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LETTER

IDALLO study: A retrospective multicenter study of the SFGM-TC evaluating the efficacy and safety of ivosidenib in relapsed IDH1-mutated AML after allogeneic hematopoietic cell transplantation

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Acute myeloblastic leukemia (AML) is a heterogeneous hematological malignancy whose prognosis depends on molecular and cytogenetic markers present at diagnosis. The ELN (European LeukemiaNet) classification, revised in 2022, distinguishes favorable, intermediate, and adverse risk AML according to the molecular and cytogenetic abnormalities identified to assess the risk of relapse and life expectancy.[1]

AML treatment is based on intensive chemotherapy, possibly followed by allogeneic hematopoietic cell transplantation (alloHCT) as consolidation for eligible patients with an identified donor.[2,3] AlloHCT is recommended for patients with intermediate and adverse risk AML and favorable risk patients with relapsed or refractory (R/R) disease or positive measurable residual disease (MRD).[1]

AML is the most common indication for alloHCT,[4] and even if it allows prolonged response in some patients, about 30% will relapse. Relapse is the leading cause of transplant failure, and the prognosis of these patients is poor with a 2-year survival rate of less than 20%, especially in patients with early relapse after alloHCT (within 6 months).[5] Although a second alloHCT appears to provide prolonged survival after a relapse,[6] few patients benefit from this management.

Hypomethylating agents and targeted therapies, given their more specific action mechanism and reduced toxicity profile compared to conventional chemotherapies, represent a therapeutic option for patients ineligible for intensive chemotherapy or alloHCT and relapsed or refractory patients.[7]

IDH1 and IDH2 are proteins that regulate DNA methylation and can also be targeted by specific treatments. These proteins are mutated in 6%–10% of AML, resulting in DNA and histone hypermethylation and blockage of cell differentiation.[8,9] These mutations are more often associated with a normal karyotype.[10] Ivosidenib is a treatment targeting the IDH1 protein and has been evaluated in several studies. In a cohort of R/R AML (including 43 patients relapsing after alloHCT), ivosidenib alone resulted in 39.1% overall response and 21.8% complete response.[11] In a randomized trial evaluating ivosidenib in combination with azacitidine in newly diagnosed AML ineligible for intensive chemotherapy, there was a better overall response (52.8% vs. 17.6%) and overall survival (median

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TABLE 1 Baseline demographics, baseline disease characteristics, and efficacy (continued on next page)outcomes.

Age	
Median age (years)	54.9 (45.9–61.2)
≤65 years old, *n* (%)	19 (86.4)
>65 years old, *n* (%)	3 (13.6)
Hematologic malignancies, *n* (%)	
Acute myeloid leukemia	21 (95)
Myelodysplastic syndrome	1 (5)
Risk (ELN 2022), *n* (%)	
Favorable	5 (22.7)
Intermediate	9 (45)
Adverse	6 (27.3)
Donor, *n* (%)	
Sibling	5 (22.7)
Unrelated	11 (50)
Unrelated	11 (50)
Haploidentical	6 (27.3)
Response before alloHCT, *n* (%)	
Complete response	17 (77.4)
Relapse	1 (5)
Primary induction failure	1 (5)
Missing	3 (13.6)
Conditioning, *n* (%)	
MAC	9 (45)
RIC/NMA	13 (55)
Stem cell source, *n* (%)	
Bone marrow	3 (13.6)
Peripheral blood	19 (86.4)
GvHD, *n* (%)	
Acute GvHD	8 (36.4)
Chronic GvHD	8 (36.4)
Relapse after alloHCT, *n* (%)	
≤6 months	12 (54.5)
>6 months	10 (45.5)
Type of relapse, *n* (%)	
Morphologic	16 (72.7)
Extramedullary	3 (13.6)
Molecular	3 (13.6)
Response to ivosidenib	
Median study follow-up time (months) [95% CI]	27.4 [19.4–28.7]
Overall response,[a] *n* (%)	9 (40.9)
CR, *n* (%)	8 (36.4)
Median duration of response (months) [95% CI]	18.3 [8.2–26.4]
Time to treatment (months) [95% CI]	1.7 [1–4.7]
Time to response (days) [95% CI]	40 [30–77]
Ivosidenib discontinuation, *n* (%)	17 (77.3)
Reason for discontinuation	
Death, *n* (%)	8 (47.1)
Progression, *n* (%)	6 (35.3)
Relapse, *n* (%)	2 (11.8)
Second alloHCT, *n* (%)	1 (5.9)
Other treatments	
DLI, *n* (%)	6 (27)
Azacitidine, *n* (%)	9 (40.9)
Venetoclax, *n* (%)	4 (18.2)

Abbreviations: AlloHCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; CR, complete response; CRi, complete response with incomplete hematologic recovery; DLI, donor lymphocyte infusion; ELN, European LeukemiaNet; GvHD, graft-versus-host disease; MAC, myeloablative conditioning; RIC/NMA, reduced intensity conditioning/nonmyeloablative conditioning.

[a]Overall response is defined by CR + CRi.

overall survival [OS] 24 vs. 7 months) with the combination compared to azacitidine alone.[12]

Few data are available on ivosidenib in relapsed AML after alloHCT. We present here the results of the retrospective IDALLO study, evaluating the efficacy and safety of ivosidenib in AML relapsed after alloHCT.

The IDALLO study is a retrospective multicenter study that included patients ≥18 years old with AML or myelodysplastic syndrome (MDS) with an IDH1 mutation in relapse after alloHCT from 12 French centers between June 2018 and April 2021.

The scientific committee of SFGM-TC (Société Francophone de Greffe de Moelle et de Thérapie Cellulaire) approved the study and data were collected through the European bone marrow transplantation (EBMT) registry. The transplantation centers verified recorded data and were asked to provide missing information. Every patient gave their consent for the EBMT/SFGM-TC registry. Cytogenetic and molecular risk categories were defined according to the ELN 2022 classification.[1]

Ivosidenib was administered as a single agent, orally at a dose of 500 mg once a day, and was available through compassionate access.

We evaluated the overall response rate (ORR), combining complete response (CR), and complete response with incomplete hematologic recovery (CRi) according to international definitions.[13] We also analyzed OS and progression-free survival (PFS) of the whole cohort and according to response to ivosidenib. Adverse events were collected and graded from 1 to 5 according to common terminology criteria for adverse events 4.0 scale.

Descriptive statistics were used to analyze baseline characteristics. Quantitative variables were presented as means and standard deviation or medians and interquartile ranges, and categorical variables as percentages were provided. Qualitative variables were compared with the χ^2 test (or Fisher's exact test) and continuous variables with Wilcoxon's test.

Time-to-event analyses were realized with the Kaplan–Meier method, and survival curves were compared with the log-rank test. Median follow-up was estimated using the reverse Kaplan–Meier method. $p < 0.05$ was considered significant. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc.).

Twenty-two patients fulfilled the inclusion criteria, 15 females and seven males. The median age at transplantation was 54.9 years [95% confidence interval, CI: 45.9–61.2]. Baseline patient characteristics are shown in Table 1. The most common molecular abnormality

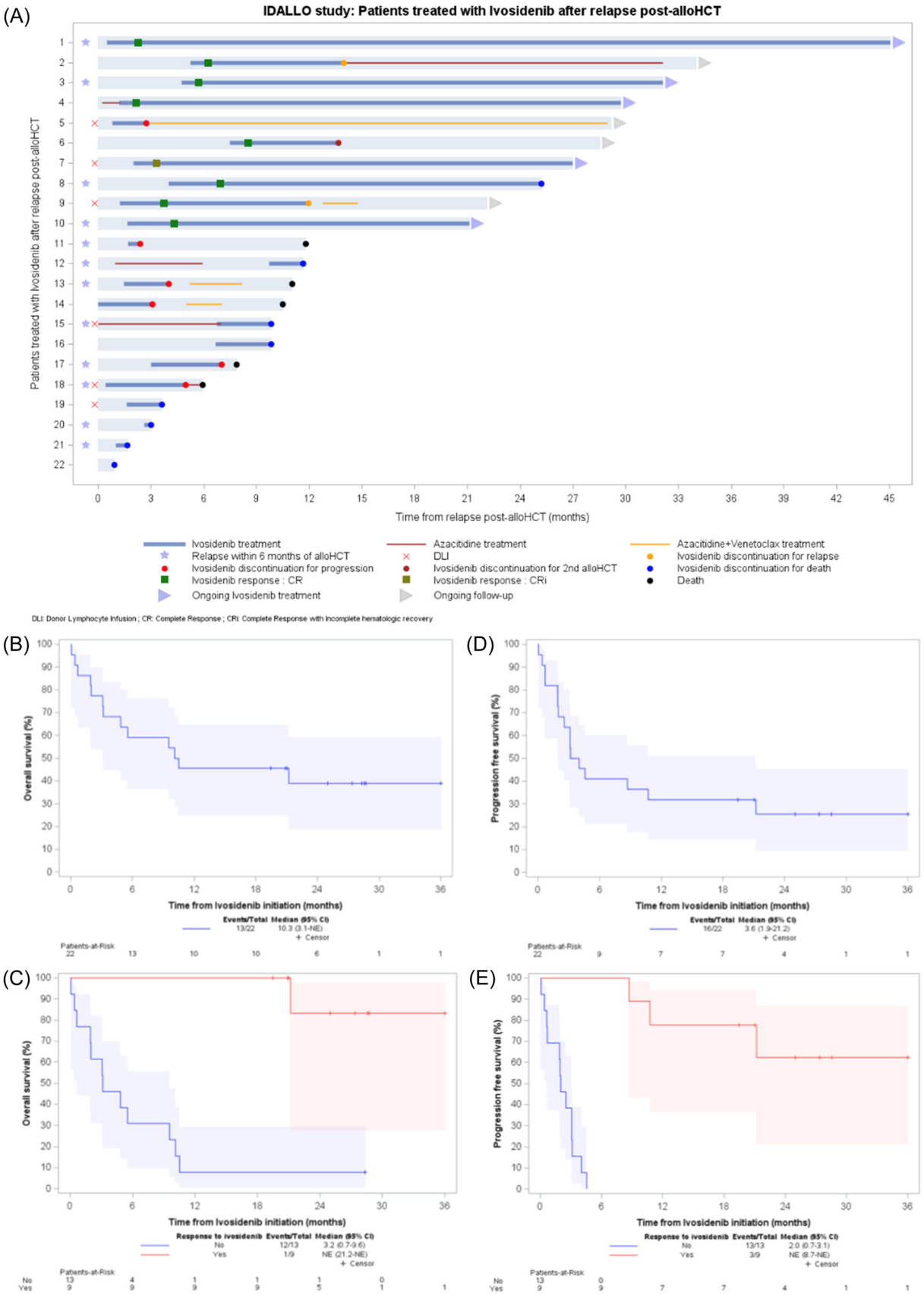

FIGURE 1 (A) Duration of ivosidenib and combination treatment. (B) Overall survival (C) Overall survival regarding response. (D) Progression-free survival. (E) Progression-free survival regarding response. AlloHCT, allogeneic hematopoietic cell transplantation; CR, complete response; CRi, complete response with incomplete hematologic recovery; DLI, donor lymphocyte infusion; NE, not evaluable.

associated with the IDH1 mutation was NPM1 mutation (five patients) and no concomitant IDH2 mutations have been identified. The median time to relapse after alloHCT was 5.8 months [95% CI: 4.6–11.5]. Nine patients (41%) received azacitidine as salvage therapy (three patients before ivosidenib and six patients after ivosidenib). Every patient treated previously with azacitidine received ivosidenib as salvage therapy. Azacitidine was combined with venetoclax in four patients (18%): all of them received this combination after ivosidenib failure. Six patients received a donor lymphocyte injection before ivosidenib introduction. The duration of ivosidenib and associated treatment are presented in Figure 1A.

ORR was 40.9% [95% CI: 20.4–61.5] (nine patients), which included 36.4% [95% CI: 16.3–56.5] of CR (eight patients) (Table 1). The median time to response was 40 days [95% CI: 30–77], and the median duration of response was 18.3 months [95% CI: 8.2–26.4].

From ivosidenib introduction, with a median follow-up of 27.4 months [95% CI: 19.4–28.7], median OS was 10.3 months [95% CI: 3.1–not evaluable (NE)] and survival rate at 18 months was 45.5% (Figure 1B).

Regarding response to ivosidenib, the median OS was not reached for responders, while the median OS for patients who did not respond to ivosidenib was 3.2 months [95% CI: 0.7–9.6] (Figure 1C). The difference between these two groups was statistically significant ($p < 0.001$).

OS was not significantly different according to the type of relapse (morphologic, extramedullary, or molecular) or time from alloHCT (before or after 6 months).

From ivosidenib introduction, the median PFS was 3.6 months [95% CI: 1.9–21.2] (Figure 1D): it was not reached in the responder group and equal to 2.0 months [95% CI: 0.7–3.1] in the nonresponder group (Figure 1E). Seventeen patients discontinued ivosidenib during the follow-up: eight patients (36%) died and did not respond, six patients (27%) progressed, two patients (9%) relapsed after the initial response, and one patient underwent a subsequent alloHCT after complete response. No patient had to discontinue ivosidenib due to toxicity and the main cause of death remained disease progression. Among responders to ivosidenib, the median duration of response was not reached [95% CI: 7.7–NE]. Among patients who discontinued ivosidenib, the median duration of treatment was 3.6 months [95% CI: 1.9–19.4] (Table 1).

Regarding safety, 10 patients (45%) had neutropenia, 12 (55%) patients had thrombocytopenia at initiation of ivosidenib, and five patients (23%) developed grade 3–4 neutropenia after initiation of ivosidenib. Thrombocytopenia grade was not consistently assessed after initiation of ivosidenib. Persistent cytopenias after initiation of ivosidenib were noticed and were related to progression. No patient presented acute graft-versus-host disease (GvHD) since the initiation of ivosidenib and two patients presented grade 1 chronic GvHD (skin and digestive system). Differentiation syndrome was not found in our cohort.

Regarding nonhematologic adverse events, three patients (14%) experienced invasive fungal infection: one patient was in CR after initiation of ivosidenib, one patient did not respond to ivosidenib, and one patient had a morphologic relapse 5 months after initial response to ivosidenib. QT prolongation was found in one patient and resolved after dosing adjustment of ivosidenib. One patient experienced grade 1 neuropathy.

AML relapse after alloHCT is associated with a poor prognosis, and patients are often ineligible for further intensive chemotherapy. Targeted therapies, thanks to their more specific action mechanism and their limited toxicity compared to conventional chemotherapy, could expand therapeutic options in this indication.

In this retrospective study, ivosidenib was associated with an ORR greater than 40%. These real-life findings confirm the one obtained by Di Nardo et al., who showed an ORR of 39.1% [95% CI: 31.9–46.7] in a study that included, notably, 43 patients presenting a relapse after alloHCT.[11] Additionally, among responders, we had mainly CR in our study characterized by rapid and prolonged response.

This study shows a median OS of about 1 year for our entire cohort, compared to a few months in previous studies in the context of R/R AML after alloHCT.[5,6] Improvement of OS was seen primarily in the ivosidenib responder group. Further investigations on predictive factors of response to ivosidenib are needed, including the impact of associated molecular and cytogenetic abnormalities.

We did not observe any serious adverse events that could lead to discontinuation of ivosidenib among all patients in this cohort. However, although survival rates are very interesting, the duration of ivosidenib was short and most patients will discontinue the treatment, mainly in the context of progression. The use of other treatments, such as azacitidine and venetoclax, might explain the good OS in some patients despite ivosidenib discontinuation. It has been shown that the subgroup of AML with an IDH1 or IDH2 mutation seems to have a better response with the combination of azacitidine and venetoclax.[12] Further analysis in a bigger cohort is needed to assess the impact of ivosidenib combination treatment more accurately.

Montesinos et al. compared event-free survival between azacitine + ivosidenib and azacitine alone in a randomized phase 3 trial in patients with IDH1-mutated newly diagnosed AML who were ineligible for intensive chemotherapy and showed better results with the combination.[14] A phase Ib/II study evaluating the combination of ivosidenib and venetoclax with or without azacitidine in R/R AML, newly diagnosed AML ineligible for induction chemotherapy, or high-risk myelodysplastic syndrome with IDH1 mutation is ongoing (NCT03471260). Preliminary results have shown a better ORR with the azacitidine combination than ivosidenib and venetoclax alone (90% vs. 83%, respectively).[15]

Furthermore, these results raise the question of the strategy to use ivosidenib in IDH1 + AML R/R: use until progression, as shown by the prolonged responses obtained in some patients as well as the good safety profile, or bridge strategy before subsequent alloHCT to spare chemotherapy cytotoxicity and improve the feasibility of alloHCT.

Finally, the use of ivosidenib as a maintenance post-alloHCT would be an interesting strategy for relapse prevention, following the example of FLT3-targeted therapies.[16] Promising results with ivosidenib were seen in a phase 1 trial.[17]

These real-life data confirm the efficacy and good safety profile of ivosidenib as a single agent in relapsed AML after alloHCT, with excellent deep and durable responses in some patients. Data are needed to identify patients most likely to respond and other studies evaluating ivosidenib in combination with other treatments such as hypomethylating agents and in the posttransplant setting as a maintenance therapy are ongoing.

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AUTHOR CONTRIBUTIONS

Ana Berceanu, Marion Simonet-Boissard, and Adrien Caillet designed the study. Adrien Caillet, Ana Berceanu wrote the manuscript. Adrien Caillet, Ana Berceanu, and Cyril Boisson analyzed and interpreted data. Ana Berceanu, Marion Simonet-Boissard, Adrien Caillet, Marie-Thérèse Rubio, Marie Robin, Edouard Forcade, Marie-Anne Couturier,

Micha Srour, Natacha Maillard, Raynier Devillier, Anne Huynh, Jean-Henri Bourhis, Célestine Simand, Sylvain Chantepie, Marie Kroemer, and Eric Deconinck collected the data and critically revised the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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