Ivosidenib: IDH1 Inhibitor for the Treatment of Acute Myeloid Leukemia

SHELBY L. MERCHANT, PharmD, KATHRYN CULOS, PharmD, BCOP, and HOUSTON WYATT, PharmD, CSP

Abstract

There is no standard therapy for refractory acute myeloid leukemia (AML), but several salvage therapies are available (National Comprehensive Cancer Network [NCCN], 2018). Recently, there have been major developments in the treatment of AML focusing on the development of targeted and novel therapies. Ivosidenib is the first approved oral, targeted, small-molecule inhibitor of the isocitrate dehydrogenase 1 (IDH1) mutation seen in AML. IDH1 mutations have been associated with significantly worse outcomes in disease-free survival, relapse-free survival, and overall survival (NCCN, 2018). This article reviews the clinical trials and dose escalation studies that led to the U.S. Food & Drug Administration approval for ivosidenib in patients with relapsed or refractory AML with a susceptible IDH1 mutation. Patient counseling and monitoring, including dosing and administration, are important steps that advanced practitioners should be aware of. The mechanism of action and pharmacokinetic information for ivosidenib is discussed, as well as recommendations for drug-drug interaction management. Adverse events and monitoring parameters are addressed in detail, as well as how to interrupt and resume treatment due to adverse events.

Acute myeloid leukemia (AML) is a hematologic malignancy originating from abnormal proliferation of immature hematopoietic cells in the bone marrow. Patient age, performance status, molecular markers, and cytogenetics determine risk stratification and prognosis. Approximately two thirds of patients under the age of 60 with newly diagnosed AML who receive standard induction therapy of daunorubicin and cytarabine achieve remission (complete response [CR]; American Cancer Society, 2018; Tamamyan et al., 2017). However, only half of patients over 60 years of age achieve a CR after intensive induction treatment (Anderson et al., 2002) due to difficulty tolerating chemotherapy and complex cytogenetic markers associated with poor prognosis (American Cancer Society, 2016; Tamamyan et al., 2017).

The curative option for most patients is a hematopoietic stem cell transplant (HCT) for patients who...
are able to achieve CR. In the 10% to 40% of newly diagnosed AML patients who do not achieve a CR and do not meet transplant criteria, salvage regimens and clinical trials should be considered (Thol, Schlenk, Heuser, & Ganser, 2015). There is no standard therapy for refractory disease, but several salvage therapies are available (National Comprehensive Cancer Network [NCCN], 2018). In the past year there have been major developments in the treatment of AML with a focus on the development of targeted and novel therapies. Ivosidenib (Tibsovo) is the first oral, targeted, small-molecule inhibitor of isocitrate dehydrogenase 1 (IDH1) mutations. Approximately 10% to 20% of patients with cytogenetically normal AML (CN-AML) have IDH1 or IDH2 mutations (“Ivosidenib deemed safe, effective in AML”, 2018; Patel et al., 2011a; Thol et al., 2015). Approximately 5% to 15% account for IDH1 mutations and 10% to 20% for IDH2 mutations, with a higher frequency of mutations seen in patients with extramedullary AML (IDH1 17%, IDH2 14%; Knepper et al., 2018). There have been conflicting reports regarding the impact of IDH mutations on survival. Comutations with IDH mutations have been seen most often with NPM1 mutations (NCCN, 2018; Papaemmanuil et al., 2016).

MECHANISM OF ACTION
Ivosidenib is a small-molecule inhibitor of IDH1 enzyme indicated for the treatment of relapsed/refractory (R/R) AML with a susceptible IDH1 mutation. Enasidenib (Idhifa) is the IDH2 inhibitor approved for the treatment of AML. Susceptible IDH1 mutations are defined as those with increased levels of oncometabolite 2-hydroxyglutarate in leukemic cells (Agios Pharmaceuticals, Inc., 2018). IDH mutations are detected via Sanger sequencing assays or high-resolution melting analysis, or both (Patel et al., 2011b).

In patients with AML, mutations in the active sites of IDH1 or 2 result in increased enzyme activity and accumulation of 2-hydroxyglutarate. Alteration of 2-hydroxyglutarate concentrations is thought to interfere with cellular metabolism and epigenetic regulation, ultimately preventing the differentiation of myeloid cells (Dhillon, 2018; “Ivosidenib deemed safe, effective in AML”, 2018). Ivosidenib targets gene mutations at position R132; the most common mutations are in R132H and R132C. Ivosidenib inhibits IDH1 R132 mutations at much lower concentrations than wild-type IDH1 in vitro. This inhibition lowers 2-hydroxyglutarate levels, inducing myeloid differentiation that reduces blast counts and increases the percentage of mature myeloid cells (Agios Pharmaceuticals, Inc., 2018; Sidaway, 2018).

CLINICAL TRIALS
Ivosidenib was approved by the U.S. Food & Drug Administration (FDA) in July 2018 for the treatment of R/R AML with a susceptible IDH1 mutation. Approval was based on a phase I dose-escalation and dose-expansion trial (DiNardo et al., 2017).

The phase I, open-label, single-arm, multicenter clinical trial assessed pharmacodynamics, pharmacokinetics, efficacy, and safety in patients receiving ivosidenib with R/R AML or myelodysplastic syndromes with excess blasts. The dose-escalation phase (N = 78) included three to six patients per cohort to establish the maximum tolerated dose. Ivosidenib was given once daily or twice daily in 28-day cycles. The maximum tolerated dose was not achieved and 500 mg daily was the recommended dose in the four expansion cohorts (N = 179). Table 1 details the four arms that were evaluated (DiNardo et al., 2017, 2018). A total of 258 patients received ivosidenib, 179 patients of whom had R/R AML. The median age

| Treatment arm | Patient qualification |
|---------------|-----------------------|
| 1             | Relapsed after HCT, second or later relapse, resistance to initial induction, reinduction treatment, relapsed within 1 year of initial treatment |
| 2             | Untreated patients with AML |
| 3             | Advanced hematologic malignancies, including myelodysplastic syndrome |
| 4             | Relapsed or refractory AML not eligible for Arm 1 |

Note. HCT = hematopoietic stem cell transplant; AML = acute myeloid leukemia. Information from DiNardo et al. (2017).
was 68, with 61% of patients with primary AML receiving a median of one previous line of therapy. The majority of prior therapy included intensive and non-intensive chemotherapy. No patients included in the trial had favorable cytogenetic risk. Ivosidenib was found to be rapidly absorbed, reaching steady state in approximately 14 days. Maximal inhibition of 2-hydroxyglutarate was observed with the 500 mg daily dose; higher doses did not achieve any additional inhibition (DiNardo et al., 2017).

In the results of the phase I dose-escalation and expansion study, 179 patients were included in the expansion phase. The median duration of exposure was 3.5 months, with 8.5% of patients discontinuing treatment to proceed to HCT. Other reasons for discontinuation include disease progression (40.3%), adverse events (12.7%), death (6.2%), and investigator decision (4.6%). Reported adverse events are described in Table 2 (DiNardo et al., 2017). Differentiation syndrome was reported in 10.6% of patients, with a median onset of 29 days (range, 5–59 days). Thirty-day all-cause mortality was 7% and 60-day all-cause mortality was 14.3%. Most deaths were attributed to disease progression and complications of the underlying disease state (DiNardo et al., 2017).

In the efficacy analysis that included 125 patients, the ORR was 41.6% (95% confidence interval [CI] = 32.9–50.8), with a CR or CRh rate of 30.4% (95% CI = 22.5–39.3). Median time and duration of CR/CRh was 2.7 months (range, 0.9–5.6 months) and 8.2 months (range, 5.5–12.0 months), respectively. The median time and duration of response was 1.9 months (range, 0.8–4.7 months) and 6.5 months (range, 4.6–9.3 months), respectively. Of the patients in remission, survival at 18 months was 50.1%. Overall survival after a median follow-up of 148 months was 8.8 months (95% CI = 6.7–10.2). Low IDH mutational and co-mutational burden in the marrow during the study was associated with CR. Patients showing response to therapy had decreases in mean levels of IDH1 mutation in the mononuclear cells in the marrow (DiNardo et al., 2018).

Ivosidenib and enasidenib have also been studied in a phase I, open-label, multicenter trial assessing IDH inhibitors in combination with induction therapy with 7 ± 3 regimen and consolidation with chemotherapy for patients with newly diagnosed AML and an IDH mutation. Addition of an IDH inhibitor resulted in CR rates of 66% and a CR rate of only 39% in patients with secondary AML. Mutation clearance occurred in 41% of patients with a CR. There was a significant association between low comutation burden with CR/CRh (p = .02) and RTK pathway mutations (NRAS, FLT3, Kras) present in non-responders (p = .003). Of note, NRAS mutational status alone had no association with response to ivosidenib, although it was not powered to detect a difference. This differs from the findings in the enasidenib trial that found an NRAS mutation was present in 86% of non-responders (p < .001; Amantangelo et al. 2017; Stein et al. 2017). The addition of an IDH inhibitor to chemotherapy was found to be safe with a median time to platelet and absolute neutrophil recovery of approximately 28 days. Adverse effects occurred at a higher frequency with induction therapy, and common adverse effects seen were febrile neutropenia (approximately 60%), hypophosphatemia (approximately 10%), and hypokalemia (approximately 8%; Stein, et al. 2018).

**DOSING AND ADMINISTRATION**

Ivosidenib is available as a 250-mg tablet that can be taken with or without food. The recommended dosage is 500 mg given orally daily until disease progression or unacceptable toxicity. Taking ivosidenib with a high-fat meal can increase the Cmax and area under the curve (AUC), and should be avoided (Agios Pharmaceuticals, Inc., 2018).

Ivosidenib is hepatically metabolized primarily by CYP3A4 with minor metabolism via N-dealkylation and hydrolytic pathways. Co-administration of strong CYP3A4 inhibitors such as posaconazole and voriconazole should be avoided; if using these agents is unavoidable, the dose of ivosidenib should be decreased to 250 mg daily per the package insert (Agios Pharmaceuticals, Inc., 2018). A population pharmacokinetic evaluation found that the use of moderate/strong CYP3A4 inhibitors voriconazole, posaconazole, and fluconazole reduced mean steady-state apparent clearance and increased the ivosidenib plasma concentration-time curve (AUC). Despite this increase in AUC, patients remained within the 5th to 95th percentile of the observed population, indicating that no adjustment in dose is
necessary, which conflicts with recommendations from the manufacturer (Le et al., 2018). Agents prolonging the QT interval should also be avoided. The use of ivosidenib in patients with moderate or severe hepatic impairment is unknown, but results assessing the use in moderate hepatic dysfunction are pending (Agios Pharmaceuticals, Inc., 2018; ClinicalTrials.gov, 2018). The half-life of ivosidenib is 93 hours, with 67% eliminated unchanged in feces and the remainder in urine (Agios Pharmaceuticals, Inc., 2018).

### ADVERSE EVENTS

IDH inhibitors induce the proliferation of differentiated leukemic cells, which can lead to differentiation syndrome; this is caused by cytokine imbalance leading to tissue damage and inflammation (Fathi et al., 2018). Differentiation syndrome is a serious adverse reaction that was identified in clinical trials at a rate of 19% in all grades and 13% in grades 3 or greater. However, only 3% required a dose reduction. Differentiation syndrome is commonly associated with other reported adverse events such as leukocytosis (38%), edema (32%), and dyspnea (33%; DiNardo et al., 2018).

The FDA performed a review to further evaluate cases of differentiation syndrome with IDH inhibitors and found a higher incidence (40%) with ivosidenib than what was identified in the phase II trial. A large portion of patient cases with differentiation syndrome was considered moderate (71%), with 12% considered severe. In addition, the FDA identified an earlier time to onset of 20 days and a higher incidence of leukocytosis at presentation (79%) with ivosidenib treatment (Norsworthy et al., 2018). Patients may present with leukocytosis, edema, dyspnea, fever, hypotension, and renal failure. Often, the signs and symptoms of differentiation syndrome are nonspecific and present similarly to other conditions common in

| Table 2. Adverse Events of Ivosidenib (N = 179) |
|-----------------------------------------------|
| ![Table 2](image) |

Note. Information from DiNardo et al. (2017).
patients with AML. Appropriate treatment is imperative, as this condition can be fatal.

Patients with suspected differentiation syndrome presenting with new onset or worsening hallmark symptoms, including fever, rapid weight gain, edema, respiratory symptoms with or without infiltrates, pleural or pericardial effusions, hypotension, and acute renal failure, should be initiated on steroid therapy (Fathi et al., 2018). For the treatment of differentiation syndrome, patients should be initiated on dexamethasone at 10 mg twice daily, which has been shown to significantly improve mortality rates to less than 1% (Fathi et al., 2018; Montesinos & Sanz, 2011). In addition, patients may receive hydroxyurea at 2 to 3 grams two or three times daily for the treatment of leukocytosis (white blood cell count > 25,000 cells/mm$^3$ or increase in white blood cell count > 15,000 cells/mm$^3$) and other supportive care measures when appropriate, including dialysis and intubation (Agios Pharmaceuticals, Inc., 2018; Fathi et al., 2018). If patients continue to have progressing symptoms despite appropriate therapy, then interruption of the IDH inhibitor is warranted. Alternatively, if patients improve on treatment, then they should be continued on dexamethasone until significant improvement or resolution of symptoms and be tapered off steroids when indicated (Fathi et al., 2018).

Other notable adverse effects of ivosidenib include Guillain-Barré syndrome (1%), QTc prolongation (26%), and tumor lysis syndrome (8%). As mentioned above, patients should avoid concomitant QTc-prolonging medications while receiving ivosidenib. Management of tumor lysis should be based on institutional protocol. Management strategies include increasing fluid intake, maintaining urine output, the initiation of prophylactic allopurinol, and in select cases, initiating rasburicase (Cairo, Coiffier, Reiter, & Younces, 2010; Coiffier, Altman, Pui, Younges, & Cairo, 2008). Adverse reactions are reported in Table 2 (Agios Pharmaceuticals, Inc., 2018).

**PATIENT MONITORING AND COUNSELING**

Monitoring parameters and dose adjustments for toxicities are listed in Table 3. Ivosidenib has not been shown to cause neutropenia, but several patients included in the clinical trial were dependent on platelet and/or red blood cell transfusions. Also, 60% of patients had a decrease in hemoglobin, with 46% having a decrease of grade 3 or greater. Ivosidenib should be interrupted for any grade 3 or higher toxicity associated with therapy and restarted when toxicity resolves. Any patient experiencing a recurrence of a grade 3 or higher toxicity should discontinue therapy and should not be reinitiated.

Patients should be counseled on toxicities while taking therapy and would likely benefit from a journal to record adverse events experienced. Patients should be instructed to contact the office if they notice any symptoms associated with differentiation syndrome, Guillain-Barré syndrome, or other serious adverse effects (Agios Pharmaceuticals, Inc., 2018).

**SUMMARY**

Ivosidenib is the first IDH1 inhibitor available for the treatment of AML. It provides another therapy option for patients with R/R disease and an IDH1 mutation. The NCCN AML guidelines recommend

| Table 3. Monitoring Parameters and Dose Adjustments for Ivosidenib |
|---------------------------------------------------------------|
| **Monitoring parameter**                                      | **Dose adjustment**                                      |
| Complete blood counts                                        | Interrupt treatment if leukocytosis is not improved with hydroxyurea. When resolved, resume ivosidenib at 500 mg once daily. Do not withhold for cytopenias. |
| Prior to initiation then weekly for the first month, every other week for second month, then monthly for duration of therapy |                                                                 |
| Chemistries                                                  | Interrupt for any grade 3 or higher toxicity. Restart when toxicity resolves. |
| Same frequency as blood counts                               |                                                                 |
| Creatine phosphokinase                                       | Interrupt for any grade 3 or higher toxicity. Restart when toxicity resolves. |
| Weekly for the first month of treatment                      |                                                                 |
| Electrocardiogram                                            | Dose interruption when QTc is > 500 msec and close monitoring when > 480 msec |
| Weekly for the first 3 weeks, then once monthly during therapy |                                                                 |
Ivosidenib monotherapy for induction therapy in older adults with R/R disease who are not candidates for or decline intense therapy (NCCN, 2018). Relapsed/refractory AML has a poor prognosis and additional therapies improving outcomes are needed. Future trials are underway to solidify its use in combination with other chemotherapy agents in the hopes of improving outcomes for patients with AML (ClinicalTrials.gov, 2019).

The advanced practitioner can provide education to patients regarding the safety and efficacy of this agent through clinical trial data. In addition, they can provide adequate safety monitoring and side-effect management for patients receiving ivosidenib therapy. Patients should be aware of the significant financial burden associated with this therapy: it costs approximately $27,000 for a 60-day supply, and health-care providers should assist in identifying resources available to patients such as a copay card and patient support program assistance offered by the manufacturer.

Disclosure
The authors have no conflicts of interest to disclose.

References
Agios Pharmaceuticals, Inc. (2018). Tibsovo (ivosidenib) package insert. Retrieved from https://www.tibsovo.pro.com/pdf/prescribinginformation.pdf
Amantangelo, M. D., Quek, L., Shih, A., Stein, E. M., Roshal, M., David, M. D.,...Levine, R. L. (2017). Enasidenib induces acute myeloid leukemia cell differentiation to promote clinical response. Blood, 130(6), 732–741. https://doi.org/10.1182/blood-2017-04-779447
American Cancer Society. (2018). Treatment response rates for acute myeloid leukemia. Retrieved from https://www.cancer.org/cancer/acute-myeloid-leukemia/treating/response-rates.html
Anderson, J. E., Kopecky, K. J., Willman, C. L., Head, D., O’Donnell, M. R., Luthardt, F. W.,...Appelbaum, F. R. (2002). Outcome after induction chemotherapy for older patients with acute myeloid leukemia is not improved with mitoxantrone and etoposide compared to cytarabine and daunorubicin: A Southwest Oncology Group study. Blood, 100(12), 3869–3876. https://doi.org/10.1182/blood-2001-02-0354
Cairo, M. S., Coiffier, B., Reiter, A.,...Younes, A. (2010). Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: An expert TLS panel consensus. British Journal of Haematology, 149(4), 578–586. https://doi.org/10.1111/j.1365-2141.2010.08143
ClinicalTrials.gov. (2018). A study of AG-120 (ivosidenib) in subjects with mild or moderate hepatic impairment or normal hepatic function. ClinicalTrials.gov identifier: NCT03282513. Retrieved from https://clinicaltrials.gov/ct2/show/NCT03282513
ClinicalTrials.gov. (2019). Ivosidenib search. Retrieved from https://clinicaltrials.gov/ct2/results?cond=&term=Ivositidin&cntry=&state=&city=&dist=
Coiffier, B., Altman, A., Pui, C.-H., Younes, A.,...Cairo, M. S. (2008). Guidelines for the management of pediatric and adult tumor lysis syndrome: An evidence-based review. Journal of Clinical Oncology, 26(16), 2767–2777. https://doi.org/10.1200/JCO.2007.15.0177
Dhillon, S. (2018). Ivosidenib: First global approval. Drugs, 78(14), 1509–1516. https://doi.org/10.1007/s40265-018-0978-3
DiNardo, C. D., de Botton, S., Stein, E. M., Roboz, G. J., Mims, A. S., Polley, D. A.,...Kantarjian, H. M. (2017). Ivosidenib (AG-120) in mutant IDH1 AML and advanced hematologic malignancies: Results of a phase 1 dose escalation and expansion study. Blood, 130(suppl 1), 725. Retrieved from http://www.bloodjournal.org/content/130/Suppl_1/725
DiNardo, C. D., Stein, E. M., de Botton, S., Roboz, G. J., Altman, J. K., Mims, A. S.,...Fathi, A. T. (2018). Durability remission with ivosidenib in IDH1-mutated relapsed or refractory AML. New England Journal of Medicine, 378, 2386–2398. https://doi.org/10.1056/NEJMoa1716984
Fathi, A. T., DiNardo, C. D., Kline, I., Kenvin, L., Gupta, I., Attar, E. C.,...de Botton, S. (2018). Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2: Analysis of a phase 1/2 study. JAMA Oncology, 4(8), 1106–1110, https://doi.org/10.1001/jamaoncol.2017.6995
Ivosidenib deemed safe, effective in AML. (2018). Cancer Discovery, 8(8), OF1. https://doi.org/10.1158/2159-8290.CD-NB2018-082
Knepper, T. C., Deutsch, Y. E., Bhagat, C. K., Watts, J. M., Bradley, T. J., Samra, W.,...Saliman, D. A. (2018). Increased frequency of IDH1/2 mutations in extramedullary acute myeloid leukemia. Blood, 123(suppl 1), 1524. https://doi.org/10.1182/blood-2018-99-113088
Le, K., Wada, R., Dai, D., Fan, B., Liu, G., Attar, E. C.,...Yang, H. (2018). Population pharmacokinetics of ivosidenib (AG-120) in patients with IDH1-mutant advanced hematologic malignancies. Blood, 132, 1394. https://doi.org/10.1182/blood-2018-99-109863
Montesinos, P.,& Sanz, M. A. (2011). The differentiation syndrome in patients with acute promyelocytic leukemia: Experience of the pethema group and review of the literature. Mediterranean Journal of Hematology and Infectious Diseases, 3(0), e2011059. https://doi.org/10.4084/MJHID.2011.059
National Comprehensive Cancer Network. (2018). NCCN Clinical Practice Guidelines in Oncology: Acute myeloid leukemia. V2.2018. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf
Norsworthy, K. J., Mulkey, F., Ward, A. F., Przepiorka, D., Deisseroth, A. R., Farrell, A. T.,...Sallman, D. A. (2018). Frequency of differentiation syndrome with ivosidenib (IVO) and enasidenib (ENA) for treatment of patients with relapsed or refractory (R/R) isocitrate dehydrogenase (IDH)1- or IDH2-mutated acute myeloid leukemia (AML): A systematic analysis by the U.S. Food and Drug Administration (FDA) [Abstract 615]. Blood (ASH Annual Meeting Abstracts), 132(suppl 1). https://doi.org/10.1182/blood-2018-99-117426
Papaemmanuil, E., Gerstung, M., Bullinger L., Gaidzik, V., Paschka, P., Roberts, N.,...,Campbell, P. (2016). Genomic classification and prognosis in acute myeloid leukemia. New England Journal of Medicine, 374, 2209–2221. https://doi.org/10.1056/NEJMa1516192

Patel, K. P., Barkoh, B. A., Chen, Z., Ma, D., Reddy, N., Medeiros, L. J., & Luthra R. (2011a). Diagnostic testing for IDH1 and IDH2 variants in acute myeloid leukemia: An algorithmic approach using high-resolution melting curve analysis. Journal of Molecular Diagnostics, 13(6), 678–686. https://doi.org/10.1016/j.jmoldx.2011.06.004

Patel, K. P., Ravandi, F., Ma, D., Paladugu, A., Barkoh, B., Medeiros, L., & Luthra, R. (2011b). Acute myeloid leukemia with IDH1 or IDH2 mutations: Frequency and clinicopathologic features. American Journal of Clinical Pathology, 135(1), 35–45. https://doi.org/10.1309/AJCPD7NR2RMNQDVF

Sidaway, R. (2018). Ivosidenib effective in IDH1-mutant AML. Nature Reviews Clinical Oncology, 15(8), 472. https://doi.org/10.1038/s41571-018-0057-4

Stein, E. M., DiNardo, C. D., Fathi, A. T., Mims, A. S., Pratz, K. W., Savona, M. R.,...,Tallman, M. S. (2018). Ivosidenib or enasidenib combined with induction and consolidation chemotherapy in patients with newly diagnosed AML with an IDH1 or IDH2 mutation is safe, effective, and leads to MRD-negative complete remissions. Blood, 132, 560. https://doi.org/10.1182/blood-2018-99-110449

Stein, E. M., DiNardo, C. D., Pollyea, D. A., Fathi, A. T., Roboz, G. J., Altman, J. K.,...,Tallman, M. S. (2017). Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood, 130, 722–731. https://doi.org/10.1182/blood-2017-04-779405

Tamamyan, G., Kadia, T., Ravandi, F., Borthakur, G., Cortes, J., Jabbour, E.,...,Konopleva, M. (2017). Frontline treatment of acute myeloid leukemia in adults. Critical Reviews in Oncology/Hematology, 110, 20–24. https://doi.org/10.1016/j.critrevonc.2016.12.004

Thol, F., Schlenk, R. F., Heuser, M., & Ganser, A. (2015). How I treat refractory and early acute myeloid leukemia. Blood, 126(3), 319–327. https://doi.org/10.1182/blood-2014-10-551911

U.S. Food & Drug Administration. (2018). FDA approves ivosidenib for relapsed or refractory acute myeloid leukemia. Retrieved from https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucms614128.htm