

Five-Year Outcomes of Olutasidenib in Patients with IDH1-Mutated Acute Myeloid Leukemia from the Phase 2 Pivotal Cohort

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Abstract

Olutasidenib is a potent, orally administered selective blocker of mutant isocitrate dehydrogenase 1 (mIDH1). It secured FDA approval for the treatment of relapsed or refractory (R/R) acute myeloid leukemia (AML) following positive results from a pivotal, open-label, multicenter phase 2 clinical study. Data from the scheduled interim review were reported earlier (data cutoff [DCO]: June 2021). This final analysis extends the follow-up by two additional years and presents updated efficacy and safety outcomes (DCO: June 2023). Upon trial completion, the entire group comprised 153 participants, with a median age of 71 years. Two-thirds had undergone at least two previous lines of therapy, and nearly 40% had prior exposure to hypomethylating agents. Of the 147 evaluable patients, 51 achieved complete remission (CR) or CR with partial hematologic recovery (CRh). This produced a CR/CRh rate of 35% ($P < 0.001$; 95% CI: 27–43), with 32% of those responders reaching full CR. The median interval to achieve CR/CRh was 1.9 months (range 0.9–5.6 months). Among those who responded, 33% did so within 2–4 months of starting treatment, while 12% needed 4 months or more. The overall response rate (ORR) was 48% ($n = 71$; 95% CI: 40–56.7). Median duration of CR/CRh reached 25.3 months (95% CI: 13.5–not reached), and median overall survival (OS) was 11.5 months (95% CI: 8.3–15.5). Patients who had received only 1–2 prior regimens demonstrated superior outcomes, with a CR/CRh rate of 41% and a median OS of 13 months, compared with 24% CR/CRh and a median OS of 8.9 months in those with three or more prior regimens. Higher CR/CRh rates were observed in individuals carrying R132C mutations (42%) and R132L/G/S variants (33%) relative to R132H mutations (17%). The likelihood of response diminished as the number of accompanying mutations rose. After the third year, minimal novel adverse events (AEs) appeared, and treatment was not stopped due to AEs in any additional cases. This extended 5-year follow-up reinforces the long-lasting clinical activity and tolerable safety profile of olutasidenib for patients with R/R mIDH1 AML, including those with extensive prior treatment. The findings indicate possible advantages to introducing this agent earlier in the treatment course and emphasize the value of maintaining therapy for at least 6 months to observe potential benefit. Further investigation is required to better define the optimal treatment sequence and the ideal candidates for therapy.

Keywords: Olutasidenib, Relapsed/refractory AML, Targeted therapy, Mutant IDH1 inhibitor

Introduction

Acute myeloid leukemia (AML) is the leading subtype of acute leukemia diagnosed in adults, comprising about

80% of such cases [1]. Even with recent therapeutic progress, long-term survival remains limited, as reflected by a 5-year relative survival rate of 32.9% [1]. Results are particularly discouraging for adults aged 65 years and above, where the 5-year relative survival rate drops to 10.5%, underscoring the urgent need for new treatment approaches [1].

Alterations in the isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) genes represent significant molecular drivers in AML, detected in roughly 20% of patients overall, with IDH1 mutations occurring in 7% to 14% of cases [2–4]. These genetic changes result in excessive production of

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the oncometabolite 2-hydroxyglutarate, which impairs normal epigenetic processes and prevents proper cell maturation, thereby fueling leukemia development [5-7]. In AML, IDH1 mutations frequently correlate with older patient age and have been associated with inferior prognosis in several, though not all, analyses [3, 8-12]. Olutasidenib is a potent, highly specific oral agent that inhibits mutant IDH1 (mIDH1). It effectively targets both mono- and bi-allelic IDH1 mutations while sparing the critical functions of the wild-type enzyme, which are involved in cellular metabolism, epigenetic regulation, differentiation, DNA repair, and redox balance [13, 14]. In the US, regulatory approval was granted for olutasidenib in adults with R/R AML harboring an IDH1 mutation, based on evidence from a dedicated phase 2 study (ClinicalTrials.gov NCT02719574) [15, 16]. The earlier interim review of the main registrational group (total $n = 153$; 147 efficacy-evaluable) showed that single-agent olutasidenib led to CR or CRh in 35% of cases (95% CI: 27–43), accompanied by a median CR/CRh duration of 25.9 months (95% CI: 13.5–not evaluable) at the June 18, 2021 data cutoff [17]. ORR was 48% ($n = 71$; 95% CI: 40–56.7), with a median response duration of 11.7 months (95% CI: 6.9–25.9). Grade 3/4 treatment-emergent adverse events occurring most often included febrile neutropenia and anemia (each 20%) [13, 17]. Differentiation syndrome was noted in 14% of participants (Grade ≥ 3 in 9%), with one associated death. Liver-related side effects affected 25% of patients but were generally reversible without progression to liver failure [17]. The current report presents complete 5-year data (DCO: June 15, 2023) from this central cohort, adding nearly 2 years of additional observation and providing a deeper understanding of the agent's extended performance and tolerability in mIDH1-mutated AML.

Materials and Methods

Study design and patient population

Study 2102-HEM-101 was designed as an open-label, international phase 1/2 investigation involving adults 18 years of age and older. Comprehensive descriptions of the protocol and assessment criteria appear in earlier publications [13, 15]. Enrollment occurred at 57 investigative sites spanning 9 nations. Phase 2 featured various patient groups diagnosed with AML or myelodysplastic syndromes. For the registrational cohort, eligibility required a centrally verified mIDH1 R132 mutation and a confirmed diagnosis of AML that

had relapsed or proven resistant to conventional therapies. Participants needed an ECOG performance status of 0–2, acceptable hepatic and renal organ function, and a QTcF interval no longer than 450 milliseconds. Key exclusion criteria encompassed symptomatic central nervous system involvement by leukemia, poorly controlled infections or metabolic conditions, and any history of prior IDH inhibitor use.

Treatment consisted of olutasidenib 150 mg taken orally twice daily on a continuous schedule in repeating 28-day cycles. Therapy continued until disease progression, excessive toxicity, or receipt of hematopoietic stem cell transplantation (HSCT). Survival monitoring in the phase 2 portion extended up to 36 months from the first day of Cycle 1 or 28 days after treatment cessation, whichever was longer.

Ethics

Institutional review boards at all participating locations approved the protocol. The trial adhered to the ethical tenets outlined in the Declaration of Helsinki and to internationally recognized Good Clinical Practice standards established by the International Conference on Harmonization. Written informed consent was secured from every enrolled patient.

Endpoints and assessments

The primary efficacy measure was the investigator-assessed proportion of patients achieving CR (including cytogenetic and molecular forms) or CRh, according to the adapted International Working Group response criteria for AML [18]. CRh criteria included a bone marrow blast percentage below 5%, a neutrophil count exceeding $0.5 \times 10^9/L$, and a platelet count above $50 \times 10^9/L$. Additional endpoints covered the broader overall response rate (ORR), which combined CR, CRh, CR with incomplete recovery (CRi), partial remission meeting neutrophil and platelet thresholds similar to CR, and morphologic leukemia-free state (MLFS). Other key measures included duration of CR/CRh, overall duration of response (DOR), achievement of transfusion independence (TI), and overall survival (OS). The investigator defined baseline transfusion dependence as receipt of at least one platelet or red blood cell transfusion in the 56 days preceding the initial olutasidenib dose. Patients were classified as transfusion-independent if they remained transfusion-free for at least 56 consecutive days while receiving study drug.

Disease assessments relied on bone marrow aspirates and peripheral blood evaluations performed at screening, on Day 1 of each cycle starting with Cycle 2, and then every other cycle beginning with Cycle 5. Time to response (TTR) was recorded from Cycle 1 Day 1 until the initial documentation of a qualifying response. DOR spanned from the date of first response until disease relapse, death, or initiation of alternative anticancer treatment (censored at the final assessment date for patients without events). For OS, follow-up was censored on the date of last confirmed survival.

Genomic testing utilized bone marrow and blood samples collected at screening and during response evaluations to explore cancer-associated mutations, including IDH1 variant allele frequency (VAF) and additional co-occurring alterations. DNA extraction was performed from whole blood and plasma preserved in PAXGene® tubes. Genomic DNA was isolated using the Maxwell® RSC Blood DNA Kit and the corresponding instrument (Promega, Madison, WI, USA) according to established protocols. Quantity was measured via Qubit™ dsDNA Broad Range Assay Kits (Invitrogen–Thermo Fisher Scientific). IDH1 mutation levels were determined through droplet digital PCR, using cloned wild-type and mutant exon 4 constructs in pCRII-TOPO vectors as controls. The targeted amplicon covered the end of exon 4 and beginning of intron 5 for the specified IDH1 variants (R132C, R132G, R132S, R132H, R132L). The detection threshold for genomic DNA was set at 0.12%. VAF analysis required over 20,000 droplets and offered sensitivity down to 0.1%. Co-mutation profiling was conducted via next-generation sequencing with HaloPlex® target enrichment (Agilent®, Santa Clara, CA) and Illumina® sequencing on a tailored 74-gene myeloid panel, providing >100× depth (IDH1 coverage > 500×), enabling reliable identification of variants at approximately 1% VAF, backed by at least 5 variant reads. Strong consistency was confirmed between NGS and droplet digital PCR methods.

Safety evaluations included all individuals who received any amount of olutasidenib. Adverse events were captured from the first dose until 28 days after the final dose, classified using MedDRA version 19.1, and severity graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Statistical analyses

The efficacy findings reported in this manuscript represent an updated evaluation of the main efficacy measures beyond those presented in the earlier interim review. The primary population for assessing efficacy was the efficacy-evaluable set, defined as all patients who had received at least one dose of olutasidenib at least 6 months before the data cutoff date.

A one-sided exact binomial test was used to evaluate the null hypothesis that the true CR/CRh rate was 15% or lower against the alternative hypothesis that the rate exceeded 15%. Rejection of the null hypothesis occurred if the one-sided p-value fell below 0.025. The CR/CRh rate, along with the corresponding number and proportion of responders, was calculated using the binomial proportion method, accompanied by Clopper-Pearson 95% confidence intervals. Kaplan-Meier (KM) methods were used to analyze duration of response (DOR), time to response (TTR), and overall survival (OS). Both OS and TTR were calculated starting from the date of the first dose until the occurrence of the relevant event.

Pre-specified clinical and genomic factors were first examined individually using univariate logistic regression to identify potential associations with achieving CR/CRh. Variables showing statistical significance were then entered into a multivariate model employing backward selection. The candidate variables included: cytogenetic risk group; AML disease status (relapsed versus refractory); AML classification (de novo versus secondary); age as a continuous variable and in categories (< 65, 65 – < 75, ≥ 75 years); specific IDH1 mutation subtype; patient sex; ECOG performance status; baseline bone marrow blast percentage (< 20%, 20%–40%, > 40%–60%, > 60%); previous exposure to hypomethylating agents (yes/no); history of hematopoietic stem cell transplantation (yes/no); renal function status (normal, mild impairment, moderate impairment); prior venetoclax use (yes/no); number of previous treatment lines (1–2 versus ≥ 3); transfusion independence at study entry (yes/no); total number of co-mutations (as a continuous variable); co-mutation burden categories (0, 1–3, 4–7); individual mutations detected in 10 or more patients (yes/no); and mutation categories grouped by biological pathway (chromatin modification, differentiation, epigenetics, receptor tyrosine kinase signaling, and splicing).

Results and Discussion

Patient characteristics and treatment course

Enrollment took place from April 2018 through June 2020, during which 153 adults with mIDH1-mutated R/R AML were recruited. All received at least 1 dose of olutasidenib at 150 mg twice daily. The median age in this group was 71 years, ranging from 32 to 89. Among them, 147 patients had centrally confirmed mIDH1 mutations and formed the efficacy-evaluable population; the remaining 6 were not included in efficacy assessments because central laboratory verification was unavailable.

Participants (n = 153) had been exposed to a median of 2 prior treatment regimens (range: 1–7). As required by study inclusion criteria, every patient had previously

received chemotherapy, with 109 out of 153 (71%) having been treated with cytarabine. Additionally, 60 patients (39%) had received a hypomethylating agent (HMA) earlier, and 12 patients (8%) had been given venetoclax. Among those 12 individuals, 8 (67%) had received venetoclax combined with an HMA (one of whom [8%] had initially started HMA monotherapy before adding venetoclax, and two [17%] had received HMA alone at a separate time), 3 (25%) had venetoclax paired with cytarabine, and 1 (8.3%) had venetoclax with dinaciclib. No participants had any previous exposure to IDH1 inhibitors. Baseline patient and disease features are presented in **Table 1**.

Table 1. Patient demographics and baseline clinical characteristics in the phase 2 pivotal cohort (n = 153)

Baseline variable	Patient characteristics
Median age, years (range)	71 (32–89)
Sex, n (%)	
Female	74 (48)
ECOG performance status ^a , n (%)	
0	53 (35)
1	71 (46)
2	28 (18)
AML classification, n (%)	
De novo/primary AML	99 (65)
Secondary AML	54 (35)
Median AML duration, months (range)	12.7 (0.7–151.5)
Disease status at enrollment, n (%)	
Treatment-refractory disease ^b	53 (35)
Disease relapse	100 (65)
Median bone marrow blast percentage (range)	40 (4–98)
Number of previous treatment regimens, n (%)	
One prior regimen	52 (34)
Two prior regimens	47 (31)
Three or more prior regimens	54 (35)
Previous therapies received, n (%)	
Hypomethylating agent-based therapy ^c	60 (39)
Cytarabine-containing therapy	109 (71)
Venetoclax exposure	12 (8)
Hypomethylating agent ^c combined with venetoclax	8 (5)
Venetoclax combined with cytarabine	3 (2)
Venetoclax combined with dinaciclib	1 (2)
Allogeneic hematopoietic stem cell transplantation	17 (11)

1. ^a Information was missing for one participant.

2. ^b The refractory classification presented in **Table 1** relies on the full safety population (N = 153). The value noted in the manuscript text (45/147) represents the count of primary refractory cases within the efficacy-evaluable set, as determined by post-hoc review.

3. ^c Includes azacitidine, decitabine, or guadecitabine.

4. AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group.

Treatment exposure and disposition

By the final data cutoff date of June 15, 2023, only 10 patients out of the total 153 (7%) were still actively receiving olutasidenib treatment. The remaining 143 patients (93%) had discontinued study drug. The leading

causes for stopping therapy were progressive disease (n = 63; 41%), adverse events (n = 27; 18%), transition to hematopoietic stem cell transplantation (HSCT) (n = 15; 10%), and death (n = 14; 9%). Overall, patients stayed

on treatment for a median of 142 days, with durations ranging from 3 to 1737 days.

Response

Among the 147 patients included in the efficacy-evaluable analysis, 51 individuals achieved either complete remission (CR) or CR with partial hematologic recovery (CRh). This translated to a response rate of 35 percent ($P < 0.0001$; 95% CI: 27–43), as detailed in

Table 2. Notably, this result matched the rate observed during the previous interim evaluation. The overall response rate (ORR) was 48% (71 patients; 95% CI: 40–56.7); (**Table 2**) and remained consistent with the interim data. After starting olutasidenib, 16 patients from this efficacy population proceeded to HSCT. These included 11 patients in CR, 1 in CRh, 3 in CR with incomplete recovery (CRi), and 1 patient who had stable disease (SD).

Table 2. Clinical response outcomes and response durability following olutasidenib treatment in the efficacy-evaluable population (n = 147).

Efficacy measure	Results
Patients evaluated for efficacy	147
Primary endpoint: CR/CRh achievement, n (%) ^a	51 (35%)
Statistical significance and confidence interval	$P < 0.0001$; 95% CI: 27–43
Median time to CR/CRh, months (range)	1.9 (0.9–5.6)
Median duration of CR/CRh, months (95% CI)	25.3 (13.5–NR)
Estimated duration of CR/CRh among responders	
Responses maintained for ≥ 6 months, % (95% CI)	84 (70–92)
Responses maintained for ≥ 12 months, % (95% CI)	67 (52–78)
Responses maintained for ≥ 18 months, % (95% CI)	52 (37–65)
Best overall response, n (%)	71 (48)
Complete remission (CR), n (%)	47 (32)
Median time to CR, months (range)	2.8 (0.9–7.4)
Median duration of CR, months (range)	25.3 (0–54.6)
CR with partial hematologic recovery (CRh), n (%)	4 (3)
CR with incomplete hematologic recovery (CRi), n (%)	15 (10)
Composite CR (CR + CRh + CRi), n (%)	66 (45)
Partial response (PR), n (%)	3 (2)
Morphologic leukemia-free state (MLFS), n (%)	2 (1)
Overall response rate ^b (ORR), n (%)	71 (48)
Median duration of response (DOR), months (95% CI)	15.5 (7.4–26.2)
Estimated duration of ORR among responders	
ORR lasting ≥ 6 months, % (95% CI)	69 (56–78)
ORR lasting ≥ 12 months, % (95% CI)	56 (44–67)
ORR lasting ≥ 18 months, % (95% CI)	42 (30–53)

^a This P-value was calculated using a one-sided exact binomial test assessing whether the CR/CRh rate was no higher than 15%. ^b ORR is calculated as the fraction of patients who achieved CR, CRh, CRi, PR (accompanied by neutrophil and platelet recovery meeting CR standards), or MLFS. Abbreviations: CI = confidence interval; CR = complete remission; CRh = CR with partial hematologic recovery; CRi = CR with incomplete recovery; DOR = duration of response; MLFS = morphologic leukemia-free state; NR = not reached; OR = overall response; ORR = overall response rate; PR = partial remission.

Of the 147 patients included in the efficacy analysis, more than half (55%; 28/51) who reached the primary study goal demonstrated an initial response by the end of the second month of treatment. In the subgroup of 51 patients who attained CR or CRh, the median time from treatment initiation to response was 1.9 months, with individual times ranging from 0.9 to 5.6 months (**Table 2**). Of these responders, 33% took 2–4 months to respond, and another 12% needed 4 months or longer to

achieve CR/CRh (**Table 3**). Among the 71 patients (48%) who recorded any level of overall response (OR), the median time to response remained 1.9 months. However, the range extended to 10.2 months (**Figure 1**). A substantial 66% of these patients responded within the first 2 months. Still, 24% required 2 to 4 months of therapy, and 10% took over 4 months (up to 10.2 months) before their overall response was documented (**Table 3**).

Table 3. Patient characteristics and time to response in responders to olutasidenib.

Patients achieving CR/CRh (n = 51)	Time to response > 4 months	Time to response 2–4 months	Time to response < 2 months
n (%)	6 (12)	17 (33)	28 (55)
Refractory, n (%)	1 (17)	9 (53)	5 (18)
Relapsed, n (%)	5 (83)	8 (47)	23 (82)
Relapsed > 12 months, n (%)	3 (50)	3 (18)	7 (25)
Number of prior regimens, median (range)	2 (1–6)	2 (1–5)	2 (1–7)
≥ 3 prior regimens, n (%)	2 (33)	3 (18)	8 (29)
Duration of response, median, months (95% CI)	NR (8.1–NR)	11.0 (4.8–15.7)	NR (14.8–NR)
Min, Max	8.1, 42.6	1.8, 50.6	3.7, 54.6
Patients Achieving OR (n = 71)	Time to response > 4 months	Time to response 2–4 months	Time to response < 2 months
n (%)	7 (10)	17 (24)	47 (66)
Refractory, n (%)	4 (57)	9 (53)	13 (28)
Relapsed, n (%)	3 (43)	8 (47)	34 (72)
Relapsed > 12 months, n (%)	1 (14)	3 (18)	13 (28)
Number of prior regimens, median (range)	1 (1–6)	2 (1–5)	2 (1–7)
≥ 3 prior regimens, n (%)	2 (29)	4 (24)	15 (32)
Duration of response, median, months (95% CI)	NR (2.8–NR)	5.6 (1.9–17.5)	25.9 (8.7–NR)
Min, Max	0, 42.6	1.8, 29	1.2, 54.6

Abbreviations: CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; NR = not reached; OR = overall response

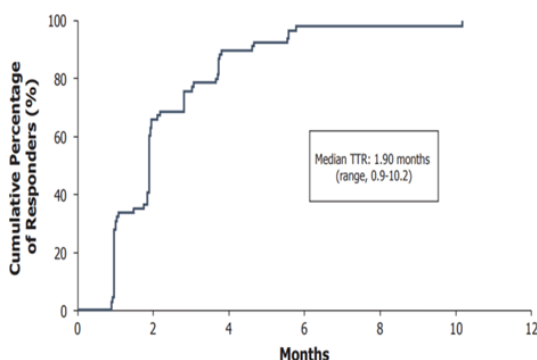


Figure 1. Time to Overall Response with Olutasidenib. N = 71 patients who achieved a response. TTR = time to response.

For the 51 patients who achieved CR or CRh, the median duration of response was 25.3 months (95% CI: 13.5–not reached [NR]), with a range of 1.8 to 54.6 months. Nearly half of them (49%, or 25/51) remained censored in the analysis (**Table 2 and Figure 2**). These figures closely align with the interim analysis, which showed a median CR/CRh duration of 25.9 months [15, 16]. Using Kaplan-Meier methods, the estimated share of patients still in CR/CRh at the 6-month point rose to 84% (from

78% previously), and at 12 months it was 67% (up from 63%) (**Table 2**) [17].

In the larger group of 71 patients who experienced any overall response (OR), the median duration of response increased from 11.7 months reported at the interim stage to 15.5 months (95 percent CI: 7.4–26.2), spanning 0 to 54.6 months (**Table 2**) [17].

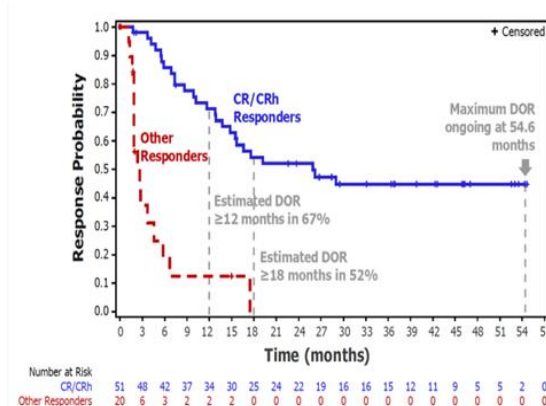


Figure 2. Duration of CR/CRh and other responses with olutasidenib. Abbreviations: CR = complete remission; CRh = complete remission with partial hematologic recovery; DOR = duration of response.

In the efficacy-evaluable group of 147 patients, the median overall survival (OS) was 11.5 months (95% CI: 8.3–15.5), with a range of 0.2 to 57.1 months. These results were in agreement with those from the prior interim evaluations (**Figure 3**) [15]. For the 51 patients who achieved CR or CRh, median OS had not been reached (95% CI: 22.8–NR), with individual survival durations extending from 6.3 to 57.1 months. In the 71 patients who attained any overall response (OR), median OS was 32.7 months (95% CI: 20.1–NR), ranging from 2.6 to 57.1 months.

A Cox proportional hazards regression analysis did not identify a meaningful association between time to response (TTR) and overall survival, whether examined across all responders or specifically in those with CR/CRh. Among the 16 patients who later underwent hematopoietic stem cell transplantation (HSCT), median OS was not reached. Kaplan-Meier estimates indicated that the 12-month survival rate in this HSCT group was 94% (95% CI: 63%–99%).

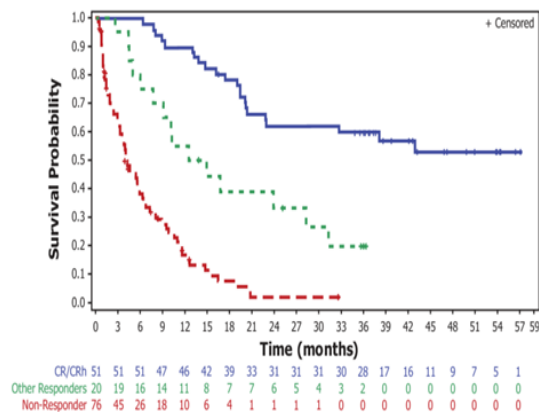


Figure 3. OS by responder status from date of first dose of olutasidenib to death from any cause.

Abbreviations: CR = complete remission; CRh = CR with partial hematologic recovery; OS = overall survival.

Response according to number of prior regimens

Among the 147 efficacy-evaluable participants, 93 had received 1 or 2 prior lines of therapy, and 54 had received 3 or more prior regimens. Median age was 72.0 years in the group with fewer prior treatments — comparable to the full efficacy population — while those with ≥ 3 prior regimens were younger on average (median 66.5 years). A larger share of the 1–2 prior regimens group had received hypomethylating agents beforehand (43% versus 33%). Venetoclax exposure was more common

among the heavily pretreated patients (11% versus 4%). 17 of the 54 patients (31%) in the ≥ 3 prior regimens category had a history of hematopoietic stem cell transplantation (HSCT).

Individuals with only 1–2 prior regimens showed improved outcomes: a CR/CRh rate of 41%, an ORR of 54%, and a median OS of 13 months. By contrast, patients with ≥ 3 prior regimens had a CR/CRh rate of 24%, ORR of 39%, and median OS of 8.9 months. Median CR/CRh duration was 25.3 months (range 1.8–54.3 months) in the 1–2 prior group and had not been reached in the ≥ 3 prior group. For patients who achieved an overall response, median DOR was 14.8 months in the 1–2 prior regimens group and 16.6 months in the ≥ 3 prior regimens group.

Response in patients with prior HSCT

The 17 patients who had received HSCT before study entry had an ORR of 29% ($n = 5$), including 2 patients (12%) with CR lasting 28.4 months and 6.4 months, respectively. The other three responders attained CRi. Two responding patients subsequently underwent a second HSCT procedure. These data should be viewed as exploratory given the restricted sample size.

Response in primary refractory patients

Post-hoc evaluation was performed in 45 patients (out of 147) who were classified as primary refractory. These patients failed to achieve CR with initial or subsequent induction treatments; eight had previously obtained a partial response (PR), but all progressed before olutasidenib initiation. Most (28/45; 62%) had only one prior regimen (overall range 1–4). Previous therapies included HMAs (25/45; 56%), cytarabine (23/45; 51%), cytarabine plus anthracycline (19/45; 42%), venetoclax regimens (3/45; 7% — two with HMA, one with cytarabine), and one allogeneic transplant (2%). In this group, the ORR was 51% (23/45; 95% CI: 35.8–66.3) with a median DOR of 6.7 months (95% CI: 3.7–17.6). CR occurred in 13 patients (29%; 95% CI: 16.4–44.3) and CR/CRh in 14 patients (31%; 95% CI: 18.2–46.6), with a median CR/CRh duration of 17.6 months (95% CI: 3.7–NR). Median OS was 8.9 months (95% CI: 5.4–13.8).

Response in post-venetoclax treatment

A total of 12 patients in the pivotal phase 2 cohort had prior venetoclax exposure, with a median duration of 6.7 months (range 2–34 months) before switching to

olutasidenib. The majority presented with intermediate or poor-risk cytogenetics (83%) and had multiple prior therapies (42% with ≥ 2 regimens). No one received venetoclax as a single agent. CR/CRh was observed in 4 of 12 patients (33%) after a median of 2.35 months (range 1–2.8 months). Kaplan-Meier analysis showed that 75% (95% CI: 13–96) of these responders maintained CR/CRh for at least 18 months. Overall response occurred in 6 patients (50%; 95% CI: 21.1–78.9). Median OS was 16.2 months (95% CI: 2.6–NR). At final analysis, three of the four CR/CRh responders remained on olutasidenib with ongoing responses, with treatment durations of 22.6, 36.9, and 50.6 months. One patient discontinued after 4.8 months in CR due to a Grade 4 liver function test abnormality. Results from this small subgroup are exploratory and should be interpreted cautiously until confirmed in larger trials.

Response in elderly patients

In the 45 patients aged 75 years and older, CR/CRh was achieved by 31 percent ($n = 14$), composite CR by 44% ($n = 20$), and ORR by 47% ($n = 21$; 95% CI 31.7–62.1). Median OS was 10 months (95% CI 4.1–14.7), and the probability of survival at 12 months was 44% (95% CI 30–57).

Hematologic analyses

At the final data cutoff, among all 153 safety population patients, 28 of 69 (41%) who received baseline platelet transfusions achieved transfusion independence for at least 56 days. Similarly, 34 of 87 (39%) patients dependent on red blood cell transfusions at baseline became independent for ≥ 56 days. Transfusion-dependent patients who attained CR/CRh showed particularly strong results, with 100% achieving platelet transfusion independence and 89% achieving red blood cell transfusion independence.

Mutational analyses

IDH1 mutation was centrally confirmed in all 147 efficacy-evaluable patients. No second-site IDH1 mutations were found at initial diagnosis, and none

developed during treatment in either refractory cases or patients who relapsed after initial response. ORR differed markedly by IDH1 variant: 26% (9/35) for R132H, 48 percent (13/27) for R132L/G/S, and 58 percent (49/85) for R132C. CR/CRh rates and response durability were superior for R132C (42% [36/85], 25.3 months) and R132L/G/S (33% [9/27], NR) compared with R132H (17% [6/35], 13.5 months). Excluding 19 R132H patients who also carried NPM1, FLT3, or TP53 co-mutations raised the CR/CRh rate to 31% for the remaining R132H cases. Data on co-mutations were missing for 33 patients. The most prevalent were NPM1 ($n = 39$), DNMT3A ($n = 35$), and ASXL1 ($n = 21$). Patients lacking any co-mutations ($n = 4$) had an ORR of 75%, while those with 4–7 co-mutations ($n = 19$) had the lowest ORR of 32%. Higher ORR was observed with JAK2 (4/7; 57%), ASXL1 (11/21; 52%), and DNMT3A (17/35; 49%) mutations. Patients with FLT3 mutations had an ORR of 31% (5/16), and those with TP53 mutations had an ORR of 40% (2/5). IDH1 mutation type significantly predicted response ($P = 0.0305$), with R132H associated with a lower probability of CR/CRh. Neither total co-mutation count nor specific co-mutations (NPM1, DNMT3A, ASXL1, FLT3, RUNX1, SRSF2) showed significant associations. In multivariate analysis, bone marrow blast percentage ($P < 0.0001$) and baseline transfusion independence ($P = 0.0019$) were significant predictors of CR/CRh. IDH1 mutation type and receptor tyrosine kinase pathway mutations were not. Although co-mutation number was not statistically significant, response rates tended to decline in patients with ≥ 4 co-mutations.

Safety

All 153 patients in the safety population experienced at least one treatment-emergent adverse event (TEAE). The incidence of TEAEs did not change significantly between the 3-year and 5-year follow-up periods, and no new safety signals emerged (**Table 4**). No additional patients discontinued treatment due to TEAEs during years 3 through 5.

Table 4. Treatment-emergent adverse events occurring in $\geq 20\%$ of patients through 5 years

Treatment-emergent adverse events (TEAEs)	Year 3 ($n = 153$) (n (%))	Year 5 ($n = 153$) (n (%))	Newly reported events by year 5, n
Nausea	58 (38)	59 (39)	1
Constipation	40 (26)	41 (27)	1
Decreased red blood cell count (RBC)	40 (26)	40 (26)	0

Increased white blood cell count (WBC)	38 (25)	38 (25)	0
Pyrexia	36 (24)	36 (24)	0
Fatigue	35 (23)	35 (23)	0
Febrile neutropenia	33 (22)	33 (22)	0
Hypokalemia	30 (20)	33 (22)	3
Diarrhea	31 (20)	32 (21)	1
Decreased platelet count	30 (20)	32 (21)	2
Dyspnea	31 (20)	31 (20)	0
Asthenia	25 (16)	30 (20)	5

Abbreviations: TEAEs = treatment-emergent adverse events; RBC = red blood cell; WBC = white blood cell.

As noted in prior reports, differentiation syndrome (DS) occurred in 21 patients (14%) through the 3-year follow-up [15]. No additional DS cases were documented between Years 3 and 5. Grade 3 DS affected 12 patients (8%), and a single patient experienced Grade 5 DS.

In the same way, 1 patient (1%) had a Grade 3 QT prolongation episode by Year 3 (deemed unrelated to the study drug) [15], and no further QT prolongation events occurred beyond Year 3.

Overall hepatotoxicity was seen in 35 patients (23%) across the full 5-year period, with a median onset of 32 days and a median resolution duration of 13 days (range, 0–1154 days). Grade 3/4 hepatotoxicity occurred in 20 patients (13%), leading to treatment discontinuation in 5 (3%). One additional hepatobiliary event—hepatic steatosis—emerged after Year 3.

Safety outcomes, analyzed by prior treatment lines in primary refractory patients and in those previously exposed to venetoclax, aligned closely with findings in the full study population, revealing no novel safety concerns. Notably, among older patients, Grade 3 or 4 adverse events occurred in 23/48 (48%) cases, and DS was observed in 3 patients (6.3%), reflecting a comparable tolerability profile to that in younger individuals.

This concluding 5-year evaluation of olutasidenib builds upon the earlier 3-year interim results, confirming its sustained effectiveness and acceptable safety in adults with relapsed/refractory (R/R) mutant IDH1 (mIDH1) acute myeloid leukemia (AML), even among those with extensive prior therapy. The complete response/complete response with partial hematologic recovery (CR/CRh) rate remained steady at 35%, with a median duration of 25.3 months. Critically, the absence of emerging safety issues underscores olutasidenib's value for extended clinical use.

Ivosidenib remains the sole other FDA-approved single-agent therapy for R/R mIDH1 AML [19]. Although both agents inhibit mutant IDH1, they possess different

molecular properties stemming from their unique chemical structures [20, 21]. Olutasidenib's smaller size and lower molecular weight allow it to occupy less volume in the IDH1 binding site, which may make it less prone to displacement by secondary IDH1 mutations [14, 20]. While both drugs potently suppress mutant IDH1, olutasidenib demonstrates strong selectivity exclusively for the mutant isoform and spares wild-type IDH1, in contrast to ivosidenib, which affects both mutant and wild-type forms [14, 20, 21]. These distinctions in structure and binding affinity could account for differences in selectivity, potency, and observed clinical performance between the two therapies [20].

Time-to-response (TTR) data indicated a median of 1.9 months to CR/CRh, yet certain patients needed as long as 6 months of therapy to reach CR/CRh and up to 10 months for any response. Importantly, TTR showed no association with overall survival (OS), including in those who attained CR/CRh. These observations align with and reinforce prescribing recommendations to maintain treatment for at least 6 months unless the disease progresses or intolerable toxicity arises, allowing sufficient time for therapeutic benefit [16].

Among responders, CR/CRh durations were generally prolonged irrespective of prior regimen count. Response rates were reduced in individuals with three or more previous lines of therapy, which may reflect a selection bias favoring patients especially responsive to the drug who then experience lasting remissions. Due to the limited sample size in this subset, these observations warrant cautious interpretation.

Findings from the pivotal cohort in this Phase 2 trial indicate that olutasidenib can deliver clinical benefits across a wide spectrum of adults with R/R mIDH1 AML, including those resistant to multiple earlier treatments, such as venetoclax-containing regimens. In the post-venetoclax context, therapeutic choices for mIDH1 R/R AML are restricted, often yielding very unfavorable results [22]. Most patients who initially respond

eventually relapse, and survival after relapse is particularly grim, with median OS reported at only 3.4 months [23]. An external real-world control analysis suggested superior performance with olutasidenib relative to ivosidenib among mIDH1 AML patients relapsed after venetoclax-based therapy, showing markedly better complete response rates (risk difference [RD]: 0.25; 95% CI: 0.01–0.49), transfusion independence (RD: 0.27; 95% CI: 0.01–0.53), and OS (hazard ratio: 0.33; 95% CI: 0.11–0.94) [24]. Although these outcomes favor olutasidenib, the modest cohort sizes (12 olutasidenib patients and 20—or 14 with stricter matching—ivosidenib patients) constrain definitive statistical inferences. This is consistent with earlier publications showing limited efficacy of ivosidenib in this setting [23, 25–27]. Collectively, the evidence supports further evaluation of olutasidenib in this challenging, high-risk group.

In the present trial, response rates (including CR/CRh) were higher in those receiving olutasidenib after 1 or 2 prior regimens than in those with 3 or more prior regimens, suggesting a possible advantage of using it earlier in the R/R phase. Prognosis following relapse after hematopoietic stem cell transplant (HSCT) is generally unfavorable, with long-term survival under 20% despite salvage approaches [28–30]. The 29% overall response rate (ORR) observed in the post-HSCT subgroup highlights olutasidenib's broad applicability, including in populations with historically limited options.

In addition to these difficult-to-treat categories, older adults with R/R mIDH1 AML—who frequently cannot endure intensive chemotherapy [31–33]—also exhibited clinically meaningful and persistent responses. Of particular importance, olutasidenib exhibited good tolerability in this elderly group, with safety characteristics mirroring those of the overall cohort, strengthening its suitability for this vulnerable population.

The analysis further examined how specific IDH1 mutation variants and the extent of co-mutations affected results. In keeping with previous studies, CR/CRh rates with olutasidenib were lower among patients harboring IDH1-R132H mutations than among those with other IDH1 variants [34–36]. Sustained responses were observed across various IDH1-R132 subtypes, especially in the absence of concurrent receptor tyrosine kinase mutations, which are associated with a worse prognosis [37, 38]. Efficacy appeared diminished in those with 4 or

more co-mutations, suggesting that greater genomic complexity might affect outcomes; however, multivariate modeling did not identify co-mutation count as a significant predictor of response. It is also noteworthy that some individuals with adverse co-mutations typically linked to inferior prognosis still achieved CR/CRh, including cases involving FLT3 and TP53 alterations [38, 39].

Olutasidenib's 5-year safety profile remained stable, with no novel signals observed compared with the 3-year interim data [13, 15]. In particular, the lack of additional DS cases through Year 5 indicates that incidence and severity remain consistent with reports on other IDH inhibitors [19, 40–42]. Likewise, the incidence of QT prolongation remained modest (8% across all grades by Year 3), and no new episodes occurred by Year 5, consistent with preclinical pharmacokinetic evidence showing plasma levels below the QTc prolongation threshold during treatment [16, 20]. Hepatotoxicity affected 23% of patients by Year 5, with only one new hepatobiliary event since the prior analysis, in accordance with labeling guidance on liver function monitoring and possible dose adjustments [16]. These patterns suggest hepatic events typically arise early and often involve asymptomatic lab changes. The consistent safety profile, including in heavily pretreated and elderly patients, supports olutasidenib's tolerability for patients needing ongoing disease management and its possible utility as a bridge to transplant when appropriate.

While the results are encouraging, certain limitations should be acknowledged. The single-arm study design restricts firm comparative interpretations. Moreover, although the data strengthen evidence of olutasidenib's lasting activity, additional investigations are required to better define optimal patient selection, treatment sequencing, and combination regimens; several such trials are in progress (e.g., NCT06668584, NCT06543381, NCT06782542, NCT06445959, NCT07032727). The post hoc nature of subgroup evaluations, modest sample sizes—especially for post-HSCT and post-venetoclax subsets—and variability in prior therapies introduce potential biases that warrant prospective confirmation in future studies.

Furthermore, although this trial offers detailed clinical insights, it does not address underlying molecular explanations for efficacy differences across IDH1 mutation subtypes or the link between hepatotoxicity and IDH1 blockade. Future preclinical and translational

studies will be valuable in clarifying these aspects of olutasidenib's profile.

Conclusion

This final 5-year review of olutasidenib offers the most thorough long-term evaluation of its performance and tolerability in adults with R/R mIDH1 AML. Sustained high CR/CRh rates, prolonged response durations, and stable survival benefits affirm its therapeutic value, including in elderly and heavily pretreated individuals. Crucially, the safety profile remained steady over time without new concerns, confirming its tolerability. These outcomes position olutasidenib as an essential therapy in this difficult-to-treat setting. Ongoing research building on these 5-year findings—particularly trials exploring combinations and sequencing—aims to refine patient selection and treatment strategies further to improve outcomes in this high-risk population.

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References

1. National Cancer Institute. Cancer stat facts: leukemia — acute myeloid leukemia (AML). 2025. <https://seer.cancer.gov/statfacts/html/amyl.html>; [accessed March 14, 2025].
2. De Botton S, Watts J, Baer M, Kye S, Schiller G, Yee K, et al. PS1051 FT-2102, an IDH1 m inhibitor, induces mutation clearance in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) treated in phase 1 dose escalation and expansion study. *HemaSphere*. 2019;3(S1):475-6.
3. DiNardo CD, Ravandi F, Agresta S, Konopleva M, Takahashi K, Kadia T, et al. Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML. *Am J Hematol*. 2015;90(8):732-6.
4. Gross S, Cairns RA, Minden MD, Driggers EM, Bittinger MA, Jang HG, et al. Cancer-associated metabolite 2-hydroxyglutarate accumulates in acute myelogenous leukemia with isocitrate dehydrogenase 1 and 2 mutations. *J Exp Med*. 2010;207(2):339-44.
5. Ward PS, Patel J, Wise DR, Abdel-Wahab O, Bennett BD, Collier HA, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell*. 2010;17(3):225-34.
6. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature*. 2009;462(7274):739-44.
7. McMurtry H, Fletcher L, Traer E. IDH inhibitors in AML—promise and pitfalls. *Curr Hematol Malig Rep*. 2021;16(2):207-17.
8. Sargas C, Ayala R, Chillón MC, Larráyo MJ, Bernal T, Rojas L, et al. Networking for advanced molecular diagnosis in acute myeloid leukemia patients is possible: the PETHEMA NGS-AML project. *Haematologica*. 2021;106(12):3079-89.
9. Paschka P, Schlenk RF, Gaidzik VI, Habdank M, Krönke J, Bullinger L, et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. *J Clin Oncol*. 2010;28(22):3636-43.
10. Marcucci G, Maharry K, Wu YZ, Radmacher MD, Mrózek K, Margeson D, et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. *J Clin Oncol*. 2010;28(14):2348-55.
11. Duchmann M, Micol JB, Duployez N, Raffoux E, Thomas X, Marceau-Renaut A, et al. Prognostic significance of concurrent gene mutations in intensively treated patients with IDH-mutated AML: an ALFA study. *Blood*. 2021;137(20):2827-37.
12. Dohner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373(12):1136-52.
13. Watts JM, Baer MR, Yang J, Prebet T, Lee S, Pigneux A, et al. Olutasidenib alone or with Azacitidine in IDH1-mutated acute myeloid leukaemia and myelodysplastic syndrome: phase 1 results of a phase 1/2 trial. *Lancet Haematol*. 2023;10(1):e46-58.
14. Caravella JA, Lin J, Diebold RB, Gokhale PC, Kattar S, Li X, et al. Structure-based design and

- identification of FT-2102 (olutasidenib), a potent mutant-selective IDH1 inhibitor. *J Med Chem.* 2020;63(4):1612-23.
15. de Botton S, Fenaux P, Yee KWL, Récher C, Wei AH, Montesinos P, et al. Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed or refractory IDH1-mutated AML. *Blood Adv.* 2023;7(13):3117-27.
 16. REZLIDHIA® (olutasidenib) capsules, for oral use [prescribing information]. South San Francisco, CA: Rigel Pharmaceuticals; April 2024.
 17. De Botton S, Récher C, Cortes J, Yee KWL, Fenaux P, Podoltsev N, et al. Olutasidenib demonstrates significant clinical activity in mutated IDH1 acute myeloid leukaemia arising from a prior myeloproliferative neoplasm. *Br J Haematol.* 2025;206(4):1121-8.
 18. Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol.* 2003;21(24):4642-9.
 19. TIBSOVO® (ivosidenib tablets), for oral use [prescribing information]. Boston, MA: Servier Pharmaceuticals LLC; October 2023.
 20. Watts JM, Shaw SJ, Jonas BA, Baer MR, de Botton S, Carvajal R, et al. Looking beyond the surface: Olutasidenib and Ivosidenib for treatment of mIDH1 acute myeloid leukemia. *Curr Treat Options Oncol.* 2024;25(11):1345-53.
 21. Popovici-Muller J, Lemieux RM, Artin E, Saunders JO, Salituro FG, Travins J, et al. Discovery of AG-120 (ivosidenib): a first-in-class mutant IDH1 inhibitor for the treatment of IDH1 mutant cancers. *ACS Med Chem Lett.* 2018;9(4):300-5.
 22. Maiti A, Rausch CR, Cortes JE, Pemmaraju N, Daver NG, Ravandi F, et al. Outcomes of relapsed or refractory acute myeloid leukemia after frontline hypomethylating agent and venetoclax regimens. *Haematologica.* 2021;106(3):894-8.
 23. Abaza Y, Winer ES, Murthy GSG, Hantel A, Pusic I, Stock W, et al. Clinical outcomes of hypomethylating agents plus venetoclax as frontline treatment in patients 75 years and older with acute myeloid leukemia: real-world data from eight US academic centers. *Am J Hematol.* 2024;99(4):606-14.
 24. Lai CE, Leahy TP, Turner AJ, Yuda S, Grunwald MR, Mariano MC, et al. Effectiveness of olutasidenib versus Ivosidenib in patients with mutated isocitrate dehydrogenase 1 acute myeloid leukemia who are relapsed or refractory to venetoclax: the 2102-HEM-101 trial versus a US electronic health record-based external control arm. *Leuk Lymphoma.* 2025;66(10):1821-32.
 25. Bewersdorf JP, Shallis RM, Derkach A, Vachhani P, Gowda L, Dembinski J, et al. Efficacy of FLT3 and IDH1/2 inhibitors in patients with acute myeloid leukemia previously treated with venetoclax. *Leuk Res.* 2022;122:106942.
 26. Khanna V, Azenkot T, Liu SQ, Young K, Saliman D, Osgood CL, et al. Outcomes with molecularly targeted agents as salvage therapy following frontline venetoclax + hypomethylating agent in adults with acute myeloid leukemia: a multicenter retrospective analysis. *Leuk Res.* 2023;131:107331.
 27. Abaza Y, McMahon C, Garcia JS, Michaelis LC, Olin RL, Agarwal S, et al. Advancements and challenges in the treatment of AML. *Am Soc Clin Oncol Educ Book.* 2024;44(3):e438662.
 28. Bejanyan N, Weisdorf DJ, Logan BR, Wang HL, Devine SM, de Lima M, et al. Survival of patients with acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: a center for international blood and marrow transplant research study. *Biol Blood Marrow Transplant.* 2015;21(3):454-9.
 29. Yerushalmi Y, Shem-Tov N, Danylesko I, Shouval R, Fein J, Shem-Tov Y, et al. Second hematopoietic stem cell transplantation as salvage therapy for relapsed acute myeloid leukemia/myelodysplastic syndromes after a first transplantation. *Haematologica.* 2023;108(7):1782-92.
 30. Lin CH, Chen TC, Shih YH, Tang JL, Tsay W, Yao M, et al. Acute myeloid leukemia relapse after allogeneic hematopoietic stem cell transplantation: a retrospective study from a single institution. *J Int Med Res.* 2022;50(2):3000605221078466.
 31. Niscola P, Gianfelici V, Catalano G, Tendas A, Cupelli L, Giordano G, et al. Acute myeloid leukemia in older patients: from new biological insights to targeted therapies. *Curr Oncol.* 2024;31(11):6632-58.
 32. Thol F, Heuser M. Treatment for relapsed/refractory acute myeloid leukemia. *Hemasphere.* 2021;5(6):e572.

33. Kantarjian H, Ravandi F, O'Brien S, Cortes J, Faderl S, Garcia-Manero G, et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. *Blood*. 2010;116(22):4422-9.
34. Wang ES, Jonas BA, Watts JM, Fathi AT, Wei AH, Baer MR, et al. Factors impacting response to olutasidenib in patients with mIDH1 acute myeloid leukemia [abstract]. *Blood*. 2023;142(Suppl 1):6047.
35. De Botton S, Yee K, Recher C, Wei AH, Fenaux P, Montesinos P, et al. Molecular characteristics of response to olutasidenib (FT-2102) in patients with relapsed/refractory mIDH1 acute myeloid leukemia [abstract]. *Blood*. 2021;138(suppl 1):2351.
36. Watts JM, Patel PA, Choe S, Bai X, Marchione DM, Stein EM, et al. Clinical and molecular characteristics of patients with AML with an exceptional response to Ivosidenib [abstract]. *J Clin Oncol*. 2023;41(suppl 16):7036.
37. Fleischmann M, Schnetzke U, Schrenk KG, Schmidt V, Sayer HG, Hilgendorf I, et al. Outcome of FLT3-ITD-positive acute myeloid leukemia: impact of allogeneic stem cell transplantation and tyrosine kinase inhibitor treatment. *J Cancer Res Clin Oncol*. 2017;143(2):337-45.
38. Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. *Blood*. 2001;98(6):1752-9.
39. Shin DY. TP53 mutation in acute myeloid leukemia: an old foe revisited. *Cancers (Basel)*. 2023;15(19):4816.
40. DiNardo CD, Stein EM, de Botton S, Altman JK, Collins R, Flinn IW, et al. Durable remissions with Ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-98.
41. Fathi AT, DiNardo CD, Kline I, Kenvin L, Gupta I, Attar EC, et al. Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2: analysis of a phase 1/2 study. *JAMA Oncol*. 2018;4(8):1106-10.
42. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130(6):722-31.