Review

Clinical Cancer Research

Targeting the *IDH2* Pathway in Acute Myeloid Leukemia

Maria L. Amaya[1] and Daniel A. Pollyea[2]

Abstract

Acute myeloid leukemia (AML) is an aggressive disease with a poor prognosis. A large percentage of patients succumb to this disease in spite of aggressive treatments with chemotherapy. Recent advances with mutational analysis led to the discovery of isocitrate dehydrogenase (*IDH*) mutations in AML. IDH2 is an enzyme that catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate; its mutated version leads to the accumulation of the oncometabolite (R)-2 hydroxyglutarate, which disrupts several cell processes and leads to a blockage in differentiation. Targeting *IDH2* is compelling, as it is an early and stable mutation in AML. Enasidenib, a specific small-molecule inhibitor of IDH2, recently gained FDA approval for the treatment of patients with relapsed/refractory *IDH2*-mutated AML. In this review, we will focus on the indications and efficacy of enasidenib in the treatment of patients with *IDH2*-mutated AML. *Clin Cancer Res; 24(20); 4931–6. ©2018 AACR.*

Introduction

Acute myeloid leukemia (AML) is diagnosed in approximately 20,000 patients each year in the United States (1). The prognosis is poor; roughly half of patients die from disease or related complications per year (1). Treatment options for AML are limited and have consisted primarily of cytarabine with anthracyclines for those able to tolerate intensive therapy (2) and, in the United States, hypomethylating agents for unfit patients (3). Cytogenetic subtypes have been the most powerful prognosticators of outcomes (4); however, given roughly half of AML patients have normal cytogenetics, mutational analysis for prognostication purposes is important (5–7). Among the initial mutations discovered via genomic sequencing was isocitrate dehydrogenase *(IDH) 1* (6), which led to great interest in this family of proteins. IDH1 and IDH2 are enzymes that mediate the oxidative decarboxylation of isocitrate to α-ketoglutarate, resulting in the production of NADPH, and are an important factor in the regulation of oxidative stress (8). IDH1 is a cytosolic enzyme, whereas its homolog, IDH2, is found in the mitochondria; both perform a critical step in the Krebs cycle (8). The first association between *IDH* mutations and malignancy was reported in gliomas (9, 10); in AML, it has been determined that *IDH1/2* mutations occur in roughly 20% of patients (7, 11, 12). In this review, we will highlight the IDH2 pathway in AML, with a specific focus on new targeted therapies.

The Mechanism of *IDH* Mutations

Pathologic *IDH* mutations are missense mutations of catalytically active arginine residues. These mutations are located in codon 132 of exon 4 (R132) in *IDH1*, and codons 140 and 172 (R140 and R172) of exon 4 in *IDH2* (13), with R140 being the most common mutation (14–16). *IDH2* mutations are more frequent in AML (17), and *IDH1* and *IDH2* tend to be mutually exclusive (18, 19). Mutations in *IDH* catalyze the reduction of α-ketoglutarate to (R)-2-hydroxyglutarate (2HG), an "oncometabolite" (20, 21), so called because it interrupts several cell pathways that lead to oncogenesis. 2HG induces epigenetic changes by inhibiting demethylases such as JMJD2A (22, 23) and competitively inhibiting several dioxygenases including TET2, a demethylating enzyme (22). As functional proof that these are overlapping pathways, *IDH2* and *TET2* mutations have been found to be mutually exclusive (24). Both *IDH2* mutations, R172 and R140, lead to the accumulation of extremely high levels of 2HG (20, 25), resulting in the reduction of α-ketoglutarate, leading to reduced prolyl hydroxylases and upregulation of HIF1α (26), disrupting adaptation to hypoxia. Finally, high levels of 2HG result in a differentiation blockade (27), contributing to the pathogenesis of AML. Figure 1 summarizes the mechanism of *IDH2* mutations.

Epidemiology and Prognosis of IDH2 Mutations

Several studies have tried to elucidate whether there is an association between *IDH* mutations and cytogenetic abnormalities, or with other mutations. It has been observed that *IDH* mutations are usually associated with cytogenetically normal patients and that they often co-occur with *NPM1* mutations (7, 11, 13, 18, 28–31). Although *IDH* mutations tend to be founder mutations (28, 32), a recent study presented at the American Society of Hematology annual meeting reported that up to 16% of *IDH*-mutant patients in a sample size of >6,000 had "progressor mutations" (subclonal mutations rather than founder mutations). In this study, *IDH1/2* mutations were mostly associated with *DNMT3A*, *SRSF2*, *NPM1*, *ASXL1*, and *RUNX1* mutations, although progressor mutations were more commonly associated with *TP53* and *FLT-3-ITD* (33). Data to support *IDH* as a prognostic marker have been conflicting and inconclusive. Patel

[1]Division of Medical Oncology, University of Colorado, Aurora, Colorado. [2]Division of Hematology, University of Colorado, Aurora, Colorado.

Corresponding Author: Daniel A. Pollyea, University of Colorado School of Medicine, 1665 Aurora Court, Aurora, CO 80224. Phone: 720-848-8084; Fax: 720-848-1786; E-mail: daniel.pollyea@ucdenver.edu

doi: 10.1158/1078-0432.CCR-18-0536

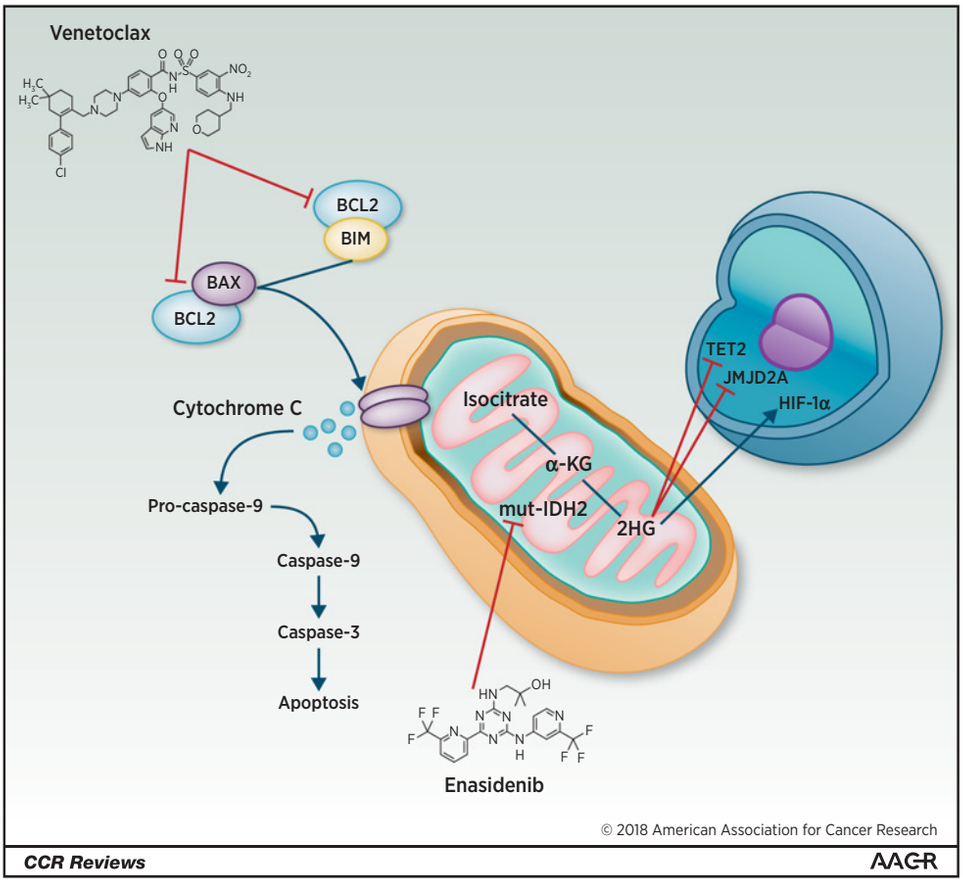

Figure 1.

Mechanism of *IDH2* mutations, and the targeted therapies enasidenib and venetoclax. Mutated *IDH2* leads to the production of 2HG, which affects several pathways including epigenetics (via disruption of TET2 and JMJD2A), and adaptation to hypoxia (HIF1α). Enasidenib directly inhibits the mutated IDH2 enzyme. Venetoclax is a Bcl-2 inhibitor, which allows activation of BAX and release of cytochrome C, leading to apoptosis. It has been shown that *IDH*-mutated cells rely on the Bcl-2 pathway, and therefore, targeting this pathway with venetoclax is beneficial.

and colleagues and others showed *IDH2* R140Q mutations had an overall improved prognosis when associated with *NPM1* mutations (7, 16). There are data to suggest that in patients with normal cytogenetics, *IDH* status did not affect overall survival (OS; refs. 11, 14, 15), whereas other data suggest it was associated with a lower remission rate (13) and lower OS (30, 34). In an effort to understand the impact of *IDH* mutations on prognosis based on all prior data, Xu and colleagues performed a meta-analysis, which showed when *IDH* mutations were pooled together, there was no change in prognosis in AML (31). *IDH2* mutations confer a better prognosis in intermediate-risk AML patients, but not within the subcategory of AML patients with a normal karyotype. The authors also noted the association between *IDH2* and *NPM1* mutations conferred a benefit based on several studies previously mentioned (31). It is possible that the conflicting reports may be a result of comutational data, or in the case of *IDH2*, due to the analysis of *IDH2* R140 and R172 together when they may prognosticate for different outcomes. This is corroborated by data showing R140 and R172 are exclusively comutated with particular genes, and they result in different levels of 2HG suppression (35). Table 1 summarizes studies that highlight the prognostic outcomes of *IDH2* mutations. Although it is inconclusive whether *IDH2* acts as a prognostic marker at diagnosis, 2HG levels do appear to have a prognostic significance after treatment, with higher levels of 2HG resulting in a decrease in OS (36, 37). *IDH* mutations have been largely studied in the adult population, but they also occur in pediatric AML cases. Although less frequent in this population (about 3%), they are also more commonly associated with normal karyotype and with high 2HG levels. These mutations confer no prognostic significance, although studies suggesting this are likely underpowered due to the low percentage of patients having this mutation (38).

Targeting IDH2

Given the incidence of *IDH* mutations in AML, there was interest in developing a specific inhibitor of cells with mutant copies of *IDH* (25). The first IDH2 inhibitor, AGI-6780, targeted the *IDH2* R140 mutation and induced differentiation of primary human *IDH2*-mutated AML cells, while decreasing 2HG (39). Another *IDH2*-mutant small-molecule inhibitor, enasidenib (previously known as AG-221), was developed and was shown to be

Table 1. Prognostic significance of *IDH2* mutations

Study	Cytogenetics or comutations	Percentage of patients with mIDH2 R140	Percentage of patients with mIDH R172	Complete response	OS
Abbas et al. (2010) 893 patients	Largely cytogenetically normal patients. Correlated with NPM1 mutations	8.3%	2.6%	NC (no distinction between R140 and R172)	NC (no distinction between R140 and R172)
Boissel et al. (2010) 502 patients	Largely cytogenetically normal patients	Not studied	3.0%	↓ R172 R140 NS	↓ R172 R140 NS
Marcucci et al. (2010) 358 patients	Cytogenetically normal patients	15.6%	3.6%	↓ R172	NC
Paschka et al. (2010) 805 patients	Largely cytogenetically normal or intermediate-risk patients	6%	2.6%	NC (no distinction between R140 and R172)	NC (no distinction between R140 and R172)
Thol et al. (2010) 272 patients	Cytogenetically normal patients	11%	1.1%	NC (no distinction between R140 and R172)	NC (no distinction between R140 and R172)
Chou et al. (2011) 446 patients	Largely intermediate-risk cytogenetics and normal karyotype. A large number were associated with trisomy 8	9.2%	2.9%	NC (no distinction between R140 and R172)	↑ (No distinction between R140 and R172)
Green et al. (2011) 1473 patients	Largely cytogenetically intermediate-risk patients. R140 correlated with NPM1 mutations	8%	1.9%	↑ R140 ↓ R172	↑ R140 ↓ R172
Chotirat et al. (2012) 230 patients (194 non-APL)	50% of patients had normal karyotype. 25% of patients had t(15;17)	8.7%	1.7%	NS	NC (no distinction between R140 and R172)
Patel et al. (2012) 398 patients	Mostly intermediate- and unfavorable-risk patients. Correlated with NPM1 mutations	6%	2.3%	NS	↑ R140 NC R172
Willander et al. (2014) 189 patients	>50% cytogenetically normal patients	11.1%	2.6%	NC (no distinction between R140 and R172)	↓ R140 ↑ R172
DiNardo et al. (2015) 826 patients	Largely intermediate-risk cytogenetics, and associated with FLT-3 and NPM1 mutations	10%	3%	NC (no distinction between R140 and R172)	NC (no distinction between R140 and R172)

Abbreviations: ↑, improved outcome; ↓, worsened outcome; APL, acute promyelocytic leukemia; NC, no change; NS, not studied.

highly selective with improved solubility and oral availability (40). Initial laboratory studies showed that enasidenib reduced serum 2HG by >90% and allowed primary myeloid cells to differentiate (40). This led to the clinical development of enasidenib, in which reduction of 2HG levels was seen in treated patients (35, 41).

Enasidenib in the Relapsed/Refractory Setting

In a phase I/II clinical trial, 239 relapsed/refractory AML patients 18 years or older were treated with enasidenib in a dose-escalation (doses ranging from 60 to 650 mg QD) and dose-expansion phase. Enasidenib had an overall response rate of 40%, with a median response duration of 5.8 months and a median OS of 9.3 months. Nineteen percent of patients achieved complete remission; these patients had a median OS of 19.7 months. The most common adverse event was indirect hyperbilirubinemia, which occurred in 35% of patients (41) and may be due to off-target inhibition of the UGT1A1 enzyme and had no clinical sequelae (41).

Significant toxicity included differentiation syndrome, tumor lysis syndrome, and leukocytosis, which all occurred in <7% of the patients (41). Differentiation syndrome is a unique complication that can occur with effective therapy in patients with AML. As described above, high levels of 2HG from *IDH2*-mutated cells can result in a differentiation blockade, and treatment with enasidenib can induce rapid differentiation of leukemia cells, resulting in differentiation syndrome, which has disparate clinical features (42). In addition, treatment-related leukocytosis, in concert with differentiation, can make it difficult to discern whether patients are progressing or responding. The treatment of differentiation syndrome involves corticosteroids, hydroxyurea for leukocytosis, and occasionally, a treatment interruption (43, 44). Based on promising results compared with historical controls in this nonrandomized clinical trial, enasidenib received FDA approval for relapsed and refractory (RR) *IDH2*-positive AML in 2017.

Enasidenib in the Upfront Setting

The 2017 American Society of Hematology meeting highlighted several studies using enasidenib in the upfront setting; none have been published in manuscript form. A phase I study used enasidenib in combination with induction chemotherapy in 56 adult patients with *IDH2* mutations who had not previously been treated. Patients with *IDH2* mutations were treated with either enasidenib plus cytarabine and daunorubicin or idarubicin, followed by consolidation with cytarabine plus enasidenib for up to four cycles. They were then maintained with single-agent enasidenib (100 mg) for up to 2 years. Ninety-one percent of patients had >1 grade 3 or higher TEAE with febrile neutropenia and elevated bilirubin being the most common adverse events. They had a total response rate of 62% with a complete remission (CR) of 50% (45). In another analysis, 38 untreated patients from the dose-escalation/-expansion study of predominantly relapsed AML patients who received single-agent enasidenib were analyzed separately; none were deemed candidates for standard treatment. The adverse event profile was similar to that of the relapsed population. The overall response was 32% with a CR of 18%. The median OS in these patients was 11.3 months (46). This regimen is also being explored in the Beat AML master trial, in which newly diagnosed older *IDH2*-mutated patients receive single-agent enasidenib, with the option to add azacitidine after the first cycle of treatment (NCT03013998, BAML-16-001-S3). The combination

of enasidenib and azacitidine was also reported in the upfront setting; 6 patients with *IDH2* mutations received enasidenib (100 or 200 mg) in combination with azacitidine. The majority of the patients had an R140 mutation, and they had a median treatment of 9 cycles. The study had an overall response rate of 4 out of 6 patients, and 2 patients in the 100-mg enasidenib arm achieved a complete remission (47).

Enasidenib amid Other Agents

Note that 2017 was a year of several FDA approvals for new agents in the treatment of AML. Among these agents is midostaurin, a multitargeted kinase inhibitor, which acts as an inhibitor against FLT3-ITD/FLT-3-TKD. Midostaurin in combination with induction and consolidation chemotherapy, followed by maintenance therapy, showed an increased OS from 25.6 versus 74.7 months; however, unlike enasidenib, midostaurin has not been shown to be effective as a single agent in the treatment of AML (48). Among other therapies with single-agent activity is sorafenib, a multikinase inhibitor that has been used in the treatment of relapsed and refractory (RR) AML. In a phase I study including 50 patients, an overall response was achieved in 10% of patients with *FLT3-ITD* mutations, with 34% of patients showing reduction of blasts, and duration of response lasting for at least two cycles (49). It has also been shown to improve duration of remission in *FLT3-ITD* patients treated with sorafenib after allogeneic transplantation (50). Another agent to gain reapproval from the FDA is gemtuzumab ozogamicin (GO), an anti-CD33 antibody used for the treatment of $CD33^{+}$ newly diagnosed AML patients. It was approved for administration in combination with induction chemotherapy, as it showed improvement in event-free survival (51). As a single agent, it can be used in newly diagnosed AML patients not fit for chemotherapy, with an improved median survival from 3.6 to 4.9 months (52). Treatment of RR AML with GO resulted in 26% of the patients achieving a CR with median duration of 11 months and OS of 8.4 months (53). Single-agent azacitidine has been shown to be beneficial in the elderly population with untreated AML, as presented in a subgroup analysis of the AZA-AML-001 study. In this study, elderly patients were randomized to azacitidine versus conventional care regimens (best supportive care, low-dose cytarabine, or intensive chemotherapy). Azacitidine resulted in a CR rate of 18%, with OS of 19.1 versus 13.4 months with conventional care regimens (54). Among experimental agents that appear to have promising single-agent activity is ivosidenib, an IDH1 inhibitor. Preliminary results from a phase I clinical trial on *IDH1*-mutated relapsed/refractory AML patients showed an overall response rate [CR/CR with incomplete count recovery (CRi)] of 30%, with a median duration of 8.2 months, which appears comparable with enasidenib efficacy in the *IDH2*-mutated population (55). Although impossible to truly compare efficacy across trials, based on response rates of above-mentioned agents, enasidenib has comparable, if not better, response rates to other single-agent therapies and appears to be a good option in a selected population of patients.

AG-881

AG-881 is an inhibitor of both *IDH1* and *IDH2* mutations and has the added benefit of penetrating the blood–brain barrier. There is currently an ongoing phase I, multicenter study with AG-881 to evaluate safety profile in advanced hematologic malignancies with *IDH1/2* mutations (NCT02492737); no results have been reported to date.

Venetoclax

B-cell Lymphoma-2 (Bcl-2) is an antiapoptotic protein that is overexpressed in several malignancies (56, 57), including AML (58), and high levels of Bcl-2 have oncogenic properties via impaired apoptosis (59). Venetoclax is a small molecule that inhibits Bcl-2, and it gained FDA approval for chronic lymphocytic leukemia in 2016. Although not a direct inhibitor of IDH, *IDH*-mutated cells may be sensitive to venetoclax. Chan and colleagues first reported the dependence of *IDH*-mutant cells on the Bcl-2 pathway (60) by using a synthetic lethal approach, taking advantage of the fact that cells that express an oncogenic mutation often depend on a particular pathway and/or other genes for survival. Using this screen, *IDH*-mutant AML cells were noted to depend on Bcl-2 for survival and were sensitive to venetoclax (60). In a study of relapsed/refractory AML patients that used single-agent venetoclax, the overall response rate for 32 patients was 19%. However, patients with *IDH1/2* mutations had a 33% CR/CRi rate (61), suggesting venetoclax may be a promising agent for AML patients with *IDH* mutations. Off-label venetoclax has also been used in combination with low-intensity chemotherapy in patients with RR myeloid malignancies. A recent study looked at with RR AML patients receiving venetoclax in combination with hypomethylating agents or low-dose cytarabine. Patients received a median of 2 cycles of treatment. Of 11 patients with *IDH* mutations, 27% responded to treatment, with 1 CR, 1 CRi, and 1 morphologic leukemia-free state. One patient quickly cleared peripheral blasts but had infectious complications leading to hospice care, and another patient had greater than 50% blasts reduction, without full hematologic recovery (62).

Discussion

The outcome for patients with AML has remained poor, in part due to a lack of new effective treatments. In a very short time from the discovery of *IDH* as a pathogenic mutation, there is now an FDA-approved targeted therapy for patients with this mutation, a very impressive accomplishment for a field that has had few victories over many years. *IDH2* has been shown to be an early and stable mutation, seen in about 8% to 19% of patients with AML. It is unclear whether and how *IDH2* mutations affect prognosis, but it is suspected that oncogenesis relies on the overproduction of the oncometabolite 2HG. The specific and potent IDH2 inhibitor enasidenib decreases 2HG and can result in differentiation of AML cells, leading to clinical responses. However, although nearly all patients treated with enasidenib have rapid and profound reductions in 2HG, not all patients respond to treatment, suggesting we do not fully understand the mechanism of action of this agent. Furthermore, not all patients achieving a CR after enasidenib treatment have a complete molecular response (35). While trying to elucidate why some patients are nonresponders, recent data suggest patients with R172 mutation have less suppression of 2HG when compared with R140, and patients with comutated genes had lower responses to enasidenib. Particularly, patients with comutation of RAS pathways achieved less CR (35). Enasidenib has been primarily studied in the relapsed/refractory setting, with overall response rates around 40%. Although this represents an

improvement over alternative treatments with respect to activity and tolerability, given that IDH2 is an early, stable mutation and enasidenib is a highly effective IDH2 inhibitor, one has to consider whether improvements will be possible from a strategy of targeting a single pathway or mutation in this very heterogeneous disease. It is conceivable that multiple mutations could be simultaneously targeted. However, considering relatively few mutations are druggable, the extreme heterogeneity of this disease, and the potential toxicity of multiple concomitant therapies, this is unlikely to be feasible. The role of targeted therapies therefore must be more clearly defined. Focusing on targeting IDH2 in the upfront treatment setting, likely in combination with conventional intensive and nonintensive treatment approaches, may result in longer remission durations, but requires upfront knowledge of the patient's mutational profile, which can be difficult for patients who present in extremis. Alternatively, targeting IDH2 may be best used as a tool to achieve a remission that would allow a patient to proceed to a potentially curative therapy, such as a stem cell transplantation, with chemorefractory disease that otherwise prevents such a maneuver. Otherwise, it may remain a medium-term and relatively nontoxic strategy for a minority of patients with RR disease. Given the clinical activity in this area, the coming years will better elucidate the ideal scenario for targeting IDH2.

Disclosure of Potential Conflicts of Interest

D.A. Pollyea reports receiving commercial research grants from Agios and is a consultant/advisory board member for Agios and Celgene. No potential conflicts of interest were disclosed by the other author.

Received February 14, 2018; revised April 17, 2018; accepted May 11, 2018; published first May 16, 2018.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.
2. Rai KR, Holland JF, Glidewell OJ, Weinberg V, Brunner K, Obrecht JP, et al. Treatment of acute myelocytic leukemia: a study by cancer and leukemia group B. Blood 1981;58:1203–12.
3. Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol 2012;30:2670–7.
4. Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, Goldstone AH, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood 2010;116:354–65.
5. Falini B, Nicoletti I, Martelli MF, Mecucci C. Acute myeloid leukemia carrying cytoplasmic/mutated nucleophosmin (NPMc+ AML): biologic and clinical features. Blood 2007;109:874–85.
6. Mardis ER, Ding L, Dooling DJ, Larson DE, McLellan MD, Chen K, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. N Engl J Med 2009;361:1058–66.
7. Patel JP, Gonen M, Figueroa ME, Fernandez H, Sun Z, Racevskis J, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med 2012;366:1079–89.
8. Molenaar RJ, Radivoyevitch T, Maciejewski JP, van Noorden CJ, Bleeker FE. The driver and passenger effects of isocitrate dehydrogenase 1 and 2 mutations in oncogenesis and survival prolongation. Biochim Biophys Acta 2014;1846:326–41.
9. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, et al. An integrated genomic analysis of human glioblastoma multiforme. Science 2008;321:1807–12.
10. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009;360:765–73.
11. Paschka P, Schlenk RF, Gaidzik VI, Habdank M, Kronke J, Bullinger L, et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J Clin Oncol 2010;28:3636–43.
12. Dohner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med 2015;373:1136–52.
13. Marcucci G, Maharry K, Wu YZ, Radmacher MD, Mrozek K, Margeson D, et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol 2010;28:2348–55.
14. Abbas S, Lugthart S, Kavelaars FG, Schelen A, Koenders JE, Zeilemaker A, et al. Acquired mutations in the genes encoding IDH1 and IDH2 both are recurrent aberrations in acute myeloid leukemia: prevalence and prognostic value. Blood 2010;116:2122–6.
15. Thol F, Damm F, Wagner K, Gohring G, Schlegelberger B, Hoelzer D, et al. Prognostic impact of IDH2 mutations in cytogenetically normal acute myeloid leukemia. Blood 2010;116:614–6.
16. Green CL, Evans CM, Zhao L, Hills RK, Burnett AK, Linch DC, et al. The prognostic significance of IDH2 mutations in AML depends on the location of the mutation. Blood 2011;118:409–12.
17. Stein EM. Molecular pathways: IDH2 mutations-co-opting cellular metabolism for malignant transformation. Clin Cancer Res 2016;22:16–9.
18. DiNardo CD, Ravandi F, Agresta S, Konopleva M, Takahashi K, Kadia T, et al. Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML. Am J Hematol 2015;90:732–6.
19. Platt MY, Fathi AT, Borger DR, Brunner AM, Hasserjian RP, Balaj L, et al. Detection of dual IDH1 and IDH2 mutations by targeted next-generation sequencing in acute myeloid leukemia and myelodysplastic syndromes. J Mol Diagn 2015;17:661–8.
20. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 2009;462:739–44.
21. Ward PS, Patel J, Wise DR, Abdel-Wahab O, Bennett BD, Coller HA, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. Cancer Cell 2010;17:225–34.
22. Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim SH, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. Cancer Cell 2011;19:17–30.
23. Chowdhury R, Yeoh KK, Tian YM, Hillringhaus L, Bagg EA, Rose NR, et al. The oncometabolite 2-hydroxyglutarate inhibits histone lysine demethylases. EMBO Rep 2011;12:463–9.
24. Figueroa ME, Abdel-Wahab O, Lu C, Ward PS, Patel J, Shih A, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. Cancer Cell 2010;18:553–67.
25. Ragon BK, DiNardo CD. Targeting IDH1 and IDH2 mutations in acute myeloid leukemia. Curr Hematol Malig Rep 2017;12:537–46.
26. Bruick RK, McKnight SL. A conserved family of prolyl-4-hydroxylases that modify HIF. Science 2001;294:1337–40.
27. Losman JA, Looper RE, Koivunen P, Lee S, Schneider RK, McMahon C, et al. (R)-2-hydroxyglutarate is sufficient to promote leukemogenesis and its effects are reversible. Science 2013;339:1621–5.
28. Chou WC, Hou HA, Chen CY, Tang JL, Yao M, Tsay W, et al. Distinct clinical and biologic characteristics in adult acute myeloid leukemia bearing the isocitrate dehydrogenase 1 mutation. Blood 2010;115:2749–54.
29. Patel KP, Ravandi F, Ma D, Paladugu A, Barkoh BA, Medeiros LJ, et al. Acute myeloid leukemia with IDH1 or IDH2 mutation: frequency and clinicopathologic features. Am J Clin Pathol 2011;135:35–45.

30. Boissel N, Nibourel O, Renneville A, Gardin C, Reman O, Contentin N, et al. Prognostic impact of isocitrate dehydrogenase enzyme isoforms 1 and 2 mutations in acute myeloid leukemia: a study by the Acute Leukemia French Association group. J Clin Oncol 2010;28:3717–23.
31. Xu Q, Li Y, Lv N, Jing Y, Xu Y, Li Y, et al. Correlation between isocitrate dehydrogenase gene aberrations and prognosis of patients with acute myeloid leukemia: a systematic review and meta-analysis. Clin Cancer Res 2017;23:4511–22.
32. Chou WC, Lei WC, Ko BS, Hou HA, Chen CY, Tang JL, et al. The prognostic impact and stability of Isocitrate dehydrogenase 2 mutation in adult patients with acute myeloid leukemia. Leukemia 2011;25:246–53.
33. Ma W, De Dios I, Funari V, Sudarsanam S, Jiang S, Agersborg S, et al. IDH1 and IDH2: founding or progressor mutations in myeloid neoplasms [abstract]. In: Proceedings of the American Society of Hematology Annual Meeting; 2017 Dec 9–12; Atlanta, GA. Blood; 2017. Abstract nr 405.
34. Willander K, Falk IJ, Chaireti R, Paul E, Hermansson M, Green H, et al. Mutations in the isocitrate dehydrogenase 2 gene and IDH1 SNP 105C >T have a prognostic value in acute myeloid leukemia. Biomark Res 2014;2:18.
35. Amatangelo MD, Quek L, Shih A, Stein EM, Roshal M, David MD, et al. Enasidenib induces acute myeloid leukemia cell differentiation to promote clinical response. Blood 2017;130:732–41.
36. DiNardo CD, Propert KJ, Loren AW, Paietta E, Sun Z, Levine RL, et al. Serum 2-hydroxyglutarate levels predict isocitrate dehydrogenase mutations and clinical outcome in acute myeloid leukemia. Blood 2013;121:4917–24.
37. Janin M, Mylonas E, Saada V, Micol JB, Renneville A, Quivoron C, et al. Serum 2-hydroxyglutarate production in IDH1- and IDH2-mutated de novo acute myeloid leukemia: a study by the Acute Leukemia French Association group. J Clin Oncol 2014;32:297–305.
38. Andersson AK, Miller DW, Lynch JA, Lemoff AS, Cai Z, Pounds SB, et al. IDH1 and IDH2 mutations in pediatric acute leukemia. Leukemia 2011;25:1570–7.
39. Wang F, Travins J, DeLaBarre B, Penard-Lacronique V, Schalm S, Hansen E, et al. Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation. Science 2013;340:622–6.
40. Yen K, Travins J, Wang F, David MD, Artin E, Straley K, et al. AG-221, a first-in-class therapy targeting acute myeloid leukemia harboring oncogenic IDH2 mutations. Cancer Discov 2017;7:478–93.
41. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood 2017;130:722–31.
42. Fathi AT, Sadrzadeh H, Borger DR, Ballen KK, Amrein PC, Attar EC, et al. Prospective serial evaluation of 2-hydroxyglutarate, during treatment of newly diagnosed acute myeloid leukemia, to assess disease activity and therapeutic response. Blood 2012;120:4649–52.
43. Birendra KC, DiNardo CD. Evidence for clinical differentiation and differentiation syndrome in patients with acute myeloid leukemia and IDH1 mutations treated with the targeted mutant IDH1 inhibitor, AG-120. Clin Lymphoma Myeloma Leuk 2016;16:460–5.
44. Fathi AT, DiNardo CD, Kline I, Kenvin L, Gupta I, Attar EC, et al. Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2: analysis of a phase 1/2 study. JAMA Oncol 2018;4:1106–10.
45. Stein E, DiNardo C, Mims A, Savona M, Pratz K, Stein A, et al. Ivosidenib or enasidenib combined with standard induction chemotherapy is well tolerated and active in patients with newly diagnosed AML with an IDH1 or IDH2 mutation: initial results from a phase 1 trial [abstract]. In: Proceedings of the American Society of Hematology Annual Meeting; 2017 Dec 9–12; Atlanta, GA. Blood; 2017. Abstract nr 726.
46. Pollyea D, Tallman M, Botton S, DiNardo C, Kantarjian H, Collins R, et al. Enasidenib monotherapy is effective and well-tolerated in patients with previously untreated mutant- IDH2 (m IDH2) acute myeloid leukemia (AML) [abstract]. In: Proceedings of the American Society of Hematology Annual Meeting; 2017 Dec 9–12; Atlanta, GA. Blood; 2017. Abstract nr 638.
47. DiNardo C, Stein A, Fathi A, Montesinos P, Odenike O, Kantarjian H, et al. Mutant isocitrate dehydrogenase (mIDH) inhibitors, enasidenib or ivosidenib, in combination with azacitidine (AZA): preliminary results of a phase 1b/2 study in patients with newly diagnosed acute myeloid leukemia (AML) [abstract]. In: Proceedings of the American Society of Hematology Annual Meeting; 2017 Dec 9–12; Atlanta, GA. Blood; 2017. Abstract nr 639.
48. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med 2017;377:454–64.
49. Borthakur G, Kantarjian H, Ravandi F, Zhang W, Konopleva M, Wright JJ, et al. Phase I study of sorafenib in patients with refractory or relapsed acute leukemias. Haematologica 2011;96:62–8.
50. Metzelder SK, Schroeder T, Finck A, Scholl S, Fey M, Gotze K, et al. High activity of sorafenib in FLT3-ITD-positive acute myeloid leukemia synergizes with allo-immune effects to induce sustained responses. Leukemia 2012;26:2353–9.
51. Castaigne S, Pautas C, Terre C, Raffoux E, Bordessoule D, Bastie JN, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet 2012;379:1508–16.
52. Amadori S, Suciu S, Selleslag D, Aversa F, Gaidano G, Musso M, et al. Gemtuzumab ozogamicin versus best supportive care in older patients with newly diagnosed acute myeloid leukemia unsuitable for intensive chemotherapy: results of the randomized phase III EORTC-GIMEMA AML-19 trial. J Clin Oncol 2016;34:972–9.
53. Taksin AL, Legrand O, Raffoux E, de Revel T, Thomas X, Contentin N, et al. High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: a prospective study of the alfa group. Leukemia 2007;21:66–71.
54. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Gattermann N, Germing U, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol 2010;28:562–9.
55. DiNardo C, De Botton S, Stein E, Roboz GJ, Mims AS, Pollyea DA, et al. Ivosidenib (AG-120) in mutant IDH1 AML and advanced hematologic malignancies: results of a phase 1 dose escalation and expansion study [abstract]. In: Proceedings of the American Society of Hematology Annual Meeting; 2017 Dec 9–12; Atlanta, GA. Blood; 2017. Abstract nr 725.
56. Yip KW, Reed JC. Bcl-2 family proteins and cancer. Oncogene 2008;27:6398–406.
57. Reed JC. Bcl-2-family proteins and hematologic malignancies: history and future prospects. Blood 2008;111:3322–30.
58. Porwit-MacDonald A, Ivory K, Wilkinson S, Wheatley K, Wong L, Janossy G. Bcl-2 protein expression in normal human bone marrow precursors and in acute myelogenous leukemia. Leukemia 1995;9:1191–8.
59. Adams JM, Cory S. The Bcl-2 apoptotic switch in cancer development and therapy. Oncogene 2007;26:1324–37.
60. Chan SM, Thomas D, Corces-Zimmerman MR, Xavy S, Rastogi S, Hong WJ, et al. Isocitrate dehydrogenase 1 and 2 mutations induce BCL-2 dependence in acute myeloid leukemia. Nat Med 2015;21:178–84.
61. Konopleva M, Pollyea DA, Potluri J, Chyla B, Hogdal L, Busman T, et al. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. Cancer Discov 2016;6:1106–17.
62. DiNardo CD, Rausch CR, Benton C, Kadia T, Jain N, Pemmaraju N, et al. Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies. Am J Hematol 2018;93:401–7.