Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed or refractory *IDH1*-mutated AML

Stéphane de Botton,[1] Pierre Fenaux,[2] Karen Yee,[3] Christian Récher,[4] Andrew H. Wei,[5] Pau Montesinos,[6] David C. Taussig,[7] Arnaud Pigneux,[8] Thorsten Braun,[9] Antonio Curti,[10] Carolyn Grove,[11] Brian A. Jonas,[12] Asim Khwaja,[13] Ollivier Legrand,[14] Pierre Peterlin,[15] Montserrat Arnan,[16] William Blum,[17] Daniela Cilloni,[18] Devendra K. Hiwase,[19] Joseph G. Jurcic,[20] Jürgen Krauter,[21] Xavier Thomas,[22] Justin M. Watts,[23] Jay Yang,[24] Olga Polyanskaya,[25] Julie Brevard,[25] Jennifer Sweeney,[25] Emma Barrett,[25] and Jorge Cortes[26]

[1]Hematologie Clinique, Institut Gustave Roussy, Villejuif, France; [2]Département (DMU) d'hématologie et immunologie, APHP Nord, Service d'hématologie séniors, Hôpital St Louis/université de Paris, Paris, France; [3]Princess Margaret Cancer Centre, Toronto, ON, Canada; [4]Service d'hématologie, CHU de Toulouse, Institut Universitaire du Cancer Toulouse - Oncopole, Toulouse, France; [5]The Alfred Hospital and Monash University, Peter Mac Callum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia; [6]Hematology Department, Hospital Universitari i Politècnic La Fe, Valencia, Spain; [7]Royal Marsden Hospital, London, United Kingdom; [8]Service d'Hématologie Clinique et Thérapie Cellulaire, CHU Bordeaux, Université de Bordeaux, Bordeaux, France; [9]Service d'Hématologie Clinique Hôpital Avicenne-APHP-Université Paris XIII, Bobigny, France; [10]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Institute of Hematology Seràgnoli, Bologna, Italy; [11]PathWest & Sir Charles Gairdner Hospital, Nedlands, Australia; [12]University of California Davis School of Medicine, Sacramento, CA; [13]Department of Haematology, University College London, London, United Kingdom; [14]Hôpital Saint-Antoine, Université Pierre et Marie Curie, Paris, France; [15]Service d'hématologie clinique, Nantes University Hospital, Nantes, France; [16]Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain; [17]Winship Cancer Institute of Emory University, Atlanta, GA; [18]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy; [19]Royal Adelaide Hospital and SA Pathology, Adelaide, Australia; [20]Columbia University Irving Medical Center and NewYork-Presbyterian Hospital, New York, NY; [21]Braunschweig Municipal Hospital, Braunschweig, Germany; [22]Lyon-Sud Hospital, Pierre-Bénite, Lyon, France; [23]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; [24]Karmanos Cancer Institute, Detroit, MI; [25]Forma Therapeutics, Inc, Watertown, MA; and [26]Georgia Cancer Center, Augusta University, Augusta, GA

Key Points

- Olutasidenib induced durable remissions in patients with m*IDH1* R/R AML; transfusion independence was achieved across all response groups.

- The side effect profile is well-characterized and manageable; olutasidenib represents a therapeutic advance in a poor-prognosis population.

Olutasidenib (FT-2102) is a potent, selective, oral, small-molecule inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1). Overall, 153 IDH1 inhibitor–naive patients with m*IDH1*[R132] relapsed/refractory (R/R) acute myeloid leukemia (AML) received olutasidenib monotherapy 150 mg twice daily in the pivotal cohort of this study. The median age of participants was 71 years (range, 32-87 years) and the median number of prior regimens received by patients was 2 (1-7). The rate of complete remission (CR) plus CR with partial hematologic recovery (CRh) was 35%, and the overall response rate was 48%. Response rates were similar in patients who had, and who had not, received prior venetoclax. With 55% of patients censored at the time of data cut-off, the median duration of CR/CRh was 25.9 months. The median duration of overall response was 11.7 months, and the median overall survival was 11.6 months. Of 86 patients who were transfusion dependent at baseline, a 56-day transfusion independence was achieved in 29 (34%), which included patients in all response groups. Grade 3 or 4 treatment-emergent adverse events (≥10%) were febrile neutropenia and anemia (n = 31; 20% each), thrombocytopenia (n = 25; 16%), and neutropenia (n = 20; 13%). Differentiation syndrome adverse events of special interest occurred in 22 (14%) patients, with 14 (9%) grade ≥3 and 1 fatal case reported. Overall, olutasidenib induced durable remissions and transfusion independence with a well-characterized and manageable side effect profile. The observed efficacy represents a

The full-text version of this article contains a data supplement.

therapeutic advance in this molecularly defined, poor-prognostic population of patients with m*IDH1* R/R AML. This trial was registered at www.clinicaltrials.gov as #NCT02719574.

Introduction

An isocitrate dehydrogenase 1 gene mutation (m*IDH1*) is present in between 7% and 14% of patients with acute myeloid leukemia (AML).[1-3] IDH1 is a metabolic enzyme that catalyzes oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG). *IDH1* gene mutations confer neomorphic enzymatic activity, promoting transformation of α-KG to the oncometabolite, 2-hydroxyglutarate (2-HG). Aberrant accumulation of 2-HG leads to competitive inhibition of α-KG−dependent dioxygenases, which are crucial to DNA and histone demethylation and may block standard differentiation of stem and progenitor cells, thereby promoting neoplastic transformation.[4-6] Inhibition of mIDH1 in tumor cells, and the concomitant reduction in 2-HG production, can restore normal cellular differentiation and provide therapeutic benefit in m*IDH1*-cancers. Inhibitors of mIDH1 have demonstrated efficacy in both newly diagnosed and relapsed/refractory (R/R) AML, and are currently being studied in patients with myelodysplastic syndromes (MDS), cholangiocarcinoma, and glioma.[7-12]

Olutasidenib (FT-2102) is a potent, selective, oral, small-molecule inhibitor of mIDH1 with the therapeutic potential to restore normal cellular differentiation.[12,13] A phase 1/2 trial was conducted to assess the safety, pharmacologic profile, and clinical activity of olutasidenib both as monotherapy and in combination with azacitidine in patients with MDS or AML harboring m*IDH1*. Here, we report results from a preplanned interim analysis in patients with m*IDH1* R/R AML who received olutasidenib monotherapy in the pivotal phase 2 cohort of the trial. Enrollment was stopped early at this second interim analysis when the efficacy stopping criteria were met.

Methods

Study design

Study 2102-HEM-101 (#NCT02719574) is an open-label, multicenter, phase 1/2 trial. During phase 1, the phase 2 dose of 150 mg twice daily was selected.[12] Phase 2 includes multiple cohorts of patients with AML and MDS and is ongoing. In this pivotal cohort, patients with m*IDH1* R/R AML were enrolled from 57 centers in 9 countries and received 150 mg olutasidenib monotherapy, twice daily, in continuous 28-day cycles.

The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. The protocol was approved by the institutional review boards or ethics committee at study sites. Written informed consent was provided by all patients.

Patients

Patients aged ≥18 years, harboring mIDH1^{R132} with pathologically proven AML, R/R to standard treatment were included. Central confirmation of mutation status was performed using pretreatment peripheral blood and/or bone marrow aspirate samples. Other criteria included Eastern Cooperative Oncology Group (ECOG) performance status 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.

Efficacy assessments

The primary efficacy end point was the rate of complete remission (CR) plus CR with partial hematologic recovery (CRh), by investigator assessment, using modified response criteria of the International Working Group in AML.[14,15] CRh was defined as bone marrow blasts <5% with an absolute neutrophil count >0.5 × 10^9/L and platelet count >50 × 10^9/L.

Overall response rate (ORR) was a secondary end point, defined as the rate of CR, CRh, CR with incomplete blood count recovery (CRi), partial remission (which required recovery of neutrophil and platelet counts consistent with a CR), or morphologic leukemia-free state (MLFS). Other secondary end points included duration of CR + CRh, duration of overall response (DOR), rate of transfusion independence (TI), and overall survival (OS). Patients were classified as transfusion dependent if platelet and/or red blood cell (RBC) transfusion was administered within 8 weeks before baseline and were transfusion independent if platelet and/or RBC transfusion was not administered for at least 56 days during treatment. For the OS, patient data were censored at the last date they were known to be alive. DOR was calculated from the time of first response until death, relapse, or new anticancer therapy; patients without an event were censored at their last response assessment.

Safety assessments

Safety data were summarized descriptively for patients who received at least 1 dose of olutasidenib. Adverse events (AEs) were recorded from the time of first dose until 28 days after the last dose of study drug. AEs were coded using MedDRA version 19.1 and graded via the NCI-CTCAE version 4.03.

Translational analyses

Peripheral blood samples were collected for pharmacodynamic assessments, including for 2-HG, a biomarker of the on-target activity of olutasidenib. Bone marrow and peripheral blood samples were collected for mutational analyses, including for *IDH1* variant allele frequency (VAF) and comutations. Methods for translational analyses are described in the supplemental Appendix.

Statistical analysis

A group sequential design using O'Brien Fleming boundaries was used with 2 planned interim analyses and a final test. A sample size of 173 patients would provide 90% power to test the null hypothesis that the true rate of CR + CRh is ≤15% with a 2.5% significance level, using a one-sided exact test for a binomial proportion, assuming the true response rate was 25%. At the first interim analysis, if ≤6 responses in 58 evaluable participants were observed, the trial would be stopped early for futility. At the second interim analysis (at 67% information or an efficacy-evaluable

population of 115), the trial may be stopped for either futility or further enrollment may be stopped for efficacy. An early stopping criterion for efficacy was met when ≤28 responses were observed in 115 evaluable participants, and enrollment was stopped.

Time to OS and time to response were measured from the first dose to the event; time to OS and DOR were measured using Kaplan-Meier methods. The survival probability and 95% confidence interval (CI) were estimated at 3, 6, 12, and 24 months based on the Kaplan-Meier product-limit method and Greenwood formula.

Results

Patient disposition and baseline characteristics

Between April 2018 and June 2020, 153 patients with m*IDH1* R/R AML were enrolled and received at least 1 dose of olutasidenib (150 mg, twice daily). Olutasidenib was administered in the outpatient setting throughout the trial, except for 2 days during which pharmacokinetic sampling was performed. Compliance with medication was tracked using patient diaries. Mean (±standard deviation) treatment compliance was 99.4% (±2.1%).

At data cut-off on 18 June 2021, 21 (14%) patients remained on treatment and 132 (86%) had discontinued. The most common reasons for discontinuation were disease progression (n = 62; 41%), AE (n = 26; 17%), hematopoietic stem cell transplantation (HSCT) (n = 15; 10%), and death (n = 14; 9%). Median treatment duration was 142 days (range, 3-1045 days).

The efficacy-evaluable population comprised 147 patients who received the first dose of olutasidenib at least 6 months before data cut-off. Patients had received a median of 2 prior regimens (range, 1-7). Most patients had received prior induction therapy (n = 143; 97%) and prior cytarabine (n = 105; 71%). Data on specific induction regimens were not collected. In total, 12 patients had received prior treatment with venetoclax. No patient had received prior IDH1 inhibitor therapy. Patient and disease characteristics are presented in Table 1.

Response

In the primary efficacy evaluation, 51 of 147 patients achieved CR or CRh, yielding a CR + CRh rate of 35% (95% CI, 27.0-43.0). Most patients who achieved CR/CRh responded early, with a median time to response of 1.9 months (range, 0.9-5.6 months). The CR rate was 32% (n = 47; 95% CI, 24.5-40.2). The ORR was 48% (n = 71; 95% CI, 40.0-56.7) (Table 2).

Median duration of CR/CRh was 25.9 months (95% CI, 13.5-NE [not evaluable]) with 55% of patients censored; all 28 censored patients were still being followed-up for duration of response at data cut-off. The estimated percentages of patients who maintained CR/CRh at 6 and 12 months were 78% and 63%, respectively. (Figure 1). Median duration of CR was 28.1 months (95% CI, 13.8-NE). Median DOR was 11.7 months (95% CI, 6.9-25.9).

For 12 patients previously treated with venetoclax, the CR + CRh rate was 33% (n = 4; 95% CI, 9.9-65.1) and the CR rate was 25% (n = 3; 95% CI, 5.5-57.2); moreover, 2 patients achieved CRi and 2 achieved stable disease, providing an ORR of 50% (n = 6; 95% CI, 21.1-78.9). Two of 3 patients who achieved CR and 1 who achieved CRh in the postvenetoclax population remained in remission and were receiving study treatment at the time of data

cut-off; 1 patient who achieved CR discontinued olutasidenib because of an AE.

OS

The median OS was 11.6 months (95% CI, 8.9-15.5) in the overall population of 153 patients. (Figure 2A). Better response was strongly associated with longer survival. In patients who achieved CR/CRh, the median OS was not reached (95% CI, 22.8-NE), and the estimated 18-month survival was 78%. For patients who responded but did not achieve CR/CRh, the median OS was 13.7 months (95% CI, 6.0-NE). In nonresponders, the median OS was 4.0 months (95% CI, 3.2-5.8) (Figure 2B).

Transplantation

In total, 16 patients underwent transplantation, including 15 who discontinued olutasidenib to receive HSCT and 1 who discontinued because of a grade 3 AE of bone marrow hypoplasia but subsequently proceeded to transplantation. Patients who received HSCT were followed-up for DOR and OS because HSCT was not an event in time-to-event analysis. To address the possibility that use of HSCT after olutasidenib treatment could favorably influence DOR and OS, sensitivity analyses were performed in which patients had censored observation at the time of transplantation (supplemental Figures 2 and 3). Similar outcomes were observed irrespective of censoring for transplantation.

Hematologic analyses

TI was observed in patients in all response groups. Of 86 patients who were RBC and/or platelet transfusion dependent at baseline, 29 (34%) achieved TI during any 56-day postbaseline period. High rates of both platelet and RBC TI (100% and 88%, respectively) were observed among patients who were transfusion dependent at baseline and achieved CR/CRh. In contrast, responders who did not achieve CR/CRh had platelet and RBC TI rates of 58% and 53%, respectively (Figure 3).

Translational analyses

IDH1 mutation subtype and comutations at baseline are presented in Table 1. Patients who achieved CR/CRh had fewer comutations compared with other responders (supplemental Table 3). Although the ORR was not significantly reduced, the rate of CR/CRh in patients with receptor tyrosine kinase pathway mutations was lower than that in patients without receptor tyrosine kinase pathway mutations. Response rates tended to be lower in patients with concurrent FLT3 mutations. Patients in CR/CRh were more likely to have VAF clearance (28%; 11 of 39) than other responders (8%, 1 of 12) or nonresponders (7%, 2 of 30). After 2 cycles of treatment, the median 2-HG concentration was reduced by 82% (83% in CR/CRh responders, and 80% in other responders). The observed reductions in 2-HG were sustained throughout subsequent treatment cycles.

Safety

At least 1 treatment-emergent AE (TEAE) was reported in all 153 patients. The most frequent TEAEs (≥20%), irrespective of relationship to olutasidenib, were nausea (n = 58; 38%), constipation and anemia (n = 40; 26% each), leukocytosis (n = 38; 25%), pyrexia (n = 36; 24%), fatigue (n = 35, 23%), febrile neutropenia

Table 1. Patient demographic and baseline disease characteristics in the efficacy-evaluable population

Parameter	Efficacy-evaluable population (n = 147)
Sex, n (%)	
Male/female	74 (50)/73 (50)
Age (y)	
Median (range)	71 (32-87)
ECOG PS, n (%)	
0	45 (31)
1	76 (52)
2	23 (16)
AML type, n (%)	
Primary de novo	97 (66)
Secondary:	50 (34)
MDS	39 (78)
Therapy related	4 (8)
Other*	7 (14)
AML cytogenetic risk category (per either NCCN or ELN guidelines),† n (%)	
Favorable	6 (4)
Intermediate	107 (73)
Poor	25 (17)
Unknown	9 (6)
Prior AML therapy outcome, n (%)	
Refractory	51 (35)
Relapsed	96 (65)
Remission duration ≤12 months	67 (70)
Remission duration >12 months	29 (30)
Number of prior regimens	
Median (range)	2 (1-7)
1 regimen, n (%)	48 (33)
2 regimens, n (%)	45 (31)
≥3 regimens, n (%)	54 (37)
Prior treatments received,‡ n (%)	
Induction therapy§	143 (97)
Cytarabine	105 (71)
Idarubicin	64 (44)
Daunorubicin	31 (21)
Fludarabine	25 (17)
Hypomethylating agent	58 (39)
As a single agent	21 (14)
In combination with venetoclax	8 (5)
Gemtuzumab based combinations	11 (7)
Venetoclax	12 (8)
Allogeneic HSCT	17 (12)
Hematologic laboratory parameters, median (range)	
Percentage of bone marrow blasts	42 (4-98)
Percentage of peripheral blood blasts	22.5 (1-96)
White blood cells ×10^9/L	2 (0.1-75)
Absolute neutrophil count ×10^9/L	0.35 (0-5.3)

Table 1 (continued)

Parameter	Efficacy-evaluable population (n = 147)
Renal function (creatinine clearance), n (%)	
Normal (≥90 mL/min)	60 (41)
Mildly impaired (60-89 mL/min)	66 (45)
Moderately impaired (30-59 mL/min)	21 (14)
Severely impaired (15-29 mL/min)	0
***IDH1* mutation type (as determined by investigator), n (%)**	
R132C	90 (61)
R132H	34 (23)
R132G	10 (7)
R132S	10 (7)
R132L	3 (2)
Number of co-occurring mutations, n (%)‖	
1 to 3	91 (62)
4 to 7	19 (13)
None	4 (3)
Not done/unknown	33 (22)
Co-occurring mutations in >5% patients, n (%)‖	
Epigenetic	80 (54)
DNMT3A	67 (46)
TET2	22 (15)
Differentiation	62 (42)
NPM1	31 (21)
RUNX1	20 (14)
PHF6	8 (5)
RTK pathways	58 (40)
FLT3	15 (10)
NRAS	14 (10)
JAK2	12 (8)
Chromatin	50 (34)
ASXL1	23 (16)
STAG2	12 (8)
BCOR	12 (8)
Splicing	43 (29)
SRSF2	25 (17)
U2AF1	10 (7)
Other	15 (10)
TP53	9 (6)

ECOG, Eastern Cooperative Oncology Group; ELN, European Leukemia Net; NCCN, National Comprehensive Cancer Network; PS, performance status; RTK, receptor tyrosine kinase.

*Other secondary AML types were essential thrombocytopenia and myelofibrosis (each 2 patients; 1%) and chronic myelomonocytic leukemia myeloproliferative neoplasm and polycythemia vera (each 1 patient; 1%).

†Data on the type of classification system of cytogenetic risk was used (either NCCN or ELN guidelines) were not collected.

‡Other prior antineoplastic agents received were lomustine (11 patients; 7%); mitoxantrone (9 patients; 6%); etoposide (5 patients; 3%); amsacrine (3 patients; 2%); cladribine, doxorubicin, durvalumab, melphalan, and midostaurin (each 2 patients; 1%); and alemtuzumab, cyclophosphamide, dinaciclib, enasidenib, glasdegib, hydroxycarbamide, idasanutlin, mercaptopurine, and methotrexate (each 1 patient; 1%).

§Data on the specific induction regimen used were not collected.

‖Mutations apart from *IDH1*.

Table 2. Response rates in the efficacy-evaluable population

Response rates	Efficacy-evaluable population (n = 147)
CR* or CRh	
n (%) [95% CI]	51 (35) [27.0-43.0]
Median time to CR/CRh, mo (range)	1.9 (0.9-5.6)
CR*	
n (%) [95% CI]	47 (32) [24.5-40.2]
Median time to CR, months (range)	2.8 (0.9-7.4)
Overall response	
N (%) [95% CI]	71 (48) [40.0-56.7]
Median time to first overall response, mo (range)	1.9 (0.9-10.2)
Best overall response, n (%)	
CR*	47 (32)
CRh	4 (3)
CRi	15 (10)
PR	3 (2)
MLFS	2 (1)
SD†	42 (29)
Progressive disease	10 (7)
Not evaluable/not done	6 (4) / 18 (12)

CRi, CR with incomplete blood count recovery; PR, partial remission; SD, stable disease (failure to achieve at least a PR but not meeting criteria for progressive disease. SD for a period of ≥8 weeks indicates clinical benefit).

*Includes patients with CR, complete cytogenetic remission, and complete molecular remission.

†Includes 3 patients considered to have clinical benefit by the treating physician and 2 patients considered to have resistant but stable disease.

(n = 33; 22%), dyspnea and diarrhea (n = 31; 20% each), and thrombocytopenia and hypokalemia (n = 30, 20% each).

Grade 3 and 4 TEAEs, irrespective of relationship to olutasidenib, were reported in 84% of patients, of which the most frequent

(≥10%) were febrile neutropenia and anemia (n = 31; 20% each), thrombocytopenia (n = 25; 16%), and neutropenia (n = 20; 13%). The most frequent TEAEs of any grade (≥5%) and grades 3 and 4 (>1%) assessed as treatment-related are summarized in Table 3.

Serious TEAEs, irrespective of relationship to olutasidenib, were reported in 111 (73%) patients, of which the most frequent (≥5%) were disease progression (n = 25; 16%), febrile neutropenia (n = 23; 15%), and pneumonia and differentiation syndrome (DS) (n = 14; 9% each).

In total, 80 (52%) patients experienced TEAEs resulting in dose interruption, including DS (n = 11; 7%), increased alanine aminotransferase (n = 8; 5%), and febrile neutropenia (n = 7; 5%). Twenty-four (16%) patients had TEAEs resulting in dose reduction, including increased alanine aminotransferase (n = 5; 3%), unspecified abnormal liver function test (n = 3; 2%), and increased aspartate aminotransferase, increased gamma-glutamyltransferase, and DS (n = 2; 1% each).

Deaths on treatment or within 28 days of the final dose were reported in 48 (31%) patients; the majority were related to progression of AML or its complications. Events leading to death in >1 patient were disease progression (n = 22; 14%), pneumonia (n = 3; 2%) and pneumonia fungal, cerebral hemorrhage, respiratory failure, sepsis (n = 2, 1% each), and death not otherwise specified. TEAEs leading to death assessed as treatment related were disease progression and DS in 1 patient each.

DS was reported as an AE among 22 (14%) patients, with grade ≥3 events in 14 (9%) patients. Concomitant leukocytosis was reported in 6 patients with DS events, all of whom had a baseline leukocyte count of <15 × 10^9/L. DS resulted in dose modifications (hold and/or reduction) in 12 patients, 11 of whom continued treatment with olutasidenib, including 1 at a reduced dose. Three patients permanently discontinued treatment because of DS, including 1 patient after a dose hold and subsequent dose reduction, and 2 patients who discontinued without prior dose modification. For most affected patients, DS occurred within the

Figure 1. Duration of response for patients with CR/CRh (n = 51).
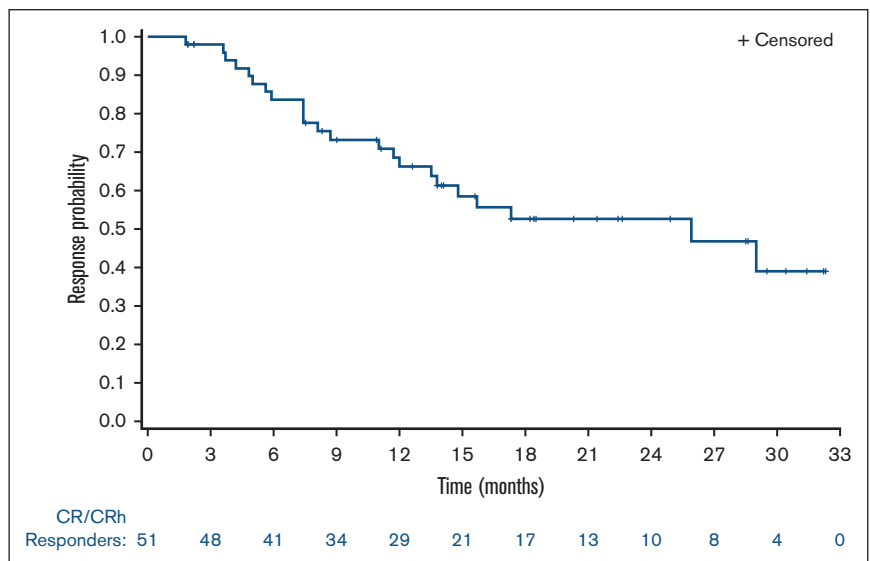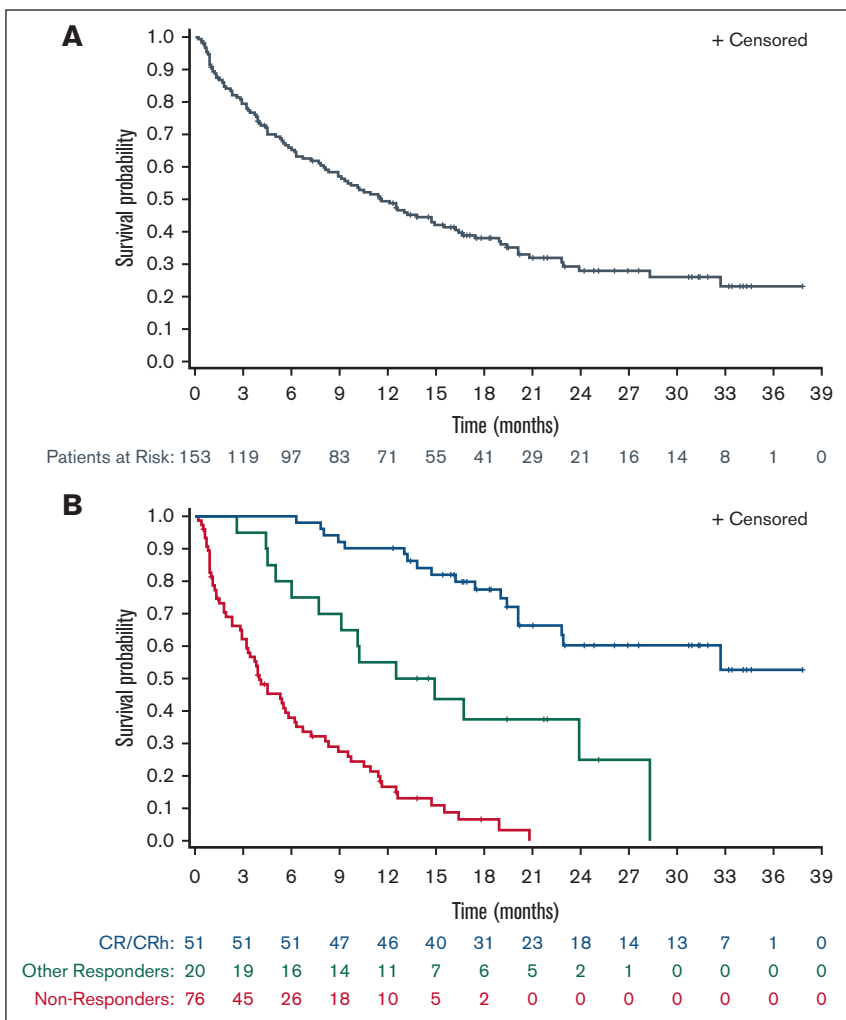
Figure 2. OS. (A) OS for patients in the full analysis population (N = 153). (B) OS for patients in the efficacy-evaluable population with CR/CRh (n = 51), other responders (n = 20), and nonresponders (n = 76). Other responders are patients with CRi, PR, or MLFS. Nonresponders are patients in response assessment categories other than CR/CRh, CRi, PR, and MLFS.
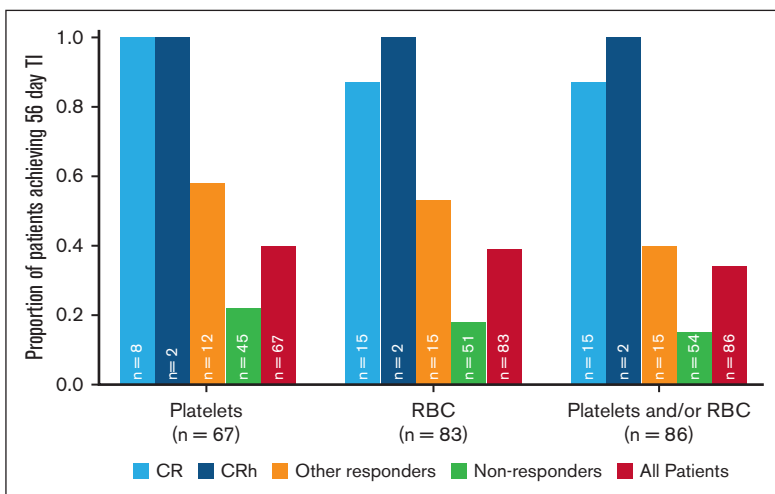
Figure 3. Patients who were transfusion dependent at baseline and achieved TI for ≥56 days. Other responders are patients with CRi, PR, or MLFS. Nonresponders are patients in response assessment categories other than CR/CRh, CRi, PR, and MLFS.

Table 3. All TEAEs of all grades (greater than or equal to 20%) and of grade 3 or 4 severity (greater than or equal to 10%); and TEAEs assessed as related to treatment with olutasidenib of all grades (greater than or equal to 5%) and of grade 3 or 4 severity (greater than 1%)

AE	All TEAEs		Treatment-related TEAEs	
	All grades (≥20%) n (%)	Grade 3 or 4 (≥10%) n (%)	All grades (≥5%) n (%)	Grade 3 or 4 (>1%) n (%)
Patients with any AE	153 (100)	129 (84)	111 (73)	59 (39)
Nausea	58 (38)	0 (0)	35 (23)	0 (0)
Anemia	40 (26)	31 (20)	9 (6)	7 (5)
Constipation	40 (26)	0 (0)	12 (8)	0 (0)
Leukocytosis	38 (25)	14 (9)	20 (13)	7 (5)
Pyrexia	36 (24)	1 (1)	2 (1)	0 (0)
Fatigue	35 (23)	2 (1)	11 (7)	1 (1)
Febrile neutropenia	33 (22)	31 (20)	2 (1)	2 (1)
Dyspnea	31 (20)	5 (3)	5 (3)	1 (1)
Diarrhea	31 (20)	2 (1)	8 (5)	1 (1)
Thrombocytopenia	30 (20)	25 (16)	8 (5)	6 (4)
Hypokalemia	30 (20)	9 (6)	3 (2)	0 (0)
Neutropenia	20 (13)	20 (13)	8 (5)	8 (5)
Decreased appetite	25 (16)	3 (2)	8 (5)	0 (0)
DS	22 (14)	13 (8)	22 (14)	13 (8)
Alanine aminotransferase increased	18 (12)	7 (5)	13 (8)	4 (3)
Aspartate aminotransferase increased	14 (9)	4 (3)	9 (6)	3 (2)
Gamma-glutamyltransferase increased	10 (7)	8 (5)	8 (5)	7 (5)
Hepatic enzyme increased	7 (5)	5 (3)	6 (4)	5 (3)
Tumor lysis syndrome	4 (3)	4 (3)	3 (2)	3 (2)
Deviating liver function test	3 (2)	3 (2)	3 (2)	3 (2)

first 2 cycles of treatment, with a median time to the first event of 17.5 days (range, 1-561 days). Most patients with DS were treated with IV or oral dexamethasone. Other medications used to manage DS included oral hydroxycarbamide, furosemide, IV methylprednisolone, oral mercaptopurine, and IV antibiotics. One patient, a 70-year-old male with refractory AML, died on study-day 31 from complications of DS. This patient presented with hypoxia requiring oxygen supplementation on day 6 associated with pulmonary edema and renal decompensation and increasing leukocytes, neutrophils, and monocytes. Dosing was interrupted on day 8 and the patient received IV dexamethasone and hydroxyurea; however, leukocytosis progressed and the patient deteriorated to a fatal outcome 23 days after receiving the last dose of olutasidenib. Further details of the patient management guidelines for DS are available in the study protocol and supplemental Table 1.

Hepatic AEs of special interest (AESI) occurred in 38 (25%) patients, with grade 3 events reported in 19 (12%) and grade 4 events in 4 (3%) patients. The most frequent grade 3 or 4 hepatic AESI were increases in laboratory liver function parameters (Table 4). A summary of shifts in liver function parameters from baseline to the highest grade reported on study is provided in supplemental Table 2. Serious hepatic AESI were primarily reports of laboratory abnormalities and occurred in 11 (7%) patients, all of which were assessed as treatment related. Hepatic AESI were managed by treatment interruptions in 19 (12%) patients, dose reductions in 10 (7%) patients, and resulted in treatment discontinuation in 7 (5%) patients. No patients met the criteria for Hy's

law, and no hepatic AESI led to liver failure. Most events occurred early, within the first 2 months of treatment, and resolved within 2 to 4 weeks, with or without dose modifications.

QT interval prolongation occurred in 12 (8%) patients; all events were of grade 1 or 2 severity, except for 1 grade 3 event assessed as unrelated to study treatment. All QT prolongation events were transient in nature. Interruption of dosing occurred in 2 patients, 1 of whom had experienced the grade 3 event assessed as unrelated to study treatment. Neither dose reduction nor treatment discontinuation was required for any patient because of QT prolongation.

Table 4. Patients with treatment-emergent hepatic AESI (greater than 1%) of all grades, and of grade 3 or 4 severity

Patients with hepatic AESI (>1%)	All grades, n (%)	Grade 3 or 4, n (%)
Patients with at least 1 treatment-emergent hepatic AESI	38 (25)	23 (15)
Investigations	33 (22)	19 (12)
Alanine aminotransferase increased	18 (12)	7 (5)
Aspartate aminotransferase increased	14 (9)	4 (3)
Gamma-glutamyltransferase increased	10 (7)	8 (5)
Blood bilirubin increased	8 (5)	2 (1)
Hepatic enzyme increased	7 (5)	5 (3)
Liver function test deviated	3 (2)	3 (2)

Of the 12 patients who experienced this AE, 6 had previously commenced treatment with a medication associated with QT prolongation either on or before the date of the event; 3 of the 12 patients had received levofloxacin, and 1 patient each had received amiodarone, fluconazole, and ondansetron.

Discussion

Olutasidenib is a targeted, oral therapy in development for the treatment of patients with *IDH1*-mutated cancers. Inhibition of mIDH1 in tumor cells and the concomitant decrease in 2-HG can restore normal cellular differentiation and provide therapeutic benefit in patients harboring *IDH1* mutations. IDH1 inhibitors have recently demonstrated efficacy in AML, with initial proof of concept in patients with MDS, solid tumor, and glioma.[7,10,16-20]

The pivotal cohort of this study comprised 153 patients with m*IDH1* R/R AML. Baseline characteristics, including the age and overall health of the population, were generally comparable with populations enrolled in similar clinical trials for this indication. Olutasidenib demonstrated a clinically meaningful CR + CRh rate of 35%, with CR representing the majority of responses. Achievement of CR/CRh is associated with clinical benefit, both through the establishment of disease control and through a reduced risk of infection and bleeding after the resumption of hematopoiesis. The CR + CRh rate was defined as the primary efficacy end point, consistent with other Food and Drug Administration (FDA)-approved IDH or FLT3 inhibitors for the treatment of R/R AML.[7,15,21-25] The CR + CRh reference rate of 15% was selected as the null hypothesis based on historical data in similar populations of patients at high risk, with rates of CR ranging from 12% to 16% and median OS from 3.3 to 6.3 months.[26-28] The observed CR + CRh rate of 35% in our study thus represents clinically meaningful efficacy in the high-risk population evaluated. The majority of patients had co-occurring mutations, were in the intermediate-to-poor AML cytogenetic risk category, had received prior induction therapy, and had a median of 2, with up to 7, prior treatment regimens. These results are also encouraging in the context of outcomes recently reported for ivosidenib, an FDA-approved IDH1 inhibitor that achieved a CR + CRh rate of 33%, with median duration of CR + CRh of 8.2 months and a median DOR of 6.5 months in a similar population of patients with R/R AML.[7] Although the CR + CRh rate of 35% in our study is similar to that reported for ivosidenib, median duration of CR + CRh for olutasidenib was 25.9 months and median DOR was 11.7 months. In this context, the efficacy of olutasidenib compares favorably with that of ivosidenib in patients with R/R AML, based on the data available to date. Furthermore, the median OS of 11.6 months for olutasidenib well exceeds that reported in historical studies, and is encouraging in the context of the 8.8 months reported for ivosidenib in a similar patient population.[7] Although olutasidenib and ivosidenib are structurally distinct, apparent differences in the overall clinical profile of these agents remain unconfirmed in the absence of a head-to-head study. In addition, although patient and disease characteristics of the ivosidenib study population appear to be similar to those of the olutasidenib population described herein, there may be some small differences in latent variables that influence outcomes. Overall, the efficacy data we present here for olutasidenib appear to be encouraging in this poor-prognostic population, particularly the duration of the responses. Further

data from ongoing studies may provide additional insights regarding differences between IDH1 inhibitors in the future.

Conversion to TI, another recognized indicator of clinical benefit, was achieved in 34% of patients (29 of 86) who received olutasidenib and had been classified as transfusion dependent at baseline. Moreover, 16 (11%) patients underwent allogeneic HSCT, indicating the potential of olutasidenib as a bridge to the only currently available therapy with curative potential. Most patients who underwent transplantation are still being followed-up for duration of response and survival, such that the median cannot yet be estimated, but long-term outcomes in this population will be explored in future reports. Results in 12 patients who received prior venetoclax were also promising; the remission rate was consistent with that of the broader study population, and most patients who achieved remission had an ongoing remission at the time of data cut-off.

The comutational profile at baseline was consistent with previous reports,[22] suggesting that the population of our study is representative of patients with m*IDH1* AML. To further explore the possibility that primary resistance to IDH inhibitors may be because of disease burden, as exemplified by comutations or VAF,[15] analyses of clinical response were conducted by baseline genetics. Achievement of CR/CRh was associated with fewer comutations and with VAF clearance. Longitudinal analyses of 2-HG concentration were performed to explore potential mechanisms of acquired resistance. The sustained on-target activity of olutasidenib observed attributable to suppression of 2-HG was consistent with previous findings,[12] indicating that acquired resistance is unlikely to be related to a loss of pharmacologic effect. Future reports will further investigate potential mutation-associated resistance pathways, including the role of *IDH1* mutation subtypes and individual comutations in the response to olutasidenib.

In this pivotal cohort, olutasidenib was well tolerated with an AE profile largely characteristic of symptoms or conditions experienced by patients undergoing treatment for AML or of the underlying disease itself. The most common AEs were gastrointestinal and hematologic in nature. These events are expected, readily recognized, and managed with dose modifications and standard-of-care measures by physicians who provide care for patients with AML. Hepatic AESI occurred in the early cycles of treatment and were generally characterized by asymptomatic laboratory elevations and AEs presenting with a mixed cholestatic-hepatocellular injury pattern. These events were manageable with dose holds or modifications and did not result in liver failure. QT prolongation was infrequently observed, with only 1 patient experiencing a grade 3 event that resolved after treatment interruption. No QT prolongation AEs led to a dose reduction or treatment discontinuation. Furthermore, because of the class potential for QT prolongation with mIDH1 inhibitors, the safety profile was further investigated in a cardiac substudy in which Holter monitoring was performed; olutasidenib showed no effects on heart rate, AV conduction, or cardiac depolarization. No new clinically relevant morphologic changes demonstrated any signal of concern. There was also no evidence of a large effect of olutasidenib on cardiac repolarization, as evidenced by concentration-QTc modeling results and time-matched and categorical outlier analyses (Forma Therapeutics, Inc. data on file; July 2021). These observations are fully in accordance with the safety profile we describe herein.

DS is a significant and potentially life-threatening risk of novel, targeted AML therapies, including inhibitors of IDH1, IDH2, and FLT3. DS may occur when normal cellular differentiation is restored, thereby promoting the maturation of leukemic blast cells and their subsequent extravasation into the lungs, skin, and other soft tissues. This can result in diverse clinical manifestations of the syndrome, such that a careful differential diagnosis is required. The signs and symptoms are generally nonspecific and can resemble infections and other complications of AML. Most frequently, these include respiratory manifestations, with symptoms including dyspnea and pulmonary infiltrates or pleuropericardial effusion. Fever or leukocytosis in the absence of infection may also occur, in addition to the potential for edema-related weight gain, hypotension, rash, or acute renal failure in some patients. Familiarity with the clinical presentation of DS is critical because early recognition and treatment of suspected cases, especially rapid intervention with corticosteroids, have been shown to be effective in this syndrome, which can otherwise prove fatal if treatment is delayed. Early intervention for DS with targeted therapies is usually effective and rarely necessitates interruption or discontinuation of therapy.[29] To characterize DS and establish practical recommendations for diagnosis and treatment more clearly, an independent review committee retrospectively evaluated 72 potential cases among 281 patients with R/R AML in a study of the FDA-approved IDH2 inhibitor enasidenib. It was concluded that DS occurred in ~12% of patients treated with enasidenib. Of note, only 33 of the 72 suspected cases were confirmed as possible or probable DS by the review committee. The study also suggested that patients who experienced the syndrome were less likely to have <20% bone marrow blasts (6% vs 22%; $P = .04$) and more likely to have received fewer prior anticancer regimens (median, 1.0 [range, 1-4] vs 2.0 [1-14]; $P = .05$) at study entry than those who did not.[30] More recently, the rate of DS was reportedly 11% for the IDH1 inhibitor ivosidenib in the registrational study in patients with R/R AML.[7] In the pivotal cohort of this study, DS was reported in 14% of patients with R/R AML, the majority of whom were successfully managed with dose interruptions and supportive treatment with steroids, diuretics, and hydroxyurea. The incidence rate of DS for olutasidenib was thus comparable with that reported for FDA-approved IDH1 and IDH2 inhibitors in similar patient populations.

Overall, the efficacy data we present herein for olutasidenib appear to be encouraging in this poor-prognostic population, particularly the durability of the responses. Further data from studies currently in progress may provide additional insights into differences between IDH1 inhibitors. Investigation of olutasidenib in other m*IDH1* hematologic malignancies is ongoing.[31]

In conclusion, olutasidenib monotherapy induced durable remissions and TI among patients with R/R m*IDH1* AML with a well-characterized and manageable side effect profile. The observed efficacy is clinically meaningful and represents a therapeutic advance in this molecularly defined patient population that has a poor prognosis and limited treatment options.

Acknowledgments

The sponsor of this study (Forma Therapeutics, Inc.) collaborated with the clinical investigators in the study design, conduct, and data collection. The study sponsor analyzed the data and conducted the statistical analyses. All authors had access to, and had the opportunity to review, the study data.

Authorship

Contribution: O.P., J.B., and J.S. designed the study and developed the protocol; J.B. developed the statistical plan; S.d.B., P.F., K.Y., C.R., A.H.W., P.M., D.C.T., A.P., T.B., A.C., C.G., B.A.J., A.K., O.L., P.P., M.A., W.B., D.C., D.K.H., J.G.J., J.K., X.T., J.M.W., and J.Y. recruited the patients; S.d.B., P.F., K.Y., C.R., A.H.W., P.M., D.C.T., A.P., T.B., A.C., C.G., B.A.J., A.K., O.L., P.P., M.A., W.B., D.C., D.K.H., J.G.J., J.K., X.T., J.M.W., J.Y., J.C., O.P., J.B., J.S., and E.B. collected the data; O.P., J.B., J.S., and E.B. participated in the analysis and interpretation of pharmacokinetic and pharmacodynamic data; and all authors participated in the analysis and interpretation of the clinical data and the development of the manuscript and were responsible for the decision to submit the article for publication.

Conflict-of-interest disclosure: S.d.B. has received honoraria and research funding from Forma Therapeutics; has received honoraria and research funding from and is a consultant to Agios; has received honoraria from, is a consultant to, and is on the speakers' bureau for Celgene; has received honoraria from and is a consult to Astellas, Daiichi Sankyo, Syros, AbbVie, Bayer, and Janssen; has received honoraria from Seattle Genetics; and is a consultant to Pierre Fabre, Novartis, Pfizer, and Servier. P.F. is a consultant to and has received honoraria and research funding from AbbVie, Janssen, Jazz Pharmaceuticals, Novartis, and Bristol Myers Squibb (BMS). K.Y. is a consultant to and has received research funding from F. Hoffman-La-Roche and Jazz Pharmaceticals; is a consultant to and has received honoraria and research funding from Novartis; is a consultant to Astellas, BMS/Celgene, GlaxoSmithKline, Pfizer, Shattuck Labs, Taiho, and Takeda; has received research funding from Astex, Forma Therapeutics, Geron, Gilead, Janssen, Karyopharm, and Treadwell; and has received honoraria from AbbVie. C.R. is a consultant to, has received honoraria and research funding from, and is a board/advisory committee member for AbbVie, BMS, and Jazz Pharmaceuticals; has received honoraria and research funding from and is a board/advisory committee member for Amgen and Astellas; is a board/advisory committee member for Novartis, Pfizer, and Takeda; and is a consultant to, has received honoraria from, and is a board/advisory committee member for Servier. A.H.W. has received honoraria and research funding from, is a consultant to, is on the speakers' bureau, and is a board/advisory committee member for Astellas; has received honoraria and research funding from, is on the speakers' bureau, and is a board/advisory committee member for AbbVie/Genentech, Amgen, Celgene/BMS, and Novartis; has received research funding and honoraria from, is a consultant to, and is a board/advisory committee member for Servier and Syndax; has received honoraria from, is a consultant to, and is a board/advisory committee member for Janssen and Gilead; has received honoraria from and is a board/advisory committee member for MacroGenetics and Pfizer; has received honoraria and research funding from and is a board/advisory committee member for AstraZeneca; has received research funding from Astex; is an

ORCID profiles: S.d.B., 0000-0002-8126-4942; K.Y., 0000-0002-2572-9952; C.R., 0000-0002-3332-4525; A.H.W., 0000-0002-7514-3298; P.M., 0000-0002-3275-5593; A.C., 0000-0002-7752-6049; C.G., 0000-0003-2788-9893; B.A.J., 0000-0002-4921-5809; D.C., 0000-0001-6346-4791; X.T., 0000-0002-5332-2404; J.C., 0000-0002-8636-1071.

Correspondence: Jorge Cortes, Georgia Cancer Center, Augusta University, 1410 Laney Walker Blvd, CN2222, Augusta, GA 30912; email: jorge.cortes@augusta.edu.

References

1. Botton SD, Watts J, Baer M, et al. PS1051 FT-2102, an IDH1 m inhibitor, induces mutation clearance in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) treated in phase 1 dose escalation and expansion study. *HemaSphere*. 2019;3(s1):475-476.

2. DiNardo CD, Ravandi F, Agresta S, et al. Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML. *Am J Hematol*. 2015;90(8):732-736.

3. Gross S, Cairns RA, Minden MD, et al. Cancer-associated metabolite 2-hydroxyglutarate accumulates in acute myelogenous leukemia with isocitrate dehydrogenase 1 and 2 mutations. *J Exp Med*. 2010;207(2):339-344.

4. Cairns RA, Mak TW. Oncogenic isocitrate dehydrogenase mutations: mechanisms, models, and clinical opportunities. *Cancer Discov*. 2013;3(7):730-741.

5. Losman JA, Looper RE, Koivunen P, et al. (R)-2-hydroxyglutarate is sufficient to promote leukemogenesis and its effects are reversible. *Science*. 2013;339(6127):1621-1625.

6. Lu C, Ward PS, Kapoor GS, et al. IDH mutation impairs histone demethylation and results in a block to cell differentiation. *Nature*. 2012;483(7390):474-478.

7. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398.

8. Fan B, Le K, Manyak E, et al. Longitudinal pharmacokinetic/pharmacodynamic profile of AG-120, a potent inhibitor of the IDH1 mutant protein, in a phase 1 study of IDH1-mutant advanced hematologic malignancies. *Blood*. 2015;126(23):1310.

9. De La Fuente MI, Colman H, Rosenthal M, et al. A phase Ib/II study of olutasidenib in patients with relapsed/refractory IDH1 mutant gliomas: safety and efficacy as single agent and in combination with azacitidine. *J Clin Oncol*. 2020;38(15 suppl):2505.

10. Lowery MA, Abou-Alfa GK, Valle JW, et al. ClarIDHy: a phase 3, multicenter, randomized, double-blind study of AG-120 vs placebo in patients with an advanced cholangiocarcinoma with an IDH1 mutation. Paper presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; 2-6 June. 2017. Chicago, IL.

11. Norsworthy KJ, Luo L, Hsu V, et al. FDA approval summary: ivosidenib for relapsed or refractory acute myeloid leukemia with an isocitrate dehydrogenase-1 mutation. *Clin Cancer Res*. 2019;25(11):3205-3209.

12. Watts JM, Baer MR, Yang J, 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-e58.

13. Caravella JA, Lin J, Diebold RB, et al. Structure-based design and identification of FT-2102 (olutasidenib), a potent mutant-selective IDH1 inhibitor. *J Med Chem*. 2020;63(4):1612-1623.

14. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards of therapeutic trials in acute myeloid leukemia. *J Clin Oncol*. 2003;21(24):4642-4649.

15. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130(6):722-731.

16. de Botton S, Pollyea DA, Stein EM, et al. Clinical safety and activity of AG-120, a first-in-class potent inhibitor of the IDH1 mutant protein, in a phase 1 study of patients with advanced, IDH1-mutant hematological malignancies. Paper presented at: 20th Congress of the European Hematology Association. 2015. Abstract P563.

17. de la Fuente MI, Colman H, Rosenthal MA, et al. Phase 1b/2 study of olutasidenib (FT-2102), an inhibitor of mutant IDH1, in patients with relapsed/refractory IDH1-mutant gliomas: preliminary safety and clinical activity. Paper presented at: 24th Annual Meeting of the Society for NeuroOncology; 20-24. November 2019. Phoenix, AZ. Abstract ACTR-52.

18. Fan B, Chen Y, Wang F, et al. Pharmacokinetic/pharmacodynamics evaluation of AG-120, a potent inhibitor of the IDH1 mutant protein, in a phase 1 study of IDH-1mutant advanced hematologic malignancies. Paper presented at: 20th Congress of the European Hematology Association. 2015. Abstract P572.

19. Mellinghoff IK, Maher EA, Wen PY, et al. A phase 1, multicenter, randomized, open-label, perioperative study of AG-120 (ivosidenib) and AG-881 in patients with recurrent, nonenhancing, IDH1-mutant, low-grade glioma. Paper presented at: 23rd Annual Scientific Meeting and Education Day of the Society for Neuro-Oncology (SNO); 15-18. November 2018. New Orleans, LA.

20. Mellinghoff IK, Touat M, Maher E, et al. AG-120, a first-in-class mutant IDH1 inhibitor in patients with recurrent or progressive IDH1 mutant glioma: updated results from the phase 1 non-enhancing glioma population. Paper presented at: Society for Neuro-Oncology Annual Scientific Meeting; 16-19. November 2017. San Francisco, CA.

21. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381(18):1728-1740.

22. Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood*. 2020;135(7):463-471.

23. IDHIFA [enasidenib]. Prescribing information. Celgene Corporation, Summit, NJ. Accessed 15 February 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209606s000lbl.pdf

24. Tibsovo [ivosidenib]. Prescribing information. Servier Pharmaceuticals LLC, Boston, MA. Accessed 15 February 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211192_s008lbl.pdf

25. US Department of Health and Human Services, Food and Drug Administration. Acute myeloid leukemia: developing drugs and biological products for treatment guidance for industry. Accessed 15 February 2023. https://www.fda.gov/media/162362/download

26. Roboz GJ, Rosenblat T, Arellano M, et al. International randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory acute myeloid leukemia. *J Clin Oncol*. 2014;32(18):1919-1926.

27. Faderl S, Ravandi F, Huang X, et al. Clofarabine plus low-dose cytarabine followed by clofarabine plus low-dose cytarabine alternating with decitabine in acute myeloid leukemia frontline therapy for older patients. *Cancer*. 2012;118(18):4471-4477.

28. Ravandi F, Ritchie EK, Sayar H, et al. Vosaroxin plus cytarabine versus placebo plus cytarabine in patients with first relapsed or refractory acute myeloid leukaemia (VALOR): a randomised, controlled, double-blind, multinational, phase 3 study. *Lancet Oncol*. 2015;16(9):1025-1036.

29. Fathi AT, Stein EM, DiNardo CD, Levis MJ, Montesinos P, de Botton S. Differentiation syndrome with lower-intensity treatments for acute myeloid leukemia. *Am J Hematol*. 2021;96(6):735-746.

30. Fathi AT, DiNardo CD, Kline I, et al. Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2: analysis of a phase 1/2 study. *JAMA Oncol*. 2018;4(8):1106-1110.

31. Cortes JE, Esteve J, Bajel A, et al. Olutasidenib (FT-2102) in combination with azacitidine induces durable complete remissions in patients with mIDH1 acute myeloid leukemia. *Blood*. 2021;138(suppl 1):698.