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RESEARCH

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Olutasidenib for mutated *IDH1* acute myeloid leukemia: final five-year results from the phase 2 pivotal cohort

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Abstract

Background Olutasidenib is an oral, selective inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1), FDA-approved for relapsed/refractory (R/R) acute myeloid leukemia (AML) based on a registrational, phase 2, open-label, multicenter trial.

Methods Results from the pre-planned interim analysis were previously published (data cut-off [DCO]: June 2021). In this final-follow up analysis, we report an additional 2 years of efficacy and safety data (DCO: June 2023).

Results At study completion, the overall population included 153 patients (median age, 71 years); 66% had received ≥ 2 prior treatment regimens, and 39% with a hypomethylating agent. Among the 147 efficacy-evaluable patients, 51 achieved complete remission (CR) or CR with partial hematologic recovery (CRh), resulting in a CR/CRh rate of 35% ($P < 0.001$; 95% CI, 27–43), with 32% of responders achieving CR. The median time to CR/CRh was 1.9 months (range, 0.9–5.6 months). Among responders, 33% achieved CR/CRh within 2–4 months and 12% required ≥ 4 months. The overall response rate (ORR) was 48% ($n = 71$; 95% CI, 40–56.7). Median duration of CR/CRh was 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 with 1–2 prior regimens had a higher CR/CRh rate (41%) and longer median OS (13 months) than those with ≥ 3 prior regimens (CR/CRh: 24%; median OS: 8.9 months). CR/CRh rates were higher among patients with R132C (42%) and R132L/G/S mutations (33%) compared with those harboring R132H mutations (17%). Response rates decreased with increasing numbers of co-mutations. Few new adverse events (AEs) and no treatment discontinuations due to AEs occurred beyond Year 3.

Conclusion These 5-year data support the durable efficacy and manageable safety profile of olutasidenib in R/R m*IDH1* AML, including heavily pretreated patients. Findings highlight the potential role of olutasidenib in earlier lines of treatment, and support sustaining therapy for at least 6 months to allow for a clinical response. Further research is warranted to optimize treatment sequencing and patient selection.

Trial registration NCT02719574.

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

Introduction

Acute myeloid leukemia (AML) is the most common type of acute adult leukemia, accounting for approximately 80% of all cases [1]. Despite advances in treatment, prognosis remains poor, with a 5-year relative survival rate of 32.9% [1]. Among patients aged ≥ 65 years, outcomes are even worse, with a 5-year relative survival rate of 10.5%, underscoring the ongoing need for novel therapeutic strategies [1].

Mutations in isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) enzymes are key drivers in AML, occurring in about 20% of cases, with *IDH1* mutations present in 7% to 14% of patients [2–4]. These mutations lead to the production of 2-hydroxyglutarate, an oncometabolite that disrupts epigenetic regulation and blocks cellular differentiation, driving disease progression [5–7]. *IDH1* mutations in AML are associated with older age and, in some but not all studies, a poorer prognosis [3, 8–12].

Olutasidenib is a potent, selective, oral inhibitor of mutant IDH1 (mIDH1), which binds and inhibits single- and double-mutated IDH1 variants, while retaining essential wild-type IDH1 function (e.g., key roles in metabolism, epigenetics, differentiation, DNA repair, redox states) [13, 14]. In the United States, olutasidenib is approved for patients with relapsed/refractory (R/R) AML with a detected *IDH1* mutation based on the results from a phase 2 trial (ClinicalTrials.gov identifier: NCT02719574) [15, 16]. In the pre-planned interim analysis of the pivotal registrational cohort (N = 153; efficacy-evaluable population: n = 147), olutasidenib monotherapy induced complete remission (CR) or CR with partial hematologic recovery (CRh) in 35% (95% confidence interval [CI], 27–43) of patients, with a median duration of CR/CRh of 25.9 months (95% CI, 13.5–not evaluable [NE]) (data cut-off [DCO]: June 18, 2021) [17]. The overall response rate (ORR) was 48% (n = 71; 95% CI, 40–56.7.7), with a median duration of response (DOR) of 11.7 months (95% CI, 6.9–25.9). Febrile neutropenia and anemia (both 20%) were the most frequently reported Grade 3 or 4 treatment-emergent adverse events (TEAEs) [13, 17]. Differentiation syndrome occurred in 14% of patients, with Grade ≥ 3 events in 9%, including one fatality. Hepatic adverse events were reported in 25% of patients, though most were reversible and did not lead to liver failure [17]. Herein, we present the final 5-year results (DCO: June 15, 2023) from this pivotal cohort, which includes an additional 2 years of data since the interim analysis, offering long-term insights into the efficacy and safety of olutasidenib in m*IDH1* AML.

Materials and methods

Study design and patient population

Study 2102-HEM-101 was an open-label, multicenter, phase 1/2 trial in adults aged 18 years and older. Trial design details and outcome measures have been previously published [13, 15]. The full study was conducted across 57 centers in 9 countries. Phase 2 included multiple cohorts of patients with AML and myelodysplastic syndrome. In brief, eligible patients in the pivotal, registrational cohort harbored m$IDH1^{R132}$ (central laboratory confirmed) pathologically proven AML, R/R to standard treatment. Patients had Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2, adequate liver and renal function, and QT interval corrected using Fridericia's formula (QTcF) ≤ 450 milliseconds. Patients with symptomatic central nervous system leukemia, uncontrolled infections or metabolic disorders, and/or prior IDH inhibitor therapy were excluded.

Olutasidenib was administered orally at the recommended phase 2 dose of 150 mg as monotherapy, twice daily, in continuous 28-day cycles until disease progression, unacceptable toxicity, or hematopoietic stem cell transplantation (HSCT). Patients in phase 2 were followed for survival for up to 36 months from Cycle 1 Day 1, or for 28 days after treatment discontinuation (whichever was longer).

Ethics

The study was approved by independent institutional review boards of each participating site and was conducted in accordance with the ethics principles of the Declaration of Helsinki and with Good Clinical Practice guidelines defined by the International Conference on Harmonization. All patients provided written informed consent.

Endpoints and assessments

The primary efficacy endpoint was the rate of CR—including cytogenetic CR and molecular CR—plus CRh, by investigator assessment, using modified response criteria of the International Working Group in AML [18]. CRh was defined as bone marrow blasts < 5% with an absolute neutrophil count > 0.5 × 10^9/L and a platelet count > 50 × 10^9/L. Secondary endpoints included the ORR, defined as the proportion of patients achieving CR, CRh, CR with incomplete blood count recovery (CRi), partial remission (requiring neutrophil and platelet recovery consistent with CR), or morphologic leukemia-free state (MLFS). Additional secondary endpoints included the duration of CR/CRh, DOR, rate of transfusion independence (TI), and overall survival (OS).

At baseline patients were classified by the investigator as transfusion-dependent if they received ≥ 1 platelet and/or ≥ 1 red blood cell transfusion within 56 days (8 weeks) prior to the first dose of olutasidenib (classified as platelet dependent, red blood cell dependent, or both). Patients were considered transfusion-independent if they remained free from platelet and/or red blood cell transfusions for at least 56 consecutive days during treatment.

Response was assessed using bone marrow aspirates/peripheral blood, which were collected at screening, on Day 1 of each 28-day cycle starting with Cycle 2, and then every other cycle starting with Cycle 5. Time to response (TTR) was measured from Day 1 of treatment to the first day on which a qualifying response was observed. DOR was measured from the first documented response until death, relapse, or initiation of new anticancer therapy, with patients without an event censored at their last response assessment. For OS analysis, patient data were censored at the last known date of survival.

Bone marrow and peripheral blood samples were collected during screening (prior to Cycle 1 Day 1), and at each timepoint when bone marrow aspirates or biopsies were obtained, for exploratory genomic analyses of cancer-associated mutations and genetic alterations, including *IDH1* variant allele frequency (VAF) and co-mutations. DNA for mutational analyses was extracted from peripheral whole blood and plasma collected in PAXGene® tubes. Blood genomic DNA (gDNA) was isolated using the Maxwell® RSC Blood DNA Kit on the Maxwell® RSC Instrument (Promega, Madison, WI, USA), according to the manufacturer's instructions. The yield of gDNA was assessed using the Qubit™ dsDNA Broad Range Assay Kits (Invitrogen–Thermo Fisher Scientific). *IDH1* mutant allele frequencies were quantified using droplet digital polymerase chain reaction. As a positive control, wild-type and mutant exon 4 fragments of the *IDH1* gene were cloned into the shuttle vector pCRII-TOPO and used as template DNA. The target sequence comprised the terminal 135 bp of exon 4 and 92 bp of the adjacent intron 5 from wild-type 5 mutated DNA samples: *IDH1* R132C (c.394C > T), R132G (c.394C > G), R132S (c.394C > A), R132H (c.395G > A), and R132L (c.395G > T). In this assay, the limit of detection was calculated as the proportion of the minimum number of droplets considered positive (threshold = 3 droplets) relative to the mean number of droplets. For gDNA, the limit of detection was 0.12% ($n = 146$, mean: 2,479 ± 1,055 droplets; median: 2,412; range: 241-9,187). VAF data were based on > 20,000 droplets with a limit of sensitivity of 0.1%. Co-mutations were assessed using next-generation sequencing. Target enrichment was performed using the HaloPlex® system (Agilent®, Santa Clara, CA), followed by Illumina® sequencing with a custom 74-gene myeloid panel, achieving > 100× coverage across the panel. The minimum sequencing depth across the broader gene panel was 100x, while coverage of *IDH1* specifically exceeded 500x. This provided sensitivity to detect variants present at ~ 1% VAF with support from ≥ 5 variant reads. Concordance analyses between next-generation sequencing and droplet digital polymerase chain reaction demonstrated high agreement in VAFs, confirming the robustness of variant detection.

Safety data were summarized descriptively for all patients who received at least one dose of olutasidenib. Adverse events (AEs) were documented from the first dose through 28 days after the last dose and were coded using MedDRA version 19.1 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Statistical analyses

Efficacy results presented here are an updated analysis of the key efficacy outcomes since the prior interim analysis. The efficacy-evaluable set, which includes all patients who received the first dose of olutasidenib ≥ 6 months before the analysis cutoff date, was the primary set for efficacy evaluations.

To test the null hypothesis that the CR/CRh rate was ≤ 15% versus 1-sided alternative hypothesis that the CR/CRh rate was > 15%, a 1-sided exact test for a binomial proportion was performed. If the exact 1-sided p-value was < 0.025, the alternative hypothesis was accepted. The number and proportion of patients achieving CR/CRh response are reported from the binomial proportion, together with the Clopper-Pearson 95% CI. Analysis of DOR, TTR, and OS were based on Kaplan-Meier (KM) methods. OS and TTR were measured from the first dose to the event.

Prespecified clinical and genomic variables were screened in a univariate logistic regression analysis for association with CR/CRh, and significant variables were included in a multivariate analysis using backward selection. Candidate variables were: cytogenetic risk classification; AML disease state (relapsed vs. refractory); AML type (primary vs. secondary); age in years (continuous) and categorized (< 65, 65–< 75, ≥ 75 years); *IDH1* mutation type; sex; ECOG performance status; bone marrow blast percentage (< 20%, 20%–40%, > 40%–60%, > 60%); prior HMA exposure (yes/no); prior HSCT (yes/no); renal function (normal, mild impairment, moderate impairment); prior venetoclax exposure (yes/no); number of prior therapies (1–2 vs. ≥ 3); transfusion independence at baseline (yes/no); number of co-mutations (continuous); co-mutation category (0, 1–3, 4–7); individual mutations present in ≥ 10 patients (yes/no); and pathway-level categories (chromatin, differentiation, epigenetics, receptor tyrosine kinase, and splicing).

Results

Patient characteristics and treatment course

Between April 2018 and June 2020, a total of 153 patients with m*IDH1* R/R AML, median age of 71 years (range, 32–89 years), were enrolled and received at least 1 dose of olutasidenib (150 mg, twice daily) (Supplemental Fig. 1). Of these, 147 had m*IDH1* confirmed by central laboratory testing and comprised the efficacy-evaluable population; 6 patients were excluded from efficacy analyses due to lack of central confirmation. Patients ($N = 153$) had received a median of 2 prior regimens (range, 1–7 regimens). Per eligibility criteria, all patients had received prior chemotherapy, and 109/153 (71%) had received prior cytarabine. In addition, 60 (39%) had prior treatment with a hypomethylating agent (HMA), and 12 (8%) had prior treatment with venetoclax. Of those 12, 8 (67%) received venetoclax in combination with an HMA (including 1 [8%] patient who initially received HMA alone before starting venetoclax and 2 [17%] who received prior single-agent HMA separately from venetoclax), 3 (25%) with cytarabine, and 1 (8.3%) with dinaciclib. No patient had received prior IDH1 inhibitor therapy. Patient and disease characteristics are summarized in Table 1.

At final DCO (June 15, 2023), 10 of 153 patients (7%) remained on treatment and 143 (93%) had discontinued. The most common reasons for discontinuation were disease progression ($n = 63$; 41%), AE ($n = 27$; 18%), HSCT ($n = 15$; 10%), and death ($n = 14$; 9%). Median treatment duration was 142 days (range, 3–1737 days).

Response

In the efficacy-evaluable population ($n = 147$), 51 patients achieved a CR/CRh for a rate of 35% ($P < 0.0001$; 95% CI, 27–43 (Table 2)), which did not change from the interim analysis. The ORR was 48% ($n = 71$; 95% CI, 40–56.7) (Table 2), also consistent with the interim analysis. Of the 147 patients, 16 (11 in CR; 1 in CRh; 3 in CRi; and 1 in stable disease [SD]) subsequently underwent HSCT following olutasidenib treatment.

Among the 147 efficacy-evaluable patients, 55% (28/51) of those who met the primary endpoint responded within 2 months. The median TTR in the 51 patients achieving CR/CRh was 1.9 months (range, 0.9–5.6 months) (Table 2), with 33% of patients requiring 2 to 4 months and 12% requiring at least 4 to achieve CR/CRh (Table 3). Among the 71 (48%) patients who achieved an overall response (OR), the median TTR was also 1.9 months (range, 0.9–10.2 months) (Fig. 1), with 66% of patients achieving an OR within 2 months. However, 24% of patients required 2 to 4 months to respond and 10% required more than 4 months (up to 10.2) months of therapy to achieve an OR (Table 3).

Among the 51 patients who achieved CR/CRh, the median duration of response was 25.3 months (95% CI, 13.5–not reached [NR]; range, 1.8–54.6 months), with 49% (25/51) of patients censored (Table 2; Fig. 2). This compares to a reported median duration of CR/CRh of 25.9 months in the interim analysis [15, 16]. The KM-estimated percentages of patients maintaining CR/CRh at 6 and 12 months increased from 78% to 63% in the interim analysis to 84% and 67% (Table 2) [17]. Among the 71 patients who achieved an OR, the median duration

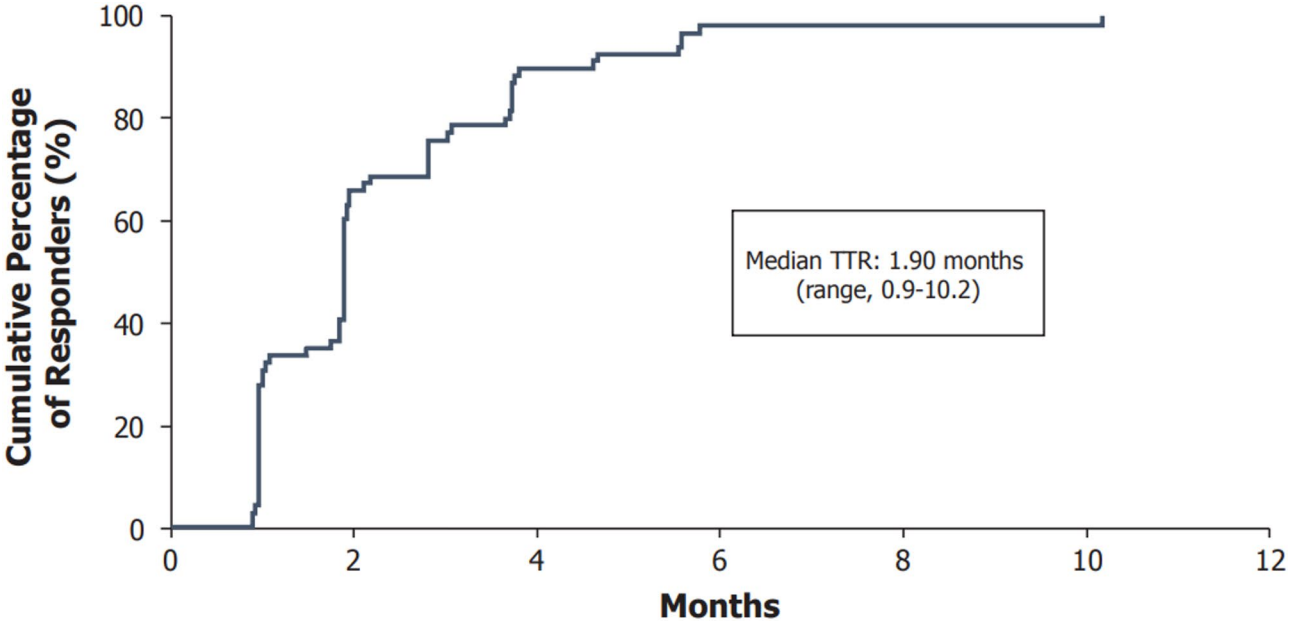

Fig. 1 Time to Overall Response With Olutasidenib. N = 71 patients who achieved a response. TTR, time to response

Table 1 Baseline demographics and disease characteristics

Pivotal Cohort	***N*** **= 153**
Median age, years (range)	71 (32–89)
Female, n (%)	74 (48)
ECOG Performance Status[a], n (%)	
0	53 (35)
1	71 (46)
2	28 (18)
AML type, n (%)	
Primary	99 (65)
Secondary	54 (35)
Duration of AML, months, median (range)	12.7 (0.7–151.5)
Disease status, n (%)	
Refractory[b]	53 (35)
Relapsed	100 (65)
Bone marrow blasts, %, median (range)	40 (4, 98)
Prior number of regimens, n (%)	
1	52 (34)
2	47 (31)
≥ 3	54 (35)
Prior regimens, n (%)	
Hypomethylating agent[c]	60 (39)
Cytarabine	109 (71)
Venetoclax	12 (8)
Hypomethylating agent[c] + venetoclax	8 (5)
Venetoclax + cytarabine	3 (2)
Venetoclax + dinaciclib	1 (2)
Allogenic stem cell transplant	17 (11)

[a]Data unavailable for 1 patient

[b]Refractory status in Table 1 is based on the safety population (*N* = 153). The figure reported in the text (45/147) reflects the number of primary refractory patients within the efficacy population used for post-hoc analyses

[c]Azacitidine, decitabine, or guandecitabine

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

Table 2 Summary of response and duration of response with olutasidenib

Efficacy-Evaluable Population	***n*** **= 147**
Primary endpoint: CR/CRh, n (%)[a]	51 (35%) (*P* < 0.0001; 95% CI, 27–43)
Time to CR/CRh, months, median (range)	1.9 (0.9–5.6)
Duration of CR/CRh, months, median (95% CI)	25.3 (13.5–NR)
Estimated % of patients with CR/CRh lasting at least:	
CR/CRh ≥ 6 months, % (95% CI)	84 (70–92)
CR/CRh ≥ 12 months, % (95% CI)	67 (52–78)
CR/CRh ≥ 18 months, % (95% CI)	52 (37–65)
Best overall response, n (%)	71 (48)
CR	47 (32)
Time to CR, months, median (range)	2.8 (0.9–7.4)
Duration of CR, months, median (range)	25.3 (0–54.6)
CRh	4 (3)
CRi	15 (10)
Composite CR (CR, CRh, CRi), n (%)	66 (45)
PR	3 (2)
MLFS	2 (1)
Overall response rate[b] (ORR), n (%)	71 (48)
DOR, months, median (95% CI)	15.5 (7.4–26.2)
Estimated % of patients with ORR lasting:	
≥6 months, % (95% CI)	69 (56–78)
≥12 months, % (95% CI)	56 (44–67)
≥18 months, % (95% CI)	42 (30–53)

[a]*P* value is from a 1-sided exact binomial test of the null hypothesis that CR/CRh ≤ 15%

[b]Defined as the proportion of patients achieving CR, CRh, CRi, PR (requiring neutrophil and platelet recovery consistent with CR), or MLFS

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 response increased from 11.7 months in the interim analysis to 15.5 months (95% CI, 7.4–26.2; range, 0–54.6 months) (Table 2) [17].

Median OS in the efficacy evaluable population (n = 147) was 11.5 months (95% CI, 8.3–15.5; range, 0.2–57.1 months), consistent with the interim analyses (Fig. 3) [15]. In the 51 patients achieving CR/CRh, median OS was NR (95%, CI, 22.8–NR; range, 6.3–57.1 months). Among the 71 patients achieving OR, the median OS was 32.7 months (95% CI, 20.1–NR; range, 2.6–57.1 months) (Supplemental Fig. 2). A Cox regression model showed no significant association between TTR and OS in the overall responders and those with a CR/CRh response. Among the 16 patients who proceeded to HSCT, the median OS was NR. The KM-estimated probability of survival at 12 months post-treatment for these 16 patients was 94% (95% CI, 63–99).

Response by number of prior regimens

Of the 147 patients in the efficacy-evaluable population, 93 received 1–2 prior regimens and 54 received ≥ 3 prior regimens (Supplemental Table 1). The median age was 72.0 years in the 1–2 prior regimens group, aligning with the efficacy-evaluable population, while the ≥ 3 prior regimens group had a notably lower median age of 66.5 years. Prior exposure to HMAs was more frequent in the 1–2 prior regimens group than in the ≥ 3 prior regimens group (43% vs. 33%, respectively), while venetoclax exposure was higher in the ≥ 3 prior regimens group (11% vs. 4%). Of the 54 patients who received ≥ 3 prior regimens, 17 (31%) had been treated with prior HSCT.

Patients with 1–2 prior regimens had a higher CR/CRh rate (41%), ORR (54%), and longer median OS (13 months) compared to those with ≥ 3 prior regimens (CR/CRh: 24%; ORR: 39%; median OS: 8.9 months). Median duration of CR/CRh was 25.3 months (range, 1.8–54.3

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

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

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

months) for 1–2 prior regimens, but NR for ≥ 3 prior regimens. Of those who achieved an overall response, the median DOR was 14.8 months for patients with 1–2 prior regimens and 16.6 months for those with ≥ 3 prior regimens.

Response in patients with prior HSCT

The ORR in the 17 patients with prior HSCT was 29% (*n* = 5), including 12% (*n* = 2) with CR; duration of CR was 28.4 and 6.4 months. The other 3 patients with a response achieved a CRi. Two patients with a response following olutasidenib therapy went on to undergo a second HSCT. Given the small sample size, these results should be considered exploratory.

Response in primary refractory patients

A post-hoc analysis was conducted on a subset of patients in the pivotal cohort (45/147) who were primary refractory, defined as patients who did not achieve a CR in response to first-line or any subsequent induction therapy; 8 patients in this sub-population achieved a PR in response to prior lines of therapy and all others had no prior response. All patients with prior PR progressed before starting olutasidenib on study. Most patients received 1 prior treatment regimen (28/45; 62%; range, 1–4 regimens). Prior treatments included HMA (25/45; 56%), cytarabine (23/45 51%), cytarabine plus anthracycline (19/45; 42%), venetoclax-based regimens (3/45; 7%, 2 combined with HMA, 1 combined with cytarabine), and allogeneic stem cell transplant (1/45; 2%). 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 was achieved 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 duration of CR/CRh of 17.6 months (95% CI, 3.7–NR). The median OS was 8.9 months (95% CI, 5.4–13.8).

Response in post-venetoclax treatment

Twelve of 147 patients from the phase 2 study pivotal cohort were previously treated with venetoclax for a median of 6.7 months (range, 2–34 months) prior to treatment with olutasidenib. Most patients had intermediate or poor cytogenetics (83%) and were heavily pretreated (42% with 2 or more prior regimens). No patient received venetoclax as monotherapy (see Baseline Characteristics for regimen details). CR/CRh was achieved in 4/12 post-venetoclax patients (33%) (Supplemental Table 2), with median time to CR/CRh of 2.35 months (range, 1–2.8 months). Among these responders, the KM estimated proportion with CR/CRh lasting at least 18 months was 75% (95% CI, 13–96). OR was achieved in 6 patients (50%; 95% CI, 21.1–78.9). Median OS was 16.2 months (95% CI, 2.6–NR). At the end of the study, 3 of the 4 patients who achieved CR/CRh were still in CR or CRh and continued treatment with olutasidenib, with treatment durations of 22.6, 36.9, and 50.6 months. One patient discontinued treatment after 4.8 months of CR due to Grade 4 abnormal liver function test. Given the small number of patients in this subgroup, these findings should be considered exploratory and interpreted with caution pending confirmation in larger studies.

Response in elderly patients

In patients ≥ 75 years (*n* = 45), CR/CRh was achieved in 31% (*n* = 14), composite CR in 44% (*n* = 20), and ORR was 47% (*n* = 21; 95% CI, 31.7–62.1) (Supplemental Fig. 3). The median OS was 10 months (95% CI, 4.1–14.7) with a 12-month survival probability of 44% (95% CI, 30–57) (Supplemental Fig. 4).

Hematologic analyses

At final DCO in the overall population (*N* = 153), platelet transfusion independence (≥ 56 days) was achieved in 28 of 69 (41%) patients who were dependent at baseline. Red blood cell transfusion independence (≥ 56 days) was achieved in 34 of 87 (39%) patients who were dependent at baseline (Supplemental Fig. 5). A high rate of

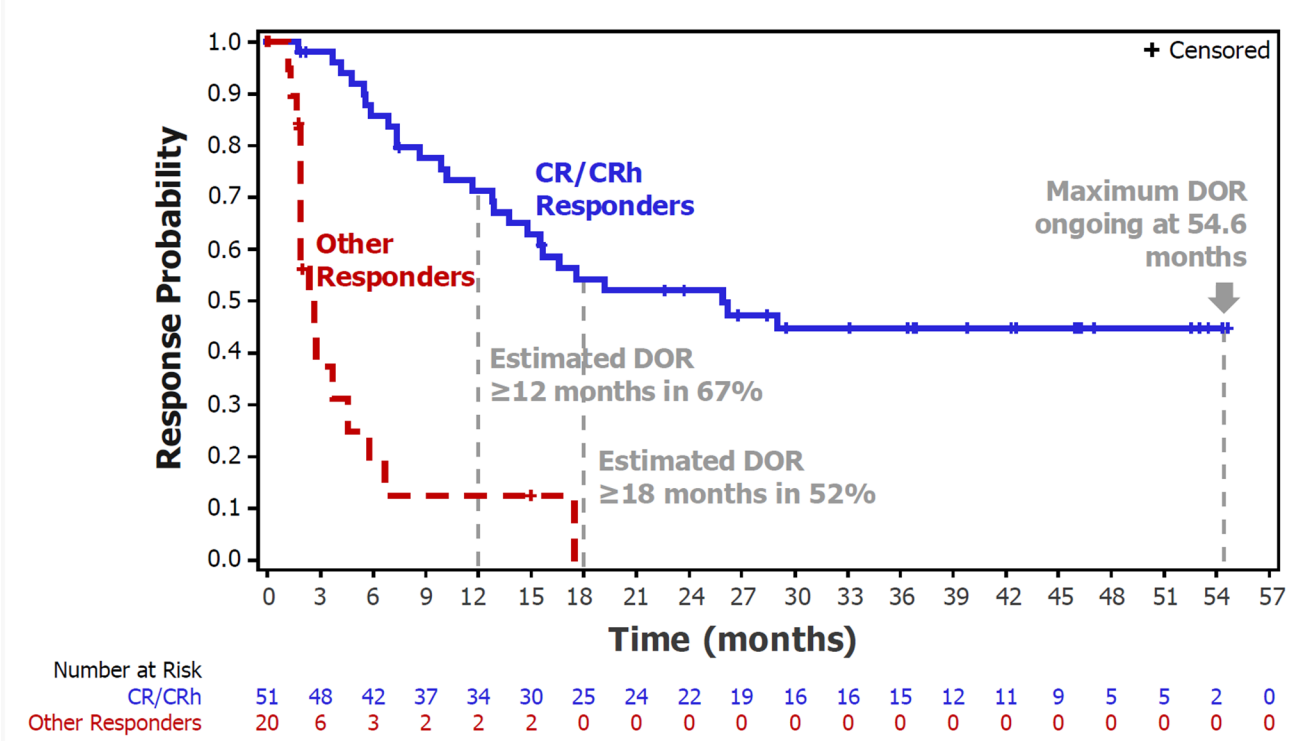

Fig. 2 Duration of CR/CRh and Other Response With Olutasidenib. CR, complete remission; CRh, complete remission with partial hematologic recovery; DOR, duration of response

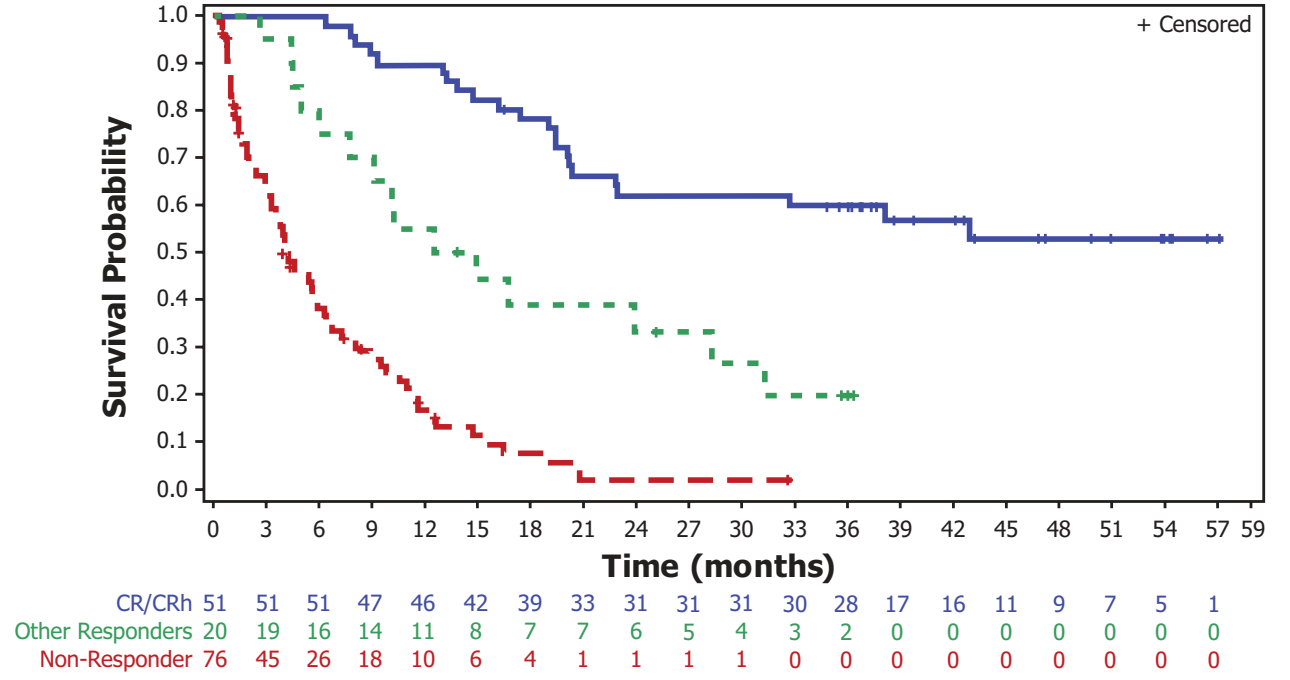

Fig. 3 OS by Responder Status From Date of First Dose of Olutasidenib to Death From Any Cause. CR, complete remission; CRh, CR with partial hematologic recovery; OS, overall survival

transfusion independence was observed among patients who were transfusion dependent at baseline and achieved CR/CRh, with 100% achieving platelet transfusion independence and 89% achieving red blood cell transfusion independence.

Mutational analyses

Central analysis confirmation of *IDH1* mutation was available for 147 patients. No second-site *IDH1* mutations were detected at the time of initial diagnosis in this phase 2 cohort. In addition, no acquired second-site *IDH1* mutations were identified upon disease reassessment either among patients refractory to olutasidenib or among those who initially responded and subsequently relapsed. ORR varied by *IDH1* mutation type: 26% (9/35) for those with R132H, 48% (13/27) for R132L/G/S, and 58% (49/85) for R132C. The CR/CRh rates and duration of CR/CRh were higher in patients with R132C (42% [36/85] and 25.3 months, respectively), R132L/G/S (33% [9/27] and NR, respectively), compared to those with R132H mutations (17% [6/35] and 13.5 months, respectively) (Supplemental Table 3). However, the CR/CRh rate increased to 31% when 19 R132H patients with *NPM1*, *FLT3*, or *TP53* co-mutations were excluded. The most common co-mutations, each observed in at least 3 patients, are detailed in Supplemental Fig. 6. Co-mutation data was not reported in 33 patients. Among these, *NPM1* ($n=39$), *DNMT3A* ($n=35$), and *ASXL1* ($n=21$) were the most frequently identified (Supplemental Table 4). Patients with no co-mutations ($n=4$) had the highest ORR at 75%, while those with 4 to 7 ($n=19$) co-mutations had the lowest at 32% (Supplemental Table 3). ORR was highest in patients with *JAK2* (4/7; 57%), *ASXL1* (11/21; 52%), or *DNMT3A* (17/35; 49%) (Supplemental Table 4). Among patients with *FLT3* or mutated *TP53*, ORR was 31% (5/16) and 40% (2/5), respectively. Supplemental Fig. 7 shows the univariate analysis for CR/CRh by mutational variables. *IDH1* mutation type was a significant predictor of response ($P=0.0305$), with patients harboring the R132H variant being less likely to achieve CR/CRh. Neither the number of co-mutations nor the presence of specific co-mutations, including *NPM1*, *DNMT3A*, *ASXL1*, *FLT3*, *RUNX1*, or *SRSF2*, was significantly associated with response. In a multivariate analysis, bone marrow blast percentage ($P<0.0001$) and transfusion independence at study entry ($P=0.0019$) were significant factors on achievement of CR/CRh. *IDH1* mutation type and presence of receptor tyrosine kinase pathway gene mutation were not significant. In addition, while the number of co-mutations was not significantly associated with response, there was a trend toward lower response rates in patients with ≥4 co-mutations compared to those with fewer co-mutations.

Table 4 Individual TEAEs reported in ≥ 20% of patients at 5 years

TEAEs	By Year 3 (*N* = 153) *n* (%)	By Year 5 (*N* = 153) *n* (%)	New Events by Year 5, *n*
Nausea	58 (38)	59 (39)	1
Constipation	40 (26)	41 (27)	1
RBC count decreased	40 (26)	40 (26)	0
WBC count increased	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
Platelet count decreased	30 (20)	32 (21)	2
Dyspnea	31 (20)	31 (20)	0
Asthenia	25 (16)	30 (20)	5

RBC, red blood cell; TEAEs, treatment emergent adverse events; WBC, white blood cell

Safety

At least one treatment-emergent adverse event (TEAE) was reported in all 153 patients in the safety population. The overall rate of TEAEs remained consistent over the 3-year and 5-year periods, with no new safety signals identified (Table 4). No additional patients discontinued treatment due to TEAEs between Years 3 and 5.

As previously reported, differentiation syndrome (DS) was observed in 21 patients (14%) by Year 3 [15]. No new DS events were reported from Year 3 to Year 5. Grade 3 DS was reported in 12 patients (8%), and Grade 5 DS was reported in 1 patient.

Similarly, as previously reported, one patient (1%) experienced a Grade 3 QT prolongation event by Year 3 (considered unrelated to study treatment) [15], with no new cases of QT prolongation reported after Year 3.

Aggregated hepatotoxicity was reported in 35 patients (23%) over the 5-year period, with a median time to onset of 32 days and a median resolution time of 13 days (range, 0–1154 days). Grade 3/4 hepatotoxicity occurred in 20 patients (13%), leading to treatment discontinuation in 5 patients (3%). One new hepatobiliary AE, hepatic steatosis, was reported after Year 3.

When evaluating safety by number of prior regimens in primary refractory patients and post-venetoclax patients, results were consistent with the overall population, with no new safety signals identified. Of note, in elderly patients, Grade 3 or 4 AEs were reported in 23/48 (48%) patients and differentiation syndrome occurred in 3 (6.3%) patients, indicating a similar safety profile to that observed in younger patients.

Discussion

This final 5-year analysis of olutasidenib extends the previous 3-year interim findings, reinforcing its durable efficacy and manageable safety in adults with R/R m*IDH1* AML, including heavily pretreated patients. The CR/CRh rate remained consistent at 35%, with a median duration of 25.3 months. Importantly, no new safety signals emerged, supporting olutasidenib's long-term clinical utility.

Ivosidenib remains the only other FDA-approved monotherapy for R/R m*IDH1* AML [19]. While both olutasidenib and ivosidenib target IDH1, they differ in molecular characteristics due to distinct chemical structures [20, 21]. Olutasidenib is smaller and has a lower molecular weight than ivosidenib enabling it to occupy less space within the IDH1 binding pocket, potentially reducing its susceptibility to displacement by IDH1 second-site mutations [14, 20]. While both olutasidenib and ivosidenib effectively inhibit mutant IDH1, olutasidenib is highly selective for the mutant form and does not inhibit wild-type IDH1, whereas ivosidenib inhibits both the mutant and wild-type forms of IDH1 [14, 20, 21]. These structural and binding differences may lead to variations in their selectivity and inhibitory activity against IDH1, potentially influencing the clinical outcomes observed with each drug [20].

TTR analysis showed that while the median time to CR/CRh was 1.9 months, some patients required up to 6 months of treatment before achieving CR/CRh and up to 10 months for an overall response. Notably, TTR did not correlate with OS, even among those achieving CR/CRh. These results support current prescribing guidelines, which recommend treatment continuation for at least 6 months in the absence of disease progression or unacceptable toxicity, ensuring adequate time for clinical benefit [16].

In patients who achieved a response, the duration of CR/CRh tended to be long regardless of the number of prior regimens. Overall response rates were lower in patients with ≥ 3 prior regimens, suggesting a responder selection effect, whereby patients particularly sensitive to treatment achieved durable remission. Given the small numbers in this subgroup, these findings should be interpreted cautiously.

The results presented for the pivotal cohort of this phase 2 study suggest that olutasidenib treatment may show clinical benefit across a broad range of patients with R/R m*IDH1* AML, including those refractory to multiple prior therapies, including venetoclax-based regimens. In the post-venetoclax setting, treatment options for patients with m*IDH1* R/R AML remain limited, with particularly poor outcomes [22]. Unfortunately, a majority of responders to initial therapy experience relapse, and the prognosis following relapse is dismal, with a reported median OS of just 3.4 months [23]. Data from a real-world external control arm analysis suggest that olutasidenib may be more effective than ivosidenib in patients with m*IDH1* AML who are R/R following venetoclax-based therapy, with significantly higher rates of complete response (risk difference [RD]: 0.25; 95% CI, 0.01–0.49), transfusion independence (RD: 0.27; 95% CI, 0.01–0.53), and OS (hazards ratio: 0.33; 95% CI, 0.11–0.94) [24]. While these results appear favorable for olutasidenib, the small sample sizes (12 olutasidenib-treated patients and 20 ivosidenib patients [or 14 when using stricter, trial-like criteria]) in both groups limit robust statistical comparisons. These findings are consistent with previously published data indicating limited clinical activity of ivosidenib in this context [23, 25–27]. Together, these data support continued investigation of olutasidenib in this high-risk population.

In the current study, response rates (including CR/CRh) were higher in patients treated after 1–2 prior regimens compared to those with ≥ 3, suggesting a potential benefit with earlier use in the R/R setting. Outcomes after relapse post-HSCT remain poor, with long-term survival rates below 20% and most patients succumbing to disease despite salvage therapies [28–30]. The observed ORR of 29% in our post-HSCT subgroup suggests olutasidenib's broad potential for efficacy across a range of patient populations, including those with traditionally poor prognoses.

Beyond these high-risk subgroups, elderly patients with R/R m*IDH1* AML, who often cannot tolerate intensive chemotherapy [31–33], also demonstrated meaningful and durable responses. Importantly, olutasidenib was well tolerated in this older population, with a safety profile consistent with the broader patient population, further reinforcing its potential role in this difficult-to-treat population.

This analysis also explored the impact of *IDH1* mutation type and co-mutation burden on treatment outcomes. Consistent with prior reports, the rate of CR/CRh in response to olutasidenib was lower in patients with *IDH1*-R132H mutations compared with other IDH1 mutation subtypes [34–36]. Durable responses were observed across multiple *IDH1*-R132 mutation subtypes, particularly in the absence of receptor tyrosine kinase co-mutations, which are associated with poor prognosis [37, 38]. Response rates declined in patients with ≥ 4 co-mutations, suggesting that additional genomic complexity may influence olutasidenib's efficacy; however, in our multivariate analysis, the number of co-mutations did not significantly predict response. It is also worth highlighting that some patients with deleterious co-mutations, typically associated with poorer outcomes, also achieved CR/CRh, including those with *FLT3* and *TP53* [38, 39].

The 5-year safety profile of olutasidenib remained consistent, with no new safety signals identified in the 5-year analysis compared to the 3-year data [13, 15]. Importantly, with no new events of DS reported by Year 5, the rates and severity of this AE align with literature reports for IDH inhibitors [19, 40–42]. Similarly, QT prolongation rates remained low (8% for all grades by Year 3), with no new events reported by Year 5, in line with pharmacokinetic data from preclinical models suggesting that, during olutasidenib treatment, plasma concentrations remain below the threshold for QTc prolongation [16, 20]. Hepatotoxicity was reported in 23% of patients by Year 5, with only one new hepatobiliary AE observed since the interim analysis, consistent with product labeling that advises liver function monitoring and potential dose modifications [16]. These findings suggest that hepatic AEs generally occurred early in treatment and were generally characterized by asymptomatic laboratory abnormalities. The stability of the safety profile, even in patients treated with multiple prior regimens and elderly populations, reinforces the tolerability of olutasidenib. These long-term safety findings further establish olutasidenib as a viable option for patients requiring prolonged disease control and support its potential role as a bridge to transplant in appropriate candidates.

Despite promising findings, several limitations must be considered. The single-arm design limits the ability to draw definitive comparative conclusions. Additionally, while these data reinforce olutasidenib's durable efficacy, further research is needed to refine patient selection and optimize treatment sequencing or combination strategies, and several studies are underway to address those questions (e.g., NCT06668584, NCT06543381, NCT06782542, NCT06445959, NCT07032727). The post hoc nature of subgroup analyses, small sample sizes —particularly in patients with prior HSCT and those treated with venetoclax—and heterogeneity in prior treatments introduce potential confounders, necessitating future prospective validation.

Additionally, while this study provides extensive clinical data, it does not explore the molecular mechanisms behind differing efficacy among IDH1 mutation subtypes or the relationship between hepatotoxicity and IDH1 inhibition. Addressing these gaps through future preclinical and translational research will be important to deepen understanding of olutasidenib's therapeutic profile.

Conclusion

This final 5-year analysis of olutasidenib provides the most comprehensive long-term assessment of its efficacy and safety in adults with R/R m*IDH1* AML. The high CR/CRh rates, extended durations of response, and consistent long-term survival outcomes reinforce its clinical benefit, including the elderly and heavily pretreated patients. Importantly, olutasidenib's safety profile remained stable over time, with no new safety signals emerging, supporting its tolerability. These findings establish olutasidenib as a critical treatment option in this challenging disease setting. Building on these 5-year results, ongoing research, including numerous studies focused on combination strategies and treatment sequencing, continues to refine patient selection and optimize therapeutic approaches, with the goal of further improving outcomes in this high-risk population.

Abbreviations

AE	Adverse events
AML	Acute myeloid leukemia
CI	Confidence interval
CR	Complete remission
CRh	Complete remission with partial hematologic recovery
Cri	Complete remission with incomplete blood count recovery
DCO	Data cut-off
DOR	Duration of response
DS	Differentiation syndrome
ECOG	Eastern cooperative oncology group
HMA	Hypomethylating agent
HSCT	Hematopoietic stem cell transplantation
MAIC	Matching-adjusted indirect comparison
mIDH1	Mutant isocitrate dehydrogenase 1
MLFS	Morphologic leukemia-free state
NR	Not reached
PR	Partial remission
OR	Overall response
ORR	Overall response rate
OS	Overall survival
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cell
R/R	Relapsed/refractory
TEAE	Treatment emergent adverse events
TI	Transfusion independence
TTR	Time to response
VAF	Variant allele frequency

Supplementary Information

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Supplementary Material 1

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Data availability
For deidentified data, requests may be sent to datasharing@rigel.com at least 24 months after clinical trial completion, provided a scientifically valid research proposal is made by qualified, academic researchers for data associated with interventions that have received regulatory approval in the US and Europe.

Declarations

Ethics approval and consent to participate
The study was approved by independent institutional review boards of each participating site and was conducted in accordance with the ethics principles of the Declaration of Helsinki and with Good Clinical Practice guidelines defined by the International Conference on Harmonization. All patients provided written informed consent.

Consent for publication
Not applicable.

Competing interests
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Supplementary Information

Supplemental Table 1. Efficacy of Olutasidenib by Number of Prior Regimens

	1-2 Prior Regimens (n=93)	≥3 Prior Regimens (n=54)
ORR, n (%); 95% CI	50 (54); 43.1-64.2	21 (39); 25.9-53.1
DOR, months, median (95% CI)	14.8 (7.4-25.9)	16.6 (5.8-NR)
CR rate, n (%); 95% CI	35 (38); 27.8-48.3	12 (22); 12.0-35.6
DOCR, months, median (95% CI)	21.3 (12.0-NR)	NR (8.7-NR)
CR/CRh rate, n (%); 95% CI	38 (41); 30.8-51.5	13 (24); 13.5-37.6
DOCR/CRh, months, median (95% CI)	25.3 (12.0-NR)	NR (8.7-NR)
OS, months, median (95% CI)	13.0 (9.3-18.9)	8.9 (5.8-14.9)

CI, confidence interval; CR, complete remission; CRh, CR with partial hematologic recovery; DOCR, duration of CR; DOCR/CRh, duration of CR/CRh; DOR, duration of overall response; NR, not reached; ORR, overall response rate; OS, overall survival.

Supplemental Table 2. Response and Survival in Patients Treated With Olutasidenib Post-Venetoclax

	n=12[a]
Overall response, n (%)	6 (50)
Best overall response, n (%)	
CR	3 (25)
CRh	1 (8)
CRi	2 (17)
SD	2 (17)
PD	2 (17)
NE/ND	2 (17)
Overall survival, median, months (95% CI)	16.2 (2.6-NR)

[a]Of the 12 patients, 8 (67%) received HMA in combination with venetoclax (including 1 [8%] patient who initially received HMA alone before starting venetoclax and 2 (17%) who received prior single-agent HMA separately from venetoclax), 3 (25%) with cytarabine, and 1 (8.3%) with dinaciclib.

CI, confidence interval; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete recovery; HMA, hypomethylating agent; NE/ND, not evaluated/not determined; NR, not reached; PD, progressive disease; SD, stable disease.

Supplemental Table 3. Response to Olutasidenib According to *IDH1* Mutation and by Number of Co-mutations

***IDH1* Mutation**	**n**	**ORR n (%, 95% CI)**	**CR/CRh n (%, 95% CI)**	**Median DOCR/CRh Months (95% CI)**
R132C	85	49 (58, 46.4-68.3)	36 (42, 31.7-53.6)	25.3 (1.9-54.3; n=36)
R132L/G/S	27	13 (48, 28.7-68.1)	9 (33, 16.5-54.0)	NR (7.4-54.6; n=9)
R132H	35	9 (26, 12.5-43.3)	6 (17, 6.6-33.6)	13.5 (1.8-29.0; n=6)
Number of Co-mutations	**n[a]**	**ORR n (%, 95% CI)**	**CR/CRh n (%, 95% CI)**	**Median DOCR/CRh Months (95% CI)**
0	4	3 (75, 19.4-99.4)	2 (50, 6.8-93.2)	14.5 (3.6-25.3; n=2)
1	42	18 (43, 27.7-59.0)	15 (36, 21.6-52.0)	NR (1.9-54.3; n=15)
2	32	14 (44, 26.4-62.3)	10 (31, 16.1-50.0)	NR (2.2-53.5; n=10)
3	17	10 (59, 32.9-81.6)	6 (35, 14.2-61.7)	NR (4.2, 46.1; n=6)
4-7	19	6 (32, 12.6-56.6)	3 (16, 3.4-39.6)	29.0 (5.9, 29.0; n=3)

[a]Co-mutation data not reported in 33 patients.

CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; DO, duration of; NR, not reached.

Supplemental Table 4. Response to Olutasidenib According to Co-mutations[a]

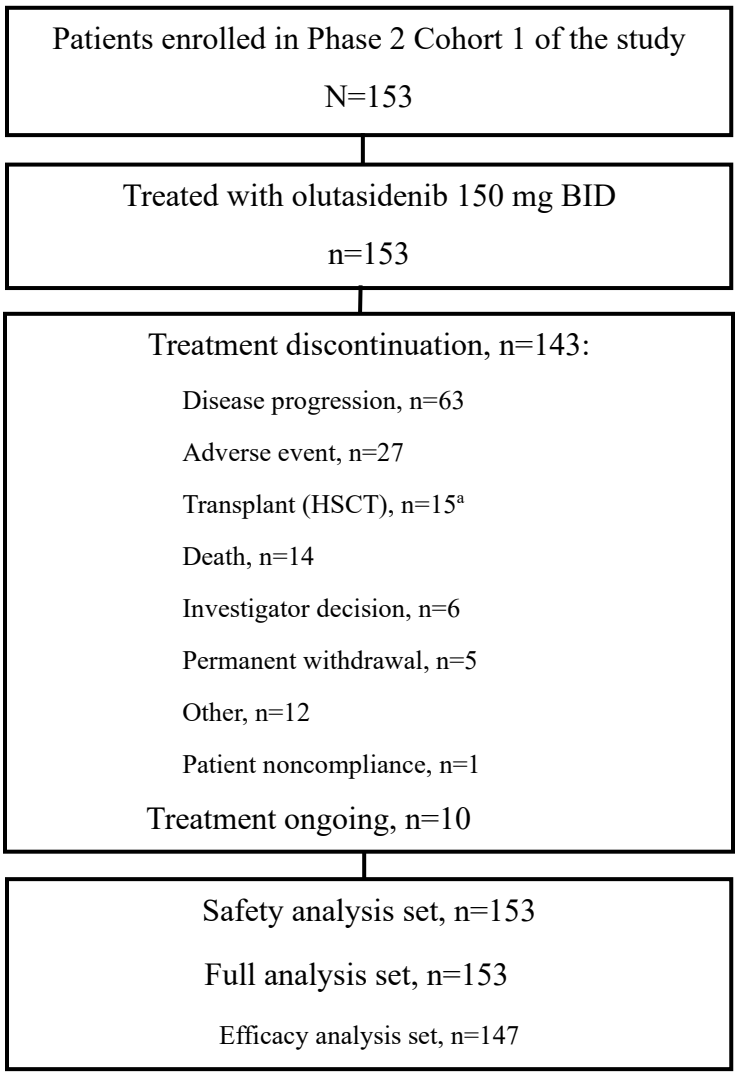
Co-mutation	n (%)[b] n=114	ORR n (%, 95% CI)	CR/CRh n (%, 95% CI)	Median DOCR/CRh months (95% CI)
NPM1	39 (34)	12 (31, 17-47.6)	9 (23, 11.1-39.3)	13.8 (4.8, NR)
DNMT3A	35 (31)	17 (49, 31.4-66.0)	12 (34, 19.1-52.2)	17.6 (2.2, 50.6)
ASXL1	21 (18)	11 (52, 29.8-74.3)	5 (24, 8.2-47.2)	NR (4.2, 47.0)
FLT3	16 (14)	5 (31, 11.0-58.7)	2 (13, 1.6-38.3)	NR (13.5, 46.1)
NRAS	10 (9)	3 (30, 6.7-65.2)	2 (20, 2.5-55.6)	9.3 (4.8, 13.8)
JAK2	7 (6)	4 (57, 18.4-90.1)	2 (29, 3.7-71.0)	29 (26.8, 29.0)
TP53	5 (4)	2 (40, 0.5-71.6)	1 (20, 0.5-71.6)	5.9

[a]Commonly reported prognostic mutations.

[b]Co-mutation data not reported in 33 of 147 patients with central analysis confirmation of *IDH1* mutation.

CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; DO, duration of; ORR, overall response rate; NR, not reached.

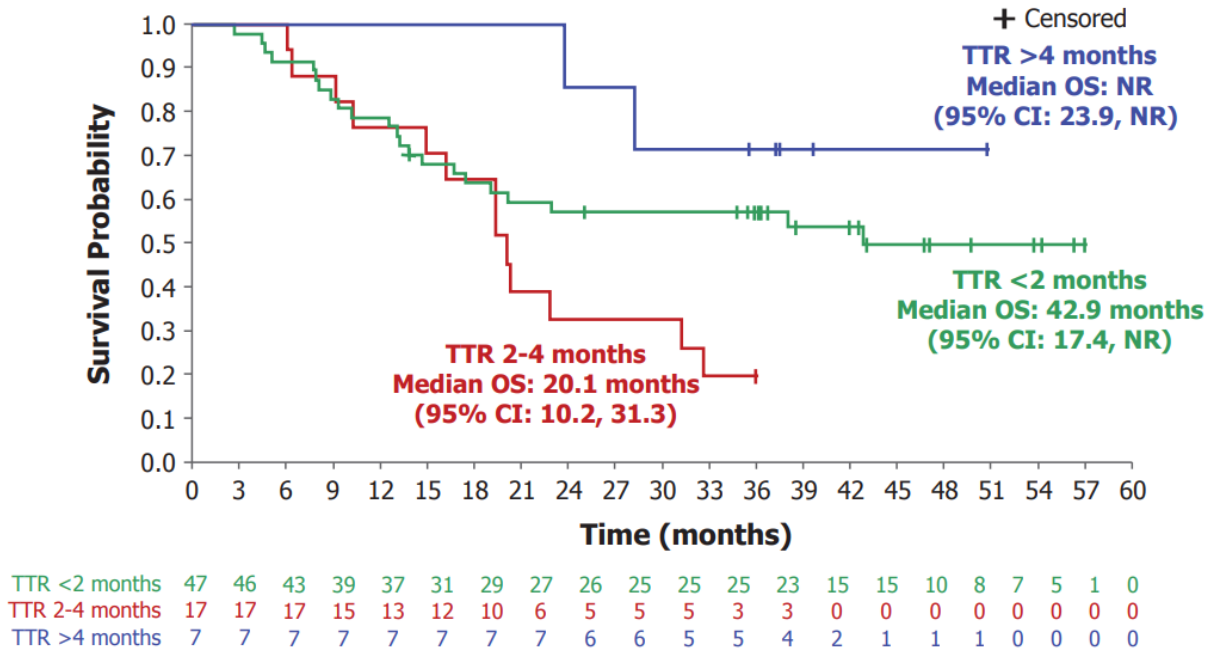
Supplemental Figure 1. CONSORT Diagram



[a]Fifteen patients discontinued olutasidenib to receive HSCT. In total, 16 patients underwent HSCT; 1 patient who discontinued olutasidenib due to a grade 3 AE of bone marrow hypoplasia subsequently underwent transplantation.

AE, adverse event; BID, twice daily; HSCT, hematopoietic stem cell transplantation.

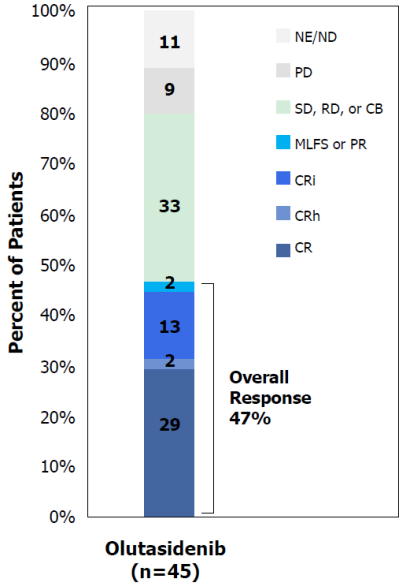
Supplemental Figure 2. Overall Survival by TTR of Patients Achieving Overall Response



CI, confidence interval; NR, not reached; OS, overall survival; TTR, time to response.

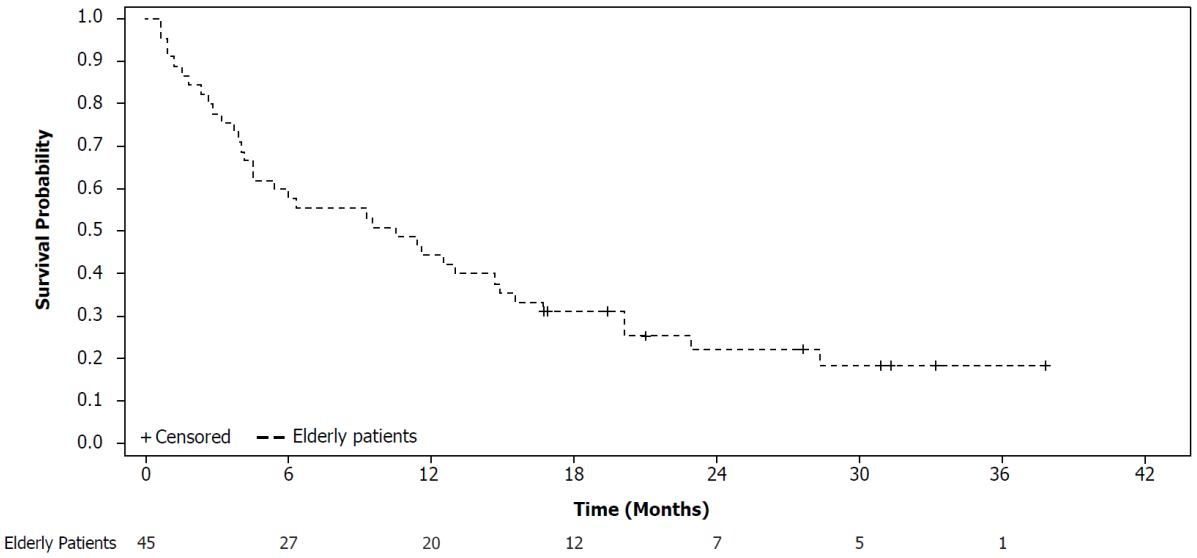
Supplemental Figure 3. Olutasidenib Outcomes in Elderly (≥75 years) Patients (n=45)

Best response, n (%)	
Overall response rate	21 (47) [95% CI: 31.7, 62.1]
CR	13 (29)
CRh	1 (2)
CRi	6 (13)
MLFS or partial remission	1 (2)
SD, RD, or CB	15 (33)
PD	4 (9)
Not evaluated/not done	5 (11)
Time to CR/CRh, months, median (range)	1.45 (0.9, 5.6)
Duration of CR/CRh, months, median (range)	25.3 (4.2, 54.6)

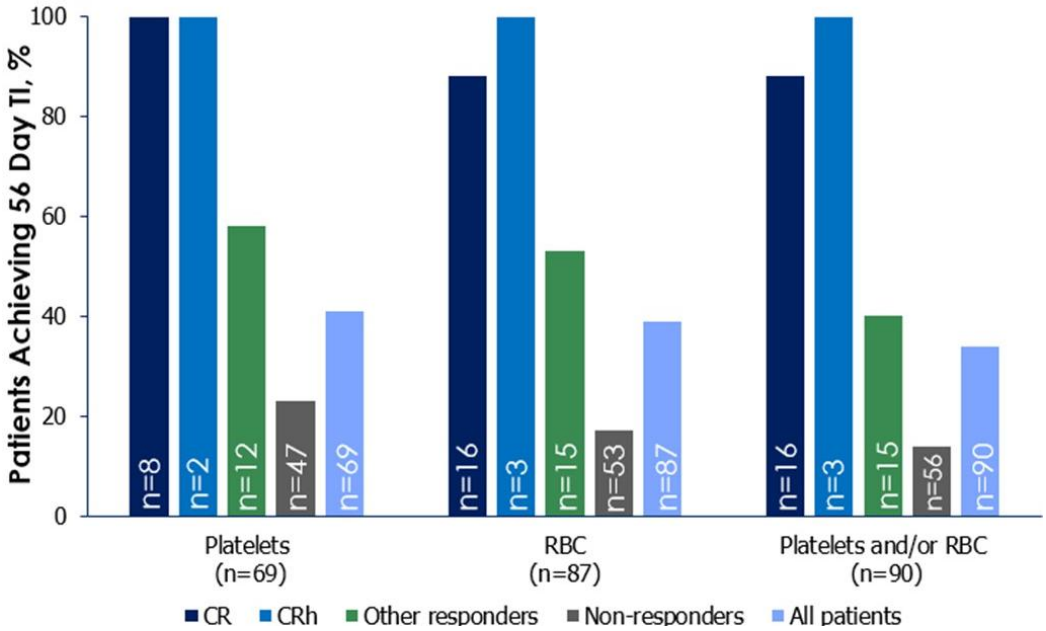


CB, clinical benefit; CI, confidence interval; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete recovery; Do, duration of; MLFS, morphologic leukemia-free state; NE/ND, not evaluated/not determined; OR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial remission; RD, resistant disease; SD stable disease.

Supplemental Figure 4. Overall Survival in Elderly Patients (≥75 years) Treated With Olutasidenib

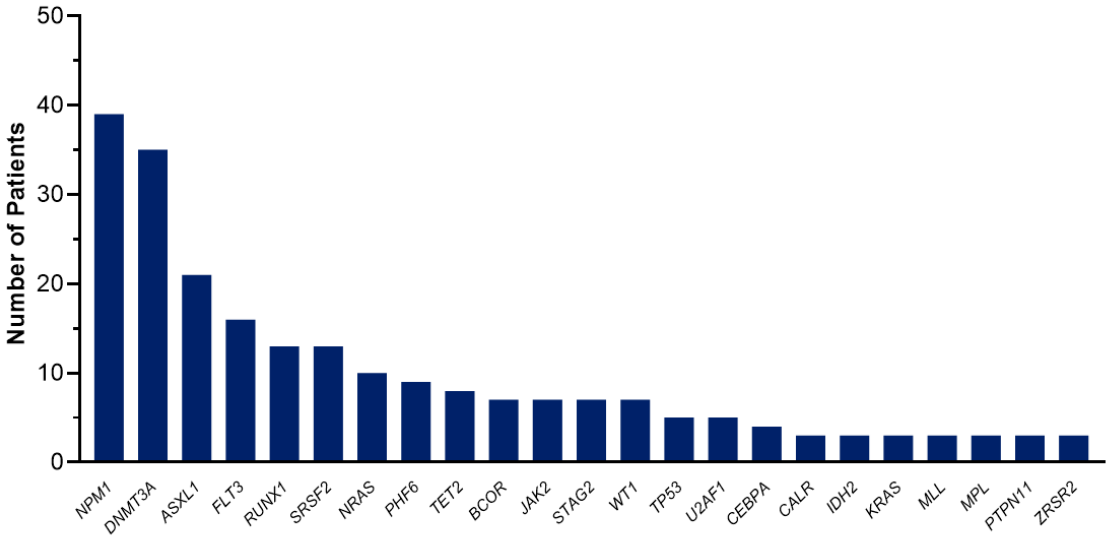


Supplemental Figure 5. Transfusion Independence During Olutasidenib Treatment



CR, complete remission; CRh, CR with partial hematologic recovery; RBC, red blood cell; TI, transfusion independence.

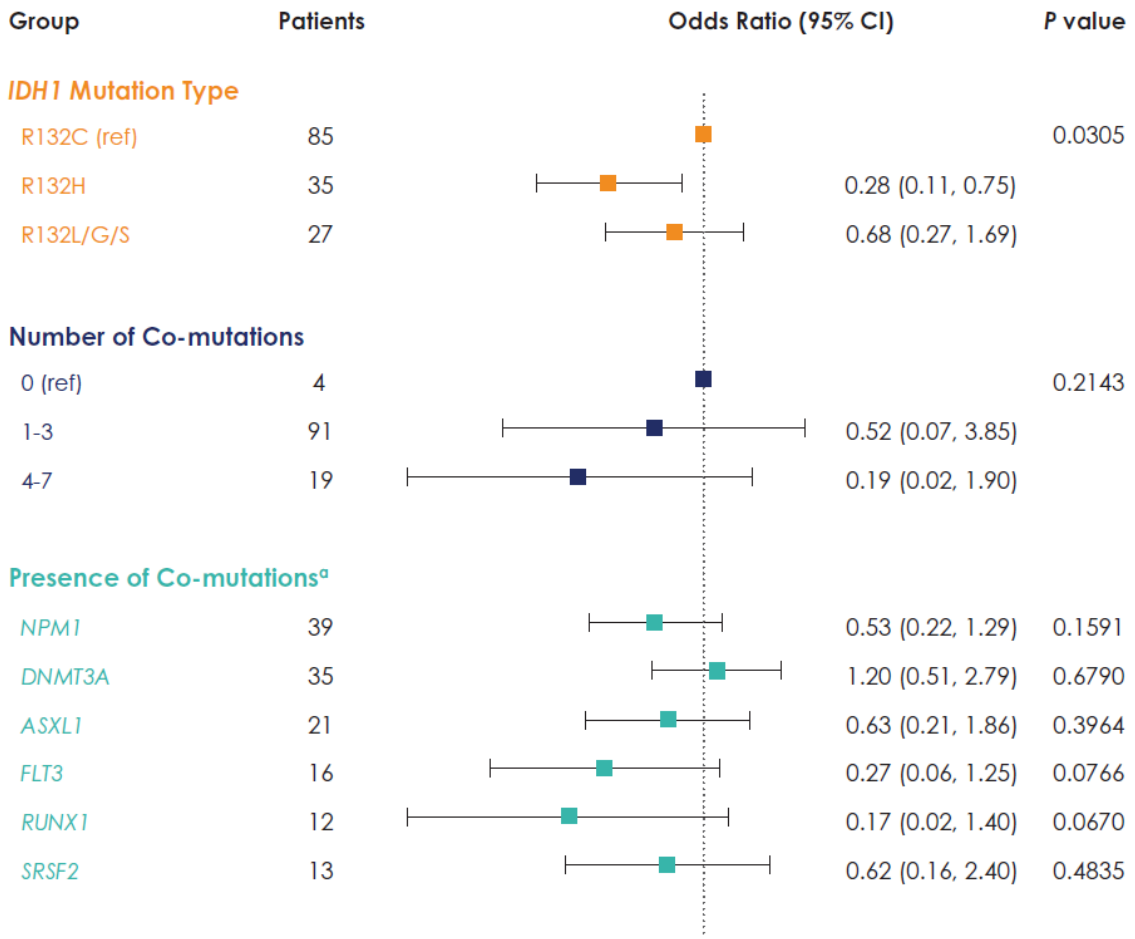
Supplemental Figure 6. Frequency of Co-mutations in Patients With R/R m*IDH1* AML



Co-mutations occurring in <3 patients not shown. Co-mutation data were not reported in 33 patients.

AML, acute myeloid leukemia; *IDH1*, isocitrate dehydrogenase 1; R/R, relapsed/refractory.

Supplemental Figure 7. Univariate Analysis of Achieving Treatment Response (CR/CRh)



[a]Genes occurring in >10 patients were included in univariate analysis. Odds ratios for this group represent the association between the presence versus absence of each gene mutation.

CR, complete remission; CRh, CR with partial hematologic recovery; IDH1, isocitrate dehydrogenase 1.