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Olutasidenib: from bench to bedside

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The discovery of isocitrate dehydrogenase 1 (*IDH1*) mutations in acute myeloid leukemia (AML) and the resounding success of molecularly targeted therapies in related myeloid malignancies swiftly prompted the development of *IDH1*^{mut} inhibitors. Olutasidenib (formerly known as FT-2102) is an orally administered novel *IDH1*^{mut} inhibitor that entered clinical development in 2016, proceeded briskly through the developmental process, and was granted regular approval to treat patients with R/R *IDH1*^{mut} AML on 1 December 2022. Single agent olutasidenib, a potent and selective *IDH1*^{mut} inhibitor, demonstrated highly durable remission rates along with meaningful outcomes, such as transfusion independence, in patients with R/R *IDH1*^{mut} AML. This review will examine the preclinical and clinical development and the positioning of olutasidenib in the *IDH1*^{mut} AML treatment landscape.

Introduction

Isocitrate dehydrogenase 1 (*IDH1*) mutations are recurrently mutated in about 10% of patients with acute myeloid leukemia (AML).[1] *IDH1*^{mut} in AML is frequently associated with older age and a normal karyotype and often co-occur with *NPM1, DNMT3A,* and *FLT3*-ITD mutations.[2,3] The prognostic impact of *IDH1*^{mut} in AML is not well defined, and there are seemingly conflicting data[4]: a Cancer and Leukemia Group B study (2010) reported that cytogenetically normal patients with AML aged <60 years (who received intensive chemotherapy but no allogeneic hematopoietic stem cell transplantation [HSCT]) with *IDH1/NPM1*$^{co\text{-}mut}$ (*FLT3*-ITD wild-type) had inferior outcomes in terms of overall survival (OS) and disease-free survival compared with those with *IDH1* or *IDH2* wild-type,[2] whereas an Eastern Cooperative Oncology Group study (2012) reported favorable outcomes in *IDH/NPM1*$^{co\text{-}mut}$ (*FLT3*-ITD wild-type) younger patients with AML (<60 years) independent of HSCT.[5] Moreover, Meggendorfer et al. reported better outcomes in patients with *IDH1*^{mut} compared with those with *IDH2*^{mut} (R140) AML, but this may have been confounded by increased rates of HSCT in *IDH1*^{mut} AML.[3] Most recently, the Acute Leukemia French Association (ALFA-2021) study reported a survival benefit with co-occurring *NPM1*^{mut} and HSCT in complete remission (CR1) in patients with *IDH1*^{mut} AML treated with intensive chemotherapy (2008-2016).[6] In patients with AML not fit for intensive chemotherapy, those with *IDH1/2* mutations appear to be particularly sensitive to venetoclax and hypomethylating agent (HMA) combination therapy (VIALE-A, 2020),[7] with longer durations of response and improved OS (particularly in *IDH2*^{mut} patients) compared with IDH wild-type patients.[8] To paraphrase Shakespeare,[9] "*IDH1*^{mut} are not prognostic by themselves, but by reflection, by some other things," meaning they appear to be context dependent.[10]

Among patients with relapsed/refractory (R/R) AML, particularly in older patients, the probability of achieving an optimal response decreases with each relapse, and the median OS is ~6 months, regardless of therapy intensity.[11-13] Historically, among patients with *IDH1*^{mut} R/R AML treated with any

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therapy (intensive chemotherapy or HMA-based without venetoclax), remission rates (CR or CR with incomplete count recovery [CRi]) were 40% and 36%, and median OS was 5.9 and 4 months in the first and second (or greater) salvage settings, respectively,[14] which sharply illustrated the need for effective and tolerable treatment options in *IDH1*^{mut} R/R AML. In older patients with *IDH1*^{mut} AML treated with frontline HMA-based therapy without venetoclax, the overall response rate (ORR) was 45% and the median OS was 9.5 months.[12] Subsequent development of *IDH1*^{mut} inhibitors led to the approval of ivosidenib in 2018, which demonstrated an ORR (ORR = CR + CR with partial hematologic recovery [CRh] + CRi + partial response + morphologic leukemia-free survival) of 41.6% and a median duration of response (ORR) of 6.5 months in patients with *IDH1*^{mut} R/R AML.[15] Subsequently, ivosidenib was also approved as monotherapy and in combination with azacitidine for patients with newly diagnosed AML unfit for intensive chemotherapy.[16] On 1 December 2022, olutasidenib became the second *IDH1*^{mut} inhibitor approved by the US Food and Drug Administration to treat adult patients with *IDH1*^{mut} R/R AML.[17]

Biology of *IDH1*-mutated AML

IDH is a key metabolic enzyme of the tricarboxylic acid cycle, comprising 2 primary isoforms: IDH1 (cytosolic) and IDH2 (mitochondrial), which are known to be recurrently mutated in a range of hematologic and solid tumor malignancies.[18] *IDH1*^{mut} are gain-of-function mutations (altered function/neomorphic activity) in the conserved arginine residues (R132 of *IDH1*) within the enzymatically active binding site.[19] Although IDH catalyzes the reversible oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) by reducing nicotinamide adenine dinucleotide phosphate (NADP+) to NADPH, the mutant *IDH1* protein facilitates the conversion of α-KG to 2-hydroxyglutarate (2-HG), an oncometabolite that consumes NADPH.[20,21] In *IDH*^{mut} AML, 2-HG (a structural analog of α-KG) competitively inhibits the pathways that use α-KG as a substrate, leading to epigenetic dysregulation with aberrant histone and DNA methylation, cellular differentiation block, and apoptosis inhibition through *BCL-2* (antiapoptotic gene) dependence.[22-24] In *IDH*-mutant malignancies, NADPH consumption promotes reprogramming of the metabolome, affecting DNA damage repair and intracellular trafficking.[18] Collectively, hypermethylation, altered metabolism, and cellular differentiation arrest drive the leukemogenic state in *IDH*^{mut} AML.

Development of olutasidenib

The distinct configuration and role of *IDH*^{mut} prompted the discovery of small-molecule inhibitors of IDH1, such as olutasidenib. A high-throughput biochemical screen for agents targeting the *IDH1*^{mut}-R132H heterodimer led to the discovery of the quinolinone class of inhibitors.[25] Through a series of optimizations, olutasidenib, a quinolinone derivative, was generated as an orally administered, highly selective, potent, and brain-penetrant inhibitor of *IDH1*^{mut}-R132 variants (50% inhibitory concentration for R132H and R132C, 24 nM and 125 nM, respectively) with no activity against wild-type *IDH1*.[26] Specifically, *IDH1*^{mut} destabilizes the α-helical structure of the regulatory segment of the IDH complex.[27] Olutasidenib, an allosteric inhibitor of *IDH*1^{mut}, binds in a hydrophobic pocket situated near the IDH1 heterodimer interface and stabilizes the mutant IDH1 enzyme in its open (inactive) conformation, thereby preventing the conformational change required for neomorphic catalytic activity and 2-HG production.[26] Although ivosidenib and olutasidenib are both allosteric type II IDH1 inhibitors[26,28] (as opposed to catalytically active site inhibitors), olutasidenib has a distinct chemical structure (quinolinone-based) and different binding properties (2:1 stoichiometry).[21,22,29] In vitro, olutasidenib treatment suppressed 2-HG production and induced granulocytic/monocytic cell differentiation in *IDH1*^{mut} primary human AML cells, and this activity was recapitulated in *IDH1*^{mut} AML xenograft models.[22-30]

Phase 1 evaluation of olutasidenib

The phase 1 portion of the study evaluated the safety and tolerability of olutasidenib as a single agent and in combination with azacitidine in patients with *IDH1*^{mut} AML or revised International Prognostic Scoring System–defined intermediate, high, or very high-risk myelodysplastic syndrome (MDS). The combination arm included patients with prior exposure to ivosidenib. Olutasidenib monotherapy was evaluated in the R/R setting (4 patients were treatment-naïve) and olutasidenib with azacitidine combination therapy was evaluated in both the treatment-naïve and R/R settings.[31]

Among the 78 enrolled patients, 32 received olutasidenib monotherapy (150 mg daily, 300 mg daily, and 150 mg twice daily), and 46 received combination therapy with azacitidine, of which 3 patients had prior exposure to ivosidenib. The median age of the monotherapy cohort was 72 years (interquartile range, 66-77), and that of the combination cohort was 67 years (interquartile range, 58-72). Grade 3 to 4 hematologic adverse events (AEs) were more common with combination therapy than monotherapy: thrombocytopenia (41% and 28%, respectively), febrile neutropenia (28% and 22%), anemia (20% and 22%), and neutropenia (28% and 6%). Common grade 1 to 2 nonhematologic AEs in patients who received monotherapy included nausea (47%), fatigue (41%), pyrexia (31%), and vomiting (25%). Class-specific AEs included differentiation syndrome (DS), liver function test abnormalities, and QT interval prolongation on ECG, which occurred in 13%, 16%, and 0% of patients in the monotherapy group, respectively, and in 13%, 11%, and 7% of patients in the combination therapy group, respectively.

Olutasidenib exhibited on-target activity with a >90% reduction of 2-HG, which was sustained over time, and the addition of azacitidine did not alter its pharmacokinetic (PK) profile. Olutasidenib demonstrated clinical activity as a single agent in R/R AML (ORR 41%) and as combination therapy (ORR, 46%). Of note, 36% of patients with AML with baseline transfusion dependence achieved durable transfusion independence (TI). For the R/R *IDH1*^{mut} AML cohort, at a median follow-up of less than 1 year, the median OS was 8.7 months (95% confidence interval [95% CI], 2.5-not estimable [NE]) for monotherapy and 12.1 months (95% CI, 4.2-NE) for combination therapy. In treatment-naïve patients with *IDH1*^{mut} AML receiving combination therapy, the ORR was 77% and the median OS was not reached (95% CI, 9.6-NE). A signal of clinical activity was also detected in patients with *IDH1*^{mut} MDS. Olutasidenib 150 mg twice daily was chosen as the recommended phase 2 dose (RP2D) because of its highest olutasidenib exposure, maximum pharmacodynamic (PD) response with an acceptable

safety profile, and preliminary clinical efficacy (the maximum tolerated dose was not reached/explored). Finally, *IDH1* mutation clearance (variant allele frequency [VAF] <1% by droplet digital polymerase chain reaction [ddPCR]) was detected in 40% of responders with AML and in 44% of those with MDS; however, an association between *IDH1* mutation clearance and response was unclear, as some patients with stable disease also demonstrated mutation clearance.

Phase 2 evaluation of olutasidenib

The preplanned interim analysis of the pivotal phase 2 cohort of patients with R/R *IDH1*^{mut} AML treated with olutasidenib monotherapy was recently reported.[32] Patients with prior IDH inhibitor therapy were excluded. The primary efficacy end point was CR + CRh per the modified response criteria of the International Working Group in AML.[33] The study used a group sequential design with 1 futility interim analysis at the time of ~33% of patients and 1 efficacy interim analysis at the time of ~67% of patients completing the first response assessment. The pivotal cohort enrolled 153 patients, 147 of whom were efficacy evaluable. Patients received a median of 2 prior AML-directed regimens (range, 1-7), of which 97% had prior exposure to induction chemotherapy, 39% prior HMA-based therapy, 12% prior HSCT, and 12 patients (8%) had received prior treatment with venetoclax. Most patients (65%) had relapsed disease (70% with remission duration ≤12 months), and 35% of patients had primary refractory disease.

Among patients evaluable for efficacy (n = 147), the CR + CRh rate was 35% (95% CI, 27.0-43.0). The median time to CR/CRh was 1.9 months (range, 0.9-5.6), and the median duration of CR/CRh was 25.9 months (95% CI, 13.5-NE). The ORR was 48% (95% CI, 40.0-56.7), and the median duration of overall response was 11.7 months (95% CI, 6.9-25.9). Among the 12 patients with prior exposure to venetoclax, the ORR was 50% with 4 patients achieving CR/CRh (33%; 95% CI, 9.9-65.1) and 2 patients having CRi. In the entire study population, the median OS was 11.6 months (95% CI, 8.9-15.5), and the median OS was not reached (95% CI, 22.8-NE) in those who achieved CR/CRh. The median OS in non-CR/CRh responders was 13.7 months (95% CI, 6.0-NE). Among 86 patients with red blood cell (RBC) and/or platelet transfusion dependence at baseline, 29 (34%) achieved TI. Of note, TI was observed regardless of response, albeit with higher rates (platelet 100%, RBC 88%) among those who achieved CR/CRh than those who did not achieve CR/CRh (platelet 58%, RBC 53%).

In the safety population (n = 153), the most common grade 3 and 4 hematologic AEs included febrile neutropenia and anemia (20% each), thrombocytopenia (16%), and neutropenia (13%). The most common causes of dose interruption were related to DS (7%), increased liver enzymes, and febrile neutropenia (5% each). DS of any grade occurred in 14% of patients, of whom 9% had grade ≥3 AE and 1 patient had fatal DS. Most commonly, DS occurred within the first 2 cycles of treatment, with a median time to first occurrence of 17.5 days (range, 1-561). Hepatic AEs occurred in 25% of patients, with grade 3 AEs in 12% and grade 4 AEs in 3% of patients, which were mostly reversible laboratory liver test abnormalities with no incidence of liver failure. Most patients were able to resume therapy after dose interruption/reduction. Transient QT prolongation occurred in 8% of patients, of which most were grade 1/2, and all cases resolved spontaneously.

Most patients (61%) had *IDH1*^{mut}-R132C, followed by R132H (23%) and other R132 variants (16%), and the most common comutations were *DNMT3A* (46%), *NPM1* (21%) and *SRSF2* (17%).[32] Receptor tyrosine kinase (RTK) pathway mutations were reported in 40% of patients (most common: *FLT3* 10%, *NRAS* 10%, and *JAK2* 8%). Patients in CR/CRh were more likely to have VAF clearance (11 of 39; 28%) than other responders 14 (1 of 12; 8%) or nonresponders (2 of 30; 7%). Data presented by de Botton et al in 2021 showed that patients with *IDH1*^{mut}-R132H had lower CR/CRh rates (17% vs 37% with the R132C variant) and harbored more *NPM1* and/or *FLT3* comutations.[34] Overall, patients with RTK mutations had significantly lower CR/CRh rates than those without (17% vs 44%, respectively, $P = .002$), which is analogous to resistance patterns that have been observed with ivosidenib.[35] Somewhat surprisingly, patients with co-occurring *NPM1* mutations were also less likely to respond (14% vs 39%, $P = .021$). At the time, no patients with *FLT3* mutations (0 of 14, $P = .005$) had responded to olutasidenib monotherapy, and patients with *DNMT3A* or *ASXL1* comutations had numerically higher rates of CR/CRh. Finally, patients with fewer comutations (mean 1.6 [standard deviation 1.4] in patients with CR/CRh, n = 40) and lower baseline *IDH1* VAF had higher rates of CR/CRh ($P < .05$ for both).

Taken together, olutasidenib is safe and compares favorably to historical CR + CRh rates (35% vs ~15% in R/R AML with conventional therapy) with a clinically meaningful duration of response (median 25.9 months) and durable TI, leading to its approval in patients with R/R *IDH1*^{mut} AML.[32] Survival in CR/CRh responders was also encouraging, with the median not yet reached and an estimated 18-month survival of 78%.

The phase 2 results of the olutasidenib and azacitidine combination (Olu-AZA) in AML were recently presented.[36] This study enrolled 4 cohorts, which included treatment-naïve patients with AML, and patients with R/R AML/MDS: with no prior exposure to HMA or IDH1 inhibitors, R/R to HMA (prior IDH1 inhibitor excluded), and patients with prior exposure to IDH1 inhibitors (including Olu-monotherapy, prior HMA excluded) as their last therapy before enrollment. At the time of presentation, 72 pts with AML/MDS (n = 63/9: R/R without prior HMA/IDH1 therapy, n = 20; R/R with prior HMA therapy, n = 21; R/R with prior IDH1 therapy, n = 20; treatment-naïve AML, n = 11) were enrolled on this ongoing study. The median age of the study cohort was 72 years (range, 28-84) and patients had received a median of 2 prior therapies (range, 1-5). In patients with AML, the CR/CRh rates were 45% (5 of 11) in the treatment-naïve setting and in the R/R setting, CR/CRh rates were 47% (9 of 19) in those without prior HMA/IDH1 inhibitor therapy, 38% (5 of 13) with prior HMA therapy, and 30% (6 of 20) with prior IDH1 inhibitor therapy. The duration of CR/CRh was highest in the treatment-naïve setting (NR [NE-NE]) followed by 16.0 months (0.9-NE) in those with R/R AML without prior HMA/IDH1 inhibitor therapy, and 8.0 months (3.0-NE) and 4.7 months (1.7-NE) in patients with prior exposure to HMA or IDH1 inhibitor, respectively. No new safety signals were detected, and the AE profile was similar to that of olutasidenib monotherapy. In patients with AML, Olu-AZA combination therapy appears to be effective in those without prior exposure to HMA or IDH1 inhibitors in both treatment-naïve and R/R settings and has demonstrated clinical activity in patients with prior HMA or IDH1 inhibitor exposure.

Positioning of olutasidenib in *IDH1*^{mut} AML

HMA therapy in combination with venetoclax has proven to be an efficacious treatment option in older patients with AML and has effectively transformed the AML treatment landscape for patients not eligible to receive intensive chemotherapy.[7,37] *IDH1*^{mut} AML is particularly sensitive to venetoclax in view of its BCL2 dependence.[24] In a pooled analysis of treatment-naïve patients with *IDH1*^{mut} AML treated with azacytidine + venetoclax, the composite CR rate (CR + CRi) was 66.7% with a median duration of CR/CRi of 21.9 months (95% CI, 7.8-NE) and a median OS of 15.2 months (95% CI, 7.0-NE).[8] In May 2022, azacitidine and ivosidenib combination therapy was also approved to treat patients with *IDH1*^{mut} AML, who are older or not able to receive intensive chemotherapy.[38] The phase 3 placebo-controlled AGILE trial, largely conducted in Europe after the approval of azacitidine+venetoclax in the United States, evaluated the azacytidine + ivosidenib combination in 72 patients with newly diagnosed *IDH1*^{mut} AML (74 patients received azacytidine + placebo). The CR + CRh rate was 54%, with a median duration of response of 22.1 months (95% CI, 13.0-NE) and a median OS of 24 months with azacitidine+ivosidenib. At a median follow-up of 12.4 months, the study achieved its primary end point of event-free survival, which was significantly longer with azacytidine + ivosidenib compared with azacytidine + placebo (hazard ratio for treatment failure, relapse from remission, or death, 0.33; 95% CI, 0.16-0.69; $P = .002$). No new safety signals were detected compared to ivosidenib monotherapy.[16]

Inevitably, most patients with AML will relapse with or without an *IDH1* mutation. Currently, ivosidenib and olutasidenib are approved as single agents to treat patients with R/R *IDH1*^{mut} AML (Table 1). With necessary caution for cross-trial comparison,[15,32] olutasidenib compares favorably to ivosidenib in terms of median duration of CR/CRh (25.9 vs 8.2 months), estimated 18-month survival in CR/CRh responders (78% vs 50%), and median OS in all patients (11.6 vs 8.8 months). Response rates also favored olutasidenib but were more similar to ivosidenib. Compared with the notable difference in CR/CRh duration and survival in responders, the more modest difference in survival in all patients likely reflects that more than half of patients do not respond to either agent (olutasidenib 52%, ivosidenib 58%) and have poor median OS (~4 months) on both studies. Importantly, olutasidenib also demonstrated clinical activity in patients with prior exposure to venetoclax.[32] Primary 2-HG–independent resistance mechanisms to olutasidenib were similar to those to ivosidenib and are likely attributable to class effects (eg, RTK pathway mutations, high mutational burden).[34,35]

Although the rates of response and rates/magnitude of 2-HG reduction[26,28] are relatively similar between the 2 drugs, which along with 50% inhibitory concentration data suggest a similar potency, the duration of response is markedly different. Reasons for disparate response patterns between olutasidenib and ivosidenib may be due to different crystal structures or binding sites or to the PK/PD profiles unique to each drug. For example, PK/PD data show that olutasidenib had stable plasma exposure throughout treatment duration with sustained 2-HG reduction until cycle 16.[39,40]

Importantly, preclinical studies also suggest that olutasidenib may possibly have a role in patients with acquired ivosidenib resistance secondary to the development of second-site *IDH1* S280F mutations in cis with the neomorphic R132C mutation.[41] Combined biochemical and structural studies have shown that the S280F substitution hinders ivosidenib binding to the IDH1 variant dimer-interface and enables more efficient 2-HG production, leading to ivosidenib resistance.[29] Cell-based inhibitor screening results (as measured by 2-HG production) have further demonstrated that ivosidenib does not effectively inhibit *IDH1* double mutants, such as R132C/S280F and R132H/S280F, as opposed to olutasidenib and other preclinical alternative dimer-interface inhibitors, which maintain potent activity against these variants.[36] Mechanistically, S280F-mediated resistance to ivosidenib may be overcome by olutasidenib because of its 2:1 binding stoichiometry (2 inhibitor molecules per *IDH1* variant dimer), unlike ivosidenib, which binds with 1:1 stoichiometry (1 inhibitor molecule per *IDH1* variant dimer).[26,27] Whether these preclinical findings are relevant clinically in preventing treatment failure is not yet known. In terms of other 2-HG dependent resistance mechanisms, rates of *IDH2* isoform switching with olutasidenib are not known.

IDH1 mutation clearance by ddPCR has been described with both drugs (28% of patients with CR/CRh tested with olutasidenib, 21% of patients with CR/CRh tested with ivosidenib) and appears to be associated with rate and depth of response,[15,32] but its association with response duration is less clear (a trend is reported with ivosidenib, and data are not reported with olutasidenib). Moreover, the definition and prognostic impact of measurable residual disease in *IDH1*^{mut} AML, including how it is assessed and by what methodology (ie, VAF clearance [ddPCR vs high sensitivity next generation sequencing] or aberrant phenotype [multiparameter flow cytometry]), remain to be fully elucidated.

Given the lack of head-to-head data, it is not possible to ascertain the superiority of olutasidenib over ivosidenib. Although the 2 studies were similar, differences in both study design and patient populations may have affected clinical outcomes (eg, the ivosidenib population had more patients with poor-risk cytogenetics and prior HSCT). However, differences in baseline characteristics may influence response rates more than duration, as patients with similar molecular features are more likely to respond to either agent, and a better understanding of mechanisms of relapse to olutasidenib is needed. These studies were also conducted 3 to 4 years apart, which could have influenced familiarity with IDH inhibitors as a class and changed the broader AML treatment landscape. We note the approval of venetoclax in the United States in 2018 while the olutasidenib study was ongoing, although the pivotal phase 2 olutasidenib cohort was enrolled primarily in Europe. To our knowledge, patients were not censored for HSCT when calculating median response duration or OS in either study, although sensitivity analysis of olutasidenib showed near identical results when censoring for HSCT.[32]

Finally, toxicity profiles may partially differentiate the 2 agents. The rates and severity of IDH-DS are remarkably similar between the 2 drugs. However, ivosidenib carries an US Food and Drug Administration warning for QTc interval prolongation, which requires monitoring upon starting therapy and possible adjustment of dose or concomitant medications, whereas olutasidenib does not. In contrast, olutasidenib carries a warning for hepatotoxicity, which also requires monitoring and could require dose interruption and/or reduction, whereas ivosidenib does not. Otherwise, both drugs are very well tolerated.[15,32,40]

Table 1. Comparison of baseline demographics and efficacy outcomes in patients with *IDH1*^{mut} R/R AML treated on the pivotal registrational trials of olutasidenib and ivosidenib

Efficacy evaluable population	Olutasidenib[32] N = 147	Ivosidenib[15] N = 125
Age, median (range or IQR)	71 (range: 32-87)	67 (range: 18-87)
Sex, n (%)		
Female	73 (50)	60 (48)
Male	74 (50)	65 (52)
AML type, n (%)		
De novo	97 (66)	83 (66)
Secondary	50 (34)	42 (34)
Hematologic malignancies, n (%)		
MDS	39 (26)	18 (14)
Other	7 (5)	10 (8)
Therapy related	4 (3)	14 (11)
Cytogenetic risk, n (%)		
Favorable	6 (4)	–
Intermediate	107 (73)	66 (53)
Poor	25 (17)	38 (30)
Missing/unknown	9 (6)	21 (17)
***IDH1* mutation, n (%)**		
R132C	90 (61)	76 (61)
R132H	34 (23)	27 (22)
R132G/S/L	23 (15)	19 (15)
Wild-type/other	–	3 (2)
Comutations, n (%)		
NPM1	31 (21)	24 (20)
FLT3	15 (10)	9 (8)
CEBPA	<10%	3 (3)
Prior regimens, median (range or IQR)	2 (range: 1-7)	2 (range: 1-6)
Venetoclax, n (%)	12 (8)	0
HSCT, n (%)	17 (12)	36 (29)
ECOG PS, n (%)		
0	45 (31)	27 (22)
1	76 (52)	64 (51)
2	23 (16)	32 (26)
3	0	2 (1)
Bone marrow blast percentage, median (range)	42 (4-98)	56 (0-98)
Response outcomes		
Composite CR rate (CR + CRh)	35%	30%
CR rate	32%	21%
ORR (CR + CRh + CRi + PR + MLFS)	48%	42%
HSCT	11%	12%
Duration of responses		
Median time to CR/CRh	1.9 mo	2.7 mo
Median duration of CR/CRh	25.9 mo	8.2 mo
Median duration of CR	28.1 mo	9.3 mo
Median duration of overall response	11.7 mo	6.5 mo

ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; MLFS, morphologic leukemia-free survival; PR, partial response.
*In the 153-patient safety population (which included the 147-patient efficacy evaluable population plus 6 patients with lack of a centrally confirmed *IDH1* mutation).

Table 1 (continued)

Efficacy evaluable population	Olutasidenib[32] N = 147	Ivosidenib[15] N = 125
Survival outcomes		
18-mo survival rate for patients with CR/CRh	78%	50%
Median OS	11.6 mo*	8.8 mo

ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; MLFS, morphologic leukemia-free survival; PR, partial response.
*In the 153-patient safety population (which included the 147-patient efficacy evaluable population plus 6 patients with lack of a centrally confirmed *IDH1* mutation).

Conclusion

The approval of olutasidenib is a critical addition to the *IDH1*^{mut} AML treatment landscape, with encouragingly durable responses. The available data support its use as monotherapy in patients with R/R AML who have failed intensive chemotherapy or venetoclax plus HMA. The choice of which IDH1 inhibitor to use first in these settings is not yet clear, although we would recommend olutasidenib in venetoclax plus HMA failures given the available data. The role of olutasidenib in patients who have failed ivosidenib monotherapy in any setting or frontline ivosidenib plus azacitidine is not known, and we would consider other treatment options (eg, venetoclax-based therapy) in this setting.

Olutasidenib is currently being evaluated in frontline and R/R settings as monotherapy and as combination therapy with azacitidine with and without prior exposure to HMA or IDH1 inhibitors (NCT02719574). These ongoing studies will hopefully clarify the role of olutasidenib in treatment-naïve *IDH1*^{mut} AML (including when given in combination with azacitidine) and in R/R *IDH1*^{mut} AML with prior IDH1 inhibitor exposure. Further studies assessing maintenance, triplet therapy, and sequencing with venetoclax and azacitidine are being considered.

Authorship

Contribution: S.V. and J.W. conceived the idea, analyzed the data, and wrote the paper.

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