Cortes *et al.*
Journal of Hematology & Oncology (2025) 18:7
https://doi.org/10.1186/s13045-024-01657-z

Journal of Hematology & Oncology

RESEARCH

Open Access

Olutasidenib in combination with azacitidine induces durable complete remissions in patients with relapsed or refractory m*IDH1* acute myeloid leukemia: a multicohort open-label phase 1/2 trial

Jorge E. Cortes[1*], Gail J. Roboz[2], Maria R. Baer[3], Brian A. Jonas[4], Gary J. Schiller[5], Karen Yee[6], P. Brent Ferrell[7], Jay Yang[8], Eunice S. Wang[9], William G. Blum[10], Alice Mims[11], Hua Tian[12], Aaron Sheppard[12], Stéphane de Botton[13], Pau Montesinos[14], Antonio Curti[15] and Justin M. Watts[16] on behalf of the Olutasidenib Combination Therapy Study Group

Abstract

Background Olutasidenib is a potent, selective, oral, small molecule inhibitor of mutant IDH1 (mIDH1) which induced durable remissions in high-risk, relapsed/refractory (R/R) m*IDH1* AML patients in a phase 1/2 trial. We present a pooled analysis from multiple cohorts of the phase 1/2 trial of patients with R/R AML who received combination olutasidenib and azacitidine therapy.

Methods Adult patients with m*IDH1*^{R132} AML received 150 mg olutasidenib twice daily plus standard-of-care azacitidine (OLU + AZA) and were evaluated for response and safety.

Results Sixty-seven patients with R/R m*IDH1*^{R132} AML received combination OLU + AZA. Median age was 66 years (range 28–82) and 54% were male. Most patients (83%) had 2 + prior regimens, including a hypomethylating agent in 40%, IDH1 inhibitor therapy in 31% (olutasidenib in 24%), and hematopoietic stem cell transplant in 10%. Cytogenetic risk was intermediate in 72%, poor in 18% and unknown in 10%. CR/CRh was achieved in 21/67 (31%; 95% CI 21–44) patients, with a median duration of 14.7 months (95% CI 4.6-not reached). CR was achieved in 18/67 (27%; 95% CI 17–39) patients, with median duration of 20.3 months (95% CI 3.7-not reached). Overall response (partial remission or better) was achieved in 34/67 (51%; 95% CI 38–63) patients. Median overall survival was 12.9 months (95% CI 18.7–19.3). In a subset analysis excluding patients who had prior OLU exposure (N = 51), CR/CRh was achieved in 19/51 (37%; 95% CI 24–52) patients, CR was achieved in 16/51 (31%; 95% CI 19–46), and overall response was achieved in 30/51 (59%; 95% CI 44–72). In patients who achieved CR/CRh and were transfusion-dependent at baseline, transfusion independence (RBC and platelets) was achieved in 64% (7/11) and 57% (4/7) of patients, respectively. The most common Grade 3 or 4 adverse events (> 20% patients) were decreased platelet count (37%), red blood cell count

*Correspondence:
Jorge E. Cortes
jorge.cortes@augusta.edu
Full list of author information is available at the end of the article

(25%), and neutrophil count (24%). Six patients (9%) experienced differentiation syndrome. Four (6%) discontinued treatment due to an adverse event.

Conclusions Olutasidenib plus azacitidine induced high response rates and durable remissions with a tolerable side effect profile in patients with R/R AML with diverse treatment histories. The results represent another therapeutic option for patients with m*IDH1* AML who may benefit from a targeted therapy.

Trial registration NCT02719574.

Keywords Isocitrate dehydrogenase-1, Hypomethylating agent, Mutant IDH1 inhibitor, Relapsed, Refractory, AML, Combination therapy

Background

Effective and well-tolerated treatments remain an area of need for patients with acute myeloid leukemia (AML), particularly in the relapsed/refractory (R/R) setting. The majority of patients with AML have inadequate response to available therapies or become refractory to first-line treatment or experience relapse after initial response [1]. Patients with R/R AML have a poor prognosis and limited treatment options. Additionally, as myeloid cancers mainly affect older adults, many patients with AML are unfit for intensive induction regimens due to age, comorbidities, or medical frailty [2]. Targeted treatments may provide an option for selected patients with AML, particularly in the R/R setting. Furthermore, targeted treatments may be appropriate for use in combination with other standard therapies and studies are underway to determine if combining targeted therapy with standard-of-care regimens may improve clinical outcomes.

About 7–14% of patients with AML have mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene [3]. Mutations in IDH1 lead to gain-of-function enzymatic activity that reduces α-ketoglutarate (α-KG) to the oncometabolite 2-hydroxyglutarate (2-HG). Abnormal accumulation of 2-HG blocks normal differentiation of stem and progenitor cells and promotes tumorigenesis. Inhibition of mIDH1 can prevent 2-HG production and restore normal cellular differentiation. Therefore, the oncogenic mIDH1 has been validated as a target for therapeutic intervention [4].

Olutasidenib (FT-2102) is a potent, selective, oral, small molecule inhibitor of mIDH1 that is FDA-approved for treatment of patients with R/R AML harboring mIDH1 [5]. Olutasidenib is highly specific for mutant IDH1, leaving wild-type IDH1 function intact [5]. Inhibition of wild-type IDH1 is detrimental to cell viability and homeostatic functions [6, 7]. Studies have shown that blocking wild-type IDH1 induces oxidative stress, which may enhance sensitivity to infections, and causes lower viability of hematopoietic stem cells under stress conditions [6, 7]. Furthermore, wild-type IDH1 catalyzes the conversion of isocitrate to α-KG and it has been shown that low levels of α-KG can block hemoglobin production and cause anemia linked to erythropoiesis disruption [8, 9]. Olutasidenib also has a low molecular weight of FW 355. A mechanism of IDH1 inhibitor resistance is the development of an *in cis* second-site mutation at S280F [10, 11]. However, the olutasidenib molecule retains the ability to bind and inhibit R132C/S280F and R132H/S280F double-mutant IDH1 [10].

A phase 1/2 trial of olutasidenib was conducted to assess its safety, pharmacologic profile, and clinical activity, with or without azacitidine, in patients with MDS or AML harboring m*IDH1*. In the phase 1 dose escalation and expansion study, the dose of 150 mg BID was established and no dose-limiting toxicities were reported [12]. The phase 2 trial included the pivotal cohort of patients with R/R AML treated with olutasidenib monotherapy, upon which the drug was approved by the US FDA in 2022 [13]. In the pivotal cohort, 35% of patients had a complete remission (CR) or CR with partial hematologic recovery (CRh), and the duration of CR/CRh in these patients was 25.9 months [13]. The phase 2 portion was a multi-cohort trial and certain cohorts have not been previously published, such as patients treated with the combination olutasidenib plus azacitidine regimen who were relapsed and/or refractory to diverse therapies at study entry.

Herein we report the results from a pooled analysis of the phase 1 and phase 2 studies of patients with R/R m*IDH1* AML who were eligible to receive azacitidine treatment and were assigned to a combination regimen of 150 mg olutasidenib plus standard-of-care azacitidine.

Methods

Study design

The study was a multicenter, open-label, phase 1/2 trial. The methodology and results for the phase 1 dose selection and dose expansion as well as the phase 2 pivotal cohort were previously reported [12, 13]. Phase 2 included multiple cohorts, and herein we report pooled analyses of three phase 2 cohorts of patients with R/R m*IDH1* AML and two cohorts of patients from phase 1 with R/R m*IDH1* AML who received combination therapy with the same olutasidenib dose plus azacitidine

(OLU + AZA). The 3 different patient cohorts from phase 2 were defined by prior treatment exposure: patients who had not been previously treated with either a hypomethylating agent (HMA) or IDH1 inhibitor (IDH1i), patients who had previously been treated with an HMA, and patients who had previously been treated with an IDH1i (Supplemental Figure S1).

In all patients in the analysis, olutasidenib was administered at 150 mg, twice daily, in continuous 28-day cycles. Azacitidine was given per standard-of-care at a starting dose of 75 mg/m^2 daily, for 7 consecutive days, in 28-day cycles. The cohorts described were enrolled across 32 sites in the United States, Canada, Europe, and Asia Pacific.

Patients

Adults (≥18y) with pathologically proven AML with confirmed *IDH1*^{R132} gene mutation, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, adequate liver and renal function, and QTcF ≤450 ms were included. The study analysis included only patients with relapsed/refractory (R/R) AML, with cohorts assigned by their treatment history, specifically whether they inadequately responded to or progressed on prior HMA, and whether they received prior single-agent IDH1i therapy (ivosidenib or olutasidenib) as their last therapy prior to study enrollment. The latter cohort included patients who progressed on single-agent olutasidenib for whom azacitidine was added and they entered this cohort.

Efficacy assessments

The primary objective of the study was to evaluate the clinical activity of olutasidenib in combination with azacitidine for treatment of R/R *mIDH1* AML. For the patients who met the analysis criteria, the full analysis set was used, which included all patients who were enrolled in the study and received at least one dose of olutasidenib.

The primary efficacy endpoint was CR/CRh rate, defined as bone marrow blasts < 5% with complete (CR) or partial (CRh) hematologic recovery, assessed by investigators. The modified response criteria of the International Working Group in AML were used [14]. Secondary efficacy endpoints included overall response, 56-day transfusion independence, time to response, duration of response, and overall survival (OS).

Safety assessments

Safety data were summarized descriptively for all patients who received at least one dose of olutasidenib. Patients were monitored for adverse events from the time of first dose until 28 days after the last dose of study drug or until resolution or stabilization of an adverse event. All adverse events were coded using MedDRA version 19.1 and graded for severity via the NCI-CTCAE version 4.03. Laboratory safety assessments, vital signs, ECG, and physical examinations were summarized by visit.

Statistical analysis

Descriptive statistics are provided and summarized. Median time to event was analyzed using Kaplan–Meier (K-M) methods for each cohort.

Results

Patients

A total of 67 enrolled patients with R/R *mIDH1* AML received combination olutasidenib plus azacitidine treatment in the trials (20 from phase 1, 47 from phase 2). All 67 patients received at least one dose of their assigned treatment and were included in both efficacy and safety analyses. Overall, 12 (18%) patients became eligible for post-remission HSCT and discontinued treatment. Other reasons for discontinuation of treatment were disease progression (n = 25), adverse event (n = 4), investigator decision (n = 10), death (n = 6), withdrawal by subject (n = 1), or an unspecified reason (n = 9).

Demographics and baseline characteristics are summarized in Table 1 for the full safety set. Median age was 66 years, 54% of the study population were male, 58% were white, 6% were black or African American, and 4% were Asian, while 31% of patients did not report race or selected "other". Patients were predominantly recruited from North America (48%) and Europe (43%), with a small percentage (9%) from Asia.

All patients in the analysis entered the study with the diagnosis of R/R AML and the median time from diagnosis to study entry was 10.2 months. Fifty-seven percent of patients (38/67) had relapsed disease, 9% had over 12-months time since relapse, and 43% (29/67) had refractory disease. Patients had received a median of 2 prior regimens (range 1–6) and 46% (31/67) had 3 or more prior regimens. All patients (100%) received induction therapy prior to study entry. Other prior regimens included HMA in 40% (27/67) (of whom 17 had azacitidine, 11 decitabine, 1 guadecitabine), IDH1 inhibitor therapy in 31% (21/67) (including 24% [16/67] who had received prior olutasidenib monotherapy and 7% [5/67] who received prior ivosidenib), HSCT in 10% (7/67) and venetoclax in 6% (4/67) of patients. Of the 4 patients with prior venetoclax treatment, 2 had received prior venetoclax and HMA regimens, and 2 had received prior venetoclax, IDH1i, and HMA. No patient in the study had a favorable cytogenetic risk classification at baseline. A total of 12 patients (18%) had poor cytogenetic risk and 48 patients had intermediate risk (72%). Seven

Table 1 Patient demographic and baseline disease characteristics in the full analysis population

Parameter	Total (N = 67)
Age, median years (range)	66 (28–82)
< 65, n (%)	29 (43)
65 to < 75, n (%)	21 (31)
≥ 75, n (%)	17 (25)
Sex, n (%)	
Male	36 (54)
Female	31 (46)
Race, n (%)	
Asian	3 (4)
Black	4 (6)
White	39 (58)
Not reported	21 (31)
Region, n (%)	
North America	32 (48)
EU	29 (43)
Asia Pacific	6 (9)
ECOG performance status score, n (%)[b]	
0	23 (34)
1	32 (48)
2	12 (18)
Prior number of regimens, n (%)[c]	
1	11 (16)
2	25 (37)
3 or more	31 (46)
Prior induction[d]	67 (100)
Prior venetoclax treatment	4 (6)
Prior HMA treatment, n (%)[e]	27 (40)
Prior IDH1i therapy, n (%)	21 (31)
Prior olutasidenib therapy, n (%)	16 (24)
Prior HSCT, n (%)	7 (10)
AML type, n (%)	
Primary de novo	44 (66)
Secondary	23 (34)
AML cytogenetic risk category, n (%)[f]	
Favorable	0
Intermediate	48 (72)
Poor	12 (18)
Unknown/Missing	7 (10)
Hematologic laboratory parameters, median (range)	
Percentage of bone marrow blasts	50 (4, 98)
Percentage of peripheral blood blasts	60 (1, 97)
White blood cells × 10^9/L	2.3 (0, 90.7)
Absolute neutrophil count × 10^9/L	0.41 (0, 17.2)
Renal function (creatinine clearance), n (%)	
Normal (≥ 90 mL/min)	36 (54)
Mildly impaired (60–89 mL/min)	22 (33)
Moderately impaired (30–59 mL/min)	9 (13)
Severely impaired (15–29 mL/min)	0
AML IDH1 mutation type, n (%)[g]	
R132C	40 (60)
R132H	19 (28)
R132G/L/S	8 (12)
AML number of co-mutations, n (%)	
None	6 (9)
1 to 3	39 (58)
4 to 10	13 (19)
Unknown	9 (13)
Co-mutations in > 10% overall patients, n (%)	
DNMT3A	22 (33)
NPM1	18 (27)
FLT3	13 (19)
SRSF2	9 (13)
ASXL1	9 (13)

[a] Patient did not identify as American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander

[b] There were no patients with ECOG performance status score of 3 or 4

[c] Most common (> 5% of total patients) prior treatments included cytarabine (81%), idarubicin (36%), daunorubicin (30%), fludarabine (30%), investigational antineoplastic drugs (27%), azacitidine (25%), decitabine (16%), granulocyte colony stimulating factor (12%), midostaurin (10%), busulfan (9%), ivosidenib (7%), venetoclax 6%)

[d] 2 patients (3%) had missing regimen type in the medical history provided by the investigator; however, both patients had azacitidine as their induction regimen

[e] Of the 27 patients with prior HMA treatment, 17 had azacitidine, 11 had decitabine, 1 had guadecitabine; there was an overlap of 2 patients who had both prior azacitidine and prior decitabine

[f] Cytogenetic risk was assessed by investigators, according to National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for AML or European Leukemia Network guidelines

[g] Mutation type as reported by investigator

patients (10%) had unknown risk classification. One to 3 co-mutations were identified in 39 (58%) patients and 4–7 co-mutations were found in 13 (19%) patients, with *DNMT3A* in 22 (33%), *NPM1* in 18 (27%), *FLT3* in 13 (19%), and *TP53* in 4 (6%) patients. Among patients with a *FLT3* co-mutation, 6 (46%) received a prior FLT3 inhibitor.

Study drug exposure

The combination therapy cohort (N = 67) received a median of 5 cycles (range 1–61) over a median treatment duration of 120 days (95% CI 86–144). A median of 262 (range 4–2974) and 35 (3–471) doses of olutasidenib and azacitidine, respectively, were received.

Response to combination therapy

In the full combination therapy cohort, the overall response rate (ORR; partial remission or better),

was 51% (34/67; Table 2). The median time to overall response was 2 months (range 0.9–7.6). CR/CRh was achieved in 31% (21/67) of patients, with a median time to CR/CRh of 3 months (range 1–9.5) and median duration of 14.7 months (95% CI 4.6-NR; Fig. 1a). The rate of CR alone was 27% (18/67), with a median duration of 20.3 months (95% CI 3.7-NR) and time to CR of 3 months (range 1–7.6) (Table 2). Among twelve patients (18%) who achieved remission and went on to receive HSCT, 9 had a best response of CR, 2 were CRi and 1 had

Table 2 Response rates to olutasidenib and azacitidine combination treatment

Response rates	R/R AML (N = 67)	R/R AML excluding prior olutasidenib (N = 51)
CR rate		
Response rate, n (%) [95% CI]	18 (27%) [95% CI 16.8 - 39.1]	16 (31%) [95% CI 19.1 - 45.9]
Time to CR, median months (range)	2.95 (1-7.6)	3.3 (1-7.6)
Duration of CR, median months [95% CI]	20.3 [95% CI 3.7 - NR][a]	20.3 (95% CI 5.6 - NR)[c]
CR/CRh rate		
Response rate, n (%) [95% CI]	21 (31%) [95% CI 20.6 - 43.8]	19 (37%) [95% CI 24.1 - 51.9]
Time to CR/CRh, median months (range)	3 (1-9.5)	3.6 (1-9.5)
Duration of CR/CRh, median months [95% CI]	14.7 [95% CI 4.6 - NR][a]	14.7 [95% CI 4.6 - NR][c]
Overall response rate		
Response rate, n (%) [95% CI]	34 (51%) [95% CI 38.2–63.2]	30 (59%) [95% CI 44.2 - 72.4]
Time to first OR, median months (range)	1.95 (0.9-7.6)	1.9 (0.9-7.6)
Duration of OR, median months [95% CI]	6.5 [95% CI 3.7 - 21.2][b]	8 [95% CI 4.5 - 21.2][d]
Best overall response, n (%)		
CR/CRh/CRi	26 (39)	23 (45)
CR	18 (27)	16 (31)
CRh	3 (4)	3 (6)
CRi	5 (7)	4 (8)
MLFS	4 (6)	4 (8)
PR	4 (6)	3 (6)
Stable disease	24 (36)[e]	15 (29)[e]
Progressive disease	2 (3)	2 (4)
Not evaluable/not done	7 (10)	4 (8)

NR not reached, *CR* complete remission, *CRh* CR with partial hematologic recovery, *CRi* CR with incomplete recovery, *MLFS* morphologic leukemia-free state, *PR* partial remission, *SD* stable disease (failure to achieve at least a PR but not meeting criteria for progressive disease)

[a] 11 patients censored

[b] 14 patients censored

[c] 10 patients censored

[d] 13 patients censored

[e] Includes 2 patients considered to have clinical benefit by the treating physician, defined as having SD for a period of ≥ 8 weeks

(See figure on next page.)

Fig. 1 Duration of response for patients with CR/CRh compared to other responders. **a** Kaplan–Meier plot of duration of response comparing patients with best overall response (BOR) of CR/CRh (n = 21) vs other responders (n = 13). Other responders include patients with BOR of CRi, MLFS, and PR. **b** Swimmer plot of individual patients by responder (PR or better) or non-responder with their duration of treatment represented by the colored bar and duration of follow-up represented by the line. The color of the bar denotes the best overall response. The open circle is the time of first response, the diamond represents a progressive disease event and the closed circle represents a death event. Prior exposure to a hypomethylating agent (HMA) or IDH inhibitor (IDH1i) therapy is marked with an X in the corresponding column next to the lane. Other responders are patients with a best overall response of CRi, MLFS, or PR. *CR*, complete remission; *CRh*, CR with partial hematologic recovery; *CRi*, CR with incomplete recover; *MLFS*, morphologic leukemia-free state; *PR*, partial remission; *NE*, not evaluable; *PD*, progressive disease; *SD*, stable disease

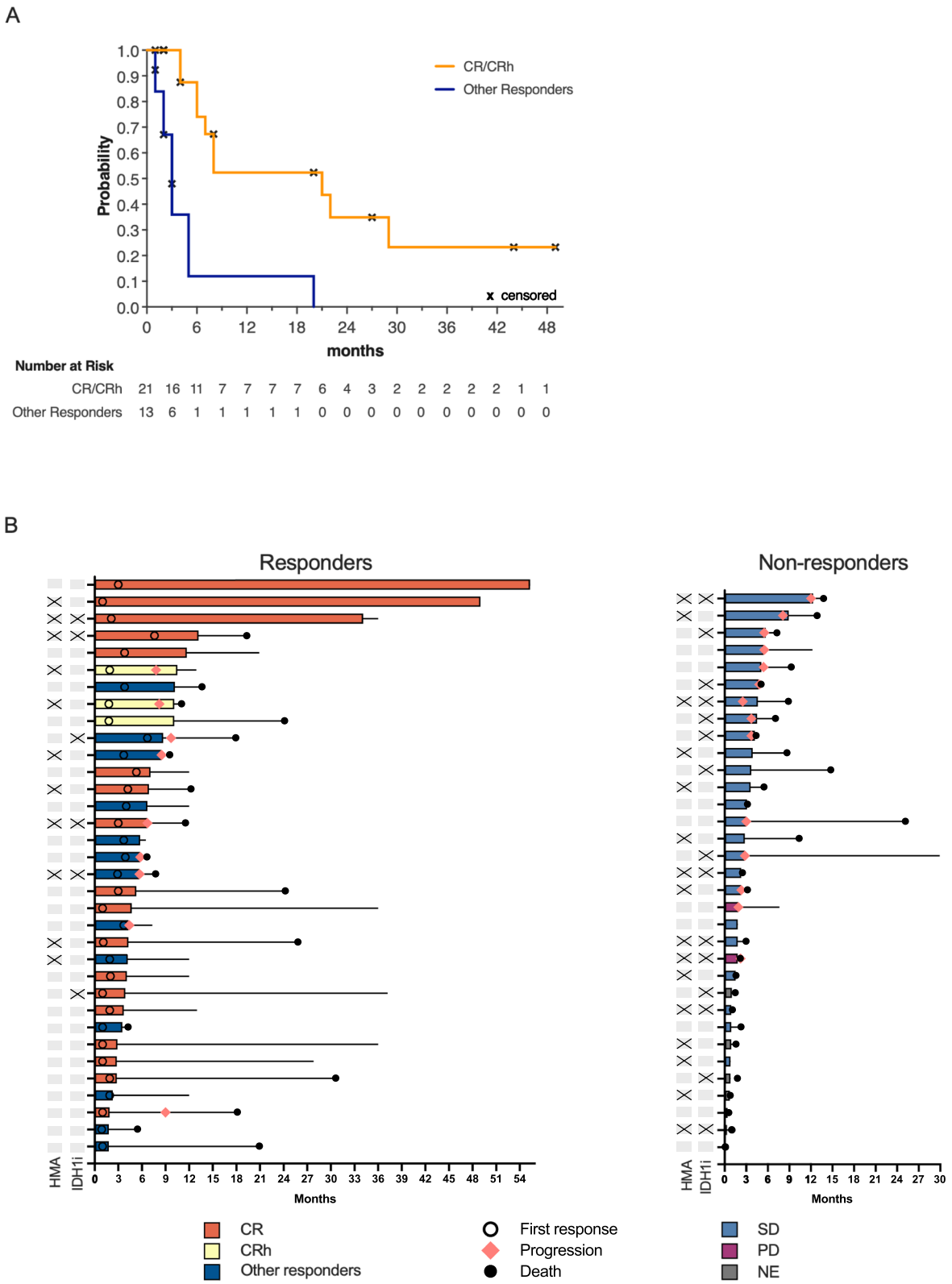

Fig. 1 (See legend on previous page.)

a PR. Seven of the 12 (58%) patients who proceeded to transplant were censored for duration of response prior to transplant.

Best response by AML cytogenetic risk classification and co-mutation profile are presented in Supplemental Table S2. Of patients in the full cohort who had a co-mutation in the *FLT3* gene, the ORR was 54% (7/13) and the rate of CR/CRh was 23% (3/13). Four of the 7 responders and all CR/CRh responders with *FLT3* co-mutation were previously treated with a FLT3 inhibitor. Of patients who had a co-mutation in *TP53*, the ORR was 50% (2/4) and one patient (25%) achieved a CR.

Overall, 6 patients had CR duration longer than 20 months, including 2 with CR duration longer than 40 months. Of the patients with CR duration > 20 months, 3 (50%) entered the study with no prior HMA and no prior IDH1i, 1 (17%) had received prior IDH1i but no prior HMA, 1 (17%) had received prior HMA but no IDH1i, and 1 (17%) had prior treatment with both an IDH1i and HMA, as well as prior venetoclax. There were 9 patients (50%) who achieved CR and discontinued treatment to undergo HSCT. Duration of CR was censored at the last recorded adequate response assessment, which occurred prior to discontinuation for transplant in 5 (56%) of the patients who proceeded to post-remission HSCT. In a post hoc analysis of the 9 patients (50%) who achieved CR but did not discontinue treatment to undergo HSCT, the median duration of CR was 27.9 months (95% CI 1.7-NR).

Response by prior IDH1

In a subset analysis of patients who had prior treatment with olutasidenib monotherapy (N = 16) prior to receiving combination OLU + AZA, the ORR was 25% (4/16), with 13% (2/16) achieving CR. In the analysis that excluded patients who had prior exposure to olutasidenib (N = 51), overall response was achieved in 59% (30/51), CR/CRh was achieved in 37% (19/51), and CR was achieved in 31% (16/51) of patients (Table 2; Fig. 1b). The duration of CR/CRh for the subset of 51 patients was identical to that of the full group receiving combination therapy (Table 2). This subset analysis included 5 patients who were R/R to prior ivosidenib, of whom 40% (2/5) responded with a CR, including one who proceeded to HSCT after 3.1 months on OLU + AZA combination therapy. The patient proceeding to transplant had 3 prior regimens (cytarabine, combination cytarabine, etoposide, mitoxantrone, and ivosidenib). The other patient who achieved a CR on OLU + AZA had 2 prior regimens (decitabine followed by ivosidenib), and experienced remission for 5.6 months before progressing. The remaining patients with prior ivosidenib therapy included 2 patients with SD and 1 with PD when given combination therapy.

Response by Prior HMA

There were 27 patients (40%) who were R/R to prior HMA treatment at study entry. Among this subset, the ORR was 41% (11/27) and the CR/CRh rate was 30% (8/27), with 22% (6/27) patients experiencing CR (Fig. 1b). The median duration of CR/CRh to OLU + AZA combination therapy among patients who had prior HMA exposure was 5.1 months (95% CI 1.7—NR). A subset analysis was also performed on patients who did not receive prior HMA (N = 40). The ORR was 58% (23/40) and CR/CRh was achieved in 33% (13/40), with 30% (12/40) attaining CR. The duration of CR/CRh in the patients who had no prior exposure to HMA was 24.1 months, which was longer compared to the full combination cohort as well as the subset with prior HMA.

Overall Survival

The median OS for all 67 patients in the full cohort was 12.9 months (95% CI 8.7–19.3; Table 3). The median follow-up time for OS was 36 months (95% CI 13.1–36.8). Among the patients who achieved CR/CRh, median OS was 30.6 months (95% CI 19.3-NR; Table 3). The 24-month KM estimated probability of survival was 73% (95% CI 46–88) for patients who achieved CR/CRh on combination therapy (Table 3, Fig. 2a). Among patients who did not receive prior olutasidenib, the median OS was 18.1 months (95% CI 9.5–24.2) compared to 7.5 months (95% CI 2.5–13.8) in patients who received prior treatment with olutasidenib (KM estimated probability in Fig. 2b). Furthermore, in patients who did not receive prior HMA, median OS was 18.1 months (95% CI 9.3–30.6), compared to 9.5 months (95% CI 3–12.2) for patients who received prior HMA (KM estimated probability in Fig. 2c).

In a sensitivity analysis of OS whereby the 12 patients who achieved remission and went on to receive HSCT were censored at transplant, there was no effect on median overall survival.

Transfusion independence

In the combination cohort (N = 67), 56-day transfusion independence of red blood cells (RBC) and platelets was achieved in 29% (12/42) and 33% (13/39) of patients, respectively, who were transfusion-dependent at baseline. In patients who achieved CR/CRh as their best overall response and were transfusion-dependent at baseline, 56-day transfusion independence (RBC and platelets) was achieved in 64% (7/11) and 57% (4/7) of patients, respectively. Transfusion independence by best overall response is summarized in Fig. 3.

Table 3 Overall survival

	R/R AML receiving combination therapy N = 67
Overall survival	
Median overall survival, all patients, months (range) [95% CI]	12.9 (0.1-55.3)[a] [95% CI 8.7–19.3]
Median overall survival, CR/CRh responder, months (range) [95% CI]	30.6 (11–55.3) [95% CI 19.3-NR]
OS Probability All Patients, % (95% CI)	
12 months	53 (40-64)
24 months	33 (21-46)
OS Probability CR/CRh responder, % (95% CI)	
12 months	90 (67-98)
24 months	73 (46-88)

NR not reached

[a] 22 patients censored

Safety

At least one treatment-emergent adverse event (TEAE) occurred in 65 of 67 (97%) patients overall, 46 (69%) of whom experienced a treatment-related TEAE (Table 4). Serious TEAEs occurred in 47 patients (70%), 15 (22%) of whom had a serious treatment-related AE. Four patients (6%) experienced a TEAE as the primary cause of discontinuation of study treatment. The AEs listed as the primary reason for discontinuation of drug were increased transaminases, increased gamma-glutamyltransferase, a cardiac arrest deemed probably not related to study drug that resulted in death, and a COVID-19 infection that led to death. Death during the treatment period or within 28 days of the final dose was reported in 17 patients (25%); the majority were related to AML disease progression (n = 9; 13%). The only event that led to death in > 1 patient was pneumonia (n = 2; 3%); none of the deaths were due to a TEAE related to study drug.

The most frequent TEAEs in patients overall were nausea (35/67, 52%), constipation (28/67; 42%), vomiting (27/67; 40%), decreased platelet count (26/67; 39%), diarrhea (21/67; 31%), and fatigue (21/67; 31%) (Table 4). Grade 3/4 adverse events occurred in 43/67 (64%) patients (Table 4). The most common grade 3 or 4 adverse events (> 20% patients) were decreased platelet count in 37% (25/67), decreased red blood cell count in 25% (17/67), and decreased neutrophil count in 24% (16/67) of patients. Six patients (9%) experienced differentiation syndrome, of which 2 (3%) were grade 3. Of the patients experiencing differentiation syndrome, 4 had their dose temporarily held; all recovered and resumed treatment. Grade 3 or 4 increases in serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and transaminases were reported in 1 patient each. QT prolongation occurred in 6 patients (9%) overall, of which 3 (4%) were grade 3 and none were higher than grade 3.

Discussion

Olutasidenib, in combination with the HMA azacitidine, induced overall responses in 51% and a durable CR or CRh in 31% of adult patients with R/R m*IDH1* AML, including those who were R/R to prior HMA and/or mIDH1 inhibitor. To our knowledge, this is the first study reporting efficacy and safety of combination therapy with an mIDH1 inhibitor and HMA in the R/R AML setting. Transfusion independence was achieved in all response groups, including patients with non-CR/CRh responses or no response. As expected, the subset of patients who were naïve to prior olutasidenib therapy

(See figure on next page.)

Fig. 2 Overall survival probability by response. **a** Kaplan–Meier estimate of overall survival for patients with CR/CRh (n = 21), other responders (n = 13), and non-responders (n = 33). Other responders are patients with CRi, MLFS, or PR. Non-responders are patients in response assessment categories other than CR, CRh, CRi, PR, and MLFS. **b** Kaplan–Meier estimate of overall survival in patients who had prior olutasidenib (OLU) therapy or no prior olutasidenib therapy. **c** Kaplan–Meier estimate of overall survival in patients who had prior hypomethylating agent (HMA) or no prior HMA. *CR*, complete remission; *CRh*, CR with partial hematologic recovery; *CRi*, CR with incomplete recover; *MLFS*, morphologic leukemia-free state; *PR*, partial remission

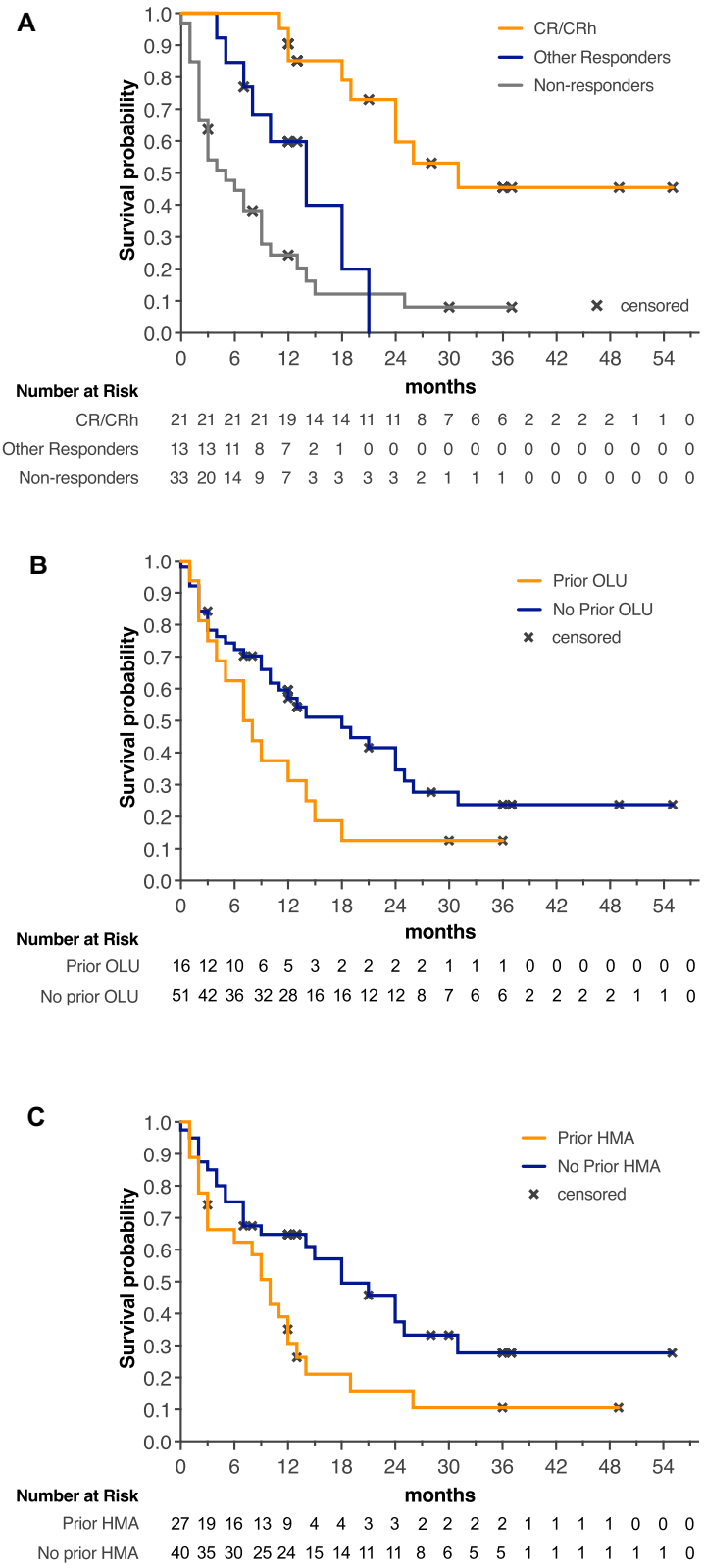

Fig. 2 (See legend on previous page.)

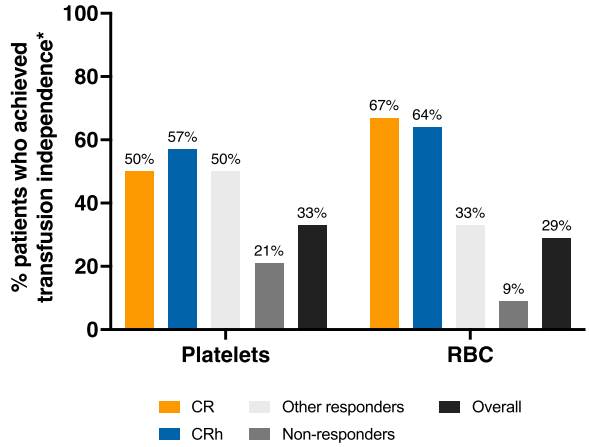

Fig. 3 Patients who achieved 56-day transfusion independence. *The proportion of patients who were transfusion-dependent at baseline and achieved transfusion independence for at least 56 consecutive days after receiving at least one dose of olutasidenib plus azacitidine combination therapy. Other responders are patients with CRi, MLFS, or PR. Non-responders are patients in response assessment categories other than CR, CRh, CRi, PR, and MLFS. *CR*, complete remission; *CRh*, CR with partial hematologic recovery; *CRi*, CR with incomplete recover; *MLFS*, morphologic leukemia-free state; *PR*, partial remission

Table 4 TEAEs of all grades (in ≥ 20% patients) and grade 3/4 severity (in ≥ 5% patients)

AE, n (%)	All Grades (N = 67)	Grade 3/4 (N = 67)
Patients with any AE	65 (97)	60 (90)
Hematologic AE		
Platelet count decreased	26 (39)	25 (37)
Red blood cell count decreased	18 (27)	17 (25)
Neutrophil count decreased	17 (25)	16 (24)
White blood cell count increased	17 (25)	7 (10)
Febrile neutropenia	16 (24)	13 (19)
White blood cell count decreased	7 (10)	4 (6)
Non-hematologic AE		
Nausea	35 (52)	3 (4)
Constipation	28 (42)	2 (3)
Vomiting	27 (40)	3 (4)
Diarrhea	21 (31)	1 (1)
Fatigue	21 (31)	7 (10)
Hypokalemia	18 (27)	4 (6)
Headache	17 (25)	1 (1)
Decreased appetite	16 (24)	0
Cough	15 (22)	1 (1)
Pyrexia	15 (22)	0
Hypertension	8 (12)	4 (6)
Pneumonia	8 (12)	4 (6)

had a higher response rate. Several patients in the study achieved remission and went on to HSCT. More evaluation is needed to understand how patients may benefit from olutasidenib maintenance therapy post-transplant, and a phase 1 study is underway to evaluate olutasidenib treatment in such a setting (NCT06543381).

A doublet regimen combining ivosidenib (an mIDH1 inhibitor) with azacitidine has been shown to have clinical activity in newly diagnosed, treatment-naïve patients with m*IDH1* AML [15]. However, there has been no published study on this doublet therapy in the m*IDH1* R/R AML population, which is more difficult to treat and typically has lower response rates compared to treatment-naive AML. The safety of olutasidenib and azacitidine doublet therapy was in line with the safety profile of the individual therapies added together. There was no concerning safety signal with olutasidenib plus azacitidine.

Emerging clinical data have demonstrated potential for combination therapy with the BCL2-inhibitor venetoclax in patients who are unfit for intensive induction therapy [16]. Studies are underway to test many doublet and even triplet therapies using targeted treatments, HMA, and venetoclax, in order to address the limited options many AML patients have based on their age or medical fitness [17, 18]. In the VIALE-A trial of venetoclax and HMA combination treatment of newly diagnosed patients with AML who were unfit for intensive chemotherapy, there was a higher rate of CR/CRi with combination therapy compared to HMA treatment alone (66.8% vs 29%, respectively; $p < 0.001$) [19]. Our study was designed before venetoclax-based treatments were widely used for AML. Four patients in the study had prior venetoclax treatment and one patient achieved a CR with a duration of > 20 months despite having been R/R to prior venetoclax, HMA, and olutasidenib. The potential use of sequential or triplet venetoclax with olutasidenib and an HMA in patients with mIDH1 needs to be addressed in future studies. A phase 1b/phase 2 study of decitabine and venetoclax in combination with olutasidenib is ongoing and recruiting patients (NCT06445959).

Limitations to note include the small sample size, the fact that this analysis was conducted post hoc and was compiled from multiple patient cohorts with different disease histories reflecting a heterogeneous patient population. Those factors may confound response to therapy. In addition, there was a potentially truncated duration of response due to patients achieving remission and discontinuing combination therapy to proceed onto HSCT. While that is a positive outcome, most patients undergoing transplant had no response assessments conducted after discontinuing the study treatment, thus prematurely shortening the length of time their response could be tracked. Indeed, in a post hoc analysis that removed the 9

patients with CR who discontinued treatment to proceed to transplant, the duration of CR was longer.

The responses reported appear similar to those reported from the pivotal phase 2 single-agent cohort [13]. de Botton et al. [13] reported an ORR of 48% and CR/CRh rate of 35% compared to 51% and 31%, respectively in the combination therapy cohort. However, it is important to note that 31% of the combination cohort received prior IDH1i therapy compared to no prior IDH1i therapy in the monotherapy cohort. When excluding the patients who had prior olutasidenib, the ORR with combination therapy was 59%, with a CR/CRh rate of 37%. In addition, the combination cohort was also more heavily pretreated overall, with 46% having 3 or more prior lines of therapy compared to 37% in the pivotal phase 2 monotherapy cohort. In light of those differences, the results obtained with the olutasidenib plus azacitidine combination in relapsed/refractory AML harboring mIDH1 are encouraging.

Conclusions

Olutasidenib in combination with azacitidine induced high response rates and durable remissions with a well-characterized and manageable side effect profile in patients with R/R mIDH1 AML. The observed efficacy is clinically meaningful and represents a new molecularly targeted therapeutic option for a patient population that has a poor prognosis and limited treatment options.

Abbreviations

AML	Acute myeloid leukemia
R/R	Relapsed or refractory
IDH1	Isocitrate dehydrogenase
α-KG	α-Ketoglutarate
2-HG	2-Hydroxyglutarate
FW	Formula weight
OLU	Olutasidenib
AZA	Azacitidine
NR	Not reached
CR	Complete remission
CRh	CR with partial hematologic recovery
CRi	CR with incomplete recovery
MLFS	Morphologic leukemia-free state
PR	Partial remission
SD	Stable disease
PD	Progressive disease
HMA	Hypomethylating agent
IDH1i	IDH1 inhibitor
HSCT	Hematopoietic stem cell transplant
ORR	Overall response rate
OS	Overall survival
KM	Kaplan-Meier
RBC	Red blood cells
TEAE	Treatment-emergent adverse event
ECOG	Eastern Cooperative Oncology Group

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-024-01657-z.

Additional file 1.

Acknowledgements

Medical writing support was provided by Jocelyn Hybiske, PhD, an independent consultant funded by Rigel Pharmaceuticals, Inc. The Olutasidenib combination therapy study group consists of: Jorge Cortes, Jay Yang, Maria Baer, Justin Watts, Thomas Prebet, Sangmin Lee, Gail Roboz, Paul Ferrell, Alice Mims, Prapti Patel, Eunice Wang, Brian Jonas, William Blum, Karen Yee, Thorsten Braun, Stephane de Botton, Ollivier Legrand, Caroline Bonmati, Xavier Thomas, and Pierre Peterlin, Christian Recher, Regis Costello, Jordi Esteve, Pau Montesinos, Montserrat Sangerman, Antonio Curti, Francesco Lanza, David Taussig, Matthias Klammer, Andrew Wei, Ashish Bajel, Carolyn Grove (see Supplemental Table for study sites).

Author contributions

JEC and JMW made substantial contributions to the design of the work, the analysis and interpretation of data, and substantively revised the work; MRB, JY, ESW and PM made substantial contributions to the analysis and interpretation of data and substantively revised the work; HT and AS made contributions to the conception of the work, acquisition and analysis of data, and revised the work; GJR, BAJ, GJS, KY, PBF, WGB, AM, SdB, and AC made substantial contributions to the interpretation of data and revised the work. All authors have approved the submitted version.

Funding

The sponsor of this study was Forma Therapeutics, Inc.; the sponsor collaborated with the clinical investigators in the study design, conduct, and data collection. Data analyses and manuscript preparation were sponsored by Rigel Pharmaceuticals, Inc. The study sponsor and Rigel Pharmaceuticals, Inc. analyzed the data and conducted the statistical analyses.

Availability of data and materials

The datasets used and/or analysed during the current study are available in redacted form to protect patient privacy from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki and in compliance with good clinical practice guidelines and applicable laws. The protocol was approved by the institutional review boards or ethics committee at study sites. Written informed consent was obtained before study entry from each patient or from the patient's legally authorized representative if the patient was unable to provide consent.

Consent for publication

Not applicable.

Competing interests

JEC has received research funding for his current or former institution from, and is a consultant to, Astellas, Amphivena, BMS, Novartis, Pfizer, Takeda, Daiichi, Jazz Pharmaceuticals, Merus, and Forma Therapeutics; and is a consultant to Rigel, BiolineRx, Biopath, Sun Pharma, and Tern. GJR has served as a consultant for Agios, Amgen, Amphivena, Astex, Celator, Celgene, Clovis Oncology, CTI BioPharma, Genoptix, Immune Pharmaceuticals, Janssen Pharmaceuticals, Juno, MedImmune, MEI Pharma, Onconova, Pfizer, Roche, and Sunesis; received research funding from AbbVie, BMS, Teva and Karyopharm; is an advisory board member or consultant for Novartis, AbbVie, BeiGene, BerGenBio, Arcellx, Jazz Pharmaceuticals, Syros, BMS, Genentech, ImmunoGen, AstraZeneca, Kura, Ryvu, Magenta, and Qihan Zentalis; has provided research support to Janssen. MRB received research funding from Abbvie, Ascnetage Pharma, Forma Therapeutics, Kite/Gilead, Kura Oncology, and Takeda. BAJ served in a consultancy/advisory role for AbbVie, Bristol Myers

Squibb, Daiichi Sankyo, Genentech, Gilead, GlycoMimetics, Kymera, Kura, Rigel, Schrodinger, Servier, Syndax and Treadwell, on a protocol steering committee for GlycoMimetics, on a data monitoring committee for Gilead, received travel reimbursement from AbbVie and Rigel, research funding to institution from AbbVie, Amgen, Aptose, AROG, Biomea, Bristol Myers Squibb, Celgene, Daiichi Sankyo, F. Hoffmann-La Roche, Forma, Forty-Seven, Genentech/Roche, Gilead, GlycoMimetics, Hanmi, Immune-Onc, Incyte, Jazz, Kymera, Loxo, Pfizer, Pharmacyclics, Sigma Tau, and Treadwell. GJS has received advisory board and/or speaker program honoraria from Agios, Stemline, GSK, AVM Biotech, Orca, Novartis, BMS, Rigel, Incyte, Gilead, Gamida, Autolus, Abbvie, Seattle Genetics, Jazz Pharmaceuticals, Kite (Gilead), Karyopharm, BMS/Celgene, Blueprint Medicine, Astellas, and Amgen; has received consultant fees from BMS, Curios, Daichi-Sankyo, and Novartis; and holds stock or stock options in Amgen, Janssen, and BMS. KY was a consultant for Bristol Myers Squibb/Celgene, F. Hoffmann-La Roche, GSK, Jazz Pharmaceuticals, Novartis, Pfizer, Shattuck Labs, Taiho Oncology, and Takeda; received research funding from Astex Pharmaceuticals, Forma Therapeutics, F. Hoffmann-La Roche, Forma Therapeutics, Genentech, Geron Corporation, Gilead Sciences, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Novartis, and Treadwell Therapeutics; and received honoraria from AbbVie, TaiHo, and Novartis. PBF received unrelated research funding from Novartis. JY received research funding from Pfizer, Puretech, and Janssen. ESW served as advisory/consulting for Abbvie, Blueprint, Daiichi Sankyo, Immunogen, Kite, Kura, Novartis, Qiagen, Rigel, Ryvu, Schrodinger, Servier, Stemline, Syndax, Takeda; speaking roles for Pfizer, Astellas, Dava (all with my own slides); served on DSMC for Gilead and Abbvie; and is section editor for UpToDate. WGB has no competing interests to declare. AM served on DSMC for Foghorn Therapeutics, Daiichi Saynko, advisory for BMS, Abbvie, Novartis, treadwell therapeutics, and is senior medical director for beat aml study for the leukemia and lymphoma society. HT and AS are employees and shareholders of Rigel Pharmaceuticals, Inc. SDB has received honoraria from AbbVie, Astellas Pharma, Bristol Myers Squibb, Jazz Pharmaceuticals, and Servier; has acted as a consultant or advisor to Bristol Myers Squibb, GlaxoSmithKline, Servier, and Syndax; has participated in speakers' bureau for AbbVie, Astellas Pharma, Bristol Myers Squibb, Jazz Pharmaceuticals, and Servier; has received research funding to his institution from Auron Therapeutics and Forma Therapeutics; and has received travel, accommodations, or expenses from AbbVie and Servier. PM has served as a consultant and has received research funding from Servier and Bristol Myers Squibb. AC received support for research/honoraria for advisory boards and meetings from Abbvie and Pfizer; received honoraria for advisory board and meetings from Menarini Stemline, Jazz Pharmaceutical and Servier. JMW has received research funding from and was a board/advisory committee member for Takeda; has received research funding from Immune System Key Ltd; and is a consultant or board/advisory committee member for Genentech, Rafael Pharma, Reven Pharma, Celgene/Bristol-Myers Squib (BMS), Servier, Rigel, Aptose, Astellas, and Daiichi-Sankyo. BAJ served in a consultancy/advisory role for AbbVie, Bristol Myers Squibb, Daiichi Sankyo, Genentech, Gilead, GlycoMimetics, Kymera, Kura, Rigel, Schrodinger, Servier, Syndax and Treadwell, on a protocol steering committee for GlycoMimetics, on a data monitoring committee for Gilead, received travel reimbursement from AbbVie and Rigel, research funding to institution from AbbVie, Amgen, Aptose, AROG, Biomea, Bristol Myers Squibb, Celgene, Daiichi Sankyo, F. Hoffmann-La Roche, Forma, Forty-Seven, Genentech/Roche, Gilead, GlycoMimetics, Hanmi, Immune-Onc, Incyte, Jazz, Kymera, Loxo, Pfizer, Pharmacyclics, Sigma Tau, and Treadwell. GJS has received advisory board and/or speaker program honoraria from Agios, Stemline, GSK, AVM Biotech, Orca, Novartis, BMS, Rigel, Incyte, Gilead, Gamida, Autolus, Abbvie, Seattle Genetics, Jazz Pharmaceuticals, Kite (Gilead), Karyopharm, BMS/Celgene, Blueprint Medicine, Astellas, and Amgen; has received consultant fees from BMS, Curios, Daichi-Sankyo, and Novartis; and holds stock or stock options in Amgen, Janssen, and BMS. KY was a consultant for Bristol Myers Squibb/Celgene, F. Hoffmann-La Roche, GSK, Jazz Pharmaceuticals, Novartis, Pfizer, Shattuck Labs, Taiho Oncology, and Takeda; received research funding from Astex Pharmaceuticals, Forma Therapeutics, F. Hoffmann-La Roche, Forma Therapeutics, Genentech, Geron Corporation, Gilead Sciences, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Novartis, and Treadwell Therapeutics; and received honoraria from AbbVie, TaiHo, and Novartis. PBF received unrelated research funding from Novartis. JY received research funding from Pfizer, Puretech, and Janssen. ESW served as advisory/consulting for Abbvie, Blueprint, Daiichi Sankyo, Immunogen, Kite, Kura, Novartis, Qiagen, Rigel, Ryvu, Schrodinger, Servier, Stemline, Syndax, Takeda; speaking roles for Pfizer, Astellas, Dava (all with my own slides); served on DSMC for Gilead and Abbvie; and is section editor for UpToDate. WGB has no competing interests to declare. AM served on DSMC for Foghorn Therapeutics, Daiichi Saynko, advisory for BMS, Abbvie, Novartis, treadwell therapeutics, and is senior medical director for Beat AML study for the Leukemia and Lymphoma Society. HT and AS are employees and shareholders of Rigel Pharmaceuticals, Inc. SDB has received honoraria from AbbVie, Astellas Pharma, Bristol Myers Squibb, Jazz Pharmaceuticals, and Servier; has acted as a consultant or advisor to Bristol Myers Squibb, GlaxoSmithKline, Servier, and Syndax; has participated in speakers' bureau for AbbVie, Astellas Pharma, Bristol Myers Squibb, Jazz Pharmaceuticals, and Servier; has received research funding to his institution from Auron Therapeutics and Forma Therapeutics; and has received travel, accommodations, or expenses from AbbVie and Servier. PM has served as a consultant and has received research funding from Servier and Bristol Myers Squibb. AC received support for research/honoraria for advisory boards and meetings from Abbvie and Pfizer; received honoraria for advisory board and meetings from Menarini Stemline, Jazz Pharmaceutical and Servier. JMW has received research funding from and was a board/advisory committee member for Takeda; has received research funding from Immune System Key Ltd; and is a consultant or board/advisory committee member for Genentech, Rafael Pharma, Reven Pharma, Celgene/Bristol-Myers Squib (BMS), Servier, Rigel, Aptose, Astellas, and Daiichi-Sankyo.

Author details
[1]Georgia Cancer Center at Augusta University, 1410 Laney Walker Rd., CN2222, Augusta, GA 30912, USA. [2]Cornell University Weill Medical College, New York, NY, USA. [3]Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, MD, USA. [4]Davis Comprehensive Cancer Center, University of California, Sacramento, CA, USA. [5]Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA. [6]Princess Margaret Cancer Centre, Toronto, Canada. [7]Vanderbilt University Medical Center, Nashville, TN, USA. [8]Karmanos Cancer Institute, Detroit, MI, USA. [9]Roswell Park Cancer Institute, Buffalo, NY, USA. [10]Emory Winship Cancer Institute, Atlanta, GA, USA. [11]The Ohio State University, Columbus, OH, USA. [12]Rigel Pharmaceuticals, Inc., South San Francisco, CA, USA. [13]Hematologie Clinique, Institut Gustave Roussy, Villejuif, France. [14]PM-Hematology Department, Hospital Universitari I Politècnic La Fe, Valencia, Spain. [15]Institute of Hematology, IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy. [16]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA.

Received: 6 November 2024 Accepted: 25 December 2024
Published online: 16 January 2025

References

1. Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM. Epidemiology of acute myeloid leukemia: recent progress and enduring challenges. Blood Rev. 2019;36:70–87.
2. Tallman MS, Wang ES, Altman JK, Appelbaum FR, Bhatt VR, Bixby D, et al. Acute Myeloid Leukemia, Version 3. 2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2019;17(6):721–49.
3. Medeiros BC, Fathi AT, DiNardo CD, Pollyea DA, Chan SM, Swords R. Isocitrate dehydrogenase mutations in myeloid malignancies. Leukemia. 2017;31(2):272–81.
4. Urban DJ, Martinez NJ, Davis MI, Brimacombe KR, Cheff DM, Lee TD, et al. Assessing inhibitors of mutant isocitrate dehydrogenase using a suite of pre-clinical discovery assays. Sci Rep. 2017;7(1):12758.
5. Caravella JA, Lin J, Diebold RB, Campbell AM, Ericsson A, Gustafson G, 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.
6. Itsumi M, Inoue S, Elia AJ, Murakami K, Sasaki M, Lind EF, et al. Idh1 protects murine hepatocytes from endotoxin-induced oxidative stress by regulating the intracellular NADP(+)/NADPH ratio. Cell Death Differ. 2015;22(11):1837–45.
7. Ye J, Gu Y, Zhang F, Zhao Y, Yuan Y, Hao Z, et al. IDH1 deficiency attenuates gluconeogenesis in mouse liver by impairing amino acid utilization. Proc Natl Acad Sci USA. 2017;114(2):292–7.
8. Cairns RA, Mak TW. Oncogenic isocitrate dehydrogenase mutations: mechanisms, models, and clinical opportunities. Cancer Discov. 2013;3(7):730–41.

9. Gu Y, Yang R, Yang Y, Zhao Y, Wakeham A, Li WY, et al. IDH1 mutation contributes to myeloid dysplasia in mice by disturbing heme biosynthesis and erythropoiesis. Blood. 2021;137(7):945–58.
10. Reinbold R, Hvinden IC, Rabe P, Herold RA, Finch A, Wood J, et al. Resistance to the isocitrate dehydrogenase 1 mutant inhibitor ivosidenib can be overcome by alternative dimer-interface binding inhibitors. Nat Commun. 2022;13(1):4785.
11. Watts JM, Shaw SJ, Jonas BA. Looking beyond the surface: olutasidenib and ivosidenib for treatment of mIDH1 acute myeloid leukemia. Curr Treat Options Oncol. 2024;25(11):1345–53.
12. Watts JM, Baer MR, Yang J, Prebet T, Lee S, Schiller GJ, 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.
13. de Botton S, Fenaux P, Yee KWL, Recher 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.
14. Cheson BD, Bennett JM, Kopecky KJ, Buchner 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.
15. Montesinos P, Recher C, Vives S, Zarzycka E, Wang J, Bertani G, et al. Ivosidenib and azacitidine in IDH1-Mutated acute myeloid leukemia. N Engl J Med. 2022;386(16):1519–31.
16. Lachowiez C, DiNardo CD, Konopleva M. Venetoclax in acute myeloid leukemia-current and future directions. Leuk Lymphoma. 2020;61(6):1313–22.
17. Edmund J, Thaliath LJ, Meleveedu K. Acute myeloid leukemia in the medically unfit elderly patients. Leuk Res. 2023;130: 107306.
18. Yilmaz M, Kantarjian H, Short NJ, Reville P, Konopleva M, Kadia T, et al. Hypomethylating agent and venetoclax with FLT3 inhibitor "triplet" therapy in older/unfit patients with FLT3 mutated AML. Blood Cancer J. 2022;12(5):77.
19. Pratz KW, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Dohner H, et al. Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. Am J Hematol. 2024;99(4):615–24.

Publisher's Note