Venetoclax in the Treatment of Younger AML Patients

Subjects: Hematology

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The combination approach based on venetoclax (VEN) with azacytidine (AZA) has significantly improved outcomes for elderly patients with acute myeloid leukemia (AML). This innovative approach has led to higher rates of overall response, measurable residual disease (MRD)-negative remissions, and overall survival compared with AZA monotherapy. As a result, this combination has emerged as the gold-standard treatment for elderly or unfit patients with AML who are not eligible for intensive therapy. In younger, fit patients with AML, intensive induction and consolidation chemotherapy is commonly used as a first-line approach; however, relapse continues to be the main reason for treatment failure in approximately 30–40% of patients. Efforts to improve MRD-negative response rates and to facilitate the transition to allogeneic hematopoietic stem cell transplantation, particularly in high-risk AML, have inspired trials exploring the combination of intensive chemotherapy with targeted agents. VEN, a first-in-class anti-BCL2 agent, combined with intensive chemotherapy regimens has shown deep MRD-negative remissions, producing prolonged event-free survival and enhancing the transition to allogeneic transplant in first-complete-remission patients. These benefits support the incremental advantages of adding VEN to intensive chemotherapy approaches across ELN risk subcategories, and provides a robust benchmark to design future trials.

acute myeloid leukemia | venetoclax plus intensive chemotherapy | high-risk patients

1. Introduction

Historically, anthracyclines and cytarabine-based regimens were the mainstay of frontline acute myeloid leukemia (AML) treatment, yielding complete remission (CR) rates of about 55% [1]. CR rates were raised to 65–78% by anthracycline selection and dose expansion [2][3][4], although mostly younger patients (i.e., under 50 years old) with favorable or intermediate-risk cytogenetics primarily benefited from these approaches [2]. Regretfully, relapses are still frequent and often occur after a median time of 24 months from diagnosis [1][2][3][4]. High-dose cytarabine consolidation or longer consolidation cycles have contributed to increasing the CR rates to about 75–85% [3][5][6]. Long-term event-free survival (EFS), however, continued to hover around 45% [4][5][6].

Measurable residual disease (MRD), assessed by either polymerase chain reaction (PCR) or multiparameter flow cytometry (MFC), has become a key biomarker for evaluating the effectiveness of AML treatment. Notably, MRD-negative remissions are correlated with a lower incidence of relapse and improved relapse-free survival (RFS) and overall survival (OS) in patients treated with less-intensive chemotherapy regimens (IC) [7][8][9][10], including consolidative HSCT. From a clinical standpoint, multi-drug IC regimens that induce MRD-negative remission in approximately 50–60% of patients [6][11], eventually leading to HSCT, are crucial for patients with an intermediate or

unfavorable risk of de novo AML, secondary or therapy-related AML [12][13] and relapsed/refractory (R/R) AML [14][15].

2. Venetoclax Plus Intensive Chemotherapy in De Novo AML

VEN, a well-known BH3 inhibitor that selectively targets BCL2, plays a pivotal role in restoring the dysregulated pathway of apoptosis in various hematological cancers. BCL-2 expression has been shown to be significantly upregulated in newly diagnosed and relapsed AML patients (with a range of 34–87%). In vitro studies showed that VEN blocks BCL-2 activity, thus reducing the apoptotic threshold of AML cells and finally leading to an improved response to chemotherapy [16]. Based on these premises, a combinatorial treatment of VEN with chemotherapy represents a reasonable approach. Recently, many studies have assessed the combination of VEN with several IC regimens, including cytarabine and daunorubicin (DA), purine-analogue-based regimens (FLAG, FLAI, CLIA), and CPX351, both in adult and pediatric patients (**Figure 1** and **Table 1**).

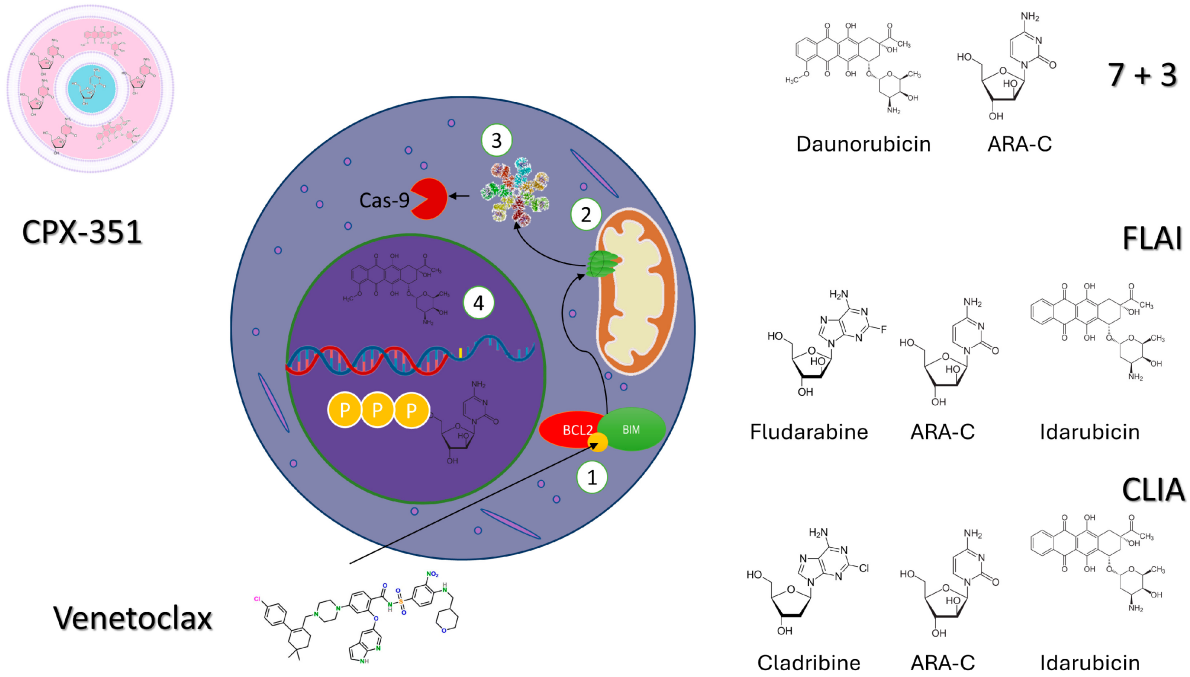

Figure 1. Vignette showing the potential mechanisms of action of intensive CHT combined with venetoclax. (1) Venetoclax is a member of a class of BH3-mimetic drugs. The BH3 domain of the anti-apoptotic protein is shown in yellow. When venetoclax is administered to AML patients, it can displace the activator protein BIM (or BID). Then, the activator protein of apoptosis in combination with the effector (BAX, BAK) proteins results in the release of cytochrome C from the outer mitochondrial membrane (2). (3) The efflux of cytochrome C promotes the formation of an apoptosome, which, in turn, activates Caspase 9 and a caspase cascade that culminates in apoptosis. The simultaneous administration of intensive chemotherapy generates intense stress and damage to nuclear DNA. In particular, (4) daunorubicin damages DNA by intercalating between base pairs, resulting in an uncoiling of the helix, ultimately inhibiting DNA synthesis and DNA-dependent RNA synthesis. At the same time, ARA-C is

phosphorylated three times in the cytoplasm and enters the nucleus, where it is incorporated into DNA, arresting DNA polymerase.

Table 1. Trials including a venetoclax and chemotherapy combination as a frontline approach.

Trial/Reference	Design	Primary Endpoint	Number of Patients	Patients Enrolled	Response	Outcomes	Early Mortality
daunorubicin + cytarabine + venetoclax (DAV)/[17]	phase II	composite complete remission rate	36	patients aged 18–60 years	CRc [6] rate: 91%	estimated 1-year OS [11]: 97% estimated 1-year EFS [12]: 72%	30-day mortality: 0%
daunorubicin + cytarabine + venetoclax (DAV 2 + 6)/[18]	phase II	overall response rate	42	patients aged 16–60 years	ORR [7]: 92.9%; 87.9% of the CR [8] patients with undetectable MRD [9]	estimated 12-month OS [11]: 83.1% estimated 12-month EFS [12]: 82.7% estimated 12-month DFS [13]: 92%	30-day mortality: 2.4%
daunorubicin + cytarabine + venetoclax	phase Ib	optimal dose schedule of venetoclax with	69	patients aged ≥65 years with de novo or s-AML [1] or t-AML [2]	overall response (CR [8]/Cri [10]) rate: 73%	median OS [11]: 15.4 months	30-day mortality: 6%

Trial/Reference	Design	Primary Endpoint	Number of Patients	Patients Enrolled	Response	Outcomes	Early Mortality
(5 + 2 + VEN)/[19]		5 + 2					
daunorubicin + cytarabine + venetoclax (5 + 2 + VEN)/[20]	retrospective clinical trial	composite complete remission	12	patients aged ≥ 60 years	CR [8] rate: 91.7% All patients with poor-risk achieved CR [8]	estimated 1-year EFS [12]: 75%. Estimated 1-year OS [11] rate: 100%	30-day mortality: 0%
cyclophosphamide + cytarabine + venetoclax (VCA)/[21]	pilot study	complete remission rate	25	adult AML [3]	CR [8]/Cri [10]: 92%; all these patients had undetectable MRD [9]	Estimated 12-month OS [11]: 79.3%.	/
fludarabine + cytarabine + idarubicin + filgastrim + venetoclax (FLAG-IDA + VEN)/[22]	phase Ib/II	overall response rate	45	patients aged ≥18 (including de novo, sAML [1], tAML [2], tsAML [4], or high-risk MDS [5])	ORR [7]: 98%; among CR [8] patients, 93% MRD [9] negative	estimated 24-month EFS [12]: 64% estimated 24-month OS [11]: 76%,	30-day mortality: 0% 60-day mortality: 0%

Trial/Reference	Design	Primary Endpoint	Number of Patients	Patients Enrolled	Response	Outcomes	Early Mortality
fludarabine + cytarabine + idarubicin + venetoclax (V-FLAI)/[23]	phase I/II trial	complete remission rate	57	European LeukemiaNet intermediate- or high-risk adult AML [3] (median age 54 years; 18–65)	CR [8] rate: 84%; MRD [9] negative: 74%	probability of 12-month OS [11]: 76%	30-day mortality: 1.8% 60-day mortality 5.3%
cladribine + cytarabine + idarubin + venetoclax (CLIA + VEN)/[24]	phase II	complete response rate	67	patients aged ≤65 years with newly diagnosed AML [3] or high-risk MDS [5]	CRc [7] rate: 96%; among CR [8] patients, 90% MRD [9] negative	estimated 12-month OS [11]: 86.5% estimated 24-month OS [11]: 86.5% estimated 12-month EFS [12]: 71.8% estimated 24-month EFS [12]: 69.7%	30-day mortality: 2% 60-day mortality 3%
CPX-351 + venetoclax	phase Ib/II	the safe dose and schedule	5	patients aged ≥ 18 years	CR [8]/CRi [10]: 80%; 75% MRD [9] negative	1-year estimated OS [11]: 75%	30-day mortality: 0%

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Trial/Reference	Design	Primary Endpoint	Number of Patients	Patients Enrolled	Response	Outcomes	Early Mortality
(CPX-351 + VEN)/[25]							60-day mortality: 0%

[1] sAML = secondary acute myeloid leukemia. [2] t-AML = therapy-related acute myeloid leukemia. [3] AML = acute myeloid leukemia. [4] ts-AML = treated secondary acute myeloid leukemia. [5] MDS = myelodysplastic syndrome. [6] CRc = composite complete remission. [7] ORR = overall response rate. [8] CR = complete remission. [9] MRD = minimal residual disease. [10] CRi = complete remission with incomplete bone marrow recovery. [11] OS = overall survival. [12] EFS = event-free survival. [13] DFS= disease-free survival.

3. Venetoclax Plus Intensive Chemotherapy in Refractory/Resistant AML

The FLAG-IDA plus VEN regimen was investigated in an R/R AML setting and showed encouraging preliminary results. After the starting 39 patients were treated [26], a protocol amendment recommended reducing the VEN-treatment days from 21 to 14 days and the cytarabine dose from 2 to 1.5 g/m^2 (phase 2 cohort) due to the occurrence of severe grade 3 and grade 4 neutropenia-related infections in the initial phase Ib study. Therefore, further trials combining VEN plus IC regimens were designed with a shorter 7-day VEN regimen [24]. Among the R/R AML patients included in the FLAG-IDA plus VEN trial phases Ib (n = 16; median age, 51 years) and IIB (n = 23; median age, 47 years) [26], the CR + Cri rate was 67% (69% were MRD-negative), and 46% proceeded to consolidative HSCT. The estimated 1-year EFS and OS rates were 41% and 68%, respectively, which represent a significant outcome amelioration in comparison with historical results for R/R AML [27][28]. The rate of adverse events resembled that observed in de novo AML trials. Febrile neutropenia and bacteremia were observed in 51% and 46% of the patients, respectively, with an increased rate of sepsis documented in the phase 1b cohort compared with the phase 2 cohorts (50% versus 43%). The 30-day and 60-day mortality among this high-risk group was 0% and 4.4%, respectively.

The FLA-IDA plus VEN (FLAVIDA) regimen (VEN given at 100 mg daily for 7 days when posaconazole was co-administered) was investigated in 13 R/R-AML patients who were predominantly in first-salvage therapy (number of previous lines of treatment: 1–5) and who were classified as ELN intermediate- and high-risk (84.6%) AML [29]. The ORR after induction was 69%, with a median time of CR/Cri maintenance of 7.3 months and an estimated 6-month EFS and OS of 52% and 76%, respectively. Afterward, a retrospective analysis of the same study analyzed the difference between 37 patients receiving FLAVIDA and a cohort of 81 patients treated with FLA-IDA but without VEN. The two cohorts were normalized according to age, genetic characteristics, R/R status, and previous HSCT [30]. Patients treated with the FLAVIDA regimen showed a more significantly improved ORR (78% vs. 47%, p =

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An approach based on the combination of VEN with high-dose cytarabine and mitoxantrone (HAM) was investigated in the phase I/II Alliance Leukemia (SAL) Relax trial [31]. Twelve patients (median age: 57 years) presenting with relapsed AML were included in this dose-finding phase study. The combination of VEN 400 mg daily (after a 3-day ramp-up) on days 3 to 14 and HAM proved secure and effective, leading 11 out of 12 patients to achieve remission.

Finally, the administration of VEN in an R/R setting has also been explored in combination with CPX-351. A phase 2 trial enrolled 26 R/R-AML patients; among them, 10 (42%) had a complex karyotype and 6 (23%) were TP53-mutated AML [25]. The CR/Cri rate was 46%. Furthermore, 78% of CR/Cri patients achieved MRD negativity. Out of the 12 responding patients, 10 (83%) underwent HSCT. The 4- and 8-week mortality was 12% and 19%, respectively, with the most common grade 3 and grade 4 adverse events including infections, pneumonia, and febrile neutropenia. The 1-year estimated OS was 39%, while in responding patients, the median OS was 26.9 months. **Table 2** summarizes these trials, including the combination of VEN and chemotherapy in an R/R setting.

Table 2. Trials including a venetoclax and chemotherapy combination in relapsed/refractory AML.

Trial/Reference	Design	Primary Endpoint	Number of Patients	Patients Enrolled	Response	Outcomes	Early Mortality
fludarabine + cytarabine + idarubicin + filgastrim + venetoclax (FLAG-IDA+ VEN)/[26]	phase Ib/II	overall response rate	49	patients aged ≥ 18	CR [1]/CRi [2] rate: 67% (69% were MRD [3]-negative); 46% proceeded to HSCT [4]	estimated 1-year EFS [7]: 41% estimated 1-year OS [8]: 68%	30-day mortality: 0% 60-day mortality: 4.4%
fludarabine + cytarabine	real-life analysis	/	24	patients aged ≥ 18	CRc [5]: 72% for the entire cohort and 91% in	12-month RFS [9]: 67%	30-day mortality: 12%; 60-day

Trial/Reference	Design	Primary Endpoint	Number of Patients	Patients Enrolled	Response	Outcomes	Early Mortality
+ idarubicin + filgastrim + venetoclax (FLAG-IDA + VEN)/[32]					patients treated for post-HCT [4] relapse	12-month OS [8]: 50%	mortality: 48%
fludarabine + cytarabine + idarubicin + venetoclax (FLAVIDA)/[29]	real-life analysis	/	13	patients aged ≥ 18	ORR [6]: 69%, with a median duration of CR [1]/CRi [2] of 7.3 months	estimated 6-month EFS [7]: 52% estimated 6-month OS [8]: 76%,	/
high-dose cytarabine + mitoxantrone + venetoclax (HAM + VEN)/[31]	phase I/II	dose-limiting toxicity	12	patients aged ≥ 18	CR [1]/CRi [2] rate: 92% (62.5% were MRD [3]-negative);	/	30-day mortality: 8.3%
CPX-351 + venetoclax (CPX-351 + VEN)/[25]	phase Ib/II	the safe dose and schedule	26	patients aged ≥ 18	CR [1]/CRi [2] rate: 46% (78% were MRD [3]-negative).	1-year estimated OS [8]: 39%; in responding patients, the median OS [8]	30-day mortality: 12% 60-day mortality: 19%

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Trial/Reference	Design	Primary Endpoint	Number of Patients	Patients Enrolled	Response	Outcomes	Early Mortality
1	2				3		
4					5		
	7			8	9	was 26.9 months	
+ cytarabine +/− idarubicin + venetoclax/[33]	phase Ib/II	the safe dose and schedule	38	patients between 2 and 22 years	ORR 6: 69%; 80% of patients who achieved a CR 1/CRi 2 proceeded to HSCT 4	/	/

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cytarabine. Overall responses were documented in 24 (69%) of 35 evaluable cases, comprising 16 CRs (11 MRD-negative). A large number (80%) of patients who reached CR/CRi, all of whom were MRD-negative after cycle 1, proceeded to a subsequent HSCT. The most frequent grade 3–4 toxicities resulted of febrile neutropenia (25 patients), bloodstream infections (6 patients), and invasive fungal infections (6 patients), with treatment-related death observed in one patient.

A recent retrospective analysis detailed the outcomes of pediatric patients with R/R AML who underwent VEN treatment before HSCT at St. Jude Children's Research Hospital [34]. Twenty-five pediatric patients (median age: 13.1 years) received VEN-based salvage therapy (VEN/cytarabine, 15; VEN/cytarabine/idarubicin, 5; VEN/cytarabine/azacytidine, 3; or VEN/decitabine, 2) prior to HSCT. Notably, 9 of the 25 patients had already undergone a prior HSCT. The last dose of VEN was administered at a median of 19 days prior to the start of the HSCT conditioning regimen. At the time of the HSCT, 14 patients were in MRD-negative CR, 9 patients were MRD+ (≥0.01%), and 2 patients had active disease (bone marrow blasts > 5%). At a median follow-up of 280 days from HSCT, the 1-year overall survival (OS) was 80% and leukemia-free survival was 74.5%. Unfortunately, six patients relapsed at a median of 143 days, and only one patient experienced non-relapse mortality.

An Italian multicenter retrospective analysis of pediatric patients (0–18 years) with R/R AML or advanced MDS arising after chemotherapy or radiation therapy who received VEN-based combination therapies was reported. Thirty-one patients (median age: 10.2 years) experiencing a median of three previous lines of therapy (31.2% relapsed after HSCT) were included in the analysis [35]. The rates of CR, partial response, and no response were 66.7%, 11.1%, and 22.2% of cases, respectively. Of note, patients who received VEN with hypomethylating agents achieved CR, a partial response, no response, and treatment failure in 36.8%, 26.3%, 31.6%, and 5.3% of cases, respectively. Twenty patients (64%) were successfully bridged to HSCT by VEN therapy after a median time of 3.3 months from the start of the VEN treatment. The estimated 30-month OS after the start of VEN was 29.9% for the whole cohort and 74.4% for patients undergoing HSCT.

According to this data, the combination of VEN plus IC therapy demonstrates efficacy in the pediatric setting for AML, with a tolerability profile similar to that observed in adult AML. Nevertheless, additional data are needed to substantiate the actual benefits of this approach and to assess its potential role in frontline regimens.

5. Molecular Markers Predicting the Response to Venetoclax and Chemotherapy-Based Regimens

The combination of VEN plus IC demonstrates significant efficacy across various genetic subgroups in AML. In patients with ELN favorable-, intermediate-, or unfavorable-risk AML, frontline treatment with FLAG-IDA plus VEN yields composite CR rates of 88%, 89%, and 89%, respectively [22]. Similarly, patients receiving CLIA plus VEN for ELN favorable-, moderate-, or high-risk AML exhibit 1-year survival rates of 78%, 93%, and 81%, respectively [24]. The efficacy of the regimen including VEN plus “2 + 6” daunorubicin and cytarabine is evident across the ELN2022 risk groups. For the favorable-risk group, the estimated 12-month OS, EFS, and DFS rates are 87.5%, 88.9%, and 100%, respectively. The intermediate-risk patients show a rate of 100% for all three endpoints, while adverse-risk patients exhibit a rate of 70.7%, 70.3%, and 79.9%, respectively [18]. The FLAG-IDA plus VEN regimen also showed efficacy in patients with extramedullary localization of the disease; indeed, among patients with extramedullary AML (three with de novo AML and one with R/R AML), all had durable responses, with three going on to HSCT [22].

According to the CAVEAT trial, a seven-day VEN pre-phase before combining the “5 + 2” regimen resulted in a significant reduction in bone marrow blasts in patients with de novo AML, especially in those patients with *NPM1* (56% reduction), *IDH2* (55% reduction), or *SRSF2* (47% reduction) mutations. As a result, patients with these mutations showed an encouraging median OS (*NPM1*: 13.2 months; *IDH2*: not reached; and *SRSF2*: 31.3 months) [19]. In a subsequent analysis of the CAVEAT study evaluating the TFR duration in patients showing CR/Cri, 75% of patients with an *NPM1* or *IDH2* mutation at diagnosis were in TFR [19]. Notably, R/R patients presenting with *NPM1, IDH1*, and *IDH2* mutations also showed promising responses when they received an intensive combination treatment with VEN. Indeed, the FLAG-IDA plus VEN approach produced 100% composite CR in these molecular subgroups, thereby allowing 71% of the patients to undergo HSCT [26]. Also, *KMT2A*-rearranged patients showed a 100% composite CR rate (80% MRD-negativity by PCR for *KMT2A*) after FLAG-IDA plus VEN, with a consequent 1-year OS of 80% [26]. However, in a pediatric trial [33], among 12 patients with *KMT2A* rearrangements, 5 patients showed no response.

While FLAG-IDA plus VEN did not predict the outcome of patients presenting with signaling pathway gene mutations (*K/NRAS*, *PTPN11*, *FLT3*, *CBL*, and *KIT*) in the frontline setting, R/R-AML patients with these mutations showed a lower median OS than patients with wild-type signaling genes. Similar findings were noted in R/R-AML patients, where tumor-suppressor gene mutations (*TP53*, *WT1*, *FBXW7*, or *PHF6*) were linked to a considerably lower rate of composite CR (38%) and a worse prognosis (median OS: 7 months) [26].

In the CAVEAT trial, the lowest blast reductions after VEN pre-phase treatment were observed in patients with *TP53* and kinase-activating mutations (*FLT3-ITD*, *FLT3-TKD*, *RAS*, and *PTPN11*). Consequently, dismal OS

outcomes were observed in patients with *TP53* (3.6 months) and *FLT3-ITD* (5.5 months) mutations [19]. In a CLIA plus VEN trial [24], 15 patients had a *FLT3-ITD* and/or -*TKD* mutation, and 9 of these patients received a concomitant FLT3 inhibitor during induction and consolidation. Patients receiving a concomitant FLT3 inhibitor had a similar OS (p = 0.38) and EFS (p = 0.20) compared with those receiving VEN plus CLIA alone. In the FLAG-IDA plus VEN trial, 10 patients (3 with de novo AML and 7 with R/R AML) showed *TP53* mutations at baseline. The overall composite CR rate was 60%, with a median duration of response and OS of 3.4 and 9 months in de novo AML and 3.2 and 7 months in R/R AML, respectively [26].

Recently, data from VIALE-A demonstrated that AML patients without specific genetic mutations (*FLT3-ITD*, *K/RAS*, *N/RAS*, and *TP53* mutations) may derive a greater benefit from the combination of VEN and AZA [36]. In this subgroup of patients, the median OS was reported to be 26 months, which represents a significant improvement compared with traditional treatment approaches. The identification of specific molecular profiles that predict a higher benefit from VEN plus IC treatments is an important goal in AML research. Indeed, the possibility of tailoring treatment based on a patient's genetic and molecular characteristics can help to optimize outcomes and to minimize potential side effects.