Introduction

In concert with the sequencing of the first AML genome in 2008, the discovery of isocitrate dehydrogenase (IDH) mutations in AML was first described. It is now recognized that approximately 8% and 12% of acute myeloid leukemias harbor an IDH1 or IDH2 mutation, respectively, with IDH mutations also present in a minority of other myeloid malignancies such as myelodysplastic syndrome (MDS) and accelerated myeloproliferative neoplasms (MPNs). These recurrent mutations in key metabolic enzymes lead to the production of the oncometabolite 2-hydroxyglutarate (2-HG), which promotes leukemogenesis through a block in normal myeloid differentiation. Since this discovery, selective oral inhibitors of mutant IDH1 and IDH2 have subsequently been developed and are now approved as single agent therapy, based on clinical efficacy observed within the original first-in-human trials. The investigation of IDH inhibitors in combination with standard therapies such as azacitidine, with intensive chemotherapy, and with other small molecule targeted therapies in rational combinations are currently under evaluation to further improve upon clinical efficacy.

Abstract

Acute myeloid leukemia is a genetically heterogeneous hematologic malignancy; approximately 20% of AML harbors a mutation in the isocitrate dehydrogenase (IDH) genes, IDH1 or IDH2. These recurrent mutations in key metabolic enzymes lead to the production of the oncometabolite 2-hydroxyglutarate, which promotes leukemogenesis through a block in normal myeloid differentiation. Since this discovery, selective oral inhibitors of mutant IDH1 and IDH2 have subsequently been developed and are now approved as single agent therapy, based on clinical efficacy observed within the original first-in-human trials. The investigation of IDH inhibitors in combination with standard therapies such as azacitidine, with intensive chemotherapy, and with other small molecule targeted therapies in rational combinations are currently under evaluation to further improve upon clinical efficacy.
This review will focus on current strategies of IDH1 and IDH2 inhibition in AML (Fig. 2). Table 1 provides a summary of the reported trials and efficacy outcomes seen with IDH1 and IDH2 inhibitors to date.

**Targeting IDH2 in AML**

Enasidenib (IDHIFA, formerly AG-221) is the first-in-class, selective and orally available mutant IDH2 inhibitor which demonstrated efficacy both in vitro and in vivo; normalizing 2-HG levels and inducing myeloid differentiation in various pre-clinical models. In the first-in-human phase 1 dose escalation and expansion study (AG221-001), 345 patients with advanced IDH2-mutated myeloid malignancies were enrolled. The recommended phase 2 dose was determined as 100 mg daily, and in 214 patients with relapsed or refractory AML treated at the 100 mg dose level, the complete remission (CR) rate was 19.6% and CR with incomplete hematologic recovery (CRi) was 9%, with an overall response rate (ORR) of 39%. The time to best response was 3.7 months, and median duration of CR/CRi lasted 8 months. The median OS among all patients was 8.8 months, with a median OS of 22.9 months for patients attaining a CR and 10.6 months for patients with a non-CR response. IDH2-mutational clearance, as assessed by digital-droplet PCR with a detection level of 0.04%, occurred in ~1/3 of patients who attained aa CR or a CR with partial hematologic recovery (CRh) demonstrating the potential for deep remission in a minority of responding patients.

Subsequent translational analysis of the original relapsed/refractory (R/R) cohort has identified that patients with co-occurring RAS pathway mutations (i.e., NRAS, KRAS, FLT3-ITD, PTPN11) are less likely to respond, as are patients with a high co-mutational burden (i.e., the presence of 6 or more co-occurring mutations).

Patients with 3 or less mutations and no RAS pathway mutation had a 55% chance of responding to enasidenib monotherapy (with a 29% CR rate) whereas patients with ≥6 co-occurring mutations had an ORR of 31% (16% CR rate).

Of interest, while effective 2HG reduction was more frequent in IDH2-R140 variants (median 93% 2HG inhibition) than in IDH2-R172 (median 28% 2HG inhibition), equivalent responses occurred in both R140 and R172 patients. Additionally and of some surprise, responses occurred independently of the size of the IDH2 clone at
treatment initiation, as measured by variant allelic frequency at enrollment.

**Newly diagnosed IDH2-mutated AML**

The original AG221-001 enasidenib monotherapy study enrolled 39 patients with newly diagnosed/treatment-naive IDH2-mutated AML, with a median age of 77 years and 23 (59%) of patients having an antecedent hematologic disorder such as MDS. In this subgroup, the CR rate was 18%, CR/CRi rate was 21%, ORR was 31%, and median OS was 11.3 months in this older and generally high-risk population. Notably, response rates with single agent enasidenib were similar in previously untreated patients and those who progressed on prior therapy as discussed above. This could reflect the fact that previous standard, non-venetoclax-based therapies used in these studies do not alter the mechanisms of response or resistance to IDH inhibition.

Synergistic activity of enasidenib in combination with the hypomethylating agent azacytidine has been demonstrated pre-clinically, leading to the AG221-005 phase II randomized study of azacytidine + enasidenib, versus azacytidine alone, for newly diagnosed patients with AML ineligible for standard intensive chemotherapy. The primary study endpoint was overall response rate, with OS and EFS as key secondary endpoints. A total of 101 patients were enrolled in a 2:1 ratio to azacytidine + enasidenib (n = 68) or azacytidine (n = 33), with a CR rate of 53% vs 12%, CR/CRi rate of 63% vs 24%, and ORR of 71% vs 42% leading to the study reaching its primary endpoint. With a median follow up of 14 months, median EFS was 17.2 months with the combination vs 10.8 months with azacytidine alone (p = NS) and OS 22 months in both groups.

When considering the overlapping survival of both frontline treatment arms, it is of particular importance to recall that the study was not blinded. The median number of cycles received of the enasidenib + azacytidine combination was 10, compared to 6 with azacytidine mono-therapy, and at least 24% of patients randomized to azacytidine alone were taken off the study to receive subsequent enasidenib, alone or in combination, potentially confounding OS results.

For newly diagnosed younger patients appropriate for cytotoxic therapy, a recently reported Phase 1 combination study evaluated enasidenib in combination with 7+3 therapy. In 91 patients with IDH2 mutations and a median age of 63 yrs, CR/CRi rates were 74% and median OS was 25.6 months. A confirmatory Phase 3 study to clarify the role of adding enasidenib to induction-consolidation chemotherapy for IDH2-mutated AML is under evaluation, in a randomized phase 3 multi-institutional trial (NCT#03839771), which importantly will also include a maintenance component of enasidenib (vs placebo) after completion of induction/consolidation (+/− allogeneic SCT) to investigate the role of enasidenib as maintenance. A combination study of the liposomal 7+3 chemotherapeutic CPX-351 with enasidenib is also enrolling (NCT03825796).

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**Table 1** Clinical activity of IDH inhibitors as single agents or in combination.

| A  | 7+3 | V | E | I | N | Md age | CR/CRi | mOS       | References |
|----|-----|---|---|---|---|--------|--------|----------|-----------|
| **Newly Diagnosed AML:** |     |    |    |    |    |        |        |          |           |
| A  | 28  | 78 yrs | 10.7% |         | 6.2 mo | 41,42 |       |          |           |
| A  | 33  | 75 yrs | 24.2% |         | 22 mo  | 24    |       |          |           |
| E  | 39  | 77 yrs | 21%   |         | 11.3 mo| 23    |       |          |           |
| I  | 33  | 76 yrs | 48.5% |         | 12.6 mo| 29    |       |          |           |
| A  | V   | 79  | 76 yrs | 78.5% (85.7% IDH2, 65.6% IDH1) | 24.5 mo (NR for IDH2, 17.5 mo IDH1) | 42    |       |          |           |
| A  | E   | 68  | 75 yrs | 63.2%  |         | 22 mo | 24    |       |           |
| A  | I   | 23  | 76 yrs | 69.6%  |         | NR (12 mo OS 82%) | 30    |       |           |
| A  | V   | I   | 12  | 67 yrs | 75%    |         | NR    | 43    |           |
| 7+3| E   | 91  | 63 yrs | 74% (80% de novo, 63% sAML) | 12-mo OS 77% | 25    |       |          |           |
| 7+3| I   | 60  | 63 yrs | 77% (88% de novo, 50% in sAML) | 12-mo OS 78% | 25    |       |          |           |
| **Relapsed/Refractory AML:** |     |    |    |    |    |        |        |          |           |
| E  | 345 | 68 yrs | 28.6% |         | 9.3 mo | 20    |       |          |           |
| I  | 258 | 68 yrs | 30%   |         | 8.8 mo | 27    |       |          |           |

A azacytidine, V venetoclax, E Enasidenib, I Iosidenib, Md age median age, yrs years, mo months, CR/CRi complete response/complete response with incomplete count recovery, mOS median overall survival, IDH Isocitrate Dehydrogenase, NR not reached, sAML secondary acute myeloid leukemia.
Targeting IDH1 in AML

Ivosidenib (TIBSOVO, formerly AG-120) is the first-in-class, selective and orally available mutant IDH1 inhibitor, with confirmed pre-clinical efficacy leading to robust 2HG inhibition and reinstatement of effective myeloid differentiation26. In the first-in-human phase 1 dose escalation and expansion study (AG120-001), 258 patients with advanced IDH1-mutated myeloid malignancies were enrolled27. The recommended phase 2 dose of ivosidenib was established at 500 mg daily, with a CR/CRh rate of 30% and ORR 42% in 125 R/R AML patients, with a median duration of CR/CRh lasting 8.2 months. The median OS among all patients was 8.8 months, with a median OS of 18 months in patients attaining a CR/CRh. IDH1-mutational clearance, as assessed by digital-droplet PCR with detection of 0.04%, occurred in 21% of responding patients, again highlighting the potential for deep remissions in a minority of patients. Patients with mutation clearance had longer durations of remission and longer overall survival with a median OS of 14.5 months vs 10.2 months in those without mutation clearance.

Similar to enasidenib, correlative translational analyses confirmed that patients with co-occurring RAS pathway mutations are less likely to respond to ivosidenib monotherapy. Interestingly, a favorable correlation was found between the presence of a JAK2 mutation and response, with 7 of 11 (64%) AML with JAK2-V617F mutations achieving a CR or CRh28.

Clonal hierarchy was investigated by examining the baseline variant allele frequency (VAF) of the IDH1 mutation in relationship to other identified gene mutations, with the IDH1 mutation defined as sub-clonal in samples where a co-mutation was present at a VAF ≥ 5% that of the IDH1 VAF, and otherwise the IDH1 was defined as clonal. The IDH1 mutation was determined to be sub-clonal in 28% of patients (and clonal in 72%), and with no association of clonal hierarchy to ivosidenib response was identified28.

Newly diagnosed IDH1-mutated AML

There were 33 patients with newly diagnosed/treatment-naïve IDH1-mutated AML that were treated on the original AG120-001 ivosidenib monotherapy trial. The median age was 77 years and 26 (76%) had secondary AML, including 16 patients who had received prior hypomethylating agents for an antecedent hematologic disorder. In this high-risk group, the CR rate was 30%, CR/CRh was 42.5%, and with a median OS of 12.6 months29. In addition to the relapsed IDH1-mutated AML population, the United States Food and Drug Administration (FDA) has approved ivosidenib as monotherapy for the newly diagnosed older and chemotherapy- ineligible population based on these results.

Pre-clinical investigation of mutant IDH1 transformed cell lines demonstrated enhanced differentiation and apoptosis with the combination of azacytidine and ivosidenib (Yen, Cancer Res 78;2018 suppl; abstr 4956). This led to a Phase 1b clinical trial which enrolled 23 patients to the combination of azacytidine and ivosidenib, demonstrating a CR rate of 61%, CR/CRh rate of 70%, and a 12-month OS of 82% (median duration of response or DOR has not been reached, with median follow-up of 16 months)30. The follow-up confirmatory Phase 3 AGILE study of ivosidenib vs placebo in combination with azacytidine in untreated AML is now ongoing (NCT 03173248) with a primary endpoint of relapse-free survival. Ultimately, data from this combination should be compared to venetoclax regimens, the current standard of care for this population. Conceptually, the combination of a hypomethylating agent with venetoclax and an IDH inhibitor should offer the highest chance of response, decrease chance of resistance and provide long-term remissions. We believe that an effective combination used early in the disease process would be superior to a sequential approach of these effective agents as we’ve learned from acute lymphoblastic leukemia or multiple myeloma.

The Phase 1 combination study of intensive chemotherapy + enasidenib for newly diagnosed patients discussed above also included an arm of IDH1-mutated AML, that received ivosidenib in combination with standard intensive chemotherapy. In 60 patients with IDH1 mutations and a median age of 63 yrs, CR/CRi rates were 77%, and 12-month OS was 78%31. A confirmatory randomized phase 3 trial (NCT#03839771) is under evaluation, which also includes maintenance ivosidenib (vs placebo) to evaluate the utility of ivosidenib as maintenance after consolidation therapy (+/− allogeneic stem cell transplant). A study of CPX-351 in combination with ivosidenib (NCT04493164) is also currently enrolling.

Second generation IDH inhibitors

Additional small molecule IDH inhibitors are under various stages of preclinical and clinical development. Compounds from Novartis (IDH305), Agios (AG881; now vorasidenib) and Bayer (BAY1436032) were previously evaluated in Phase 1 clinical trials, and are not currently under clinical development in hematologic malignancies31,32. The brain-penetrant dual inhibitor of IDH1 and IDH2, vorasidenib, is currently under development in recurrent/refractory IDH1-mutated glioma.

Olutasidenib, formerly FT-2102, warrants specific mention as a well-tolerated and effective mutant IDH1 inhibitor33. At the recommended dose of 150 mg twice daily in R/R AML, an ORR of 41% (18% CR) as monotherapy, and ORR of 46% (12% CR) in combination with azacytidine was reported. (Watts ASH 2019) A recent
press release in October 2020 of top-line data from a planned interim analysis of the pivotal Phase 2 olutasid- 
denib monotherapy arm for R/R AML stated positive 
results; in 123 R/R AML patients, a CR/CRh rate of 33.3% 
(30% CR and 3% CRh) and an impressive DOR (censored 
at H SCT) of 13.8 months was attained. This data has not 
yet been presented.

Adverse events

In general, the IDH inhibitors are well tolerated oral 
therapies. Enasidenib is associated with an indirect 
hyperbilirubinemia which occurs in approximately 
15–20% (grade ≥3 in 8%), related to off-target 
UGT1A1 inhibition. This is clinically similar to Gil-
bert’s syndrome and is generally not clinically sig-
nificant. Ivosidenib is associated with grade ≥3 QTc 
prolongation in 7–8%, and routine EKG assessment is 
recommended along with discontinuation of other 
offending QTc prolonging concomitant medications 
when possible.

Both IDH inhibitors are associated with development of 
differentiation syndrome (DS), which is reported in 
approximately 12–15% of patients receiving an IDH 
inhibitor as monotherapy and is most frequently mani-
fested as dyspnea, culture-negative fevers, pulmonary 
infiltrates, and/or hypoxia. IDH-inhibitor related DS 
occurs at a median of 30 days of treatment, however DS 
can be delayed and can occur several months into therapy, 
so attention is warranted. In a review by the FDA of the 
pivotal trials of ivosidenib and enasidenib, DS was iden-
tified in 19% of patients receiving either of those agents.

Discontinuation of the IDH inhibitor in the setting of a 
severe IDH-DS is often recommended, however the half-
life of the IDH inhibitors is measured in days (not hours) 
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of patients attaining minimal or measurable residual disease (MRD) negativity\(^43\). Updated trial results with longer follow-up are anticipated in the coming year. In addition, a trial of enasidenib in combination with venetoclax (NCT04092179) is now enrolling.

**Conclusion**

In conclusion, the development of oral, potent, small molecule and mutant specific IDH1 and IDH2 inhibitors represents an early success story of the cancer genome-sequencing era, and signifies an important advance for AML therapy in the era of personalized therapeutics. Evaluation of strategies to increase efficacy and prevent relapse with IDH inhibitors are ongoing, including clinical investigations of treatment combinations with standard anti-leukemia therapies (i.e., intensive chemotherapy, hypomethylating agents) as well as rational combinations (venetoclax) and agents targeted against AML resistance pathways (i.e., FLT3, RAS, other RTK pathway inhibitors). In addition, second generation and “pan” IDH1/IDH2 inhibitors are also under development, providing further hope in the promise of increasingly improved outcomes in patients with IDH-mutated AML.

**Acknowledgements**

G.C.I. received funding through the K12 Paul Calabresi Clinical Scholarship Award (NIH/NCI K12 CA089894).

**Conflict of interest**

G.C.I. received research funding from Celgene, Kura Oncology, Syndax and Novartis, and received consultancy fees from Novartis and Kura Oncology. C.D. D. received research funding from AbbVie, Agios, Novartis, Celgene, Daiichi-Sankyo, Calithera Biosciences, Jazz Pharmaceuticals, Notable Laboratories, and received consultancy fees from AbbVie, Agios, Novartis, Celgene, Daiichi-Sankyo, and Jazz Pharmaceuticals.

**Publisher’s note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Received:** 19 February 2021 **Revised:** 28 April 2021 **Accepted:** 5 May 2021 **Published online:** 03 June 2021

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