

Efficacy and Safety Profile of Ivosidenib in the Management of Patients with Acute Myeloid Leukemia (AML): An Update on the Emerging Evidence

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Abstract: The isocitrate dehydrogenase enzyme, catalyzing isocitrate conversion to α -ketoglutarate (α KG) in both the cell cytoplasm and mitochondria, contributes to the production of dihydronicotinamide-adenine dinucleotide phosphate (NADPH) as a reductive potential in various cellular processes. *IDH1* gene mutations are revealed in up to 20% of the patients with acute myeloid leukemia (AML). A mutant IDH enzyme, existing in the cell cytoplasm and possessing neomorphic activity, converts α KG into oncometabolite R-2-hydroxyglutarate (R-2-HG) that accumulates in high amounts in the cell and inhibits α KG-dependent enzymes, including epigenetic regulators. The resultant alteration in gene expression and blockade of differentiation ultimately lead to leukemia development. Myeloid differentiation capacity can be restored by obstruction of the mutant enzyme, inducing substantial reduction in R-2-HG levels. Ivosidenib, a potent selective inhibitor of mutant *IDH1*, is a differentiating agent shown to be clinically effective in newly diagnosed AML (ND-AML) and relapsed/refractory (R/R) AML harboring this mutation. The drug is approved by the Food and Drug Administration (FDA) as a single-agent treatment for R/R AML. Significance of mutated *IDH1* targeting and a potential role of ivosidenib in AML management, when used either as a single agent or as part of combination therapies, will be reviewed herein.

Keywords: mutant *IDH1*, acute myeloid leukemia, ivosidenib

Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematological malignancy distinguished by a variety of recurring mutated genes.^{1,2} The past decade has witnessed considerable advances in unraveling molecular, genetic, and epigenetic underpinnings of AML and in the identification of its new diagnostic and prognostic markers.

In the past years, new drugs, including a wide range of small-molecule inhibitors, have been developed and approved by the Food and Drug Administration (FDA), thus extending the therapeutic landscape for AML.³

Recurrent mutations in isocitrate dehydrogenase 1 and 2 (*IDH1* and *IDH2*) are among most prevalent in AML (found in about 20% of the patients).⁴

The breakthrough in the identification of targetable genetic aberrations in AML, has provided a unique platform for the development of targeted therapeutic agents

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for the management of this aggressive disease. Ivosidenib, a potent selective inhibitor of the *IDH1* mutant protein has been currently approved in the United States (US) for the treatment of adult AML patients harboring this mutation who are relapsed or refractory (R/R) to prior therapy and individuals ≥ 75 years of age or those with comorbidities, precluding the use of intensive induction chemotherapy.⁵

This review will focus on *IDH1* mutations and discuss the mechanism of action of ivosidenib, as well as its role in AML treatment.

The Role of *IDH1* Mutation in Leukemogenesis

Isocitrate dehydrogenase 1 (*IDH1*) is one of the key enzymes that plays a role in cellular metabolism. It catalyzes the reversible oxidative decarboxylation of isocitrate to alpha ketoglutarate (α KG) in the cell cytoplasm, with simultaneous reduction of NADP^+ to NADPH .²

Alteration in cellular metabolism is one of the key characteristics of cancer cells. This phenomenon is known as the “Warburg effect”, first described in 1924.⁶ Cancer cells, including those of AML, preferentially utilize glucose to generate energy, ie, use the tricarboxylic acid (TCA) cycle⁶ even in the presence of oxygen.⁷

A loss-of-function mutation in *IDH1* shifts the products of the TCA cycle, such as α KG, towards the production of 2-hydroxyglutarate (2HG).⁸ In AML cells that harbor an *IDH1* mutation a significant elevation in 2HG levels is seen. The most common *IDH1* mutation recurrently occurring in glioma and leukemia is the one that leads to the replacement of arginine located at position 132 of the *IDH1* gene by histidine.⁹ Mutations at position 132 (*IDH1*^{R132}) are the most prevalent recurrent *IDH1* mutations. The mutated *IDH* is capable of cell transformation through alteration of the activity of 2HG-dependent enzymes.⁵ The mutated *IDH* preferably produces the (R) 2HG enantiomer.¹⁰ The (R) enantiomer accumulation leads to differentiation arrest and leukemia development. Fortunately, and fundamental to the therapeutic potential of *IDH* inhibition, this effect on cell differentiation is reversible when levels of (R) 2HG are restored to normal.^{10,11} Additionally, a decrease in α KG levels is accompanied with an increase in 2HG levels. Consequently, 2HG acts as a competitive inhibitor of α KG-dependent reactions. The resultant hypermethylation of DNA and histones leads to the differentiation blockade ultimately promoting leukemogenesis.⁵

These findings have given rise to a hypothesis that inhibition of *IDH1* activity in *IDH1*^{R132} cases could reverse this abnormal accumulation and induce differentiation of leukemic cells.¹²

Prognostic Significance of *IDH1* R132 Mutation

IDH1^{R132} was first determined to be a recurring oncogenic mutation in glioblastoma. Parsons et al, exploring the genomic landscape of glioblastoma multiforme (GBM), have identified mono-allelic, missense, point mutations in *IDH1* as the most frequent aberration in this disease.¹³ *IDH1*^{R132} is reported to be present in $>80\%$ of the adult patients with secondary GBMs and in over 70% of the adults with grade 2 and grade 3 gliomas.¹⁴ Notably, *IDH* mutations have also been observed in over 50% of chondrosarcoma cases as well as in up to 20% of cholangiocarcinomas and in rare cases of paraganglioma, colon, prostate, and lung cancers.¹⁴

The prognostic significance of *IDH-1* mutations varies among different cancer types. For instance, in GBM, *IDH* mutations are associated with a longer overall survival (OS), amounting to 31 months, relative to only 15 months in patients with *IDH* wild-type.¹⁵ While being frequent among patients with cholangiocarcinoma, the *IDH1* mutation has not been found to affect their OS.¹⁶

In AML, the *IDH1*^{R132} mutation is revealed as a recurring event¹⁷ in 6–10% of the patients.¹⁸ Notably, among AML patients presenting with normal cytogenetics, the incidence of *IDH1* mutation has been reported to reach 16%.^{4,19} *IDH1* mutations are known to frequently coexist with other molecular aberrations, such as nucleophosmin 1 (*NPM1*) mutations and partial tandem duplication of mixed lineage leukemia gene (*MLL-PTD*).^{12,20} Mutations in the *IDH1* gene are also found, albeit at a lower rate, in other myeloid malignancies, equating to up to 12% and 8% among patients with myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs), respectively,^{10,21,22} and their significant presence changes among the different hematologic malignancies. This will be discussed in detail herein.

IDH1 mutations are considered driver mutations that play a role in leukemogenesis and are observed in pre-leukemic hematopoietic stem cells (HSCs) and progenitors.²¹ Notably, acquisition of an *IDH1* mutation may promote transformation of MDS and MPN to AML.^{21,23,24}

IDH1 Mutations in MDS

A recent analysis of genetic abnormalities reported *IDH1* mutations in about 3%²⁵ of the samples obtained from 944 MDS patients. These mutations often co-existed with *SRSF2* and *DNMT3A* mutations, while being mutually exclusive with *TET2* mutations.²⁵

Molenaar et al, evaluating the incidence of *IDH1* mutations in 868 low-risk and 536 high-risk patients with MDS,¹⁵ reported increased frequency of these aberrations in high-risk compared to low-risk patients. The presence of *IDH1* mutations appeared to be associated with shorter survival, particularly in individuals with low-risk disease.^{26,27} Moreover, high-risk MDS patients harboring mutated *IDH1*^{R132} were reported to be more prone to AML transformation.²⁸ Notably, in such cases, typical AML mutations such as *FLT3*, *PTPN11*, *WT1*, *NPM1*, were also present.²⁸ In a recent study from the MD Anderson Cancer Center, 1.6% (n = 17) out of 1042 MDS patients displayed the *IDH1*^{R132} mutation² and demonstrated unique clinical and pathologic features, including elevated absolute neutrophil counts, a higher percentage of bone marrow blasts, and a trend towards increased platelet counts relative to those observed in MDS patients with normal *IDH1*.² Overall, all these studies point to an association between *IDH* mutations and a more advanced disease stage.

Over the last decade, several studies assessed the prognostic impact of *IDH1* mutations in MDS. A study from the Mayo Clinic, evaluating a cohort of 277 MDS patients, identified *IDH* mutations in 12% of the patients, 2.6% of whom displayed *IDH1* alterations (mostly R132-S).²⁹ While the frequency of *IDH1* mutations varied between MDS subtypes, all but one patient in that study had a normal karyotype.²⁹ Importantly, in a multivariate analysis, these mutations emerged as the only factor associated with reduced leukemia-free survival.²⁹ A later study, incorporating 97 patients with MDS, confirmed an association of *IDH1* mutations with shorter OS and progression-free survival (PFS).³⁰

In summary, the incidence of *IDH1* mutations in MDS is lower than that reported in AML and appears to increase with a rising MDS risk score, implying involvement of these mutations in disease progression.²⁷

The mechanisms underlying MDS transformation to secondary AML (sAML) can be explained by one of the following two models^{2,27}:

(a) A linear model, using results of bulk sequencing analysis, suggests accumulation of serial mutations during

disease development from non-mutated HSCs to clonal hematopoiesis, MDS and ultimately to sAML.

(b) A nonlinear model of clonal evolution suggests that mutation accumulation in various stem cell compartments results in vast subclonal diversity in MDS stem cells. While some of such subclones induce MDS, others first function as pre-AML and later as AML stem cells.

In both situations, the low prevalence of *IDH1* mutation in MDS is in favor of its strong leukemogenesis potential.

IDH1 Mutations in MPN

The World Health Organization (WHO) classifies the following types of myeloproliferative neoplasms (MPNs) related to *JAK2*, *CALR*, and *MPL* gene mutations: polycythemia vera (PV), essential thrombocytopenia (ET), primary myelofibrosis (PMF) and prefibrotic PMF (pre-PMF).³¹ In general, *IDH1* mutations are rare in chronic-phase MPNs and have been reported in 0% of PV and ET patients and only in 1% of PMF patients.³² Several studies demonstrated that the frequency of *IDH1* mutations in MPN increased during the blast phase. Green et al evaluating 16 patients with blast/leukemic phase of pre-existing *JAK2*-mutated MPN, identified *IDH* mutations in five of these patients, three of whom harbored *IDH1*^{R132}.¹⁷ In a study from the Mayo Clinic, *IDH* mutations were detected in 9 (4%) of the 227 patients with either chronic or blast-phase MPN, screened for these aberrations. Of note, five of the nine individuals displayed *IDH1*^{R132} (2.2%).³³ The cumulative *IDH* (I+2) mutational frequency was found to be about 4% for patients in the chronic phase of the disease and 21% for those with blast-phase MPN.³³

IDH1^{R132} has been recently established as one of the mutations associated with rapid progression to myelofibrosis³⁴ and AML transformation.²⁴

The co-occurrence of mutated *IDH1* with other mutations, specifically *SRSF2*, may accelerate progression to AML and shorten leukemia-free survival.³⁵ This is particularly true of PMFs with mutated *SRSF2*-, where 13% of the patients have been reported to display *IDH1* mutations relative to only 1% observed in *SRSF2* wild-type PMFs.³⁵ Likewise, PMF patients presenting with concurrent *JAK2* and *IDH1*^{R132} mutations are suggested to be at risk of disease progression.³⁶

A recent analysis from the MD Anderson Cancer Center, evaluating the role of *IDH1/2* inhibitors in the management of post-MPN AML, included five patients with *IDH1* mutation who were treated with ivosidenib either as a single agent or as part of a combination

regimen.³⁷ Although none of the patients receiving ivosidenib monotherapy achieved complete remission, they demonstrated a significant reduction in the percentage of blasts along with a clinical benefit of over 6 months.

In summary, *IDH1*^{R132} mutation has been associated with poor prognosis in both MDS and MPN. The incidence of *IDH1*^{R132} is increased in late-stage MPN and high-risk MDS (20%) compared to early-stage and low-risk disease (<4%). *IDH1*^{R132} is frequently present in secondary AML, and is thus considered as one of the factors contributing to the evolution of chronic MDS and MPN to full-blown leukemia.^{29,36}

IDH1 Mutations in AML

IDH1 mutations are recognized as one of the most common genetic abnormalities in AML.

In a study conducted at the Washington University, *IDH1* mutations emerged as recurring genetic alterations in 16 of 188 AML patient samples (8.5%).⁴ This finding was further confirmed by Paschka et al in 14% of the AML patients included in that study.³⁸ In a retrospective mutational analysis from the Memorial Sloan Kettering Cancer Center, including 398 AML patient samples from E1900 study [by the Eastern Cooperative Oncology Group (ECOG)] and 104 validation cohort samples, somatic alterations were found in 97.3% of the samples, with *IDH1* mutation revealed in 7% of these cases.³⁹ Notably, among patients with intermediate-risk normal cytogenetics, this prevalence could reach 15–20%.⁴⁰ It was also found, in the ECOG-AML cohort, that *IDH1* (and *IDH2*) mutations were mutually exclusive. Expression of *IDH* mutants disrupted TET2 catalytic function in cells and impaired hematopoietic differentiation causing facilitation of stem/progenitor cell marker expression, suggesting a leukemogenic effect.⁴¹

The prognostic significance of *IDH1* mutations in AML is not fully elucidated. Similar to other genetic interactions in AML, there seems to be a difference in the prognosis depending on whether the *IDH1* mutation appears in isolation or in combination with other mutations. In the Medical Research Council (MRC) 10 and 12 studies, among 1333 young adult patients with AML, *IDH1*^{R132} was found to be associated with high relapse rates.⁴² At the same time, another large study including 826 AML patients reported comparable OS for *IDH-WT* and *IDH*-mutated AMLs.⁴³ In the aforementioned ECOG E1900 study, patients with intermediate-risk AML harboring both *NPM1* and *IDH1* mutations demonstrated

a superior 3-year OS relative to that observed in patients with mutant *NPM1* and wild-type *IDH1* (89% vs 31%, $P < 0.001$).³⁹ A recent meta-analysis incorporating data of 33 reported studies⁴⁴ concluded that in AML, the presence of mutant *IDH1* was associated with reduced OS (HR, 1.17; $P = 0.0047$) and event-free survival (EFS; HR 1.29; $P = 0.0110$) compared to those found in patients with wild-type *IDH1*, particularly in normal-karyotype AML (CN-AML). Likewise, *IDH1* single-nucleotide-polymorphism (SNP) rs11554137 appeared to correlate with an inferior OS (HR 1.34; $P = 0.0294$).

Given the genetic heterogeneity of AML, Dunlap et al made an attempt to assess the clinical impact of coexisting mutations on the outcome of forty patients (median age 60 years) with normal cytogenetics and mutated *NPM1* who were *FLT3-ITD* negative.⁴⁵ The 5-year OS and disease-free survival (DFS) of the study group were 54.8% and 42.8%, respectively. The presence of triple mutations in *NPM1* + *DNMT3a* and *IDH1* was associated with a trend towards reduced OS, irrespective of potential confounders such as age and WBC at presentation.⁴⁵

Ivosidenib Mechanism of Action

Ivosidenib (known as AG-120 and AGI-16,678) is a highly specific, allosteric, reversible inhibitor of mutated *IDH1* (Tibsovo, Agios Pharmaceuticals). According to the criteria of the FDA Biopharmaceutical Classification System (BCS) it is defined as a Class II compound (low solubility, high permeability, is mainly metabolized by CYP3A4, and inducing CYP3A enzyme activity).

In a chondrosarcoma cell line model, harboring an endogenous *IDH1* mutation was demonstrated to result in a 100-fold increase of both intracellular and extracellular D-2-HG levels, compared to *IDH1* wild-type cell lines. Specific inhibition of mutant *IDH1* with AGI-5198 led to a >90% reduction of D-2-HG levels in a dose-dependent manner and a moderate decrease in the viability of mutant *IDH1* cell lines. However, this did not significantly affect the tumorigenic properties of these cell lines, which precluded the use of this compound in clinical studies.⁴⁶ Ivosidenib was the first *IDH1* enzyme inhibitor that demonstrated a proof of concept in clinical trials. A US multicenter Phase 1 study, including 168 patients with various types of *IDH1*-mutant solid tumors who received at least one dose of ivosidenib with dose escalation (range 100mg-1200mg), demonstrated 98% inhibition of plasma 2-HG in patients with chondrosarcoma and cholangiocarcinoma after continuous ivosidenib treatment for 1 week.

The resultant 2-HG levels appeared to be comparable to those observed in healthy subjects and persisted throughout the treatment period.⁴⁷ Likewise, in patients with glioma, mean post-treatment plasma 2-HG levels remained within the normal range.⁴⁷

To determine the effect of mutant *IDHI* inhibition in primary human AML blast cells, Popovici-Muller et al investigated mutant *IDHI-R^{132H}*, mutant *IDHI-R^{132C}*, and *IDHI* wild type in the bone marrow and peripheral blood samples derived from patients that were treated with ivosidenib in an ex vivo assay. In mutant *IDHI* samples, ivosidenib was found to decrease the level of intracellular 2-HG by 96% at the lowest administered dose of 0.5 μ M and by 98.6% and 99.7%, respectively, when 1 and 5 μ M doses were used. Ivosidenib induced differentiation of primary mutant *IDHI-R^{132H}* and mutant *IDHI-R^{132C}* blast cells obtained from AML patients treated ex vivo. This was evidenced by enhanced ability of the cells to form differentiated colonies, as well as elevation in the expression of cell-surface differentiation markers and a rise in the proportion of mature myeloid cells.¹²

Pharmacokinetics

Ivosidenib is rapidly absorbed, reaching a steady state at 14 days and a protein-bound range of 92–96%. High-fat meals may interfere with its absorption and should not precede drug swallowing.⁴⁸ The drug is metabolized in the liver by CYP3A4, being mainly excreted in the feces (77% unchanged) and in the urine (10% unchanged and 7% metabolized). Concomitant use with moderate/strong CYP3A4 inhibitors, especially antifungal azoles, reduces ivosidenib clearance.⁴⁹ Co-administration of strong CYP3A4 inducers is not recommended and if strongly indicated, a dose reduction of ivosidenib from 500 to 250 mg/day is advised. No dose adjustments of ivosidenib are needed in concomitant use of weak CYP3A4 inhibitor or inducers.^{48,49} Concomitant application of ivosidenib and CYP substrates with narrow therapeutic windows (eg, warfarin, phenytoin) is contraindicated.⁴⁹ Given that ivosidenib is a P-glycoprotein inhibitor, patients should avoid concurrent use of P-glycoprotein substrates (such as verapamil or cyclosporine) while on treatment with ivosidenib.

Ivosidenib for Relapsed AML with *IDHI* Mutation

On July 20, 2018, the FDA approved ivosidenib (TIBSOVO, Agios Pharmaceuticals, Inc.) for the use in AML patients harboring an *IDHI* mutation, while in

relapse. The approval was granted based on the findings of a non-randomized, open-label, single-arm, multicenter, phase 1, dose-escalation and dose-expansion study of ivosidenib prescribed as monotherapy.⁵⁰ Included in that study were patients who could not receive conventional therapy, so the label was limited to patients older than 75 years or those who had comorbidities precluding the use of intensive induction chemotherapy.⁵

Two hundred and fifty-eight patients received ivosidenib in that trial. The median age of enrolled patients was 68 years, 39% of them were diagnosed with secondary AML, and adverse cytogenetics was reported in 31%. The maximum prescribed ivosidenib dose was 1200 mg per day, while the maximum tolerable dose was not reached. However, no clinical benefit associated with the dose increase was observed and 500 mg was identified as the optimal daily dose.⁵⁰

The efficacy of ivosidenib was assessed based on complete remission (CR) + CR with partial hematologic recovery (CRh) rate, duration of CR + CRh, as well as conversion of transfusion dependence to transfusion independence. At a median follow-up of 8.3 months, in 174 adult patients with *IDHI*-mutated R/R AML, the CR+CRh rate was 33% [95% confidence interval (CI), 26–40] with median response duration of 8.2 (95% CI, 5.6–12) months, and transfusion independence acquired in 37% of the patients.⁵¹

Although the results show a short-term benefit in patients with an unmet medical need, responses to ivosidenib may appear only after several months, as was reported by DiNardo et al in a cohort of 125 R/R AML patients, treated with ivosidenib.⁵² Responses developed within up to 8 months, with a median response duration of more than 6 months. The CR rate was 22% with a median duration of over 9 months. Median OS for the total cohort was 9 months, while it equated to 18 months for those who achieved CR.⁵²

The most frequent (20%) adverse reactions of any grade recorded in patients receiving ivosidenib included diarrhea, febrile neutropenia, leukocytosis, fatigue, nausea, dyspnea, prolongation of the QT interval, edema, anemia, pyrexia, and cough.⁵⁰ Among serious adverse reactions, observed in 5% of the cases, were QTc interval prolongation (7.8%), leukocytosis (10%) and differentiation syndrome (3.9%).

Concomitant use of ivosidenib and other drugs with the potential of prolonging the QTc interval should be avoided, and these drugs should be replaced with

alternative treatments if possible. Otherwise, the subjects receiving such drugs should be adequately monitored with electrocardiogram (ECG) control and measurement of serum electrolyte levels, particularly those of potassium and magnesium.

In case the QTc interval is >480 ms (grade 2) or >500 ms (grade 3), treatment with ivosidenib should be discontinued and restarted after the values return to ≤ 480 ms, with the recommended drug doses of 500 mg/day and 250 mg/day for grade 2 and grade 3 events, respectively. In addition, ECG should be monitored at least once weekly for 2 weeks following resolution. The main drugs that could prolong the QTc interval are fluoroquinolones (eg, ciprofloxacin, moxifloxacin), 5-HT₃ antagonists (eg, granisetron, ondansetron), and azole antifungals (eg, fluconazole, voriconazole, posaconazole), which are also strong or moderate CYP3A4 inhibitors and may increase ivosidenib plasma concentrations (worsening potential QTc interval prolongation).

In patients for whom antifungal therapy is necessary, alternative treatments should be considered like aerosolized liposomal amphotericin B, added to systemic antifungal treatment, despite limited data,^{53,54} intravenous agents such as echinocandins (caspofungin, micafungin, and anidulafungin) or low-dose amphotericin B. Another option may be the use of isavuconazole as an oral agent with a spectrum of activity similar to that of posaconazole or voriconazole, which are moderate CYP3A4 inhibitors, without QTc prolongation effects.⁴⁹

As mentioned above, differentiation syndrome (DS) was identified as another serious adverse effect⁵⁰ in patients treated with ivosidenib, who experienced the symptoms, similar to those observed in patients receiving all-*trans* retinoic acid (ATRA) for acute promyelocytic leukemia (APL). These reactions were apparently caused by cytokine release from differentiating myeloid blasts.^{55,56} DS was reported to evolve late during therapy,⁵⁷ with median onset time of 29 days (range 5–59 days) and with 37% of the patients developing leukocytosis. There were also reports of patients presenting with treatment-related myopericarditis and cardiogenic shock.⁵⁷

The recommended DS treatment included use of steroids, diuretics with or without hydroxyurea, and non/invasive ventilation. These measures led to the resolution of symptoms in almost 90% of the cases. Of note, none of the patients experienced grade 4 or lethal events. Treatment with ivosidenib that has been withheld in some patients,

could be safely renewed at the standard daily dose of 500 mg.^{21,50,57,58} Yet, caution is advised since there is no agreement regarding the optimal timing and dosage for ivosidenib re-introduction after DS.

A recent systematic analysis of DS in R/R AML patients treated with ivosidenib (NCT02074839) or the *IDH2* inhibitor, enasidenib (NCT01915498), conducted by the FDA⁵⁸ estimated potential DS risk associated with ivosidenib therapy in a multivariable model. The assessed parameters included baseline bone marrow and peripheral blood blast percentages, secondary versus *de novo* AML, WBC count, and LDH levels. Other parameters evaluated in the multivariate analysis were prior hematopoietic stem cell transplantation (HSCT) and the presence of *TET2* mutations. Peripheral blast count $\geq 25\%$ and bone marrow blast count $\geq 48\%$ along with a median WBC count above 10×10^3 , LDH above the upper limit of normal, prior HSCT and the presence of *TET2* mutations were associated with higher relative risk of DS. Potential DS risk was suspected when two or more criteria were found to be positive within 7 days of appearance. DS was considered moderate when fulfilled two or three criteria and severe when fulfilled four or more criteria.^{51,58,59} It is noteworthy that morphological evidence of cellular differentiation in blood or bone marrow was not considered a requirement for potential DS.

Despite the imminent potential for the development of DS with possible fatal complications, the reported data from different studies suggest that this phenomenon is infrequent, occurs late during exposure to ivosidenib and the assumption of a favorable outcome with prompt early treatment is fair.^{50,56,57,60,61}

Ivosidenib as First-Line Therapy for AML with Mutant *IDH1*

On May 2, 2019, the FDA approved ivosidenib (TIBSOVO, Agios Pharmaceuticals, Inc.) for the application in newly-diagnosed AML with a susceptible *IDH1* mutation, in patients ≥ 75 years of age or those with comorbidities precluding the use of intensive induction chemotherapy.

The approval was granted based on the data from an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) of single-agent ivosidenib used for newly diagnosed AML with an *IDH1* mutation.⁶⁰ Patients aged ≥ 75 years or those who met at least one of the following criteria were enrolled in the study: baseline

ECOG performance status (ECOG PS) ≥ 2 , severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, or creatinine clearance <45 mL/min. Twenty-eight patients were treated (median age 77 years; range: 64–87 years); 22 (79%) of them had therapy-associated AML or AML with myelodysplasia-related alterations. Ivosidenib was given orally at a daily dose of 500 mg and was discontinued due to disease progression, unacceptable toxicity, or HSCT. CR +CRh was achieved in 12/28 patients (42.9%); 7/17 (41.2%) transfusion-dependent patients acquired transfusion independence that maintained for a minimum of 8 weeks. Two of the 28 patients received HSCT. Based on the results of that study, the FDA recommended an oral once-daily ivosidenib dose of 500 mg (with or without food) that could be administered until AML progression or unacceptable toxicity. To ensure clinical response in patients who did not experience disease progression or unacceptable toxicity, the therapy duration of a minimum of 6 months was recommended.⁶²

Adverse events, recorded in at least 25% of the study participants, included the following: nausea, diarrhea, decreased appetite, fatigue, edema, leukocytosis, arthralgia, abdominal pain, dyspnea, DS and myalgia. Prescribing information contained a warning addressed to both healthcare practitioners and patients regarding the risk of DS that could be life-threatening or fatal.

A recently conducted multicenter, open-label, phase 1 study assessed safety and tolerability of induction and consolidation combination regimens, including ivosidenib (or enasidenib) and intensive chemotherapy, in ND-AML patients with mutant *IDH1* or *IDH2*.⁶¹ The study also analyzed clinical responses. Next-generation sequencing (NGS) was used to evaluate the mutational profile at the starting point of treatment with ivosidenib as well as at the time of the best response. Responses were assessed by multi-parameter flow cytometry and digital polymerase chain reaction (PCR) assay to evaluate measurable minimal residual disease (MRD). Despite the fact that only a small number of patients were assessed by both methods, the promising findings of *IDH1* clearance in 39% of the patients (16/41) and MRD achievement in 80% of them (16/20) could make ivosidenib combined with intensive chemotherapy an attractive treatment option for newly diagnosed AML patients with mutated *IDH1*.⁶¹

Prospective studies are still needed to identify the optimal method for the assessment of mutant *IDH1*

clearance that would provide the most accurate information, especially in clinical practice.

A number of ongoing clinical trials are evaluating potential expansion of the indications for the use of ivosidenib in *IDH1*-mutated AML and MDS (Table 1).

In contrast to the FDA, ivosidenib has not yet been approved in Europe. The European Medicines Agency (EMA) had reservations about the data, partly related to efficacy and lack of better control, leading the sponsor in November 2020 to withdraw the application. The lack of approval in Europe relates to both relapsed and newly diagnosed AML patients.

Resistance to Ivosidenib

Several studies have addressed the issue of resistance mechanisms to ivosidenib. Based on patient response, the following two types of drug resistance are defined: primary resistance refers to the lack of response to initial therapy; secondary resistance refers to the development of drug resistance following initial response to treatment.

Data from a recently published international phase 1 study, exploring molecular mechanisms underlying primary and secondary resistance to ivosidenib in R/R AML with mutant *IDH1*⁶³ demonstrate an association of mutations in receptor tyrosine kinase (RTK) pathway genes with both primary and secondary resistance in this patient population. Notably, *KRAS* mutations appear to be more frequent at relapse/progression than at baseline.⁶³

These findings are in line with previously reported evidence of an association between baseline mutations in RTK pathway genes and primary resistance to ivosidenib.⁵⁰ The biological processes explaining a causal link between RTK pathway mutations and both primary and secondary resistance to ivosidenib remain to be elucidated.

According to one hypothesis, proliferative and pro-survival impacts of RTK pathway stimulation could be potent oncogenic signals sufficient to diminish 2-HG dependence. Another hypothesis suggests involvement of RTK pathway-activating mutations in differentiation inhibition, which remains enforced after the start of ivosidenib therapy. It is also hypothesized that *IDH1/2* mutations could contribute to the activation of certain components in RTK signaling, that might be irreversible in response to ivosidenib in patients with co-existing RTK pathway mutations.⁶³

A mechanism mediating secondary resistance could be attributed to the restoration of 2-HG caused by mutations

Table I Current Clinical Trials in AML and MDS

NCT Number	Title	Conditions	Interventions	Estimated Patient Enrollment	Characteristics
NCT04493164	CPX-351 and ivosidenib for the treatment of IDH1 mutated acute myeloid leukemia or high-risk myelodysplastic syndrome	<ul style="list-style-type: none"> Acute myeloid leukemia with gene mutations Myelodysplastic syndrome Myeloproliferative neoplasm Recurrent/Refractory acute myeloid leukemia 	<ul style="list-style-type: none"> Drug: Ivosidenib Drug: Liposome-encapsulated daunorubicin–cytarabine 	30	Phase 2
NCT04250051	Ivosidenib and combination chemotherapy for the treatment of IDH1 mutant relapsed or refractory acute myeloid leukemia	<ul style="list-style-type: none"> Recurrent/Refractory acute myeloid leukemia Recurrent/Refractory myelodysplastic syndrome Recurrent Myeloproliferative neoplasm 	<ul style="list-style-type: none"> Drug: Cytarabine Biological: Filgrastim Drug: Fludarabine Drug: Fludarabine Phosphate Drug: Ivosidenib 	25	Phase I
NCT04176393	A China bridging study of ivosidenib in r/r AML subjects with an IDH1 mutation	<ul style="list-style-type: none"> Relapsed/Refractory acute myeloid leukemia 	<ul style="list-style-type: none"> Drug: Ivosidenib 	30	Phase I
NCT03839771	A study of ivosidenib or enasidenib in combination with induction therapy and consolidation therapy, followed by maintenance therapy in patients with newly diagnosed acute myeloid leukemia or myelodysplastic syndrome EB2, with an IDH1 or IDH2 mutation, respectively, eligible for intensive chemotherapy	<ul style="list-style-type: none"> Acute myeloid leukemia Myelodysplastic syndrome with excess blasts-2 	<ul style="list-style-type: none"> Drug: AG-120 Drug: Placebo or AG-120 Drug: AG-221 Drug: Placebo for AG-221 	968	Phase 3
NCT03503409	IDH1 (AG 120) inhibitor in patients with IDH1-mutated myelodysplastic syndrome	<ul style="list-style-type: none"> Myelodysplastic syndromes Acute myeloid leukemia 	<ul style="list-style-type: none"> Drug: AG-120 	68	Phase 2
NCT03471260	Ivosidenib and venetoclax with or without azacitidine in treating participants with IDH1-mutated hematologic malignancies	<ul style="list-style-type: none"> High-risk myelodysplastic syndrome IDH1.R132X Myeloproliferative neoplasm Recurrent/Refractory acute myeloid leukemia 	<ul style="list-style-type: none"> Drug: Azacitidine Drug: Ivosidenib Other: Pharmacokinetic Study Drug: Venetoclax 	48	Phase I/2
NCT03245424	Ivosidenib expanded access program in relapsed/refractory aml with an IDH1 mutation	<ul style="list-style-type: none"> Acute myeloid leukemia Relapsed adult AML Relapsed pediatric AML 	<ul style="list-style-type: none"> Drug: Ivosidenib (AG-120) 		
NCT03173248	Study of AG-120 (ivosidenib) vs placebo in combination with azacitidine in patients with previously untreated acute myeloid leukemia with an IDH1 mutation	<ul style="list-style-type: none"> Newly diagnosed acute myeloid leukemia Untreated AML AML arising from myelodysplastic syndrome 	<ul style="list-style-type: none"> Drug: AG-120 (ivosidenib) with azacitidine Drug: Placebo with azacitidine 	200	Phase 3

(Continued)

Table 1 (Continued).

NCT Number	Title	Conditions	Interventions	Estimated Patient Enrollment	Characteristics
NCT02677922	A safety and efficacy study of oral AG-120 plus subcutaneous azacitidine and oral AG-221 plus subcutaneous azacitidine in subjects with newly diagnosed acute myeloid leukemia (AML)	<ul style="list-style-type: none"> • Leukemia, myeloid, acute 	<ul style="list-style-type: none"> • Drug: AG-120 • Drug: Azacitidine • Drug: AG-221 	131*	Phase I/2
NCT02632708	Safety study of AG-120 or AG-221 in combination with induction and consolidation therapy in participants with newly diagnosed acute myeloid leukemia (AML) with an IDH1 and/or IDH2 mutation	<ul style="list-style-type: none"> • Newly diagnosed acute myeloid leukemia • Untreated AML • AML arising from myelodysplastic syndrome (MDS) • AML arising from antecedent hematologic disorder • AML arising after exposure to genotoxic injury 	<ul style="list-style-type: none"> • Drug: AG-120 • Drug: AG-221 • Drug: Cytarabine • Drug: Daunorubicin • Drug: Idarubicin • Drug: Mitoxantrone • Drug: Etoposide 	153*	Phase I
NCT02074839	Study of orally administered AG-120 in subjects with advanced hematologic malignancies with an IDH1 mutation	<ul style="list-style-type: none"> • Relapsed/Refractory acute myeloid leukemia • Untreated AML • Other IDH1-mutated Positive Hematologic Malignancies • Myelodysplastic Syndromes 	<ul style="list-style-type: none"> • Drug: AG-120 	291	Phase I

Notes: Data from www.clinicaltrials.gov (January 2021). *Actual enrollment.

blocking drug/cofactor binding and/or occurrence of *IDH2* mutations, whose incidence is similar to that of mutations in the RTK pathway.⁶³

Furthermore, data presented in a recently published review and case series, point to mutant *IDH* isoform switching, from cytoplasmic mutant *IDH1* to mitochondrial mutant *IDH2* or in the reverse order, as the primary mechanism responsible for acquired resistance to IDH inhibitors.^{27,64} 2-HG production in AML with mutated *IDH* is suggested to be mediated by selective pressure. To circumvent drug resistance in this setting, consecutive administration of IDH inhibitors (either *IDH1*>*IDH2* or *IDH2*>*IDH1*) is proposed.⁶⁴

One of the ways to prevent the development of secondary resistance in AML is through the use of combination therapy. Several recent studies have demonstrated the synergistic effect of the combination of the BCL-2 inhibitor, venetoclax, either with hypomethylation agents or with

low-dose cytarabine.^{65–67} The most responsive patients to both combination treatments were found to be those with *IDH1/IDH2* and *NPM1* mutations.

Based on the established efficacy of both IDH inhibitors and venetoclax in AMLs with mutant *IDH1*, potential synergistic action of their combinations is hypothesized. This issue is being currently investigated in a Phase Ib/II clinical trial assessing the use of venetoclax and ivosidenib with/without azacytidine in mutant *IDH1* R/R AML patients (NCT 03471260) (Table 1).

Preliminary results demonstrated an ORR of 75% with no significant added toxicity, suggesting a favorable risk/benefit profile of these triplet combinations.⁶⁸ These findings are promising, although Chan et al suggest an antagonist effect of the mentioned combination in human AML blast cells.⁶⁹

Another promising combination therapy that might provide a synergistic effect could comprise mutant IDH

inhibitors and RTK pathway inhibitors (including *FLT3* inhibitors). Along the same lines, the currently investigated joint effect of mutant IDH1 and mutant IDH2 inhibition may also have a therapeutic potential in this patient population.⁷⁰

Among other open issues related to AML management are the safety and efficacy of combinations including novel agents only or those incorporating standard chemotherapy for AML. Prospective clinical studies are warranted to address these questions.

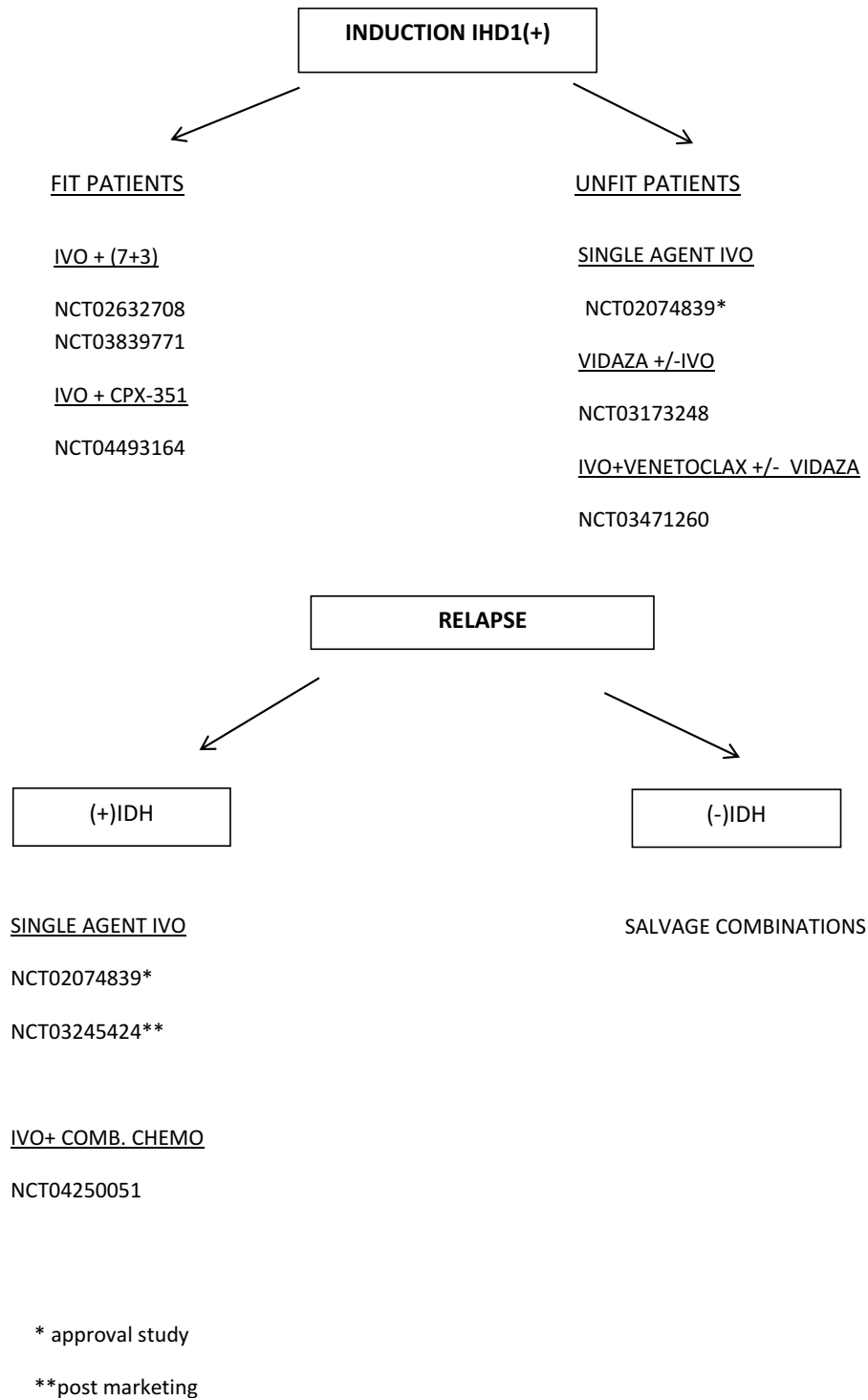


Figure 1 How to incorporate ivosidenib in AML treatment.

Summary and Conclusions

The general therapeutic strategy in patients with AML has significantly changed in the last years. Although younger patients are still mainly treated with the combination of an anthracycline and cytosine–arabinoside, as induction therapy, the growing knowledge of molecular and genetic landscape of AML has led to novel treatment options, for both younger and older patients.^{71–74} *IDH1* mutations occur in up of 20% patients with AML.^{4,18,19}

The mutated IDH1 enzyme causes the formation of 2HG instead of α KG, which entails a decrease in α KG levels with an increase in 2HG. The latter metabolite functions as a competitive inhibitor of α KG-dependent reactions and causes hypermethylation of DNA and histones resulting in differentiation block. It is postulated that this sequence of events promotes leukemogenesis.

The availability of a large number of novel drugs for the treatment of newly diagnosed AML makes it possible to explore new treatment combinations. Yet, choosing the optimal drug combination and schedule of its administration, not associated with excessive toxicity, is challenging.

Ivosidenib is the first IDH mutated inhibitor that was approved by FDA for R/R mutated *IDH* AML patients, based on results from NCT02074839 study and was administered as monotherapy.⁵⁰

Other randomized phase I/II trials are currently being conducted to evaluate the efficacy and safety of ivosidenib as monotherapy or in combinations in this group of patients (NCT04250051, NCT04176393) (Table 1).

Several clinical trials are studying the combined effect of ivosidenib with intensive chemotherapy (NCT04493164, NCT02632708), hypomethylating agents (NCT03173248) or with other targeted therapies (NCT 0341260) in newly diagnosed *IDH1*-mutated AML patients.

Results from these trials will provide the necessary data whether to incorporate ivosidenib in the first-line treatment as standard of care for patients with *IDH1*-mutated AML. It is reasonable to assume that the addition of ivosidenib can lead to improvement in long-term survival.^{2,37,61,68,75}

Maintenance treatment is also being studied in several trials. The optimal duration of maintenance treatment and how effective it will be, is yet to be evaluated. Data on *IDH1* mutation clearance and MRD might be of help to resolve this question, as was demonstrated by Chifotides et al³⁷ and other studies.

A correlation between the MRD status and the cumulative risk for relapse in AML patients was demonstrated by several studies. The long-term clinical impact of *IDH* mutation clearance is under investigation. Preliminary data suggest that clearance of the mutation results in a prolonged duration of response and improved overall survival.^{5,37,61}

With ivosidenib, adverse events of special interest are the IDH-DS, leukocytosis and prolongation of the QT interval, which can be managed with appropriate guidance.

The drug is well tolerated and the majority of treated patients achieve composite complete remission (hematologic improvement, remission without hematologic improvement and complete remission). This finding correlates with a prolongation in overall survival – as was demonstrated by the above mentioned studies.

Figure 1 summarizes the role of Ivosidenib in the treatment of AML.

Resistance to ivosidenib^{50,63} may lead to disease progression with increased 2-HG concentration in plasma and re-emergence of leukemic blasts. This emphasizes the need for therapeutic approaches enabling prevention of drug resistance.

In conclusion, ivosidenib is a promising novel agent for the treatment of *IDH1*-mutated AML in the era of targeted therapy for AML. Yet, there is still a need for prospective double-blind studies to confirm its role and timing in the treatment of AML.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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