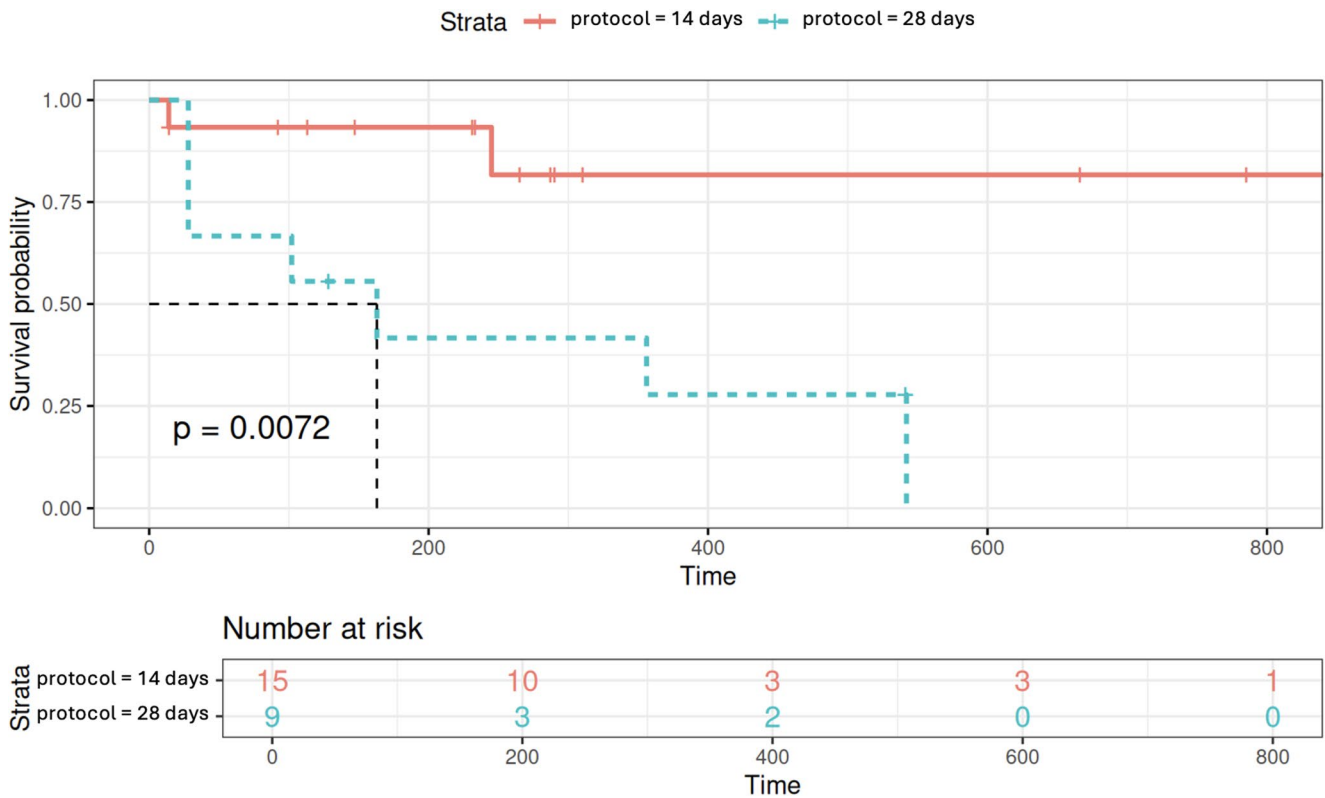
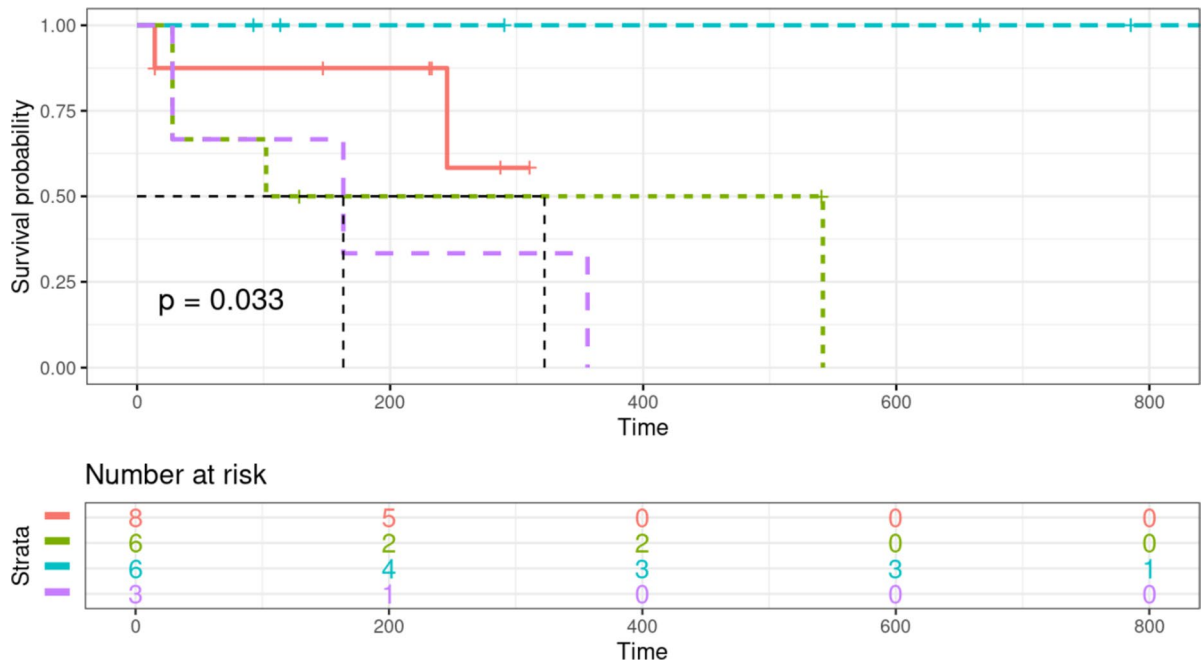
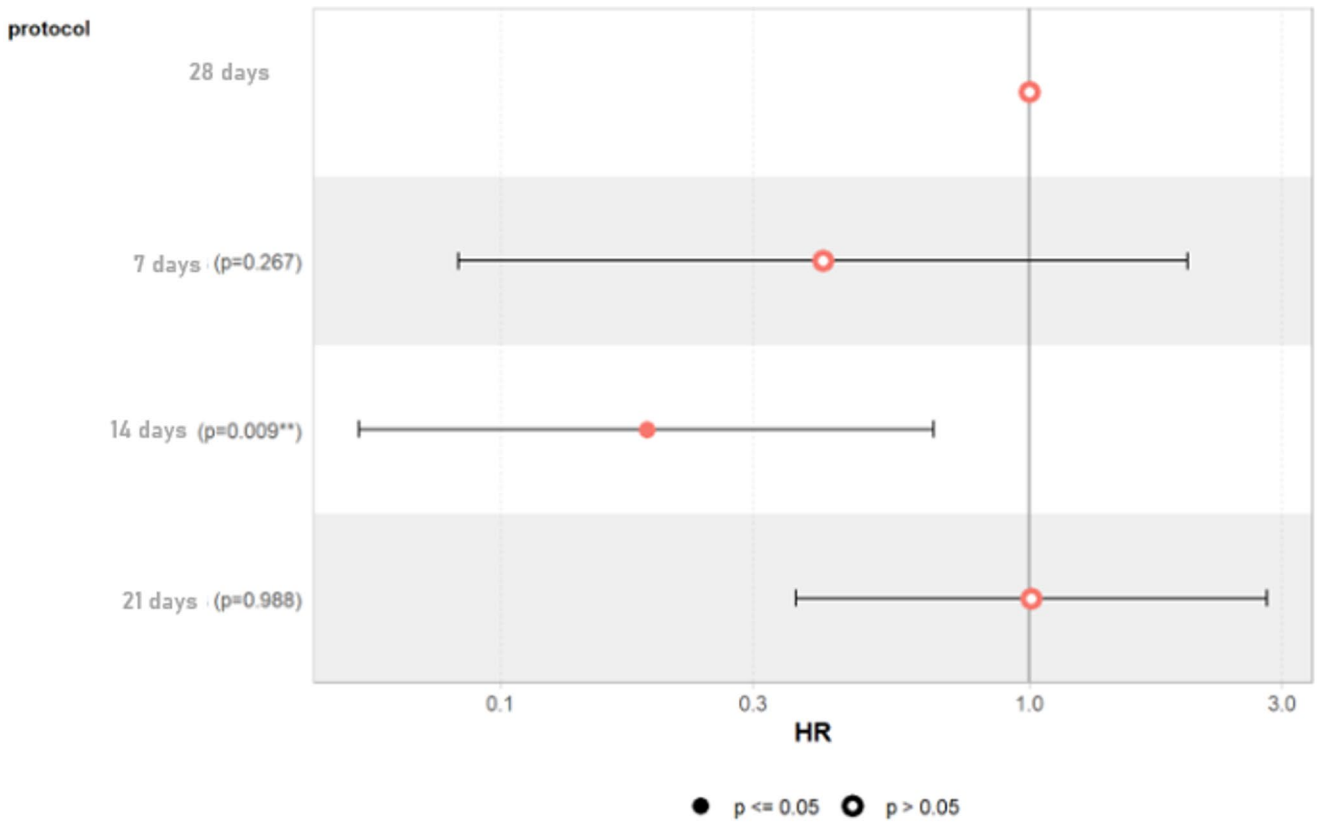


Fig. 5 Overall survival versus protocol



**Fig. 6** Overall survival by protocol and 1818ng/mL cutoff. OS red corresponds below threshold protocol 14 day. OS green corresponds below threshold protocol 28 day. OS blue corresponds above threshold protocol 14 day. OS purple corresponds above threshold protocol 28 day



**Fig. 7** Hazard ratio as a function of protocol

ml compared to a mean Ctrough of  $1018 \pm 729.4$  ng/mL in the Asian patients of Yang et al. [12]. However, another publication comparing the exposure of Asians and non-Asians shows no difference in exposure [22]. As already shown by Yang et al., our study confirmed that VEN pharmacokinetics shows a high inter-individual variability of >68%, with Ctrough ranging from 150 to 7743 ng/mL. In addition, repeated dosing in different patients showed intra-individual variability of VEN of 39%. Studies have shown that diet has a significant effect on the bioavailability of VEN [23]. Here patients were taking VEN with meals according to the prescribing information, limiting the effect of food intake. In addition, pharmaceutical analysis and search for drug-drug interactions helped to limit causes of variability. Our study shows a slight difference in concentration between patients treated and not treated with posaconazole, which is consistent with the dose recommendation in the study by Agarwal et al. There was less variability (24%) when VEN was combined with posaconazole at a dose of 100 mg than at 400 mg. Which is expected given the recommended 75% dose reduction with the enzyme inhibitor. One hypothesis is that there is either a high degree of variability in the absorption phase or a smoothing of variability at the hepatic level with posaconazole, which inhibits CYP3A4 thus reducing its own variability.

One of the main issues with VENZA is that patients are at risk for hematologic toxicities, which leads to additional infections requiring further adjustment in dose or duration of treatment, with some patients having to discontinue treatment for 7 to 14 days [4]. These dose or duration adjustments may apply to patients with myelodysplastic syndromes, for whom an increase in cytopenias has been observed. In our cohort, MDS patients accounted for 19% of the VEN14 group and 37% of the VEN28 group. Although the VEN14 group was found to be more exposed than the VEN28 group, our data showed no difference in toxicity between the two groups. Brackmann et al. found no association between exposure and toxicity [24]. Additional data support this, showing that changing the duration and dose of VEN does not alter patient outcomes [5]. In this real-world study, we first demonstrated a Ctrough threshold associated with hematological response.

In the DiNardo et al. cohort, 42% of patients had grade 3–4 neutropenia, whereas in our cohort, 69% had grade >3 neutropenia (with 37% of febrile aplasia) after the first treatment all protocols combined. Median survival was 17.8 months, in line with published results. We hypothesize that the median survival of 5.4 months in the 28-day group is explained by the high proportion of secondary AML compared to the overall population. The complete response rate (CR+Cri) in our study was 62%, which was comparable to data in the literature [4].

In practice, we have observed a reduction in the duration of VEN treatment due to the occurrence of severe toxicities. According to various studies, the duration of VEN treatment is not predictive of response [5, 7]. However, our results show an association between plasma exposure and response. Looking at plasma exposure as a function of treatment duration, we found a significant difference in plasma concentrations after prolonged continuous exposure for 28-day VEN compared to exposure for 14-day VEN. Furthermore, when looking at survival as a function of 1818ng/mL concentration, the best protocol would be 400 mg/14d if the concentration is above the cut-off. However, due to the small number of patients and the fact that the trajectories are not the same, we must remain cautious.

This observation, correlated with an 89% response rate in the subset of patients treated with VEN 400 mg/14 days at the end of cycle 1, paves the way for this alternative regimen. In addition, a significant difference in overall survival was seen in the 14-day VEN protocol compared to the 28-day VEN protocol ( $p=0.0072$ ).

One hypothesis we propose to explain this decrease in plasma concentration with chronic use of the VEN 28 protocol is an increase in the expression of intestinal efflux pumps, leading to a reduction in absorption [25].

Given the lower response rates with the 28-day administration protocol and its reported association with similar toxicities to the 14-day VEN protocol, our results support that intermittent/discontinuous administration of VEN could improve the toxicity-efficacy ratio. The main limitation of our study is its single-center nature, and the fact that consequently only a small number of patients were monitored. It will thus be necessary to confirm our findings with a multi-centric, larger study. Because exposure-response relationships have been found both on efficacy and safety endpoints, this could pave the way for PK-guided dosing of VEN, so as to ensure an optimal toxicity-efficacy ratio at bedside.

## Conclusion

Our study showed marked inter- and intra-individual variability with VEN. We cannot conclude that the 400/14-day protocol is superior to the 400/28-day protocol due to the small number of patients. However, in view of the results, a treatment duration of 14 days does not appear to be unfavorable in terms of patient survival. The article examines the pharmacokinetics of VENZA in real-world patients, finding a link between exposure and patient response rate that suggests the clinical relevance of TDM in AML patients treated with VEN. At present, the duration of the VENZA protocol varies significantly between centers and patients.

Our primary objective was to ascertain whether a protocol such as 400/14-day would yield superior outcomes for patients in terms of response.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00277-025-06531-7>.

**Acknowledgements** Loïc Osanno performed, designed the research and wrote the paper.

Lucy Brocque performed the research.

Carla Delpech, Jacques Chiaroni, Caroline Izard, Mathilde Dacos, Chems Djeddar contributed to the data.

Laurent Bourguignon analysed the data.

Laure Farnault, Julien Colle, Pauline Roche, Régis Costello, Caroline Solas, Joseph Ciccolini, Thomas Cluzeau read the research paper and made corrections.

Geoffroy Venton and Raphaëlle Fanciullino designed the research study, wrote the paper and made corrections.

**Author contributions** Loïc Osanno performed, designed the research and wrote the paper Lucy Brocque performed the research Carla Delpech, Jacques Chiaroni, Caroline Izard, Mathilde Dacos, Chems Djeddar contributed to the data Laurent Bourguignon analysed the data Laure Farnault, Julien Colle, Pauline Roche, Régis Costello, Caroline Solas, Joseph Ciccolini, Thomas Cluzeau read the research paper and made corrections Geoffroy Venton and Raphaëlle Fanciullino designed the research study, wrote the paper and made corrections.

**Funding** No funding declared.

**Data availability** No datasets were generated or analysed during the current study.

**Competing interests** The authors declare no competing interests.

**Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

- Deschler B, Lübbert M (2006) Acute myeloid leukemia: epidemiology and etiology. *Cancer* 107(9):2099–2107
- Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM (2019) Epidemiology of acute myeloid leukemia: recent progress and enduring challenges. *Blood Rev* 36:70–87
- Prassek VV, Rothenberg-Thurley M, Sauerland MC, Herold T, Janke H, Ksienzyk B et al (2018) Genetics of acute myeloid leukemia in the elderly: mutation spectrum and clinical impact in intensively treated patients aged 75 years or older. *Haematologica* 103(11):1853–1861
- DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH et al (2020) Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med* 383(7):617–629
- Vachhani P, Flahavan EM, Xu T, Ma E, Montez M, Gershon A et al (2022) Venetoclax and hypomethylating agents as first-line treatment in newly diagnosed patients with AML in a predominantly community setting in the US. *Oncologist* 27(11):907–918
- Karrar O, Abdelmagid M, Rana M, Iftikhar M, McCullough K, Al-Kali A et al (2024) Venetoclax duration (14 vs. 21 vs. 28 days) in combination with hypomethylating agent in newly diagnosed acute myeloid leukemia: comparative analysis of response, toxicity, and survival. *Am J Hematol* 99(2):E63–E66
- Pratz KW, DiNardo CD, Selleslag D, Li J, Yamamoto K, Konopleva M et al (2022) Postremission cytopenia management in patients with acute myeloid leukemia treated with venetoclax and azacitidine in VIALE-A. *Am J Hematol* 97(11):E416–E419
- Willekens C, Chraïbi S, Decroocq J, Carpentier B, Lebon D, Bonnet S et al (2022) Reduced venetoclax exposition to seven days of Azacitidine is efficient in treatment-naïve patients with acute myeloid leukemia. *Blood* 140(Supplement 1):537–538
- Aiba M, Shigematsu A, Suzuki T, Miyagishima T (2023) Shorter duration of venetoclax administration to 14 days has same efficacy and better safety profile in treatment of acute myeloid leukemia. *Ann Hematol* 102(3):541–546
- García-Ferrer M, Wojnicz A, Mejía G, Koller D, Zubiatur P, Abad-Santos F (2019) Utility of therapeutic drug monitoring of imatinib, nilotinib, and dasatinib in chronic myeloid leukemia: A systematic review and Meta-analysis. *Clin Ther* 41(12):2558–2570e7
- Cheung TT, Salem AH, Menon RM, Munasinghe WP, Bueno OF, Agarwal SK (2018) Pharmacokinetics of the BCL-2 inhibitor venetoclax in healthy Chinese subjects. *Clin Pharmacol Drug Dev* 7(4):435–440
- Yang X, Mei C, He X, He L, Lu X, Tong H et al (2022) Quantification of venetoclax for therapeutic drug monitoring in Chinese acute myeloid leukemia patients by a validated UPLC-MS/MS method. *Molecules* 27(5):1607
- Recherches n'impliquant pas la personne humaine études et évaluations dans le domaine de la santé [Internet]. [cited 2023 Aug 22]. Available from: <https://www.cnil.fr/fr/declaration/mr-004-recherches-nimpliquant-pas-la-personne-humaine-etudes-et-evaluations-dans-le>
- Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM et al (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 127(20):2391–2405
- Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H et al (2022) Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood* 140(12):1345–1377
- Common Terminology Criteria for Adverse Events (CTCAE) | Protocol Development | CTEP [Internet]. [cited 2023 Aug 29]. Available from: [https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/ctc.htm#ctc\\_60](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_60)
- ich-guideline-m10 -bioanalytical-method-validation-study-sample-analysis-frequently-asked-questions\_en.pdf [Internet]. [cited 2023 May 22]. Available from: [https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m10-bioanalytical-method-validation-study-sample-analysis-frequently-asked-questions\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m10-bioanalytical-method-validation-study-sample-analysis-frequently-asked-questions_en.pdf)
- van Eerden RAG, Oomen-de Hoop E, Noordam A, Mathijssen RHJ, Koolen SLW (2021) Feasibility of extrapolating randomly taken plasma samples to trough levels for therapeutic drug

- monitoring purposes of small molecule kinase inhibitors. *Pharmaceuticals (Basel)* 14(2):119
19. Kassambara A, Kosinski M, Biecek P (2024) `_survminer`: Drawing Survival Curves using 'ggplot2'. R package version 0.5.0.999. <https://github.com/kassambara/survminer>
  20. Lausen B, Schumacher M (1992) Maximally selected rank statistics. *Biometrics* 48(1):73–85
  21. Agarwal SK, DiNardo CD, Potluri J, Dunbar M, Kantarjian HM, Humerickhouse RA et al (2017) Management of Venetoclax-Posaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. *Clin Ther* 39(2):359–367
  22. Gong JQX, Suleiman AA, Menon R, Deng R, Mensing S, Salem AH (2023) Pooled population pharmacokinetic analyses of venetoclax in patients across indications and healthy subjects from phase 1, 2, and 3 clinical trials. *J Clin Pharmacol* 63(8):950–960
  23. Jones AK, Freise KJ, Agarwal SK, Humerickhouse RA, Wong SL, Salem AH (2016) Clinical predictors of venetoclax pharmacokinetics in chronic lymphocytic leukemia and non-Hodgkin's lymphoma patients: a pooled population pharmacokinetic analysis. *AAPS J* 18(5):1192–1202
  24. Brackman D, Eckert D, Menon R, Salem AH, Potluri J, Smith BD et al (2022) Venetoclax exposure-efficacy and exposure-safety relationships in patients with treatment-naïve acute myeloid leukemia who are ineligible for intensive chemotherapy. *Hematol Oncol* 40(2):269–279
  25. Burger H, van Tol H, Brok M, Wiemer EAC, de Bruijn EA, Guetens G et al (2005) Chronic imatinib mesylate exposure leads to reduced intracellular drug accumulation by induction of the ABCG2 (BCRP) and ABCB1 (MDR1) drug transport pumps. *Cancer Biol Ther* 4(7):747–752

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.