

# IDH1-mutated relapsed or refractory AML: current challenges and future prospects

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**Abstract:** The prognosis of patients with relapsed or refractory acute myeloid leukemia (R/R AML) is discouraging with salvage standard approaches. Mutations of isocitrate dehydrogenase 1 (IDH1<sup>mut</sup>), present in 7–14% of AML patients, have been discovered recently, opening the door to targeted agents aiming to improve the outcomes in this setting. Several oral selective IDH1<sup>mut</sup> inhibitors are under investigation, ivosidenib being the first approved for R/R AML. We performed a systematic review to analyze the clinical outcomes and safety reported with IDH1<sup>mut</sup> inhibitors and other agents in adult patients with IDH1<sup>mut</sup> R/R AML. Ivosidenib in monotherapy achieved complete remission (CR) of 24%, overall response of 42%, and median overall survival of 9 months in R/R AML, and promising outcomes were reported with IDH305 and FT-2102. IDH1<sup>mut</sup> inhibitors were generally well tolerated, but some therapy-related toxicities should be monitored, including IDH-differentiation syndrome, prolongation of the QT interval, and leukocytosis, all manageable and reversible. Also, venetoclax, CB-839, PARP inhibitors, and IDH1 peptide vaccine are being studied in IDH1<sup>mut</sup> AML. The results of the ongoing and upcoming clinical trials will bring new evidence to establish the role of IDH1<sup>mut</sup> inhibitors in therapeutic strategies of AML.

**Keywords:** isocitrate dehydrogenase 1, acute myeloid leukemia, relapsed/refractory, ivosidenib, FT-2102, venetoclax

## Introduction

Despite improvements in chemotherapy over the last years, the majority of adult patients with acute myeloid leukemia (AML) will show primary refractory disease or relapse after achieving complete remission (CR).<sup>1</sup> The prognosis of relapsed/refractory (R/R) AML patients is particularly poor, but in a subset of patients salvage therapy followed by allogeneic hematopoietic stem cell transplantation (alloHSCT) was shown to be possibly curative.<sup>2</sup>

Whole-genome sequencing of AML has revealed some acquired mutations in such genes as isocitrate dehydrogenase 1 (IDH1) or 2 (IDH2) genes, encoding for two enzymes that catalyze the conversion of isocitrate to  $\alpha$ -ketoglutarate ( $\alpha$ KG) and reduce nicotinamide adenine dinucleotide phosphate (NADP<sup>+</sup>) to NADPH. In mutated IDH1 (IDH1<sup>mut</sup>) and IDH2 (IDH2<sup>mut</sup>), NADPH is oxidized to NADP<sup>+</sup> and  $\alpha$ KG transformed into the oncometabolite D-2-hydroxyglutarate (2HG). When levels of 2HG are increased, they interfere with cellular metabolism and epigenetic regulation and hence contribute to leukemogenesis. Somatic mutations of IDH1 and IDH2 genes are found in 7–14% and 8–19% of AML cases, respectively.<sup>3,4</sup>

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The recent discovery of new mutations in AML has opened the door to targeted agents that are actually in use or under investigation. This is the case for *IDH1<sup>mut</sup>* and *IDH2<sup>mut</sup>* inhibitors for patients with IDH mutations. Enasidenib was the first inhibitor of IDH2 to be approved by the US Food and Drug Administration (FDA) in August 2017 for R/R AML that carries *IDH2<sup>mut</sup>*. More recently, in July 2018, ivosidenib which inhibits mutated cytosolic IDH1 was also approved for R/R AML. Following this path, there are other *IDH1<sup>mut</sup>* and *IDH2<sup>mut</sup>* inhibitors and their combinations with other therapies under investigation (ie, intensive chemotherapy and hypomethylating agents).<sup>5</sup> Our aim was to perform a systematic review of the literature and to analyze the clinical outcomes reported with *IDH1<sup>mut</sup>* inhibitors and other agents in adult patients with *IDH1<sup>mut</sup>* R/R AML.

## Materials and methods

### Search strategy and selection of studies

In accordance with the PRISMA guidelines, two independent reviewers (JMV and PM) conducted this systematic review.<sup>6</sup> The following databases were searched without restrictions: Pubmed, EMBASE, the Cochrane Central Register, the ProQuest Medical Library, the EBSCOhost Online Research Databases, the Web of Science, and the Database of Abstracts of Reviews of Effects (DARE). In addition, the reference lists of important studies and reviews were hand-searched. Available abstracts and oral communications from conferences of the American Society of Hematology, the American Society of Clinical Oncology, and the European Hematology Association were also reviewed. Reference lists of relevant reviews and studies were searched manually. The last literature search was on November 12, 2018.

Similar keywords were used in different databases: “isocitrate dehydrogenase inhibitor 1” or “inhibitor of mutant isocitrate dehydrogenase 1” or “IDH1 mutated” and “acute myeloid leukemia” [Mesh] and relapse or refractory or resistance or recurrence or recrudescence or “salvage therapy” or “salvage treatment”.

The study selection was conducted by both authors independently. In cases of disagreement, a third reviewer (EB) adjudicated. Inclusion criteria were studies using *IDH1<sup>mut</sup>* inhibitors in IDH1mut adult AML patients, especially in the subset of R/R AML, studies evaluating effectiveness and/or safety of *IDH1<sup>mut</sup>* inhibitors in IDH1mut R/R AML, with at least CR rate or overall survival (OS), studies analyzing combinations of *IDH1<sup>mut</sup>* inhibitors with

other agents in R/R AML, and studies analyzing untargeted therapies that might be employed in the treatment of *IDH1<sup>mut</sup>* R/R AML.

Our systematic search obtained 59 citations from databases and journals, and 19 records were identified through other sources (Figure 1). Of the 78 citations selected for full reading, 46 fulfilled the inclusion criteria and 22 were included. Agreement on study selection among the reviewers was excellent (kappa =0.97).

### Data extraction

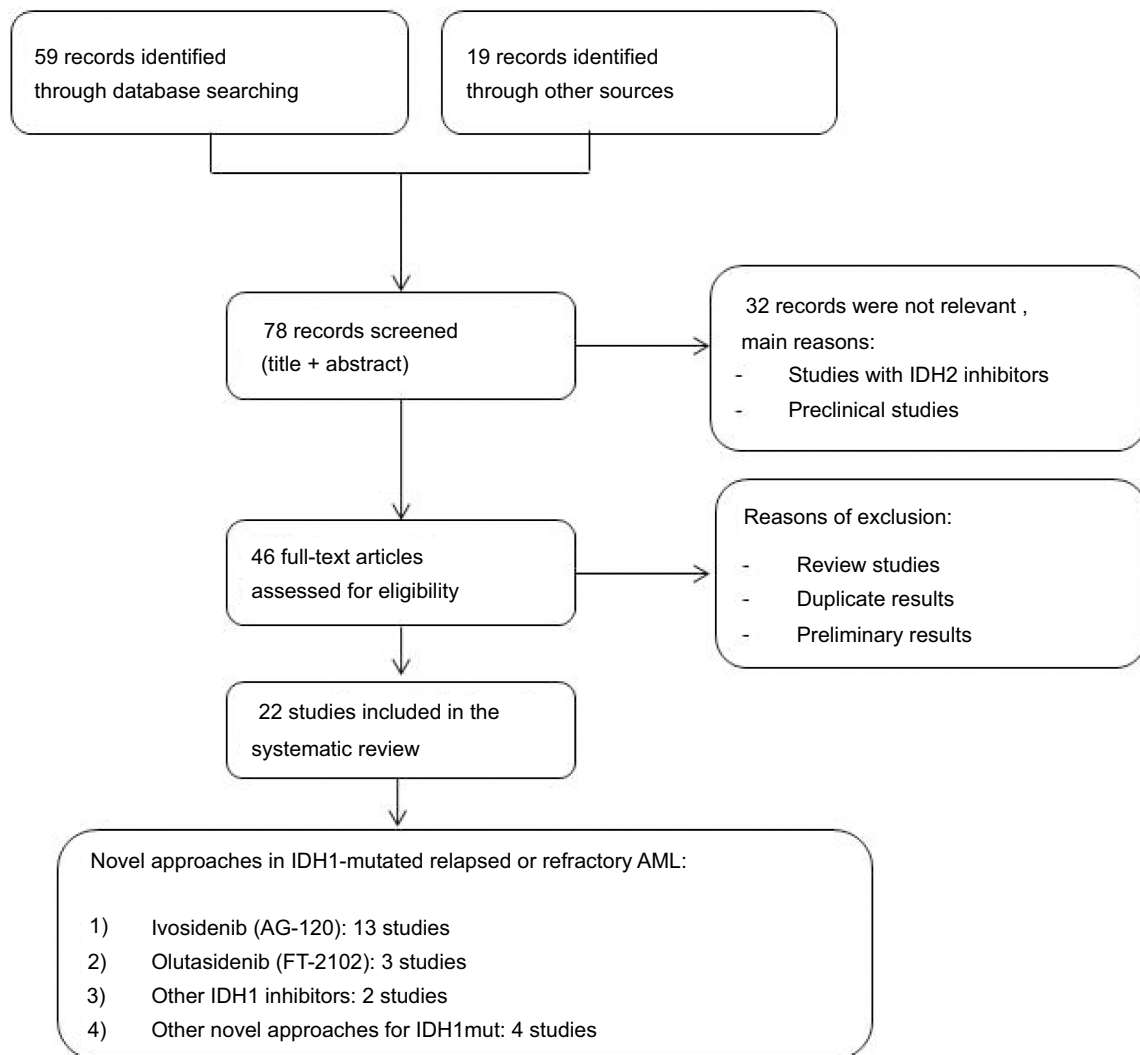
From the selected studies, we extracted data on study design, chemotherapy scheme, AML status, median age, CR, OS, and safety data. Different CR rates were reported in the included studies, including CR with incomplete blood count recovery (CRi), CR without platelet recovery (CRp), and CR with partial hematological recovery (CRh). Median CR duration (mCRD) is reported when data were available.

## Diagnosis and epidemiology of *IDH1<sup>mut</sup>* AML

### *IDH1* mutation

The IDH1 enzyme is encoded by the *IDH1* gene on chromosome 2q33.3 and localized in the cytoplasm and peroxisomes.<sup>3,7,8</sup> The *IDH1* gene normally encodes NADPH-dependent enzyme that catalyze the conversion of isocitrate to  $\alpha$ KG. *IDH1<sup>mut</sup>* reduces  $\alpha$ KG to the onco-metabolite D2HG, causing its accumulation.<sup>3,9,10</sup> Biochemical studies have shown that D2HG production can potentially affect epigenetic regulation and cell differentiation through inhibition of both histone and DNA demethylation.<sup>11</sup>

In AML, the most frequently detected *IDH1<sup>mut</sup>* is located in the Arg132 residue (R132), modifying the substrate-binding arginine of the enzyme catalytic domain for R132H, R132C, R132G, R132L, or R132S residues. The results of R132 *IDH1<sup>mut</sup>* are hypermethylation of DNA and histones and a block in differentiation that implies the presence of leukemogenic myeloid progenitor cells.<sup>7</sup> Despite these effects, *IDH1<sup>mut</sup>* enzymes alone do not cause leukemic transformation in mice. Several studies have demonstrated that *IDH* mutations tend to occur in combination with other mutations, suggesting cooperation to drive leukemogenesis in human AMLs.<sup>12</sup> Mutations in *IDH1* and *IDH2* are thought to be mutually exclusive, although occasionally in rare AML, patients have concurrent mutations in both *IDH1* and *IDH2*.<sup>8,13</sup>



**Figure 1** Summary of evidence search and selection.

**Abbreviations:** AML, acute myeloid leukemia; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; *IDH1<sup>mut</sup>*, isocitrate dehydrogenase 1 mutated.

## IDH1 epidemiology

Several studies have demonstrated that *IDH1<sup>mut</sup>* and *IDH2<sup>mut</sup>* are associated with older age and confer an adverse prognosis, especially *IDH1<sup>mut</sup>* in AML with a cytogenetically normal karyotype (CN-AML).<sup>8,14</sup> Other covariants are associated with *IDH1<sup>mut</sup>*, including intermediate-risk cytogenetics, a higher platelet count, increased bone marrow–blast percentage at diagnosis, *FLT3-ITD* and *NPM1* mutations,<sup>3,8,14,15</sup> and rarely related to therapy-related AML, *TET2*, and *WT1* mutations.<sup>3,16,17</sup>

## IDH1 comutations

A meta-analysis performed by Patel et al found that *NPM1* is the most frequent concurrent mutation (87/144; 60.4%), followed by *FLT3-ITD* (37/146; 25.3%) and *CEBPA* (14/

155; 9.0%).<sup>18</sup> In several studies, it has been shown that a heterogeneous pattern of certain gene mutations is associated with different prognostics. In CN-AML, a favorable genotype is defined by the association of *NPM1* or *CEBPA* mutation without either *FLT3-ITD* nor *IDH1* mutations.<sup>16</sup> Furthermore, *IDH1* mutations confer adverse prognoses in CN-AML with *NPM1* mutation without *FLT3-ITD*.<sup>8,14,19</sup>

## *IDH1<sup>mut</sup>* diagnosis

*IDH1<sup>mut</sup>* testing is essential in the clinical setting to identify AML patients who may benefit from targeted IDH treatments. Several methods are used to test *IDH* mutations from patients with hematologic malignancies, including Sanger sequencing, PCR-based methods, and next-generation sequencing (NGS).<sup>3,20–25</sup> Sanger sequencing has been the classical way to detect IDHmut. However, this

procedure is low sensitive and produces slow turnaround, and thus might be less suitable as a molecular diagnostic tool.

PCR-based methods are rapid and not expensive methods to detect known mutations. Because *IDH1<sup>mut</sup>* are recurrently located at codon 132 in exon 4 of the *IDH1* gene, several PCR-based methods have been developed to detect them.<sup>3,20,21</sup> Recently, new digital PCR technology (BEAMing) enabled *IDH1<sup>mut</sup>* detection up to 5 different mutations (R132S, R132G, R132C, R132H, and R132L) from a single sample with higher sensitivity than NGS (lower limit of detection 0.02–0.04%).<sup>24</sup> NGS is used as a substitute for PCR and Sanger sequencing in many academic medical centers, and gene panels are used for diagnostic and prognostic purposes. It allows quantification of variant allele frequency (VAF) and the detection of co-occurring mutations.<sup>25</sup> Serial monitoring by NGS has been employed in clinical trials to detect minimal residual disease (MRD) after therapy with *IDH<sup>mut</sup>* inhibitors.<sup>26</sup>

## Prognostic impact of *IDH1* mutations in AML patients receiving standard chemotherapy

The prognostic impact of *IDH1<sup>mut</sup>* has been widely studied in newly diagnosed AML with contradictory results, suggesting adverse outcomes,<sup>7,14,19</sup> no influence,<sup>3,8,27–33</sup> or a favorable outcome in one study.<sup>15</sup> A meta-analysis of 8 studies found a lower event-free survival (EFS) in patients with *IDH1<sup>mut</sup>*, but there were no differences in OS.<sup>17</sup> However, two meta-analyses including 15 studies<sup>34</sup> and 24 studies<sup>35</sup> obtained significant associations between *IDH1<sup>mut</sup>* and lower OS, as well as a lower event-free survival and CR rate in the last meta-analysis.<sup>35</sup> These associations were reproduced in the subset of CN-AML *IDH1<sup>mut</sup>* patients.<sup>34,35</sup> Furthermore, the *IDH1* single-nucleotide polymorphism rs11554137 was also related to a poor OS.<sup>35</sup>

The influence of these mutations in R/R AML remains scarcely reported. Mutation of *IDH1* was an unfavorable factor for survival in a large cohort of 761 R/R AML treated with intensive salvage therapy.<sup>36</sup> The main schemes employed were based on a high dose of Ara-C (HiDAC), used in 71.2% of the patients. Unfortunately, specific data regarding the outcomes of *IDH1<sup>mut</sup>* with each salvage scheme were not provided. The next large study analyzing the clinical outcomes of *IDH* mutations did not find any differences in the CR/CRi and the median OS

(mOS) among *IDH1<sup>mut</sup>*, *IDH2<sup>mut</sup>*, and wild-type *IDH* (*wtIDH*) for AML induction or the first salvage therapy (S1) and the second or beyond salvage therapy (S2). This study employed at S1 and S2 schemes based on HiDAC (36% and 41%), hypomethylating agents (HMA) (32% and 27%), and low-dose Ara-C (24% and 3%). Specifically, *IDH1<sup>mut</sup>* showed a CR/CRi of 40% vs 41% and 36% vs 27% at S1 and S2 against *wtIDH*, respectively, and a mOS of 5.9 and 7.7 months at S1 and 4.0 and 4.8 months at S2, respectively.<sup>3</sup> Lower survival rates were reported in a French cohort of 185 R/R AML patients treated with standard salvage therapies (intensive chemotherapy in 68%, azacitidine in 18%, and other therapies in 14%) comparing *IDH1<sup>mut</sup>* versus *wtIDH* and *IDH2<sup>mut</sup>* (mOS 5.9, 7.6, and 11 months; 3-year OS 8%, 19%, and 23%), whereas no differences were reported in CR (50%, 43%, and 52%, respectively).<sup>4</sup> Recently, the outcomes of R/R AML with *IDH1<sup>mut</sup>* from the UK NCRI AML trials treated with nontargeted therapy were analysed, showing mOS of 4.4 months, 1-year OS of 32%, 2-year OS of 17%, and remission rate of 23%. Age and AML subtypes (refractory, relapsed post-HSCT, second relapse, and relapsed within 1 year of remission) were not associated with differences in survival rates.<sup>37</sup>

## Novel approaches in *IDH1*-mutated relapsed or refractory AML

Several targeted therapy agents are currently under development for *IDH1<sup>mut</sup>* R/R AML patients, and are showing promising results.

### Ivosidenib (AG-120)

#### Drug development and pharmacokinetics

Ivosidenib (AG-120) is the first oral selective small molecule inhibitor of the *IDH1-R132<sup>mut</sup>*, resulting in inhibition of mutant *IDH1* enzyme and decreased D2HG levels. The efficacy, safety, and pharmacokinetics of ivosidenib were evaluated in Phase I/II clinical trial in patients with *IDH1<sup>mut</sup>* advanced hematologic malignancies, including R/R AML [NCT02074839].<sup>38,39</sup> Besides, this agent is being tested for advanced cholangiocarcinoma [NCT02989857], glioma [NCT03343197], and advanced solid tumors [NCT02073994]. In July of 2018, the FDA approved ivosidenib for the treatment of R/R AML patients with *IDH1<sup>mut</sup>*.<sup>40</sup>

The selected oral dose was 500 mg/24 hrs (maximum tolerated dose was not reached). It was rapidly absorbed (median 3 hrs to peak plasma concentration) and a steady

state reached at 14 days. The steady-state mean apparent volume of distribution was 234 L and the protein bound was near 92–96%. CYP3A4 was the main way of metabolism, although 77% was excreted unchanged in the feces and 17% in the urine (10% unchanged), obtaining a clearance of 4.3 L/hr and a terminal elimination half-life of 93 hrs.<sup>38,41</sup> A population pharmacokinetic model of ivosidenib has been recently performed, suggesting that no dose adjustments were needed according to the patient and disease conditions, and only the concomitant use of azoles (moderate/strong CYP3A4 inhibitors) was able to reduce ivosidenib clearance.<sup>42</sup>

### Efficacy

The Phase I dose-escalation and dose-expansion clinical trial included 179 AML R/R *IDH1*<sup>mut</sup> patients treated with 500 mg of ivosidenib every 24 hrs in a 28-day cycle (cutoff date May 12, 2017;<sup>38</sup> second cutoff date November, 2017<sup>39</sup>) (Table 1). The primary endpoint of this study, CR or CRh, was achieved in 30.2% for an mCRD of 6.5 months (31.8% and 8.2 months at the second cutoff). In addition, the CR rate was 21.8% with an mCRD of 9.3 months (24.0% and 10.1 months at second cut-off) and overall response (OR) of 39.1% and mCRD of 6.5 months (41.9% and 6.5 months at second cutoff). The mOS in the first primary efficacy cohort of 125 patients treated with 500 mg/24 hrs was 8.8 and 9.0 months after a median follow-up of 14.8 and 15.3 months. Transfusion independence  $\geq 56$  days was achieved in 35% of patients with previous transfusion dependence and maintained in 56% of the patients who were transfusion-independent at baseline.

After ivosidenib therapy, 21% *IDH1*<sup>mut</sup> clearance was detected using digital PCR among the 34 patients who had CR or CRh<sup>38</sup> (23%, 11 of 47 at the second cutoff).<sup>39</sup> This subset of patients showed longer CRD (11.1 vs 6.5 months) and mOS (14.5 vs 10.2 months) than those without *IDH1*<sup>mut</sup> clearance. The role of the baseline comutated genes was also evaluated, and a significant association between CR or CRh and a lower comutational burden was found ( $P=0.02$ ). However, no specific preexisting mutations were identified as predictors of CR or resistance, although mutations in receptor tyrosine-kinase pathway genes were enriched in patients without response.<sup>38</sup>

### Safety

Ivosidenib monotherapy of 500 mg/24 hrs in R/R AML had acceptable tolerance and was not related to any dose-limiting toxic effects, although adverse events (AEs) were

reported in 99% of the patients enrolled in Phase I clinical trial and the dose-expansion study [NCT02074839].<sup>38,39</sup> Table 1 summarizes the AEs reported in >20% patients in all the grades, as well as AE grades  $\geq 3$ . Treatment-related AEs from ivosidenib were IDH differentiation syndrome (IDH-DS), prolongation of the QT interval, and leukocytosis. All these AEs are manageable and reversible, without needing permanent discontinuation of treatment. There were no deaths related to ivosidenib dose of 500 mg/24 hrs, whereas at 800 mg/24 hrs one AE-related death (cardiac tamponade) was reported as possibly associated with ivosidenib.

IDH-DS is a potentially fatal AE that produces a rapid increase in the differentiation of neutrophils after the removal of the differentiation block in the malignant myeloid clone. It was initially described in acute promyelocytic leukemia and it is a common AE of *IDH1*<sup>mut</sup> inhibitors.<sup>43,44</sup> IDH-DS showed similar incidence with enasidenib (ivosidenib, total: 19 [10.6%], grade  $\geq 3$ : 9 [5.0%];<sup>38</sup> enasidenib, total: 33 [11.7%]; grade  $\geq 3$ : 15 [6.3%]),<sup>45</sup> an *IDH2* inhibitor, and in more than a third of the cases it could be accompanied with leukocytosis. A recent systematic analysis performed by the FDA<sup>46</sup> obtained a higher incidence of 19% of IDH-DS in clinical trials of ivosidenib and enasidenib in R/R AML using the diagnosed criteria of Montesinos et al.<sup>47</sup> IDH-DS could be managed by discontinuation and treatment with glucocorticoids and/or hydroxyurea, and these patients had clinical responses.<sup>38,42</sup>

### Future directions

After the FDA approval of ivosidenib monotherapy in R/R AML with *IDH1*<sup>mut</sup>, an expanded-access program has been promoted by manufacturing company including adult patients and children  $\geq 12$  years of age who weigh at least approximately 100 lb [NCT03245424]. Combinations of ivosidenib with HMAs or intensive chemotherapy in R/R AML *IDH1*<sup>mut</sup> patients have not been evaluated yet. However, the addition of venetoclax to ivosidenib is under investigation in this subset of patients in a Phase I/II trial [NCT03471260].

The use of ivosidenib as a front-line therapy as a single agent<sup>38,48</sup> has been analyzed in a Phase Ib clinical trial [NCT02074839] (Table 2), and it has shown a promising 42.4% CR/CRh rate among the 33 subjects. Ongoing clinical trials are testing in *IDH1*<sup>mut</sup>-untreated AML patients, the safety and efficacy of different combinations of ivosidenib with azacitidine [NCT03173248; NCT02677922]<sup>49–51</sup> or intensive chemotherapy [NCT02632708]<sup>52</sup> (Table 2). It

**Table 1** Studies using IDH1 inhibitors in IDH1-mutated relapsed or refractory AML

IDH1 inhibitor	Ivosidenib (AG-120)	IDH305	Olutasidenib (FT-2102)	Olutasidenib (FT-2102) + azacitidine
Schedule	500 mg/24 hrs (28-day cycle)	75–150–300–450–550–750–900 mg/12 hrs (21-day cycle)	150–300 mg/24 hrs or 150 mg/12 hrs or 100 mg/24 hrs with food; selected dose 150 mg/12 hrs	150 mg/24 hrs or 150 mg/12 hrs + AZA 75 mg/m <sup>2</sup> 7 days (28-day cycle)
Design	PROSP, Phase I, MC <sup>38,39</sup>	PROSP, Phase I, MC <sup>57</sup>	PROSP, Phase I, MC <sup>53</sup>	PROSP, Phase I/II, MC <sup>56</sup>
Clinical trial	NCT02074839	NCT02381886	NCT02719574	NCT02719574
Inclusion criteria	IDH1 <sup>mut</sup> R/R AML; ≥18 years and ECOG-PS score of 0 to 2	IDH1 <sup>mut</sup> R/R AML and MDS; also evaluated in glioma and other solid tumors	IDH1 <sup>mut</sup> R/R AML with no prior therapy with IDH1 inhibitors	IDH1 <sup>mut</sup> R/R AML
<b>N</b>	179: 106 RF; 17 ER, 43 R HSCT, 26≥2 <sup>nd</sup> R-LR	21 (NA distribution of R and RF AML); 3 MDS	21	19
Median age	67.0 (18–87)	NA	71 (35–87) <sup>b</sup>	66 (31–88) <sup>c</sup>
CR [n (%)]; mCRD	CR: 43 (24.0); 10.1 months CR-CRi: 57 (31.8); 8.2 months OR: 75 (41.9); 6.5 months	CR: 2 (9.5); NA CRi: 1 (4.8); NA PR: 4 (19); NA	CR: 3 (14); NA CRi/MLFS: 4 (19); NA OR: 7 (33); NA	CR: 0 (0); NA CRi/MLFS: 6 (32); NA OR: 6 (32); NA
Median OS	9.0 months (follow-up 15.3 months)	NA	NA	NA

(Continued)

Table 1 (Continued).

IDH1 inhibitor	Ivosidenib (AG-120)	IDH305	Olutasidenib (FT-2102)	Olutasidenib (FT-2102) + azacitidine
Safety: AE in >20% patients all grades (%) AE grade ≥3: [n (%)] IDH-DS: [n (%)]	AEs in >20% patients, all grades (%): Diarrhea (34); 4 (2) Leukocytosis (31); 14 (8) Nausea (31); 1 (1) Febrile neutropenia (29); 52 (29) Fatigue (29); 3 (2) Prolong QT interval (26); 18 (10) Dyspnea (25); 7 (4) Peripheral edema (24); 0 (0) Pyrexia (23); 2 (1) Anemia (22); 36 (20) Cough (21); 1 (0) AE grade ≥3: [n (%)] IDH-DS G ≥3: 7 (4) Thrombocytopenia G ≥3: 3 (2) Platelet count decreased G ≥3: 3 (2) Hypoxia G ≥3: 2 (1) IDH-DS 19 (11); G ≥3: 9 (5)	AEs in >10% patients, all grades (%) in AML, glioma or other solid tumors: Bilirubin increased (31) AST increased (17) ALT increased (16) Nausea (14) In AML/MDS, AEs >5% patients: Bilirubin increased (8) Lipase increased (8) In AML/MDS, grade ≥3: Bilirubin increased (4) IDH-DS: NA	AEs in >5% patients G ≥3 (%): Thrombocytopenia (26) Febrile neutropenia (23) Anemia (19) Pneumonia (13) Neutropenia (7) Hypokalemia (7) Pyrexia (7) Leukocytosis (6) IDH-DS: 3 (11) Prolong QT interval: 1 (4)	AEs in >5% patients G ≥3 (%): Febrile neutropenia (27) Anemia (19) Thrombocytopenia (19) Leukocytosis (19) Fatigue (15) Hypertension (15) Neutropenia (15) Nausea (12) Pneumonia (12) Hypokalemia (12) Abdominal pain (8) IDH-DS: 3 (13)

**Notes:** OS and CR estimated in months in cases reported in days (1 month = 30 days) and weeks (1 month = 4.3 weeks). <sup>a</sup>Evaluated after a median follow-up of 14.8 m in primary efficacy population, which included the first 125 IDH1<sup>mut</sup> relapsed or refractory AML receiving 500 mg daily at least 6 months before cutoff. <sup>b</sup>AEs of the entire cohort including 21 relapsed or refractory AML, 3 untreated AML, and 4 MDS. <sup>c</sup>AEs of entire cohort including 19 relapsed or refractory AML, 4 untreated AML, and 1 MDS.

**Abbreviations:** ≥2<sup>nd</sup> R, second or beyond relapse; AML, acute myeloid leukemia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, complete remission with partial hematologic recovery; Cri, complete remission with incomplete recovery; ECOG-PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; ER, early relapse <1 year; HSCT, hematopoietic stem cell transplantation; IDH, isocitrate dehydrogenase; IDH1<sup>mut</sup>, isocitrate dehydrogenase 1 mutated; IDH-DS, IDH differentiation syndrome; LR, late relapse >1 year; mCRD, median CR duration; mDFS, median disease-free survival; MDS, myelodysplastic syndrome; MLFS, morphologic leukemia-free state; mOS, median overall survival; MC, multicenter; N, population of the cohort; NA, not available; OR, overall response; OS, overall survival; PROSP, prospective study; R, relapse; RETROSP, retrospective study; RF, refractory; RFS, relapse-free survival; R/R AML, relapsed/refractory AML; UC, unicentric or single center.

Table 2 Studies using IDH1 inhibitors in IDH1-mutated untreated AML

IDH1 inhibitor	Ivosidenib AG-120	Ivosidenib or enasidenib + intensive chemotherapy	Ivosidenib + azacitidine	Ivosidenib or enasidenib + azacitidine	Olutasidenib (FT-2102)	Olutasidenib (FT-2102) + azacitidine
<b>Schedule</b>	500 mg/24 hrs (28-day cycle)	IVO 500 mg/24 hrs or ENA 100 mg/24 hrs + Ara-C (200 mg/m <sup>2</sup> /d x7d) + DNR (60 mg/m <sup>2</sup> /day x3 days) or IDA (12 mg/m <sup>2</sup> /day x3 days) <sup>a</sup>	IVO 500 mg/24 hrs or placebo + AZA 75 mg/m <sup>2</sup> 7 days (28-day cycle)	IVO 500 mg/24 hrs or ENA 100–200 mg/24 hrs + AZA 75 mg/m <sup>2</sup> 7 days	150–300 mg/24 hrs or 150 mg/12 hrs or 100 mg/24 hrs with food; selected dose 150 mg/12 hrs	150 mg/24 hrs or 150 mg/12 hrs + AZA 75 mg/m <sup>2</sup> 7 days (28-day cycle)
<b>Design</b>	PROSP, Phase I, MC <sup>38,48</sup>	PROSP, Phase I, MC <sup>52</sup>	RCT, PROSP, Phase III, MC <sup>49</sup>	PROSP, Phase Ib/II, MC <sup>50,51</sup>	PROSP, Phase I, MC <sup>53</sup>	PROSP, Phase I/II, MC <sup>56</sup>
<b>Clinical trial</b>	NCT02074839	NCT02632708	NCT02677922	NCT03173248	NCT02719574	NCT02719574
<b>Inclusion criteria</b>	IDH1 <sup>mut</sup> -untreated AML; ≥18 years and ECOG-PS score of 0 to 2	IDH1/2 <sup>mut</sup> newly diagnosed AML (we will be focused in IDH1 treated with IVO)	IDH1 <sup>mut</sup> -untreated AML ineligible for intensive chemotherapy	IDH1/2 <sup>mut</sup> newly diagnosed AML ineligible for intensive chemotherapy (we will be focused in IDH1 treated with IVO)	IDH1 <sup>mut</sup> -untreated AML with no prior therapy with IDH1 inhibitors	IDH1 <sup>mut</sup> -untreated AML
<b>N</b>	34: 7 de novo, 27 sAML Prior HMA: 14	60; 42 de novo, 18 sAML Prior HMA: 4	NA (plans to enroll 392 patients)	23	3	4
<b>Median age</b>	76.5 (64–87)	62.5 (24–76)	NA	76 (61–88)	71 (35–87) <sup>b</sup>	66 (31–88) <sup>c</sup>
<b>CR [n (%)]; mCRD</b>	n=33 CR: 10 (30.3); NE: CR1y: 77.8% CR-CRt: 14 (42.4); NE: CR-CR1y: 66.7% OR: 19 (57.6); 8.3; OR1y: 59.5%	N=49; de novo 34; sAML 15 CR: 35 (71); NA De novo CR: 27 (79) sAML CR: 8 (53) CR-CR1/CRp: 39 (80); NA De novo CR-CR1/CRp: 31 (91) sAML CR-CR1/CRp: 8 (53)	NA	CR: 10 (44); NA CR1/CRp: 5 (22); NA PR: 0 (0); NA MLFS: 3 (13); NA OR: 18 (78); NA	CR: 0 (0); NA CR1/MLFS: 1 (33); NA OR: 1 (33); NA	CR: 2 (50); NA CR1/MLFS: 1 (25); NA OR: 3 (75); NA
<b>Median OS</b>	12.6 m (23 m follow-up)	NE; OS1y: 79%	NA	NE	NA	NA

(Continued)



Table 2 (Continued).

IDH1 inhibitor	Ivosidenib AG-120	Ivosidenib or enasidenib + intensive chemotherapy	Ivosidenib + azacitidine	Ivosidenib or enasidenib + azacitidine	Oltasidenib (FT-2102)	Oltasidenib (FT-2102) + azacitidine	
Safety; AE in >20% patients all grades (%) AE grade ≥3: [n (%)] IDH-DS: [n (%)]	AEs in >20% patients, all grades (%); AE grade ≥3: [n (%)] Diarrhea (53); 2 (6) Fatigue (44); 3 (9) Nausea (38); 2 (6) Decreased appetite (32); 1 (3) Leukocytosis (27); 1 (3) Anemia (27); 4 (12) Peripheral edema (27) Thrombocytopenia (24); 5 (15) Dyspnea (24); 1 (3) Hypomagnesemia (24) Dizziness (24) Arthralgia (21); 1 (3) Hypokalemia (21); 1 (3) Constipation (21); 1 (3) Abdominal pain (21); 1 (3) Insomnia (21) Serious AEs (≥5%) IDH-DS 5 (14.7) Febrile neutropenia 3 (8.8) Pneumonia 3 (8.8) Prolong QT interval 2 (5.9) IDH-DS, total 6 (18); G≥3: 3 (9)	Induction period AE grade ≥3: [n (%)] IDH-DS 2 (3) Leukocytosis 0 (0) Prolong QT interval 1 (2) Bilirubin increased 4 (7) 30-day mortality: 3 (5) 60-day mortality: 5 (8) AEs in >10% patients G ≥3 (%): Febrile neutropenia (62) Hypophosphatemia (13) Hypokalemia (10) Colitis (10) Hypertension (10) Bilirubin increased (7) Lung infection (5) Sepsis (7) IDH-DS G ≥3: 2 (3)	NA	AEs in >20% patients, all grades (%); AE grade ≥3: [n (%)] Nausea 14 (61); 1 (4) Anemia 12 (52); 10 (44) Thrombocytopenia 11 (48); 10 (44) Febrile neutropenia 9 (39); 9 (39) Constipation 9 (39); 1 (4) Diarrhea 9 (39); 1 (4) Vomiting 8 (35); 1 (4) Dizziness 8 (35); 1 (4) Pyrexia 7 (30); 1 (4) Fatigue 7 (30); 0 (0) Insomnia 7 (30); 0 (0) Hypokalemia 7 (30); 0 (0) QT interval prolongation 6 (26); 3 (13) Back pain 5 (22); 0 (0) Headache 5 (22); 0 (0) Cough 5 (22); 0 (0) Serious AEs: Febrile neutropenia 8 (35) IDH-DS: 3 (13)	AEs in >5% patients G ≥3 (%): Thrombocytopenia (26) Febrile neutropenia (27) Anemia (19) Leukocytosis (19) Fatigue (15) Hypertension (15) Neutropenia (15) Nausea (12) Pneumonia (12) Hypokalemia (12) Abdominal pain (8) IDH-DS: 3 (13)	AEs in >5% patients G ≥3 (%): Thrombocytopenia (26) Febrile neutropenia (23) Anemia (19) Pneumonia (13) Neutropenia (7) Hypokalemia (7) Pyrexia (7) Leukocytosis (6) IDH-DS: 3 (11) Prolong QT interval: 1 (4)	AEs in >5% patients G ≥3 (%): Febrile neutropenia (27) Anemia (19) Thrombocytopenia (19) Leukocytosis (19) Fatigue (15) Hypertension (15) Neutropenia (15) Nausea (12) Pneumonia (12) Hypokalemia (12) Abdominal pain (8) IDH-DS: 3 (13)

**Notes:** OS and CR has been estimated in months in the cases that it was reported in days (1 month =30 days) and weeks (1 month =4.3 weeks). <sup>a</sup>Consolidation chemotherapy: ≤4 cycles while continuing treatment with the mutated IDH1 inhibitor. Those who complete or are ineligible for consolidation may continue maintenance treatment with ivosidenib or enasidenib for ≤2 years from the start of induction. <sup>b</sup>AEs of the entire cohort including 21 relapsed or refractory AML, 3 untreated AML, and 4 MDS. <sup>c</sup>AEs of the entire cohort including 19 relapsed or refractory AML, 4 untreated AML, and 1 MDS.

**Abbreviations:** ≥2<sup>nd</sup>°R, second or beyond relapse; AML, acute myeloid leukemia; ALT, alanine aminotransferase; Ara-C, cytarabine; AST, aspartate aminotransferase; AZA, azacitidine; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission without platelet recovery; DNR, daunorubicin; ECOG-PS, Eastern Cooperative Oncology Group performance-status; EFS, event-free survival; ENA, enasidenib; ER, early relapse <1 year; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; IDA, idarubicin; IDH, isocitrate dehydrogenase; IDH<sup>mut</sup>, isocitrate dehydrogenase 1 mutated; IDH-DS, IDH differentiation syndrome; IVO, ivosidenib; LR, late relapse >1 year; MC, multicenter; mCRD, median CR duration; mDFS, median disease-free survival; MDS, myelodysplastic syndrome; MLFS, morphologic leukemia-free state; mOS, median overall survival; MRD, measurable residual disease; N, population of the cohort; NA, not available; NE, relapse-free survival; OS, overall survival; PROSP, prospective study; R, relapse; RCT, randomized clinical trial; RETROSP, retrospective study; RF, refractory; RFS, relapse-free survival; sAML, secondary AML; UC, unicentric or single center; Y, year.

is worth noting that a new international Phase III randomized clinical trial aiming to enroll a large number of patients will compare AZA+IVO vs AZA in newly diagnosed *IDH1<sup>mut</sup>* patients unfit for intensive chemotherapy [NCT03173248]. Moreover, ivosidenib is being tested as maintenance therapy after allo-HSCT in *IDH1<sup>mut</sup>* myeloid malignancies in a Phase I dose-escalation trial [NCT03564821].

## Olutasidenib (FT-2102)

### Drug development and pharmacokinetics

Olutasidenib (FT-2102) is a new *IDH1<sup>mut</sup>* inhibitor that is being tested in an ongoing Phase I/II clinical trial in patients with *IDH1<sup>mut</sup>* AML (R/R or untreated) and MDS [NCT02719574] in monotherapy and combined with azacitidine. Preclinical studies in rats and human tissue showed a major excretion route through the hepatic metabolism by CYP enzymes (CYP3A4, 2C9 and 1A1). Pharmacokinetic, pharmacodynamic, and safety data have supported the selection of a 150 mg/12 hr dose, reaching a durable steady state at 2 weeks without a low threshold for QTc-prolongation risk and achieving prompt and durable 2-HG reductions.<sup>53</sup> FT-2102 is also being tested in advanced solid tumors and gliomas with *IDH1<sup>mut</sup>* [NCT03684811].

### Efficacy

The first set of data of the Phase I/II clinical trial was recently presented, including 31 patients treated with FT-2102 as a single agent with a median of 3 months (range 0.2–20 months), 22 of them with R/R AML with no prior therapy with *IDH1<sup>mut</sup>* inhibitors (Table 1).<sup>53</sup> Preliminary endpoints reported were CR rate of 14%, a CRi and morphologic leukemia-free state (MLFS) of 19%, and OR of 33%.

### Safety

Regarding the safety of olutasidenib, severe AEs occurring in >5% of patients of the entire cohort are included in Table 1. IDH-DS was reported in 3 patients and resolved after temporary discontinuation and treatment with dexamethasone, hydroxyurea, and supportive care. There were no deaths related to FT-2102 therapy.<sup>53</sup>

### Future directions

Combinations of HMA and *IDH<sup>mut</sup>* inhibitors are being evaluated in several clinical trials because this combination increases hemoglobinization and the expression of erythroid differentiation markers, reduces leukemic stem

cell populations, and potentiates apoptosis.<sup>54,55</sup> The addition of azacitidine had no impact on FT-2102 pharmacokinetics.

At data cutoff (April 7, 2018), 26 patients had been treated with FT-2102 (150 mg/24 hrs or 150 mg/12 hrs) plus azacitidine (75 mg/m<sup>2</sup> for 7 days) for a median of 3 months (range 0.2–12 months), 20 of them with R/R AML<sup>56</sup> (Table 1). Preliminary end points reported were CR rate of 0%, CRi + MLFS of 32%, and OR of 32%. AEs with a grade  $\geq 3$  occurring in >5% of patients of the entire cohort are summarized in Table 1. IDH-DS developed in 3 patients, all of which remitted after temporary interruption and treatment (glucocorticoids, hydroxyurea, and supportive care). No deaths related to FT-2102 were reported.

Untreated AML patients were also included in a Phase I/II clinical trial, with scarce reported data [NCT02719574] (Table 2): 3 patients were treated with FT-2102 monotherapy<sup>53</sup> and 4 patients had it in combination with azacitidine.<sup>56</sup> At the first cutoff, these schemes had obtained CR of 0% and 50%, CRi/MLFS of 33% and 25%, and OR of 33% and 75%, respectively. Safety profiles were analyzed together with the subsets of R/R AML and MDS.

FT-2102 monotherapy at 150 mg/12 hrs will be analyzed in an ongoing Phase II study with three cohorts [NCT02719574]: R/R AML, AML/MDS with CR/CRi (ie, with MRD), and R/R MDS/AML with a prior exposure to an *IDH1m* inhibitor. Moreover, three Phase 2 combination-therapy (FT-2102 150 mg/12 hrs plus azacitidine 75 mg/m<sup>2</sup> 7 days) cohorts are currently open [NCT02719574]: patients <60 years with R/R AML or MDS naïve to HMA and *IDH1m* inhibitors; R/R AML or MDS with inadequate response/PD on HMA; and R/R AML or MDS who have progressed on a prior *IDH1m* inhibitor.

## Other *IDH1<sup>mut</sup>* inhibitors

### IDH305

IDH305 is an oral small-molecule *IDH1<sup>mut</sup>* inhibitor active against the *IDH1R132* mutation and assayed in a Phase I dose-finding clinical trial [NCT02381886] in AML/MDS (including R/R AML; Table 1), gliomas, and other/non-central nervous system (CNS) solid tumors. Preliminary results in 21 AML patients were reported at cutoff on March 30, 2016, showing promising antitumoral activity:<sup>57</sup> a CR of 9.5%, a CRi of 4.8%, and partial remission (PR) of 19%. Hepatotoxicity was detected in the 3 malignancies (Table 1), although in AML/MDS the incidence

was lower. Unfortunately, 3 subsequent clinical trials [NCT02987010, NCT02977689, NCT02826642] were withdrawn before enrolling the first participant, and no new clinical data about this drug have been reported.

### Vorasidenib (AG881)

Vorasidenib (AG-881) is an oral inhibitor of *IDH1<sup>mut</sup>* and *IDH2<sup>mut</sup>* which is being evaluated in a Phase I trial in solid tumors, including gliomas, as it penetrates the blood–brain barrier [NCT02481154], with the first report of the safety profile in 93 of the patients.<sup>58</sup> Furthermore, AG-881 is being tested in advanced hematologic malignancies after progression with a prior *IDH<sup>mut</sup>*-inhibitor treatment [NCT02492737].

### BAY1436032

BAY1436032 is an oral pan-mutant *IDH1* inhibitor, active against *IDH1<sup>R132H</sup>*, *IDH1<sup>R132C</sup>*, *IDH1<sup>R132G</sup>*, *IDH1<sup>R132L</sup>*, and *IDH1<sup>R132S</sup>*, which has demonstrated, in preclinical in vitro and in vivo studies strong antileukemic activity in *IDH1<sup>mut</sup>* patient-derived xenograft (PDX) models.<sup>59</sup> BAY1436032 is being tested in Phase I trials as a single agent in R/R AML [NCT03127735] and advanced solid tumors [NCT02746081], but the clinical reports have not been presented yet. Also, synergistic activity has been detected in PDX *IDH1<sup>mut</sup>* models with a combination of BAY-1436032 and azacitidine through inhibition of the cell cycle by dysregulating EGR, GF11, and NFκB signaling.<sup>60</sup>

### DS-1001

DS-1001 is a new oral *IDH1<sup>mut</sup>* inhibitor being studied in patients with recurring or progressing gliomas [NCT03030066]. Potentially, DS-1001 could be active in R/R AML *IDH1<sup>mut</sup>* patients.

## Non-targeted therapies tested in *IDH1<sup>mut</sup>* AML

### Venetoclax

Venetoclax is an oral selective inhibitor of the antiapoptotic B-cell lymphoma-2 (BCL-2) that is being tested in R/R AML. Preclinical studies have obtained activity against *IDH<sup>mut</sup>* cells mediated by the intracellular accumulation of the oncometabolite D2HG.<sup>61</sup> This finding was reproduced in clinical trials of venetoclax monotherapy in R/R or untreated AML<sup>62</sup> and combined with HMA or low-dose cytarabine in R/R myeloid malignancies,<sup>63</sup> achieving a CR/CRi of 33% and a 27% response rate in *IDH<sup>mut</sup>* patients, respectively. This study revealed that venetoclax

could be an alternative treatment after *IDH*-inhibitor failure (7 of 11 patients were pretreated with *IDH<sup>mut</sup>* inhibitors).<sup>63</sup> In elderly untreated AML patients who are unfit for intensive therapies, combinations of HMA and venetoclax obtained in an *IDH<sup>mut</sup>* subgroup a CR/CRi rate of 71% and a median OS of 24.4 months.<sup>64</sup> Combinations of venetoclax and ivosidenib will be tested in this subset of patients in a Phase I/II trial [NCT03471260].

### CB839

CB-839 is an oral glutaminase inhibitor under investigation. Glutaminase is an enzyme which generates glutamine, the main source of α-KG in *IDH1<sup>mut</sup>* cells. Preclinical and in vivo studies demonstrated that CB839 reduced the growth of *IDH1/2<sup>mut</sup>* AML cells.<sup>65–67</sup> In R/R AML *IDH<sup>mut</sup>* patients, CB-839 is being tested in monotherapy and in combinations with azacitidine [NCT02071927].<sup>68</sup>

### PARP inhibitors: olaparib and talazoparib

The D2HG produced by *IDH1/2<sup>mut</sup>* enzymes is associated with increased DNA damage and improved responses to poly (ADP-ribose) polymerases (PARP) inhibitors in solid tumor cells. In an in vitro study, AML *IDH1/2<sup>mut</sup>* cells were sensitive to monotherapy with PARP inhibitors (olaparib and talazoparib). This activity was potentiated in combination with daunorubicin, a DNA-damaging agent. However, the combination of PARP and *IDH1/2<sup>mut</sup>* inhibitors decreased and antagonized their efficacy.<sup>69</sup> Monotherapy with olaparib is being studied in glioma, cholangiocarcinoma, and other solid tumors with *IDH1<sup>mut</sup>* or *IDH2<sup>mut</sup>* [NCT03212274], and BGB-290 (PARP inhibitor) combined with temozolomide in glioma, but these agents have not been tested in R/R AML yet.

## *IDH1*-peptide vaccine

The mutation-specific vaccination of *IDH1* (R132H) has been tested as a novel target for immunotherapy in glioma, as this neoantigen shows high uniform expression and penetrance in glioma cells. Preclinical studies in mice with *IDH1*-peptide vaccination obtained an effective mutation-specific antitumour immune response against *IDH1<sup>R132H</sup>*-expressing tumor cells and reduced the growth of gliomas.<sup>70,71</sup> Three different clinical trials are evaluating the safety and efficacy of *IDH1*-peptide vaccine in different grades of glioma alone [NCT02454634, NCT02771301] or combined with temozolomide [NCT02193347].

## Conclusion

R/R is the subset of AML with worse long-term outcomes with standard salvage therapies. The investigation of new targeted therapies (*IDH* and *FLT3*) has shown promising results, achieving a better antileukemic efficacy and safety profile in comparison with salvage regimens. In this review, we have analyzed the impact of *IDH1<sup>mut</sup>* inhibitors, a new targeted therapy with positive results in R/R AML.

Two *IDH<sup>mut</sup>* inhibitors (ivosidenib and enasidenib) have achieved fast approval with Phase I/II clinical trial results in the subgroup of *IDH1/2mut* R/R AML, pending further studies to demonstrate a significant improvement in survival and/or other long-term outcomes. Nevertheless, with the advent of new targeted therapies, the diagnostic workup of R/R AML will now include a systematic screening for *IDH1* mutations, in order to personalize treatments. Ongoing clinical trials are testing the use of *IDHmut* inhibitors as single agent or in combination with HMAs or intensive chemotherapy as frontline therapy and the role of these inhibitors in post-transplant maintenance.

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## Disclosure

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